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The PREHAB Study: A protocol for a prospective randomized clinical trial of exercise therapy for people living with frailty having cancer surgery

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Manuscripts

Title: The PREHAB Study: A protocol for a prospective randomized clinical trial of exercise therapy for people living with frailty having cancer surgery

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The OHRI and funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT02934230
Date of registration in primary registry	August 22, 2016
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Source(s) of monetary or material support	International Anesthesia Research Society The University of Ottawa Department of Anesthesiology and Pain Medicine
Primary sponsor	The Ottawa Hospital Research Institute
Secondary sponsor	Investigator-led, Dr. Daniel McIsaac
Contact for public queries	DM, dmcisaac@toh.ca
Contact for scientific queries	DM, dmcisaac@toh.ca
Public title	The Prehabilitation Study: Exercise Before Surgery to Improve Patient Function in People
Scientific title	The Prehabilitation Study: Exercise Before Surgery to Improve Patient Function in People
Countries of recruitment	Canada
Health condition(s) or problem(s) studied	Cancer, Frailty
Intervention(s)	Prehabilitation
Key inclusion and exclusion criteria	Ages eligible for study: ≥ 60 years Sexes eligible for study: both Accepts health volunteers: no
	Inclusion criteria: adult patient (≥ 60 years), elective surgery for intraabdominal or thoracic cancer, Clinical Frailty Score ($\geq 4/9$)
	Exclusion criteria: unable to communicate in written or oral form in official languages serviced by The Ottawa Hospital (English or French), unwilling to participate in home-based prehabilitation, major cardiac risk factors, scheduled to undergo surgery in fewer than 3 weeks from randomization
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: double blind (investigator and outcome assessors)
	Primary purpose: prevention
Date of first enrolment	January 19, 2017
Target sample size	200
Recruitment status	Recruiting
Primary outcome(s)	Postoperative functional capacity (6-Minute Walk Test)
Key secondary outcomes	Functional mobility, patient-reported health related quality of life and disability free survival

ABSTRACT

Introduction: Exercise before surgery (prehabilitation) may improve outcomes. Frailty is a key predictor of adverse postoperative outcomes in older people; the multidimensional nature of frailty makes this a population who may derive substantial benefit from prehabilitation. The objective of this trial is to test the efficacy of prehabilitation to improve postoperative functional outcomes for people living with frailty having cancer surgery with curative intent.

Methods and analysis: We will conduct a single center, parallel-arm randomized controlled trial of home-based prehabilitation vs. standard care among consenting patients ≥ 60 years having elective cancer surgery (intraabdominal and intrathoracic) and who are frail (Clinical Frailty Scale ≥ 4). The intervention consists of ≥ 3 weeks of prehabilitation (strength, aerobic, and stretching). The primary outcome is the 6-minute walk test at the first postoperative clinic visit. Secondary outcomes include the short physical performance battery, health related quality of life, disability free survival, complications and health resource utilization. The primary outcome will be analyzed by intention to treat using analysis of covariance. Outcomes up to one year after surgery will be ascertained through linkage to administrative data.

Ethics and dissemination: Ethical approval has been granted by our ethics review board (Protocol Approval #2016009-01H). Results will be disseminated through presentation at scientific conferences, through peer-reviewed publication, stakeholder organizations, and engagement of social and traditional media.

Trial registration: NCT02934230; Pre-results.

Strengths and limitations of this study

- Adequately powered and blinded for a patient-centered functional outcome.
- Intervention based on a pragmatic intervention with proven efficacy.
- Complex intervention, possible risk of contamination.
- Feasibility of prehabilitaion in older people with frailty before surgery unproven.

For peer review only

INTRODUCTION

Our population is aging rapidly, a demographic shift that directly impacts perioperative care. People aged ≥ 60 years are the fastest growing group of surgical patients,(1) and experience adverse outcomes at a rate two- to four-times higher than younger patients.(2,3) However, amongst older surgical patients, research suggests that 25-40% of adverse outcomes are attributable to the presence of frailty.(4–6) Frailty is a multidimensional syndrome based on an aggregate susceptibility to adverse health outcomes due to age- and disease-related deficits that accumulate across multiple domains.(7,8) Independent of age, gender, and other confounders, people with frailty have significantly higher rates of postoperative morbidity, mortality and healthcare resource use. People living with frailty are also significantly more likely to develop a new disability after elective surgery than older surgical patients without frailty.(9)

Despite the growing observational literature that links the presence of preoperative frailty with adverse outcomes across different surgical procedures, the literature evaluating interventions to improve the postoperative outcomes of people living with frailty is sparse.(6) Frailty-related risk is manifest through vulnerability to stressors.(7) Surgery induces substantial physiological stress, and some data suggest that people with frailty experience a significantly increased risk of early mortality (over 30 times higher than non-frail patients on postoperative day 3).(10) These findings support the hypothesis that the limited physical reserve of frail patients may contribute to their risk of adverse outcomes. Therefore, interventions that target the physical reserve of people with frailty may contribute to improved outcomes. Exercise training in non-surgical people with frailty improves functional capacity, muscle strength and may decrease frailty itself.(11,12) Prehabilitation (preoperative exercise training) of people without frailty having colorectal surgery improves postoperative function when compared to postoperative

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3 exercise alone(13), an effect that may be especially pronounced in people who are older or who
4
5 have multimorbidity. Therefore, we hypothesize that prehabilitation may be an appropriate
6
7 intervention to improve the postoperative outcomes of people living with frailty.
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11 The primary objective of this study is to test the efficacy of home-based prehabilitation
12
13 for older people with frailty having elective surgery with curative intent for intraabdominal or
14
15 intrathoracic cancer, to improve postoperative function as measured by the 6-minute walk test (6-
16
17 MWT) at their first postoperative clinic visit in a parallel-arm superiority trial with equal
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19 allocation between arms. Our secondary objective is to measure this intervention's efficacy in
20
21 improving other important outcomes, including patient-reported and health system measures.
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25 **METHODS AND ANALYSIS**

26 27 28 **Study design and setting**

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31 We will conduct a single center, parallel arm randomized controlled trial of home-based
32
33 prehabilitation vs. standard perioperative care in people living with frailty undergoing elective
34
35 surgery for intraabdominal and intrathoracic known or suspected cancer at The Ottawa Hospital
36
37 (TOH). This will be a superiority trial to test the hypothesis that home-based prehabilitation will
38
39 result in improved postoperative functional outcomes compared to standard care plus a generic
40
41 activity guide. This protocol is reported in keeping with the Standard Protocol Items:
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43 Recommendations for Intervention Trials guidelines.(14) TOH is a 900-bed tertiary care
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45 academic health sciences center serving a catchment area of 1.2 million people. TOH is the
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47 regional cancer referral center for the Eastern portion of the Canadian province of Ontario. On
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49 average, intraabdominal and intrathoracic cancer patients are seen 4 weeks prior to surgery (as
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3 this is a provincial benchmark for cancer care). Research ethics board (REB) approval has been
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5 granted by the study center.
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8 **Eligibility criteria**

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11 All consenting patients 60 years or older who are: scheduled to undergo elective surgery
12
13 for intraabdominal and intrathoracic cancer (colorectal, thoracic, hepatobiliary or urologic); able
14
15 to communicate in French or English; willing to participate in home-based exercise; and
16
17 identified with frailty based on the Clinical Frailty Scale (CFS; score of $\geq 4/9$) will be included.
18
19 The CFS is a 9-point global frailty scale based on clinical evaluation in the domains of mobility,
20
21 energy, physical activity and function.(8) A multitude of frailty instruments exist to diagnose
22
23 frailty. We have chosen the CFS as it is easily administered, has excellent inter-rater reliability,
24
25 and has been shown to accurately identify older patients at high risk of adverse outcomes in a
26
27 variety of acute care settings (8,15,16). The CFS will be administered by trained clinicians and
28
29 clinical researchers.
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35 **Intervention**

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37 The intervention will be a home-based total-body exercise training program
38
39 (prehabilitation), based on a protocol with proven efficacy in improving the function of people
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41 without frailty in less than 4 weeks before surgery (13,17) (see supplemental methods 1).
42
43 Prehabilitation will consist of three components: 1) strength training; 2) aerobic exercise and 3)
44
45 flexibility. Prehabilitation will be prescribed as 1-hour sessions performed a minimum of 3 times
46
47 per week. Intervention group patients will also be provided with standard nutritional advice. In
48
49 addition to paper-based materials outlining the prehabilitation program, participants will have an
50
51 individualized teaching session at the time of recruitment as well as being provided with a take
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3 home video. Furthermore, activity logs and weekly phone calls will be used to encourage and
4
5 measure compliance and to answer questions.
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8 The strength training component consists of one set of 10 repetitions of 10 strength
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10 exercises. The exercises include; push ups, seated rows, chest fly, deltoid lift, bicep curls, triceps
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12 extensions, chair squats, hamstring curls, standing calf raises and abdominal crunches. The
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14 participants will be provided with an elastic band in order to complete these exercises at home.
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16 In addition, participants will be encouraged to modify the exercises based on ability. The
17
18 aerobics component consists of the participants' choice of cardio (e.g. walking, biking, or
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20 swimming) for 20 minutes at moderate intensity. Lastly, the flexibility component consists of 6
21
22 stretches each to be held for 20 seconds, done for 2 repetitions. The stretches target the chest,
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24 arms, legs and truck.
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30 Participants randomized to the control group will receive the World Health Organization
31
32 (WHO) Global Recommendations for Physical Activity for Health for people 60 years and above
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34 pamphlet, as well as Canada's Food Guide. Both groups will receive pedometers to track their
35
36 daily step-count before surgery.
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40 All other pre-, intra- and postoperative care will be at the discretion of each patient's care
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42 team for both intervention and control arm participants. Specifically, intraoperative anesthesia
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44 interventions and intraoperative and postoperative surgical care will be at the discretion of
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46 treating physicians.
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49 **Outcomes**

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52 The primary outcome will be postoperative functional capacity, measured using the 6-
53
54 MWT. The 6MWT will be administered at baseline and at the first postoperative clinic visit. The
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2
3 6-MWT has been widely used for preoperative and postoperative evaluation and for measuring
4 the response to therapeutic interventions for pulmonary and cardiac disease (18). A clinically
5 relevant difference in this outcome is a change of 25 meters walked over 6 minutes.(17,19) All
6 patients will perform a standardized, self-paced 6-minute walk test in a 30-meter long corridor.
7 They will be instructed to walk as far as possible for 6 minutes. Patients will be allowed to stop
8 at any time, but will be encouraged to restart as soon as possible. Covered distance after 6
9 minutes will be measured to the nearest meter.

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Secondary outcomes will reflect four specific domains, 1) function; 2) patient-reported health outcomes and complications; 3) healthcare resource utilization and 4) patient experience with prehabilitation. Outcome assessment windows are shown in Figure 1.

Secondary functional outcomes will be assessed using the Short Physical Performance Battery (SPPB), measured at baseline and at the first postoperative clinic visit. This is a validated, objective assessment which evaluatea lower extremity functioning in older individuals through assessment of balance, gait speed and lower limb functional strength (20–22). Individuals unable to complete a task, receive a score of 0.

Patient-reported Health Related Quality of Life using the EQ-5D(23) (5-level version) will be measured at baseline, first clinic visit and 90 days after surgery. The EQ-5D assesses domains of self-perceived mobility, self-care, usual activity participation, pain/discomfort, and anxiety depression, as well as a 0 to 100-point scale relating the person's current health status to their best imaginable status. Patient-reported disability will be measured using the WHO Disability Assessment Schedule (WHODAS) 2.0 instrument (24), a 12-item, 30-day look-back multidimensional disability scale that is validated in a variety of disease states, including surgery (25)(26)(27)(28)(24). Disability scores will be measured at baseline, first clinic follow-up and 90

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3 days after surgery. Disability free survival will be assessed at 90 days, based on an individual
4 surviving to 90 days after surgery without developing a new disability.(29) Complications will
5 be identified during the index hospitalization using the Postoperative Morbidity Survey
6 (POMS).(30)
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13 Healthcare resource utilization measures will include length of hospital stay, discharge to
14 an institution, readmissions within 30 days of discharge, and total healthcare costs (using a
15 validated algorithm in our administrative data (31)).
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20 Patient experience with prehabilitation will be examined. The validated 10-item version
21 of the positive and negative affect schedule (PANAS) will be used to measure participants'
22 feelings and emotions after exercise (32). A subset of questions taken from the basic
23 psychological needs in exercise scale (BPNES) will be used to measure participants' competence
24 and autonomy felt in relation to their participation in the prehabilitation program (33). We will
25 conduct semi-structured interviews using an interview guide informed by the Theoretical
26 Domains Framework (TDF)(34) to provide insight into the barriers and facilitators to performing
27 prehabilitation in this population. All participants will be asked how likely they would be to
28 recommend the prehab program to a similar patient going for a similar surgery as themselves.
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42 **Sample size**

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45 To detect a clinically important 25 meter difference in the mean 6-MWT between study
46 arms, using a two-sided two-sample equal-variance t-test at the 5% level of significance with
47 80% power, and assuming a standard deviation of 55 meters based on a previously published
48 trial (13), we will require 77 patients per arm. This sample size calculation is conservative as it
49 does not account for the increased efficiency due to adjustment for the baseline 6-MWT in an
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3 ANCOVA. Assuming a conservative estimate of a 0.5 correlation with baseline 6-MWT, power
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5 to detect the minimum important difference increases to 90%. To account for up to 20% attrition
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7 we will enroll 100 patients per arm.
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10 **Recruitment**

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12 Patients will be recruited from our hospital's Cancer Assessment Center. Following
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14 cancer diagnosis, patients are seen by a surgeon 3-4 week prior to their scheduled operation.
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16 Following surgical assessment and confirmation of the decision to operate, patients who consent
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18 to consideration for research contact, and who meet all inclusion criteria except for frailty score,
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20 will be assessed by a trained clinician or clinical assistant using the Clinical Frailty Scale (CFS)
21
22 (8). Patients who score $\geq 4/9$ on the CFS will then be offered the opportunity to provide written
23
24 informed consent.
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30 **Assignment of the intervention**

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32 The random allocation sequence will be computer-generated by the study biostatistician
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34 using permuted blocks of randomly varying lengths, stratified on planned open vs. minimally
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36 invasive surgery. Study personnel will access the randomization sequence via a central secure
37
38 internet-based application to ensure adequate allocation concealment.
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43 **Blinding**

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45 Clinicians and outcome assessors will be blinded to treatment allocation. All participants
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47 will be informed that they are being enrolled in a study to increase their level of physical activity
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49 prior to surgery. Control arm patients will be provided the WHO activity pamphlet and
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51 encouraged to be active prior to surgery; however, treatment status cannot be fully concealed to
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53 participants.
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Data collection and management

Data will be collected in three ways. All preoperative functional assessments, and demographics will be collected by trained study personnel using a secure, iPad-based application that has been specifically designed for this study. Post-operative functional outcomes, HRQoL, and disability will also be collected with this application, either in-person or by phone. Patients will keep a daily activity log during the prehabilitation phase. Length of stay, discharge disposition, readmissions, and healthcare costs and mortality will be calculated through linkage to our hospital data warehouse and provincial health administrative data system, which contain validated measures of these outcomes. All study data will be stored on a secure server in our hospital data warehouse in a privacy legislation compliant manner. Patient diaries will be entered into the data collection system and stored in the same way; paper copies will be maintained in an appropriately locked and secured filing cabinet. The Principal Investigator will have access to the blinded data set. Data linked to our provincial health administrative data system will be stored and managed according to specific privacy legislation which governs use of this data.

Data Analysis

All outcomes will be analyzed according to intention to treat. Descriptive statistics (mean and standard deviation for continuous variables or median and inter-quartile range for skewed distributions, and frequency and proportion for categorical variables) will be used to compare characteristics of participants at baseline.

The primary outcome will be measured at baseline and first postdischarge clinic visit. The response at the first post-discharge visit will be analyzed using linear regression analysis with the baseline measure entered as a covariate (i.e., using analysis of covariance or

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3 ANCOVA). The model will include the stratification factors (planned open vs. minimally
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ANCOVA). The model will include the stratification factors (planned open vs. minimally
invasive surgery), and pre-specified covariates: age, sex, surgery type, preoperative chemo, ASA
score, and frailty score. The intervention effect will be estimated using the adjusted least square
mean difference between arms and presented together with 95% confidence interval. Every effort
will be made to avoid missing outcome data; nevertheless, to assess the potential for differential
attrition, the characteristics of patients dropping out will be compared between arms, as well as
to the characteristics of patients completing the study. To adjust for potential bias due to attrition
under a missing at random mechanism, the regression model will include baseline characteristics
found to be associated with attrition. Sensitivity analyses will additionally be carried out to
examine the potential impact of non-random missingness under a pattern-mixture model.⁽³⁵⁾ We
will also perform a per protocol analysis with $\geq 80\%$ compliance based on activity logs (i.e.
completion of $\geq 80\%$ of prescribed exercise sessions) considered as adherent to the protocol.

The SPPB will be analyzed in the same manner as the primary outcome. Secondary
outcomes measured at >2 -time points (EQ-5D, disability) will be analyzed using repeated
measures linear regression. Binary secondary outcomes (disability free survival, complications,
readmissions and institutional discharge) will be analyzed using logistic regression. Time to
hospital discharge will be analyzed using Cox regression with in-hospital mortality as a
competing risk. Total healthcare costs will be compared using a generalized linear model with
gamma distributed errors and a log link to account for the skewed nature of cost data. Overall
survival will be analyzed using Cox regression. All secondary analyses will include the same
covariates as described for the primary outcome.

Patient experience with prehabilitation data will be analyzed descriptively (mean and
standard deviation for continuous variables or median and inter-quartile range for skewed

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3 distributions, and frequency and proportion for categorical variables). Interview data will be
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5 transcribed and then coded in duplicate to identify responses relevant to the theoretical domains.
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7 The coded data will then be used to identify consistent belief statements, which represent an
8
9 underlying theme that impacts behaviour. The frequency of each belief statement will be
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11 calculated.
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14 15 **ETHICS AND DISSEMINATION**

16 17 18 **Ethics Approval**

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21 Prior to the commencement of the study, the protocol was presented to the independent
22
23 ethics committee of The Ottawa Health Sciences Network – Research Ethics Board and ethics
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25 approval was subsequently granted (Protocol #20160091-01H). Each participant will be given
26
27 the opportunity to read, consider, and ask questions about the information in the informed
28
29 consent form. The trained Research Assistant must obtain written informed consent (see
30
31 supplemental material) from the participant before any study procedures occur. Any
32
33 modifications to the protocol which may impact on the conduct of the study, potential benefit of
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35 the patient or may affect patient safety, including changes of study objectives, study design,
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37 patient population, sample sizes, study procedures, or significant administrative aspects will
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39 require a formal amendment to the protocol. Such amendments will be reviewed and approved
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41 by the local REB.
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46 47 **Confidentiality**

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50 Patients' data will be anonymized using a study identification number that will be stored
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52 using a protected file separated from the research data. This file will be stored on a secured
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54 hospital server where only the researchers in this study will have access to the research data.
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Monitoring

A Data and Safety Monitoring Board (DSMB) has been established. During the period of recruitment, interim analyses and safety outcomes will be supplied in confidence to the DSMB, along with any other analyses that the committee may request. The purpose of the DSMB is to protect participant safety, safeguard the credibility and integrity of the trial for subjects, and to ensure the timely conclusion of the trial so its results can be disseminated.

All adverse events that occur after enrollment during in-person data collection and throughout the prehabilitation period will be documented. Serious adverse events that the Principal Investigator deems related to the study protocol will be reported to the Research Ethics Board within 15 days (7 days if the related-SAE resulted in death or was life threatening). Adverse events related to the participants underlying cancer and related treatment will not be collected as part of this study.

Dissemination

Results will be disseminated through presentation at scientific conferences, through peer-reviewed publication, stakeholder organizations, and engagement of social and traditional media.

DISCUSSION

Older people living with frailty represent a growing and high-risk stratum of the perioperative population. Interventions to improve the outcomes of older surgical patients living with frailty are urgently needed.⁽⁶⁾ This prospective randomized clinical trial will address multiple knowledge gaps in the perioperative frailty literature. The findings will provide novel insights into improving patient- and system-centered outcomes. Due to the increasing prevalence

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3 of older adults living with frailty in the perioperative setting, and associated adverse outcomes,
4 interventions tailored for, and tested in, this population are a priority.
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9 Several studies have demonstrated that prehabilitation in patients going for cancer
10 surgery may reduce length of stay and improve postoperative function (14, 20, 22). However, to
11 our knowledge, no studies have measured the impact of prehabilitation on postoperative
12 outcomes in surgical patients living with frailty. Furthermore, studies that have evaluated the
13 impact of prehabilitation on outcomes in any surgical patients have typically been underpowered
14 for many important outcomes (median sample size 54 participants), and at significant risk of
15 several biases (16). Additionally, most studies have focused on younger and relatively well
16 patients, populations who may be less likely to derive benefit from prehabilitation. In contrast,
17 our study focuses on individuals with lower baseline functional capacity (i.e. frailty), who we
18 hypothesize may have the most to gain from preoperative exercise, is adequately powered to
19 detect an important difference in a patient-centered outcome, and has been designed to be at low
20 risk of bias through use of robust methods of allocation concealment, blinding, and outcome
21 adjudication. Furthermore, collection of our more distal patient-reported secondary outcome
22 measures (disability, HRQoL) will allow for accurate sample size estimations for future, multi-
23 center studies of exercise prehabilitation in older people living with frailty.
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43 **Limitations**

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46 Exercise therapy is a complex intervention that we will test in a population of patients
47 who tend to have low baseline activity levels; feasibility of the intervention in this population has
48 not been evaluated previously. This could lead to issues with protocol compliance that could lead
49 to underestimation of the efficacy of the intervention, although our study processes have been
50 designed to minimize this risk through regular compliance and support calls to intervention arm
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3 participants, and per protocol analyses. There is also the possibility that new introduction of
4 increased activity in previously sedentary and functionally limited individuals could cause
5 adverse effects such as falls or myocardial ischemia. However, in addition to monitoring for
6 these potential adverse effects, exercise will be introduced in a graded fashion and supported by
7 regular calls to advance activity as appropriate. Furthermore, participants will have already been
8 deemed fit for major surgery, which typically involves tolerance of 4 metabolic equivalents
9 (consistent with moderate intensity activity). Contamination could also occur between the control
10 and intervention groups as physicians and nurses practicing at the site may be influenced by the
11 research study and may incorporate exercise prescription as part of their practice. To mitigate the
12 risk that knowledge of which arm a patient has been allocated to influence their behaviour,
13 participants in both study arms will be told that they are being enrolled in an exercise trial and
14 age-appropriate activity guidelines are being provided to control arm participants. While this
15 could reduce the relative impact of the intervention through increasing activity levels in the
16 control group, we believe that the reduction in the risks of bias from knowledge of their
17 allocation status more than outweighs the concern about attenuation of the intervention effect.
18 Furthermore, relative activity levels between study arms will be monitored through use of a
19 pedometer in all study participants.
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43 **Conclusion**

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46 In summary, we propose to evaluate the efficacy of a home based prehabilitation program
47 in frail elderly patients in preparation for cancer surgery to improve postoperative function. We
48 plan to disseminate the results of this randomized clinical trial in peer reviewed journals and
49 presentations at scientific meetings. The results of this study will inform current perioperative
50 practice and will provide direction for future research.
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3 **Author's Contributions:** DM is the Principal Investigator. DM was involved in the conception
4 and design of the study and initial draft of the protocol. CS contributed to the draft of the
5 protocol. CS and EH participated in the implementation of the study (submissions to ethics
6 committee, daily management of the trial) and EH critically reviewed the protocol and its
7 contents. JN provided her expertise in kinesiology and contributed to the knowledge needed for
8 the prehabilitation program. HM, LL, ML, GB, AH, and SG provided their experience in
9 epidemiology, quality improvement, and clinical practice to the study design and procedures, and
10 writing of the protocol. BP provided her knowledge for the care of aging patients and provided
11 insight into the intervention design. AF contributed heavily to the study design and methodology.
12 CSB contributed to the study design and the details of the intervention and control groups. CVW
13 was involved in the study methodology and provided his expertise on data linkage. MT
14 developed the analysis plan. CM provided mentorship oversight and helped draft the protocol.
15 All authors have read and approved the final protocol.
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38

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42
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44 **Competing Interests Statement:** All authors have completed the ICMJE disclosure form at
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46 reports grants from Sanofi, personal fees from Sanofi and Ferring, outside the submitted work.
47 CJLM reports other from Teleflex Medical, outside the submitted work. DIM, CS, EH, JN, HM,
48 ML, GLB, AH, SG, BP, AJF, CSB, CVW, MT, have nothing to disclose.
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Figure legend

Figure 1: Study flow

*CFS: Clinical Frailty Scale; 6 MWT: 6-Minute Walk Test; SPPB: Short Physical Performance Battery; EQ-5D: Health Related Quality of Life Measure; WHODAS: WHO Disability Assessment Schedule measuring Disability Free Survival; Baseline Activity Questionnaire; Fear of Falling Questionnaire; BPNES: Basic Psychological Needs in Exercise Scale; PANAS: Positive and Negative Affect Schedule; TDF: Theoretical Domains Framework; Healthcare resource utilization: length of hospital stay, discharge to an institution, readmissions within 30 days of discharge, and total healthcare costs.

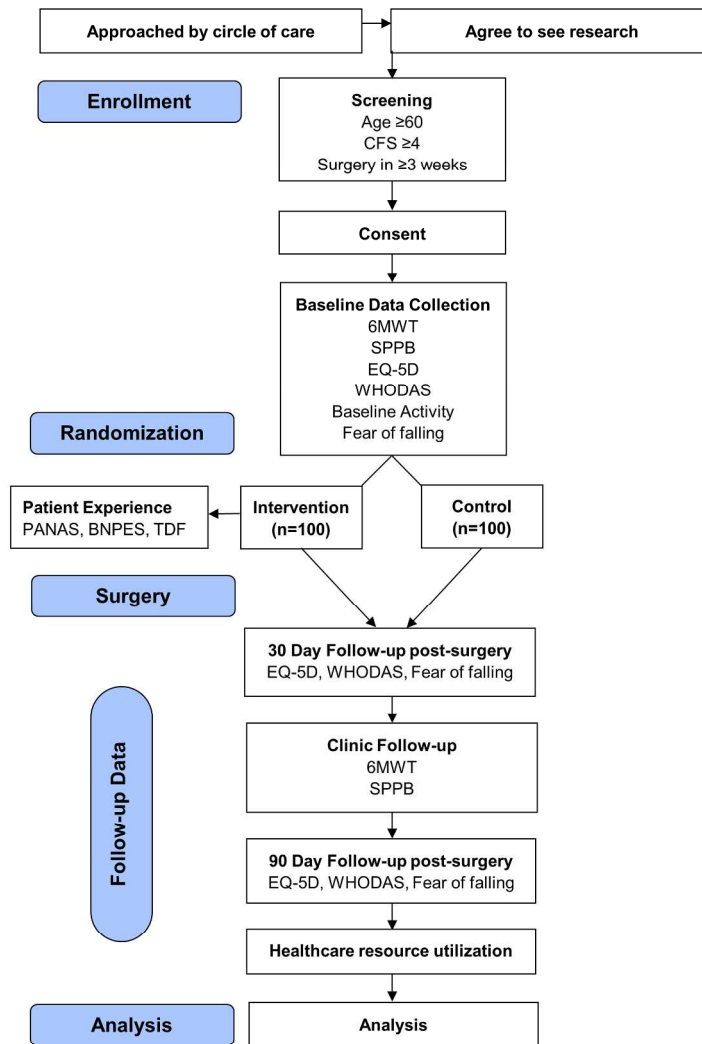


Figure 1: Study flow

*CFS: Clinical Frailty Scale; 6 MWT: 6-Minute Walk Test; SPPB: Short Physical Performance Battery; EQ-5D: Health Related Quality of Life Measure; WHODAS: WHO Disability Assessment Schedule measuring Disability Free Survival; Baseline Activity Questionnaire; Fear of Falling Questionnaire; BPNES: Basic Psychological Needs in Exercise Scale; PANAS: Positive and Negative Affect Schedule; TDF: Theoretical Domains Framework; Healthcare resource utilization: length of hospital stay, discharge to an institution, readmissions within 30 days of discharge, and total healthcare costs.

190x254mm (300 x 300 DPI)

Exercise protocol

Intervention

The intervention will be a home-based total-body exercise training program (prehabilitation) based on a protocol with proven efficacy in improving the function of non-frail surgical patients in less than 4 weeks of preoperative utilization(13,17). Prehabilitation will consist of 3 components: 1) strength training; 2) aerobic exercise and 3) flexibility. Prehabilitation will be prescribed as 1-hour sessions performed a minimum of 3 times per week. Patients will be provided with paper-based materials outlining the prehabilitation program, access to a video tutorial, and nutritional advice. The trained Research Assistant will provide individualized prehabilitation teaching for patients randomized to the intervention group. Activity logs and weekly phone calls will be used to measure compliance and to answer questions. Patients will also be asked to wear a pedometer from the time they are enrolled until their surgical date. Patients will also be able to call study personnel with any questions that may arise.

Strength training: This component consists of 1 set of 10 repetitions of each exercise: **a. push-ups** (modified to the individual's level of function as either wall push-ups or knee push-ups); **b. seated row** (performed with an elastic resistance band); **c. chest fly** (performed with an elastic resistance band); **d. deltoid lift** (performed with an elastic resistance band); **e. biceps curls** (performed with an elastic resistance band); **f. triceps extensions** (performed with an elastic resistance band); **g. chair squats**; **h. hamstring curls**; **i. standing calf raises**; **j. abdominal crunches** (modified to be performed seated in a chair). All exercises will be modified to meet the abilities of participants and to ensure their comfort with the exercises through regular telephone follow up by team members.

Aerobics: Participants' choice of cardio (i.e. walking, biking, swimming, exercise machine) for 20 minutes at moderate intensity (as defined by perceived exertion). Patients will be provided with and oriented to a BORG scale to guide their exertion perception. They will be asked to wear their pedometer from the time they are enrolled in the study until their surgical date.

Flexibility: Chest, arm, leg and trunk stretches, with each stretch to be held for 20 seconds, done for 2 repetitions.



INFORMATION SHEET AND CONSENT FORM

The Prehabilitation Study:

Exercise before Surgery to Improve Patient Function in People with Cancer

Principal Investigator: Dr. D. McIsaac (Anesthesiology) 613-798-5555 x 18253

Funding Agencies: The International Anesthesia Research Society
The University of Ottawa Anesthesia Research Grant

INTRODUCTION / BACKGROUND

You are being asked to participate in this study because you are at least 60 years of age and you are or are soon to be scheduled for intra-abdominal or intra-thoracic cancer surgery.

Before you make your decision, it is important for you to understand what the research involves. This information sheet and consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. Please take time to read the following information carefully and discuss it with your family and/or friends before you decide.

WHY IS THIS STUDY BEING DONE?

People aged 60 years and older are the fastest growing part of the population and undergo surgery at a higher rate than any other age group. This is of particular concern as frailty becomes more common with advancing age. Frailty is a condition that describes the build-up of weakness across multiple body systems, and is a known risk factor for unfavorable outcomes after surgery.

Given the high rate of frailty, and the strong link between frailty and how patients do after surgery, the care of older patients who demonstrate frailty has been identified as a key area of focus to improve the quality of care for people having surgery. Specifically, the role of exercise before surgery (prehabilitation) is a priority for patients, clinicians, and the healthcare system. Our plan is to explore the usefulness of a home-based prehabilitation program.

To answer these questions, the Departments of Anesthesiology, Surgery, and Geriatrics with the assistance of the Faculty of Health Sciences will be doing a study of patients before and after surgery. We will compare the results between those who participate in a home-based prehabilitation program before surgery to those who do not.

HOW IS THE STUDY DESIGNED?

Our study is a two-group, randomized, controlled, single-blind trial. This means that you are put into a group by chance (like flipping a coin). Neither you, nor the research team can choose the group you will be in. You will have an equal (50:50) chance of being assigned to either of the

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3 programs (the intervention program or control program). The purpose of randomization is to
4 ensure that those receiving the study intervention and those who are not are identical in every
5 other respect, or at least any differences are accounted for when it is time to look at the results.
6 That way, we can be sure that any differences we observe between the two groups are due to
7 the study intervention and nothing else.
8

9 **WHAT IS EXPECTED OF ME?**

10 **Before Your Surgery**

11 You will be asked to complete a standardized set of paper-based questionnaires to document
12 your own report of your health status. We will also measure your function with a 6-minute walk
13 test and a short physical performance measure which includes a chair stand, balance tests, and
14 walking speed. We will also ask you if you have any fear of falling. Altogether, this should take
15 approximately 30-45 minutes of your time.
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19 You will be asked if you wish to complete the 6-minute walk test with sensors attached to your
20 body to measure the way you walk and the way you hold your body. It is entirely your choice to
21 do the 6-minute walk test with or without the sensors.
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25 If you are randomized to the interventional group (the prehabilitation program); you will be
26 asked to complete 1-hour prehabilitation sessions a minimum of 3 times per week. The
27 prehabilitation sessions include walking for exercise, and strength and flexibility training. You will
28 be provided with a pedometer for walking and an elastic resistance band for the strength and
29 exercise training. In-person teaching sessions will be provided at The Ottawa Hospital, but you
30 will also be sent home with a video tutorial on the exercises in the event that you cannot attend
31 the teaching sessions. You will also be sent home with nutritional advice. You will be asked to
32 complete daily logs of your activity. A research team member will phone you once a week to ask
33 you how you are doing with the program, what exercises you have completed, if you have
34 attended a teaching session or watched the video, if you have experienced any discomforts or
35 challenges with the program or have experienced any extra concerns about falling. During the
36 last phone call before your surgery, you will be asked to answer a few additional questions to
37 better understand your experience with the program. This will take about 10 minutes of your
38 time. Your responses to some of these questions will be audio-recorded for research analysis
39 purposes only. The research assistant will inform you when the recording starts. Your recordings
40 will be kept confidential.
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45 If you are randomized to the control group, you will be provided the exact standard of care as per
46 our hospital practice. You will receive the pamphlet: 'World Health Organization (WHO) Global
47 Recommendations for Physical Activity for Health for People 65 Years and Above', as well as
48 Canada's Food Guide.
49

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52 Regardless of what group you are assigned to, all of your in-hospital care around the time of
53 surgery will be in accordance with our hospital standards as prescribed by your surgeon and
54 anesthesiologist.
55

Day of Your Surgery

All aspects of your medical, surgical and anesthetic care will be routine and will not be affected in any way by your participation in this study.

After your surgery

A trained research assistant will review your hospital chart to determine your date of hospital discharge and to document whether you had any complications.

The research assistant will call you 30 days after surgery to ask you a few questions over the phone and to see how you have been feeling since your surgery. These will be the same set of questions that you answered at the cancer assessment clinic before your surgery.

On the day of your standard surgical follow-up appointment, approximately 30-45 days after surgery, a research assistant will meet with you to complete the same set of the function tests that you did before surgery (6-minute walk test and short physical performance measures). The research assistant will phone the necessary administrative staff to confirm your scheduled appointment time. If you chose to wear the sensors during your initial 6-minute walk test, you will be asked if you could wear them again at this time point.

If you were randomized to the intervention group, you will be asked to bring your activity logs to this follow-up appointment so the research assistant can file them accordingly.

Lastly, a research assistant will phone you 90 days after surgery to ask you the same set of questions that you had previously answered on the iPad, but this time it will be over the phone. To remind you, these questions will ask you about your health status and fear of falling.

If you are in hospital at the time of the 30 and 90 day calls, the research assistant will call you in hospital or will meet with you in person if you are at The Ottawa Hospital in order to ask you these questions.

HOW LONG WILL I BE INVOLVED IN THE STUDY?

Your participation will begin at the time of your routine surgical consultation, and will conclude 3 months after your surgery.

WILL MY RESEARCH DATA BE USED IN FUTURE RESEARCH?

The data collected from the current study will not be used in future research.

POTENTIAL RISKS AND/OR DISCOMFORTS

There is no added risk related to being in this study. The questionnaires and function tests will take some added time during your clinic visits. You are able to skip any questions and any aspects of the function test that you do not feel comfortable with.

In order to be cleared for surgery, you had to pass a pre-operative functional status evaluation. The exercises in the prehabilitation program are associated with much less risk than surgery, suggesting that you are also qualified to participate in the prehabilitation program.

1
2
3 However, exercise can be associated with heart and breathing problems, especially if you haven't
4 exercised regularly and start out with exercises that are too intense. For this reason, our
5 recommended activities allow you to gradually increase your intensity over time.
6

7 **However, if you ever experience chest pain or have serious shortness of breath during or after**
8 **exercise you should seek emergency medical help.** If you are randomized to the control group,
9 there are no foreseeable risks involved for not participating in the prehabilitation program, as
10 you will receive the same care that you would get if you were not in the study.
11
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13 **POTENTIAL BENEFITS**

14 We are encouraged by the previous research to date which suggests the usefulness of
15 prehabilitation before surgery. Therefore, if you are randomized to the intervention group, you
16 may benefit in terms of how well you do after surgery, though this is not yet conclusive.
17 Furthermore, some research has found that for those who are frailer, exercise may decrease the
18 risk of falls.
19
20

21 **VOLUNTARY PARTICIPATION & WITHDRAWAL**

22 Your participation in this research study is entirely voluntary. You are free to choose to
23 participate or not to participate in this research study. If you agree to participate in this study,
24 you may choose to withdraw at any time. This will not affect your present or future care at The
25 Ottawa Hospital. You may also choose not to answer any specific questions. The study doctors
26 may also decide to discontinue the study at any time, or withdraw you from the study, if they feel
27 that it is in your best interests or if your surgery ends up not taking place for any reason. If you
28 choose to enter the study and then withdraw at a later time, all data collected about you during
29 your enrolment in the study will be retained for analysis, however no further information will be
30 collected from the time of withdrawal, onward.
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34 **NEW INFORMATION**

35 You will be advised of any new information during this study that may affect your desire to
36 remain in the study. If more effective techniques become available, they will be offered to you.
37
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40 **COMPENSATION**

41 In the event of a study-related injury you will be provided with appropriate medical treatment
42 and care. Financial compensation for lost wages, disability or discomfort due to an injury is not
43 generally available. You are not waiving any of your legal rights by agreeing to participate in this
44 study. The study doctor and The Ottawa Hospital still have their legal and professional
45 responsibilities.
46
47
48

49 **WILL I BE PAID FOR MY PARTICIPATION OR WILL THERE BE ANY ADDITIONAL COSTS TO ME?**

50 You will not be paid for participating in this study. However, your hospital parking will be
51 reimbursed since your hospital visits will be longer in time as a result of being in the study.
52
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CONFIDENTIALITY

- All information collected during your participation in this study will be identified with a unique study number, and will not contain information that identifies you, such as your name, address, etc.
- The link between your unique study number and your name and contact information will be stored securely and separate from your study records, and will not leave this site.
- Any documents leaving The Ottawa Hospital will contain only your unique study number. This includes publications or presentations resulting from this study.
- The audio-recording of the interview done before your surgery will be sent to an off-site company to be transcribed into a written document. The audio file will be password protected and encrypted. The person assigned to transcribe your interview will not be told your identity.
- Information that identifies you will be released only if it is required by law.
- For audit purposes only, your original medical records and study records may be reviewed under the supervision of Dr. McIsaac's staff by representatives from:
 - the Ottawa Health Science Network Research Ethics Board (OHSN-REB),
 - the Ottawa Hospital Research Institute
- Research records will be kept for 10 years, after this time they will be destroyed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This research study can be found on the above listed website by using the clinical trial registration number NCT02934230.

QUESTIONS ABOUT THE STUDY

If you or your family members have any questions, if you feel that you have experienced a study-related injury or if you desire further information about this study before or during participation, you may contact Dr. Dan McIsaac at 613-798-5555, extension 18253.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the plans for this research study. The Board considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital. If you have any questions about your rights as a study participant, you may contact the Chairperson at 613-798-5555, extension 16719.



The Prehabilitation Study:
Exercise before Surgery to Improve Patient Function in People with Cancer

Consent to Participate in Research

- I understand that I am being asked to participate in a research study about the usefulness of a home-based prehabilitation program on outcomes after surgery.
- This study was explained to me by _____.
- I have read, or have had read to me, each page of this Participant Informed Consent Form.
- All of my questions have been answered to my satisfaction.
- If I decide later that I would like to withdraw my participation and/or consent from the study, I can do so at any time.
- I voluntarily agree to participate in this study.
- I will be given a copy of this signed Participant Informed Consent Form.

Participant's Printed Name

Participant's Signature

Date

Investigator or Delegate Statement

I have carefully explained the study to the study participant. To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.

Investigator/Delegate's Printed Name

Investigator/Delegate's Signature

Date

Assistance Declaration

Was the participant assisted during the consent process? Yes No

The consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, and consent was freely given by the participant/substitute decision-maker.

The person signing below acted as a translator for the participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that the participant/substitute decision-maker has understood the information translated.

Name of Person Assisting (Print)

Signature

Date



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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	___1___
	2b	All items from the World Health Organization Trial Registration Data Set	___3___
Protocol version	3	Date and version identifier	___1___
Funding	4	Sources and types of financial, material, and other support	___1___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1,2,25___
	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	___1___
	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)	___16,25___

1 **Introduction**

2

3 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 _____ 6 _____

4

5

6 6b Explanation for choice of comparators _____ 7 _____

7

8 Objectives 7 Specific objectives or hypotheses _____ 7 _____

9

10 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) _____ 7 _____

11

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 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 _____ 7 _____

17

18

19 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) _____ 8 _____

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____ 8 _____

23

24

25 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) _____ 9 _____

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____ 9 _____

29

30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ 9 _____

32

33

34 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 _____ 9 _____

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40 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) _____ 10 _____

41

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____ 11 _____
 2 clinical and statistical assumptions supporting any sample size calculations

3
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____ 12 _____
 5

6 **Methods: Assignment of interventions (for controlled trials)**

7
 8 Allocation:

9
 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____ 12 _____
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions
 14
 15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____ 12 _____
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism
 19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____ 12 _____
 21 interventions
 22
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____ 12 _____
 25 assessors, data analysts), and how
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____ 12 _____
 28 allocated intervention during the trial
 29
 30

31 **Methods: Data collection, management, and analysis**

32
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____ 13 _____
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol
 37

38
 39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____ 13 _____
 40 collected for participants who discontinue or deviate from intervention protocols
 41
 42

1	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	_____13_____
2				
3				
4				
5	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	_____13_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____14_____
9				
10		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)	_____14_____
11				
12				
13				
14	Methods: Monitoring			
15				
16	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	_____16_____
17				
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22		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	_____16_____
23				
24				
25	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	_____16_____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____16_____
29				
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31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____15_____
35				
36				
37	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)	_____15_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____15_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
5				
6				
7	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	_____15_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____25_____
11				
12				
13	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	_____13_____
14				
15				
16	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	__consent form__
17				
18				
19				
20	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	_____16_____
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____25_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__supplemental__
32				
33				
34	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_____
35				
36				

37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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BMJ Open

The PREHAB Study: A protocol for a prospective randomized clinical trial of exercise therapy for people living with frailty having cancer surgery

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Geriatric medicine
Keywords:	Geriatrics, Exercise, Functional outcomes, Frailty, SURGERY

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Title: The PREHAB Study: A protocol for a prospective randomized clinical trial of exercise therapy for people living with frailty having cancer surgery

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Trial registration: ClinicalTrials.gov identifier NCT02934230

Protocol, version dated November 3, 2017

Funding: International Anesthesia Research Society, University of Ottawa Department of Anesthesiology & Pain Medicine

Trial Sponsor: The Ottawa Hospital Research Institute; 501 Smyth Box 511, Ottawa, ON, K1H 8L6; 613-761-4395; info@ohri.ca

Sponsor-Investigator: Daniel I McIsaac

The OHRI and funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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Word count: 3,921

ABSTRACT

Introduction: Exercise prehabilitation may improve outcomes after surgery. Frailty is a key predictor of adverse postoperative outcomes in older people; the multidimensional nature of frailty makes this a population who may derive substantial benefit from exercise prehabilitation. The objective of this trial is to test the efficacy of exercise prehabilitation to improve postoperative functional outcomes for people living with frailty having cancer surgery with curative intent.

Methods and analysis: We will conduct a single center, parallel-arm randomized controlled trial of home-based exercise prehabilitation vs. standard care among consenting patients ≥ 60 years having elective cancer surgery (intraabdominal and intrathoracic) and who are frail (Clinical Frailty Scale ≥ 4). The intervention consists of ≥ 3 weeks of exercise prehabilitation (strength, aerobic, and stretching). The primary outcome is the 6-minute walk test at the first postoperative clinic visit. Secondary outcomes include the short physical performance battery, health related quality of life, disability free survival, complications and health resource utilization. The primary outcome will be analyzed by intention to treat using analysis of covariance. Outcomes up to one year after surgery will be ascertained through linkage to administrative data.

Ethics and dissemination: Ethical approval has been granted by our ethics review board (Protocol Approval #2016009-01H). Results will be disseminated through presentation at scientific conferences, through peer-reviewed publication, stakeholder organizations, and engagement of social and traditional media.

Trial registration: NCT02934230; Pre-results.

Strengths and limitations of this study

- Adequately powered and blinded for a patient-centered functional outcome.
- Intervention based on a pragmatic intervention with proven efficacy.
- Complex intervention, possible risk of contamination.
- Feasibility of prehabilitation in older people with frailty before surgery unproven.

INTRODUCTION

Our population is aging rapidly, a demographic shift that directly impacts perioperative care. People aged ≥ 60 years are the fastest growing group of surgical patients,(1) and experience adverse outcomes at a rate two- to four-times higher than younger patients.(2,3) However, amongst older surgical patients, research suggests that 25-40% of adverse outcomes are attributable to the presence of frailty.(4–6) Frailty is a multidimensional syndrome based on an aggregate susceptibility to adverse health outcomes due to age- and disease-related deficits that accumulate across multiple domains.(7,8) Independent of age, gender, and other confounders, people with frailty have significantly higher rates of postoperative morbidity, mortality and healthcare resource use. People living with frailty are also significantly more likely to develop a new disability after elective surgery than older people without frailty.(9)

Despite the growing observational literature that links the presence of preoperative frailty with adverse outcomes across different surgical procedures, the literature evaluating interventions to improve the postoperative outcomes of people living with frailty is sparse.(6) Frailty-related risk is manifest through vulnerability to stressors.(7) Surgery induces substantial physiological stress, and some data suggest that people with frailty experience a significantly increased risk of early mortality (over 30 times higher than non-frail patients on postoperative day 3).(10) These findings support the hypothesis that the limited physical reserve of frail patients may contribute to their risk of adverse outcomes. Therefore, interventions that target the physical reserve of people with frailty may contribute to improved outcomes. Exercise training in non-surgical people with frailty improves functional capacity, muscle strength and may decrease frailty itself.(11–13) In particular, structured multicomponent programs demonstrate superior outcomes to other types of programs in older people with frailty.(12) Exercise prehabilitation

1
2
3 (preoperative exercise training) of people without frailty having colorectal surgery improves
4 postoperative function when compared to postoperative exercise alone(14), an effect that may be
5 especially pronounced in people who are older or who have multimorbidity. A recent
6 randomized trial of personalized prehabilitation in high-risk older people having abdominal
7 surgery reduced complications by 50%.(15) Therefore, we hypothesize that exercise
8 prehabilitation may be an appropriate intervention to improve the postoperative outcomes of
9 people living with frailty.
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20 The primary objective of this study is to test the efficacy of home-based exercise
21 prehabilitation for older people with frailty having elective surgery with curative intent for
22 intraabdominal or intrathoracic cancer, to improve postoperative function as measured by the 6-
23 minute walk test (6-MWT) at their first postoperative clinic visit in a parallel-arm superiority
24 trial with equal allocation between arms. Our secondary objective is to measure this
25 intervention's efficacy in improving other important outcomes, including patient-reported and
26 health system measures.
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37 **METHODS AND ANALYSIS**

38 **Study design and setting**

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40 We will conduct a single center, parallel arm randomized controlled trial of home-based
41 exercise prehabilitation vs. standard perioperative care in people living with frailty undergoing
42 elective surgery for intraabdominal and intrathoracic known or suspected cancer at The Ottawa
43 Hospital (TOH). This will be a superiority trial to test the hypothesis that home-based exercise
44 prehabilitation will result in improved postoperative functional outcomes compared to standard
45 care plus a generic activity guide. This protocol is reported in keeping with the Standard Protocol
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3 Items: Recommendations for Intervention Trials guidelines.(16) TOH is a 900-bed tertiary care
4 academic health sciences center serving a catchment area of 1.2 million people. TOH is the
5 regional cancer referral center for the Eastern portion of the Canadian province of Ontario. On
6 average, intraabdominal and intrathoracic cancer patients are seen 4 weeks prior to surgery (as
7 this is a provincial benchmark for cancer care). Research ethics board (REB) approval has been
8 granted by the study center.
9

17 **Eligibility criteria**

20 All consenting patients 60 years or older who are: scheduled to undergo elective surgery
21 for intraabdominal and intrathoracic cancer (colorectal, thoracic, hepatobiliary or urologic); able
22 to communicate in French or English; willing to participate in home-based exercise; and
23 identified with frailty based on the Clinical Frailty Scale (CFS; score of $\geq 4/9$) will be included.
24 The CFS is a 9-point global frailty scale based on clinical evaluation and judgement of an
25 individual's mobility, energy, physical activity and function.(8) The CFS is highly correlated (ρ -
26 0.80) with the Canadian Study of Health and Ageing Frailty Index. A multitude of frailty
27 instruments exist to diagnose frailty. We have chosen the CFS as it is easily administered, has
28 excellent inter-rater reliability, and has been shown to accurately identify older patients at high
29 risk of adverse outcomes in a variety of acute care settings (8,17,18). The CFS will be
30 administered by trained clinicians and clinical researchers.
31

46 **Intervention**

49 The intervention will be a home-based total-body exercise training program (exercise
50 prehabilitation), based on a protocol with proven efficacy in improving the function of people
51 without frailty in less than 4 weeks before surgery (14,19) (see supplemental methods 1). All
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3 intervention group participants will be exposed to at least 3 weeks of exercise, as previous use of
4 this exercise protocol was shown to be efficacious with a median of 24 days participation,(14)
5
6 and because provincial benchmarks require less than 4 weeks from diagnosis to cancer surgery.
7
8 However, because some individuals will undergo neoadjuvant chemotherapy, diagnosis to
9 surgery timeframes may vary. Therefore, we will take a pragmatic approach and allow for
10 variable exposure periods for the intervention. Exercise prehabilitation will consist of three
11 components: 1) strength training; 2) aerobic exercise and 3) flexibility. Exercise prehabilitation
12 will be prescribed as 1-hour sessions performed a minimum of 3 times per week. Intervention
13 group patients will also be provided with standard nutritional advice. In addition to paper-based
14 materials outlining the exercise prehabilitation program, participants will have an individualized
15 teaching session at the time of recruitment as well as being provided with a take home video.
16
17 Furthermore, activity logs and weekly phone calls will be used to encourage and measure
18 compliance and to answer questions.
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34 The strength training component consists of one set of 10 repetitions of 10 exercises. The
35 exercises include; push ups, seated rows, chest fly, deltoid lift, bicep curls, triceps extensions,
36 chair squats, hamstring curls, standing calf raises and abdominal crunches. The participants will
37 be provided with an elastic band in order to complete these exercises at home. In addition,
38 participants will be encouraged to modify the exercises based on ability. The aerobics component
39 consists of the participants' choice of cardio (e.g. walking, biking, or swimming) for 20 minutes
40 at moderate intensity. Lastly, the flexibility component consists of 6 stretches each to be held for
41 20 seconds, done for 2 repetitions. The stretches target the chest, arms, legs and truck.
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53 Participants randomized to the control group will receive the World Health Organization
54 (WHO) Global Recommendations for Physical Activity for Health for people 60 years and above
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3 pamphlet, as well as Canada's Food Guide. Both groups will receive pedometers to track their
4
5 daily step-count before surgery.
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8 All other pre-, intra- and postoperative care will be at the discretion of each patient's care
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10 team for both intervention and control arm participants. Specifically, intraoperative anesthesia
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12 interventions and intraoperative and postoperative surgical care will be at the discretion of
13
14 treating physicians.
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17 18 **Outcomes** 19

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21 The primary outcome will be postoperative functional capacity, measured using the 6-
22
23 MWT. The 6-MWT will be administered at baseline and at the first postoperative clinic visit.
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25 The 6-MWT has been widely used for preoperative and postoperative evaluation and for
26
27 measuring the response to therapeutic interventions for pulmonary and cardiac disease (20). A
28
29 clinically relevant difference in this outcome is a change of 25 meters walked over 6
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31 minutes.(19,21) All patients will perform a standardized, self-paced 6-MWT test in a 30-meter
32
33 long corridor. They will be instructed to walk as far as possible for 6 minutes. Patients will be
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35 allowed to stop at any time but will be encouraged to restart as soon as possible. Covered
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37 distance after 6 minutes will be measured to the nearest meter.
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43 Secondary outcomes will reflect four specific domains, 1) function; 2) patient-reported
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45 health outcomes and complications; 3) healthcare resource utilization and 4) patient experience
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47 with exercise prehabilitation. Outcome assessment windows are shown in Figure 1.
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51 Secondary functional outcomes will be assessed using the Short Physical Performance
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53 Battery (SPPB), measured at baseline and at the first postoperative clinic visit. This is a
54
55 validated, objective assessment which evaluates lower extremity functioning in older individuals
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3 through assessment of balance, gait speed and lower limb functional strength (22–24).
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5 Individuals unable to complete a task, receive a score of 0.
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8 Patient-reported Health Related Quality of Life using the EQ-5D(25) (5-level version)
9
10 will be measured at baseline, first clinic visit and 90 days after surgery. The EQ-5D assesses
11
12 domains of self-perceived mobility, self-care, usual activity participation, pain/discomfort, and
13
14 anxiety depression, as well as a 0 to 100-point scale relating the person's current health status to
15
16 their best imaginable status. Patient-reported disability will be measured using the WHO
17
18 Disability Assessment Schedule (WHODAS) 2.0 instrument (26), a 12-item, 30-day look-back
19
20 multidimensional disability scale that is validated in a variety of disease states, including surgery
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22 (27)(28)(29)(30)(26). Disability scores will be measured at baseline, first clinic follow-up and 90
23
24 days after surgery. Disability free survival will be assessed at 90 days, based on an individual
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26 surviving to 90 days after surgery without developing a new disability.(31) Complications will
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28 be identified during the index hospitalization using the Postoperative Morbidity Survey
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30 (POMS).(32)
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36 Healthcare resource utilization measures will include length of hospital stay, discharge to
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38 an institution, readmissions within 30 days of discharge, and total healthcare costs (using a
39
40 validated algorithm in our administrative data (33)).
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44 Patient experience with exercise prehabilitation will be examined. The validated 10-item
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46 version of the positive and negative affect schedule (PANAS) will be used to measure
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48 participants' feelings and emotions after exercise (34). A subset of questions taken from the
49
50 basic psychological needs in exercise scale (BPNES) will be used to measure participants'
51
52 competence and autonomy felt in relation to their participation in the exercise prehabilitation
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54 program (35). We will conduct semi-structured interviews using an interview guide informed by
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3 the Theoretical Domains Framework (TDF)(36) to provide insight into the barriers and
4
5 facilitators to performing exercise prehabilitation in this population. All participants will be
6
7 asked how likely they would be to recommend the prehab program to a similar patient going for
8
9 a similar surgery as themselves.

13 **Sample size**

16 To detect a clinically important 25 meter difference in the mean 6-MWT between study
17
18 arms, using a two-sided two-sample equal-variance t-test at the 5% level of significance with
19
20 80% power, and assuming a standard deviation of 55 meters based on a previously published
21
22 trial (14), we will require 77 patients per arm. This sample size calculation is conservative as it
23
24 does not account for the increased efficiency due to adjustment for the baseline 6-MWT in an
25
26 ANCOVA. Assuming a conservative estimate of a 0.5 correlation with baseline 6-MWT, power
27
28 to detect the minimum important difference increases to 90%. To account for up to 20% attrition,
29
30 we will enroll 100 patients per arm.
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35 **Recruitment**

37 Patients will be recruited from our hospital's Cancer Assessment Center. Following
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39 cancer diagnosis, patients are seen by a surgeon 3-4 week prior to their scheduled operation.
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41 Following surgical assessment and confirmation of the decision to operate, patients who consent
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43 to consideration for research contact, and who meet all inclusion criteria except for frailty score,
44
45 will be assessed by a trained clinician or clinical assistant using the Clinical Frailty Scale (CFS)
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47 (8). Patients who score $\geq 4/9$ on the CFS will then be offered the opportunity to provide written
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49 informed consent.
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Patient and public involvement

A James Lind Alliance Research Priority Partnership has identified the role of exercise and care of older people having surgery as two of the top ten priorities in perioperative research.(37)

These priorities directly informed our research question. We also ensured that our study was powered to address a patient-centered primary outcome which also reflected function, an outcome of key importance for older people.(38) Patients were not, however, directly involved in design, recruitment or conduct of the study. As described in the *Outcomes* section above, patient experience with the intervention will be measured quantitatively and qualitatively. Study results will be disseminated to participants through social media and our hospital patient and family advisory council.

Assignment of the intervention

The random allocation sequence will be computer-generated by the study biostatistician using permuted blocks of randomly varying lengths, stratified on planned open vs. minimally invasive surgery. Study personnel will access the randomization sequence via a central secure internet-based application to ensure adequate allocation concealment.

Blinding

Clinicians and outcome assessors will be blinded to treatment allocation. All participants will be informed that they are being enrolled in a study to increase their level of physical activity prior to surgery. Control arm patients will be provided the WHO activity pamphlet and encouraged to be active prior to surgery; however, treatment status cannot be fully concealed to participants.

Data collection and management

Data will be collected in three ways. All preoperative functional assessments, and demographics will be collected by trained study personnel using a secure, iPad-based application that has been specifically designed for this study. Post-operative functional outcomes, HRQoL, and disability will also be collected with this application, either in-person or by phone. Patients will keep a daily activity log during the exercise prehabilitation phase. Length of stay, discharge disposition, readmissions, and healthcare costs and mortality will be calculated through linkage to our hospital data warehouse and provincial health administrative data system, which contain validated measures of these outcomes. All study data will be stored on a secure server in our hospital data warehouse in a privacy legislation compliant manner. Patient diaries will be entered into the data collection system and stored in the same way; paper copies will be maintained in an appropriately locked and secured filing cabinet. The Principal Investigator will have access to the blinded data set. Data linked to our provincial health administrative data system will be stored and managed according to specific privacy legislation which governs use of this data.

Data Analysis

All outcomes will be analyzed according to intention to treat. Descriptive statistics (mean and standard deviation for continuous variables or median and inter-quartile range for skewed distributions, and frequency and proportion for categorical variables) will be used to compare characteristics of participants at baseline.

The primary outcome will be measured at baseline and first postdischarge clinic visit. The response at the first post-discharge visit will be analyzed using linear regression analysis with the baseline measure entered as a covariate (i.e., using analysis of covariance or

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3 ANCOVA). The model will include the stratification factors (planned open vs. minimally
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ANCOVA). The model will include the stratification factors (planned open vs. minimally
invasive surgery), and pre-specified covariates: age, sex, surgery type, preoperative chemo, ASA
score, and frailty score. The intervention effect will be estimated using the adjusted least square
mean difference between arms and presented together with 95% confidence interval. Every effort
will be made to avoid missing outcome data; nevertheless, to assess the potential for differential
attrition, the characteristics of patients dropping out will be compared between arms, as well as
to the characteristics of patients completing the study. To adjust for potential bias due to attrition
under a missing at random mechanism, the regression model will include baseline characteristics
found to be associated with attrition. Sensitivity analyses will additionally be carried out to
examine the potential impact of non-random missingness under a pattern-mixture model.⁽³⁹⁾ We
will also perform a per protocol analysis with $\geq 80\%$ compliance based on activity logs (i.e.
completion of $\geq 80\%$ of prescribed exercise sessions) considered as adherent to the protocol.

The SPPB will be analyzed in the same manner as the primary outcome. Secondary
outcomes measured at >2 -time points (EQ-5D, disability) will be analyzed using repeated
measures linear regression. Binary secondary outcomes (disability free survival, complications,
readmissions and institutional discharge) will be analyzed using logistic regression. Time to
hospital discharge will be analyzed using Cox regression with in-hospital mortality as a
competing risk. Total healthcare costs will be compared using a generalized linear model with
gamma distributed errors and a log link to account for the skewed nature of cost data. Overall
survival will be analyzed using Cox regression. All secondary analyses will include the same
covariates as described for the primary outcome.

Patient experience with exercise prehabilitation data will be analyzed descriptively (mean
and standard deviation for continuous variables or median and inter-quartile range for skewed

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3 distributions, and frequency and proportion for categorical variables). Interview data will be
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5 transcribed and then coded in duplicate to identify responses relevant to the theoretical domains.
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7 The coded data will then be used to identify consistent belief statements, which represent an
8
9 underlying theme that impacts behaviour. The frequency of each belief statement will be
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11 calculated.
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15 **ETHICS AND DISSEMINATION**

18 **Ethics Approval**

21 Prior to the commencement of the study, the protocol was presented to the independent
22
23 ethics committee of The Ottawa Health Sciences Network – Research Ethics Board and ethics
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25 approval was subsequently granted (Protocol #20160091-01H). Each participant will be given
26
27 the opportunity to read, consider, and ask questions about the information in the informed
28
29 consent form. The trained Research Assistant must obtain written informed consent (see
30
31 supplemental material) from the participant before any study procedures occur. Any
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33 modifications to the protocol which may impact on the conduct of the study, potential benefit of
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35 the patient or may affect patient safety, including changes of study objectives, study design,
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37 patient population, sample sizes, study procedures, or significant administrative aspects will
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39 require a formal amendment to the protocol. Such amendments will be reviewed and approved
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41 by the local REB. All items from the World Health Organization Trial Registration Data Set can
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43 be viewed as a Supplementary File.
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49 **Confidentiality**

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3 Patients' data will be anonymized using a study identification number that will be stored
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5 using a protected file separated from the research data. This file will be stored on a secured
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7 hospital server where only the researchers in this study will have access to the research data.
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10 **Monitoring**

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13 A Data and Safety Monitoring Board (DSMB) has been established. During the period of
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15 recruitment, interim analyses and safety outcomes will be supplied in confidence to the DSMB,
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17 along with any other analyses that the committee may request. The purpose of the DSMB is to
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19 protect participant safety, safeguard the credibility and integrity of the trial for subjects, and to
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21 ensure the timely conclusion of the trial so its results can be disseminated.
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26 All adverse events that occur after enrollment during in-person data collection and
27
28 throughout the exercise prehabilitation period will be documented. Serious adverse events that
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30 the Principal Investigator deems related to the study protocol will be reported to the Research
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32 Ethics Board as soon as possible. Local protocols mandate that reporting occur within 7 days if
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34 the study-related serious adverse event is unexpected and involves greater risk. Adverse events
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36 related to the participants underlying cancer and related treatment will not be collected as part of
37
38 this study.
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43 **Dissemination**

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45 Results will be disseminated through presentation at scientific conferences, through peer-
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47 reviewed publication, stakeholder organizations, and engagement of social and traditional media.
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51 **DISCUSSION**

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3 Older people living with frailty represent a growing and high-risk stratum of the
4 perioperative population. Interventions to improve the outcomes of older surgical patients living
5 with frailty are urgently needed.(6) This prospective randomized clinical trial will address
6 multiple knowledge gaps in the perioperative frailty literature. The findings will provide novel
7 insights into improving patient- and system-centered outcomes. Due to the increasing prevalence
8 of older adults living with frailty in the perioperative setting, and associated adverse outcomes,
9 interventions tailored for, and tested in, this population are a priority.
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20 Several studies have demonstrated that exercise prehabilitation in patients going for
21 abdominal or cancer surgery may reduce adverse events and improve postoperative
22 function(14,15) However, to our knowledge, no studies have measured the impact of exercise
23 prehabilitation on postoperative outcomes in surgical patients living with frailty. Furthermore,
24 studies that have evaluated the impact of exercise prehabilitation on outcomes in any surgical
25 patients have typically been underpowered for many important outcomes (median sample size 54
26 participants), and at significant risk of several biases (16). Additionally, most studies have
27 focused on younger and relatively well patients (mean age 63 years), populations who may be
28 less likely to derive benefit from exercise prehabilitation.(40–42) In several studies of surgical
29 patients with an average age <65 years, function and health related quality of life were not
30 consistently improved (41–43). In contrast, a recent study of high risk older people (mean age 71
31 years) demonstrated improvements in postoperative function and a decreased rate of
32 complications.(15) In keeping with these findings, our study focuses on individuals with lower
33 baseline functional capacity (i.e. frailty). Such individuals, we hypothesize, may have the most to
34 gain from preoperative exercise. Our study is also adequately powered to detect an important
35 difference in a patient-centered outcome and has been designed to be at low risk of bias through
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3 use of robust methods of allocation concealment, blinding, and outcome adjudication.
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5 Furthermore, collection of our more distal patient-reported secondary outcome measures
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7 (disability, HRQoL) will allow for accurate sample size estimations for future, multi-center
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9 studies of exercise prehabilitation in older people living with frailty.
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16 **Limitations**

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19 Exercise therapy is a complex intervention that we will test in a population of patients
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21 who tend to have low baseline activity levels; feasibility of the intervention in this population has
22
23 not been evaluated previously. This could lead to issues with protocol compliance that could lead
24
25 to underestimation of the efficacy of the intervention, although our study processes have been
26
27 designed to minimize this risk through regular compliance and support calls to intervention arm
28
29 participants, and per protocol analyses. There is also the possibility that new introduction of
30
31 increased activity in previously sedentary and functionally limited individuals could cause
32
33 adverse effects such as falls or myocardial ischemia. However, in addition to monitoring for
34
35 these potential adverse effects, exercise will be introduced in a graded fashion and supported by
36
37 regular calls to advance activity as appropriate. Furthermore, participants will have already been
38
39 deemed fit for major surgery, which typically involves tolerance of 4 metabolic equivalents
40
41 (consistent with moderate intensity activity).(44) Contamination could also occur between the
42
43 control and intervention groups as physicians and nurses practicing at the site may be influenced
44
45 by the research study and may incorporate exercise prescription as part of their practice. To
46
47 mitigate the risk that knowledge of which arm a patient has been allocated to influence their
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49 behaviour, participants in both study arms will be told that they are being enrolled in an exercise
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51 trial and age-appropriate activity guidelines are being provided to control arm participants. While
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3 this could reduce the relative impact of the intervention through increasing activity levels in the
4 control group, we believe that the reduction in the risks of bias from knowledge of their
5 allocation status more than outweighs the concern about attenuation of the intervention effect.
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7 Furthermore, relative activity levels between study arms will be monitored through use of a
8 pedometer in all study participants.
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14 15 **Conclusion**

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18 In summary, we propose to evaluate the efficacy of a home based exercise prehabilitation
19 program in frail elderly patients in preparation for cancer surgery to improve postoperative
20 function. We plan to disseminate the results of this randomized clinical trial in peer reviewed
21 journals and presentations at scientific meetings. The results of this study will inform current
22 perioperative practice and will provide direction for future research.
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9 **Author's Contributions:** DM is the Principal Investigator. DM was involved in the conception
10 and design of the study and initial draft of the protocol. CS contributed to the draft of the
11 protocol. CS and EH participated in the implementation of the study (submissions to ethics
12 committee, daily management of the trial) and EH critically reviewed the protocol and its
13 contents. JN provided her expertise in kinesiology and contributed to the knowledge needed for
14 the prehabilitation program. HM, LL, ML, GB, AH, and SG provided their experience in
15 epidemiology, quality improvement, and clinical practice to the study design and procedures, and
16 writing of the protocol. BP provided her knowledge for the care of aging patients and provided
17 insight into the intervention design. AF contributed heavily to the study design and methodology.
18 CSB contributed to the study design and the details of the intervention and control groups. CVW
19 was involved in the study methodology and provided his expertise on data linkage. MT
20 developed the analysis plan. CM provided mentorship oversight and helped draft the protocol.
21 All authors have read and approved the final protocol.
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43
44

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51 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). LTL
52 reports grants from Sanofi, personal fees from Sanofi and Ferring, outside the submitted work.
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3 CJLM reports other from Teleflex Medical, outside the submitted work. DIM, CS, EH, JN, HM,
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5 ML, GLB, AH, SG, BP, AJF, CSB, CVW, MT, have nothing to disclose.
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8 **Figure legend**

9 **Figure 1: Study flow**

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14 *CFS: Clinical Frailty Scale; 6 MWT: 6-Minute Walk Test; SPPB: Short Physical Performance
15 Battery; EQ-5D: Health Related Quality of Life Measure; WHODAS: WHO Disability
16 Assessment Schedule measuring Disability Free Survival; Baseline Activity Questionnaire; Fear
17 of Falling Questionnaire; BPNES: Basic Psychological Needs in Exercise Scale; PANAS:
18 Positive and Negative Affect Schedule; TDF: Theoretical Domains Framework; Healthcare
19 resource utilization: length of hospital stay, discharge to an institution, readmissions within 30
20 days of discharge, and total healthcare costs.
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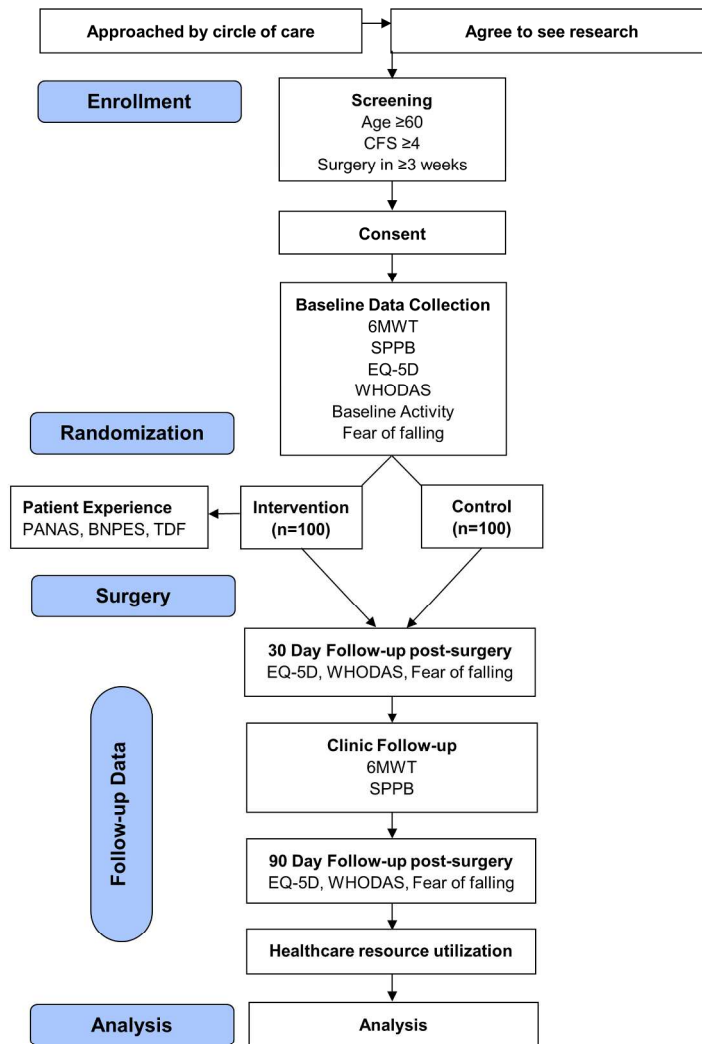


Figure 1: Study flow

*CFS: Clinical Frailty Scale; 6 MWT: 6-Minute Walk Test; SPPB: Short Physical Performance Battery; EQ-5D: Health Related Quality of Life Measure; WHODAS: WHO Disability Assessment Schedule measuring Disability Free Survival; Baseline Activity Questionnaire; Fear of Falling Questionnaire; BNPES: Basic Psychological Needs in Exercise Scale; PANAS: Positive and Negative Affect Schedule; TDF: Theoretical Domains Framework; Healthcare resource utilization: length of hospital stay, discharge to an institution, readmissions within 30 days of discharge, and total healthcare costs.

190x254mm (300 x 300 DPI)

Exercise protocol

Intervention

The intervention will be a home-based total-body exercise training program (prehabilitation) based on a protocol with proven efficacy in improving the function of non-frail surgical patients in less than 4 weeks of preoperative utilization(13,17). Prehabilitation will consist of 3 components: 1) strength training; 2) aerobic exercise and 3) flexibility. Prehabilitation will be prescribed as 1-hour sessions performed a minimum of 3 times per week. Patients will be provided with paper-based materials outlining the prehabilitation program, access to a video tutorial, and nutritional advice. The trained Research Assistant will provide individualized prehabilitation teaching for patients randomized to the intervention group. Activity logs and weekly phone calls will be used to measure compliance and to answer questions. Patients will also be asked to wear a pedometer from the time they are enrolled until their surgical date. Patients will also be able to call study personnel with any questions that may arise.

Strength training: This component consists of 1 set of 10 repetitions of each exercise: **a. push-ups** (modified to the individual's level of function as either wall push-ups or knee push-ups); **b. seated row** (performed with an elastic resistance band); **c. chest fly** (performed with an elastic resistance band); **d. deltoid lift** (performed with an elastic resistance band); **e. biceps curls** (performed with an elastic resistance band); **f. triceps extensions** (performed with an elastic resistance band); **g. chair squats**; **h. hamstring curls**; **i. standing calf raises**; **j. abdominal crunches** (modified to be performed seated in a chair). All exercises will be modified to meet the abilities of participants and to ensure their comfort with the exercises through regular telephone follow up by team members.

Aerobics: Participants' choice of cardio (i.e. walking, biking, swimming, exercise machine) for 20 minutes at moderate intensity (as defined by perceived exertion). Patients will be provided with and oriented to a BORG scale to guide their exertion perception. They will be asked to wear their pedometer from the time they are enrolled in the study until their surgical date.

Flexibility: Chest, arm, leg and trunk stretches, with each stretch to be held for 20 seconds, done for 2 repetitions.



INFORMATION SHEET AND CONSENT FORM

The Prehabilitation Study:

Exercise before Surgery to Improve Patient Function in People with Cancer

Principal Investigator: Dr. D. Mclsaac (Anesthesiology) 613-798-5555 x 18253

Funding Agencies: The International Anesthesia Research Society
The University of Ottawa Anesthesia Research Grant

INTRODUCTION / BACKGROUND

You are being asked to participate in this study because you are at least 60 years of age and you are or are soon to be scheduled for intra-abdominal or intra-thoracic cancer surgery.

Before you make your decision, it is important for you to understand what the research involves. This information sheet and consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. Please take time to read the following information carefully and discuss it with your family and/or friends before you decide.

WHY IS THIS STUDY BEING DONE?

People aged 60 years and older are the fastest growing part of the population and undergo surgery at a higher rate than any other age group. This is of particular concern as frailty becomes more common with advancing age. Frailty is a condition that describes the build-up of weakness across multiple body systems, and is a known risk factor for unfavorable outcomes after surgery.

Given the high rate of frailty, and the strong link between frailty and how patients do after surgery, the care of older patients who demonstrate frailty has been identified as a key area of focus to improve the quality of care for people having surgery. Specifically, the role of exercise before surgery (prehabilitation) is a priority for patients, clinicians, and the healthcare system. Our plan is to explore the usefulness of a home-based prehabilitation program.

To answer these questions, the Departments of Anesthesiology, Surgery, and Geriatrics with the assistance of the Faculty of Health Sciences will be doing a study of patients before and after surgery. We will compare the results between those who participate in a home-based prehabilitation program before surgery to those who do not.

HOW IS THE STUDY DESIGNED?

Our study is a two-group, randomized, controlled, single-blind trial. This means that you are put into a group by chance (like flipping a coin). Neither you, nor the research team can choose the group you will be in. You will have an equal (50:50) chance of being assigned to either of the

1
2
3 programs (the intervention program or control program). The purpose of randomization is to
4 ensure that those receiving the study intervention and those who are not are identical in every
5 other respect, or at least any differences are accounted for when it is time to look at the results.
6 That way, we can be sure that any differences we observe between the two groups are due to
7 the study intervention and nothing else.
8

9 **WHAT IS EXPECTED OF ME?**

10 **Before Your Surgery**

11 You will be asked to complete a standardized set of paper-based questionnaires to document
12 your own report of your health status. We will also measure your function with a 6-minute walk
13 test and a short physical performance measure which includes a chair stand, balance tests, and
14 walking speed. We will also ask you if you have any fear of falling. Altogether, this should take
15 approximately 30-45 minutes of your time.
16

17
18 You will be asked if you wish to complete the 6-minute walk test with sensors attached to your
19 body to measure the way you walk and the way you hold your body. It is entirely your choice to
20 do the 6-minute walk test with or without the sensors.
21

22
23 If you are randomized to the interventional group (the prehabilitation program); you will be
24 asked to complete 1-hour prehabilitation sessions a minimum of 3 times per week. The
25 prehabilitation sessions include walking for exercise, and strength and flexibility training. You will
26 be provided with a pedometer for walking and an elastic resistance band for the strength and
27 exercise training. In-person teaching sessions will be provided at The Ottawa Hospital, but you
28 will also be sent home with a video tutorial on the exercises in the event that you cannot attend
29 the teaching sessions. You will also be sent home with nutritional advice. You will be asked to
30 complete daily logs of your activity. A research team member will phone you once a week to ask
31 you how you are doing with the program, what exercises you have completed, if you have
32 attended a teaching session or watched the video, if you have experienced any discomforts or
33 challenges with the program or have experienced any extra concerns about falling. During the
34 last phone call before your surgery, you will be asked to answer a few additional questions to
35 better understand your experience with the program. This will take about 10 minutes of your
36 time. Your responses to some of these questions will be audio-recorded for research analysis
37 purposes only. The research assistant will inform you when the recording starts. Your recordings
38 will be kept confidential.
39

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41 If you are randomized to the control group, you will be provided the exact standard of care as per
42 our hospital practice. You will receive the pamphlet: 'World Health Organization (WHO) Global
43 Recommendations for Physical Activity for Health for People 65 Years and Above', as well as
44 Canada's Food Guide.
45

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47 Regardless of what group you are assigned to, all of your in-hospital care around the time of
48 surgery will be in accordance with our hospital standards as prescribed by your surgeon and
49 anesthesiologist.
50

Day of Your Surgery

All aspects of your medical, surgical and anesthetic care will be routine and will not be affected in any way by your participation in this study.

After your surgery

A trained research assistant will review your hospital chart to determine your date of hospital discharge and to document whether you had any complications.

The research assistant will call you 30 days after surgery to ask you a few questions over the phone and to see how you have been feeling since your surgery. These will be the same set of questions that you answered at the cancer assessment clinic before your surgery.

On the day of your standard surgical follow-up appointment, approximately 30-45 days after surgery, a research assistant will meet with you to complete the same set of the function tests that you did before surgery (6-minute walk test and short physical performance measures). The research assistant will phone the necessary administrative staff to confirm your scheduled appointment time. If you chose to wear the sensors during your initial 6-minute walk test, you will be asked if you could wear them again at this time point.

If you were randomized to the intervention group, you will be asked to bring your activity logs to this follow-up appointment so the research assistant can file them accordingly.

Lastly, a research assistant will phone you 90 days after surgery to ask you the same set of questions that you had previously answered on the iPad, but this time it will be over the phone. To remind you, these questions will ask you about your health status and fear of falling.

If you are in hospital at the time of the 30 and 90 day calls, the research assistant will call you in hospital or will meet with you in person if you are at The Ottawa Hospital in order to ask you these questions.

HOW LONG WILL I BE INVOLVED IN THE STUDY?

Your participation will begin at the time of your routine surgical consultation, and will conclude 3 months after your surgery.

WILL MY RESEARCH DATA BE USED IN FUTURE RESEARCH?

The data collected from the current study will not be used in future research.

POTENTIAL RISKS AND/OR DISCOMFORTS

There is no added risk related to being in this study. The questionnaires and function tests will take some added time during your clinic visits. You are able to skip any questions and any aspects of the function test that you do not feel comfortable with.

In order to be cleared for surgery, you had to pass a pre-operative functional status evaluation. The exercises in the prehabilitation program are associated with much less risk than surgery, suggesting that you are also qualified to participate in the prehabilitation program.

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3 However, exercise can be associated with heart and breathing problems, especially if you haven't
4 exercised regularly and start out with exercises that are too intense. For this reason, our
5 recommended activities allow you to gradually increase your intensity over time.
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7 **However, if you ever experience chest pain or have serious shortness of breath during or after**
8 **exercise you should seek emergency medical help.** If you are randomized to the control group,
9 there are no foreseeable risks involved for not participating in the prehabilitation program, as
10 you will receive the same care that you would get if you were not in the study.
11
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13 **POTENTIAL BENEFITS**

14 We are encouraged by the previous research to date which suggests the usefulness of
15 prehabilitation before surgery. Therefore, if you are randomized to the intervention group, you
16 may benefit in terms of how well you do after surgery, though this is not yet conclusive.
17 Furthermore, some research has found that for those who are frailer, exercise may decrease the
18 risk of falls.
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22 **VOLUNTARY PARTICIPATION & WITHDRAWAL**

23 Your participation in this research study is entirely voluntary. You are free to choose to
24 participate or not to participate in this research study. If you agree to participate in this study,
25 you may choose to withdraw at any time. This will not affect your present or future care at The
26 Ottawa Hospital. You may also choose not to answer any specific questions. The study doctors
27 may also decide to discontinue the study at any time, or withdraw you from the study, if they feel
28 that it is in your best interests or if your surgery ends up not taking place for any reason. If you
29 choose to enter the study and then withdraw at a later time, all data collected about you during
30 your enrolment in the study will be retained for analysis, however no further information will be
31 collected from the time of withdrawal, onward.
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35 **NEW INFORMATION**

36 You will be advised of any new information during this study that may affect your desire to
37 remain in the study. If more effective techniques become available, they will be offered to you.
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40 **COMPENSATION**

41 In the event of a study-related injury you will be provided with appropriate medical treatment
42 and care. Financial compensation for lost wages, disability or discomfort due to an injury is not
43 generally available. You are not waiving any of your legal rights by agreeing to participate in this
44 study. The study doctor and The Ottawa Hospital still have their legal and professional
45 responsibilities.
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49 **WILL I BE PAID FOR MY PARTICIPATION OR WILL THERE BE ANY ADDITIONAL COSTS TO ME?**

50 You will not be paid for participating in this study. However, your hospital parking will be
51 reimbursed since your hospital visits will be longer in time as a result of being in the study.
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CONFIDENTIALITY

- All information collected during your participation in this study will be identified with a unique study number, and will not contain information that identifies you, such as your name, address, etc.
- The link between your unique study number and your name and contact information will be stored securely and separate from your study records, and will not leave this site.
- Any documents leaving The Ottawa Hospital will contain only your unique study number. This includes publications or presentations resulting from this study.
- The audio-recording of the interview done before your surgery will be sent to an off-site company to be transcribed into a written document. The audio file will be password protected and encrypted. The person assigned to transcribe your interview will not be told your identity.
- Information that identifies you will be released only if it is required by law.
- For audit purposes only, your original medical records and study records may be reviewed under the supervision of Dr. McIsaac's staff by representatives from:
 - the Ottawa Health Science Network Research Ethics Board (OHSN-REB),
 - the Ottawa Hospital Research Institute
- Research records will be kept for 10 years, after this time they will be destroyed.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This research study can be found on the above listed website by using the clinical trial registration number NCT02934230.

QUESTIONS ABOUT THE STUDY

If you or your family members have any questions, if you feel that you have experienced a study-related injury or if you desire further information about this study before or during participation, you may contact Dr. Dan McIsaac at 613-798-5555, extension 18253.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the plans for this research study. The Board considers the ethical aspects of all research studies involving human participants at The Ottawa Hospital. If you have any questions about your rights as a study participant, you may contact the Chairperson at 613-798-5555, extension 16719.



The Prehabilitation Study:
Exercise before Surgery to Improve Patient Function in People with Cancer

Consent to Participate in Research

- I understand that I am being asked to participate in a research study about the usefulness of a home-based prehabilitation program on outcomes after surgery.
- This study was explained to me by _____.
- I have read, or have had read to me, each page of this Participant Informed Consent Form.
- All of my questions have been answered to my satisfaction.
- If I decide later that I would like to withdraw my participation and/or consent from the study, I can do so at any time.
- I voluntarily agree to participate in this study.
- I will be given a copy of this signed Participant Informed Consent Form.

Participant's Printed Name

Participant's Signature

Date

Investigator or Delegate Statement

I have carefully explained the study to the study participant. To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.

Investigator/Delegate's Printed Name

Investigator/Delegate's Signature

Date

Assistance Declaration

Was the participant assisted during the consent process? Yes No

The consent form was read to the participant/substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, and consent was freely given by the participant/substitute decision-maker.

The person signing below acted as a translator for the participant/substitute decision-maker during the consent process. He/she attests that they have accurately translated the information for the participant/substitute decision-maker, and believe that the participant/substitute decision-maker has understood the information translated.

Name of Person Assisting (Print)

Signature

Date

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All items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT02934230
Date of registration in primary registry	August 22, 2016
Secondary identifying numbers	Not Applicable
Source(s) of monetary or material support	International Anesthesia Research Society The University of Ottawa Department of Anesthesiology and Pain Medicine
Primary sponsor	The Ottawa Hospital Research Institute
Secondary sponsor	Investigator-led, Dr. Daniel McIsaac
Contact for public queries	DM, dmcisaac@toh.ca
Contact for scientific queries	DM, dmcisaac@toh.ca
Public title	The Prehabilitation Study: Exercise Before Surgery to Improve Patient Function in People
Scientific title	The Prehabilitation Study: Exercise Before Surgery to Improve Patient Function in People
Countries of recruitment	Canada
Health condition(s) or problem(s) studied	Cancer, Frailty
Intervention(s)	Exercise prehabilitation
Key inclusion and exclusion criteria	Ages eligible for study: ≥ 60 years Sexes eligible for study: both Accepts health volunteers: no
	Inclusion criteria: adult patient (≥ 60 years), elective surgery for intraabdominal or thoracic cancer, Clinical Frailty Score ($\geq 4/9$)
	Exclusion criteria: unable to communicate in written or oral form in official languages serviced by The Ottawa Hospital (English or French), unwilling to participate in home-based exercise prehabilitation, major cardiac risk factors, scheduled to undergo surgery in fewer than 3 weeks from randomization
Study type	Interventional
	Allocation: randomized intervention model. Parallel assignment masking: double blind (investigator and outcome assessors)
	Primary purpose: prevention
Date of first enrolment	January 19, 2017
Target sample size	200
Recruitment status	Recruiting
Primary outcome(s)	Postoperative functional capacity (6-Minute Walk Test)
Key secondary outcomes	Functional mobility, patient-reported health related quality of life and disability free survival



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	___1___
	2b	All items from the World Health Organization Trial Registration Data Set	__supplemental__
Protocol version	3	Date and version identifier	___1___
Funding	4	Sources and types of financial, material, and other support	___1___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1,2,27___
	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	___1___
	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)	___16,27___

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____5_____
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	_____6_____
7				
8	Objectives	7	Specific objectives or hypotheses	_____6_____
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____6_____
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	_____6_____
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____7_____
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____7_____
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____8_____
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____8_____
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____8_____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	_____9_____
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	_____10_____
39			participants. A schematic diagram is highly recommended (see Figure)	
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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	_____11_____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____11_____
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

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10	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	_____12_____
11				
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16	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	_____12_____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____12_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____12_____
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____12_____
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31 **Methods: Data collection, management, and analysis**

32				
33	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	_____13_____
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39		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	_____13_____
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1	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	_____13_____
2				
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5	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	_____13_____
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____14_____
9				
10		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)	_____14_____
11				
12				
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14	Methods: Monitoring			
15				
16	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	_____16_____
17				
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22		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	_____16_____
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25	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	_____16_____
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____16_____
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____15_____
35				
36				
37	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)	_____15_____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____15_____
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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7	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	_____15_____
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____27_____
11				
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13	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	_____13_____
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16	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	__consent form__
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20	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	_____16_____
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____27_____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__supplemental__
32				
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34	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_____
35				
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*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.