BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022057
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2018
Complete List of Authors:	McIsaac, Daniel; The Ottawa Hospital, Anesthesiology and Pain Medicine Saunders, Chelsey; The Ottawa Hospital Research Institute , Anesthesiology and Pain Medicine Hladkowicz , Emily ; The Ottawa Hospital Research Institute , Anesthesiology and Pain Medicine Bryson, Gregory; The Ottawa Hospital, Anesthesiology and Pain Medicine; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Forster, Alan; The Ottawa Hospital , Internal Medicine ; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Gagne , Sylvain; The Ottawa Hospital, Anesthesiology and Pain Medicine Huang, Allen; The Ottawa Hospital, Geriatric Medicine; The Ottawa Hospital Research Institute , Clinical Epidemiology Lalu, Manoj; The Ottawa Hospital, Anesthesiology and Pain Medicine; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Lavallee, Luke; The Ottawa Hospital, Surgical Oncology ; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Moloo, Husein; The Ottawa Hospital, Surgical Oncology; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Nantel, Julie; University of Ottawa, Health Sciences Power , Barbara; The Ottawa Hospital, Geriatric Medicine; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Scheede-Bergdahl, Celena; McGill University , Kinesiology and Physical Education Taljaard, Monica; Ottawa Hospital Research Institute, Clinical Epidemiology Program van Walraven, Carl; Ottawa Hospital Research Institute, Clinical Epidemiology; Institute for Clinical Evaluative Sciences, McCartney, Colin; University of Ottawa Faculty of Medicine, Anesthesiology
Keywords:	Geriatrics, Exercise, Functional outcomes, Frailty, SURGERY

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

Corresponding Author: Daniel I McIsaac MD, MPH, FRCPC
Assistant Professor of Anesthesiology and Pain Medicine, University of Ottawa; Associate Scientist, Ottawa Hospital Research Institute
Email: dmcisaac@toh.ca
Phone-613-761-4940/Fax-613-761-5209
Department of Anesthesiology, The Ottawa Hospital Civic Campus
Room B311, 1053 Carling Ave
Ottawa, ON K1Y 4E9

Authors: Daniel I. McIsaac[1,2], Chelsey Saunders[3], Emily Hladkowicz[4], Gregory L. Bryson[2,5], Alan J. Forster[6,7], Sylvain Gagne[5], Allen Huang[8,9], Manoj Lalu[1,2], Luke T. Lavallée[2,11], Husein Moloo[2,12], Julie Nantel[13], Barbara Power[9,10], Celena Scheede-Bergdahl[14], Monica Taljaard[7,15], Carl van Walraven[7,16,17], Colin J.L. McCartney[18,19]

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.

Affiliations:

1 Staff Anesthesiologist and Assistant Professor; Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

2 Associate Scientist; Clinical Epidemiology Program; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

3 Research Assistant; Department of Anesthesiology and Pain Medicine, the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

4 Research Coordinator; Department of Anesthesiology and Pain Medicine, the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

5 Staff Anesthesiologist and Associate Professor; Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

6 Staff General Internist and Full Professor; Division of General Internal Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

7 Senior Scientist; Clinical Epidemiology Program; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

8 Division Head and Associate Professor; Division of Geriatric Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

9 Clinician Investigator; Clinical Epidemiology Program; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

10 Chief; Division of Geriatric Medicine; The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

11 Staff Surgical Oncologist and Assistant Professor; Division of Urology, The Ottawa Hospital, University of Ottawa, 501 Smyth Rd, Ottawa, ON, Canada, K1H 8L6

12 Staff Surgical Oncologist and Associate Professor, Division of General Surgery, The Ottawa Hospital, University of Ottawa, 737 Parkdale Ave, Ottawa, ON, K1Y IJ8

13 Associate Professor; School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, 125 University, ON, Canada, K1N 6N5

14 Faculty Lecturer, Department of Kinesiology and Physical Education, McGill University, 475 Pine Ave West, Montreal, QC, Canada, H2W 1S4

15 Associate Professor, School of Epidemiology, Population Health and Preventative Medicine, University of Ottawa, 125 University, ON, Canada, K1N 6N5

16 Staff Physician and Professor; Department of Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K17 4E9

17 Site Director; Institute for Clinical Evaluative Sciences @uOttawa, ASB 1st Floor, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

18 Department Head and Full Professor; Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

19 Scientist; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

Word count: 3,921

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)	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 (≥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.

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

exercise alone(13), an effect that may be especially pronounced in people who are older or who have multimorbidity. Therefore, we hypothesize that prehabilitation may be an appropriate intervention to improve the postoperative outcomes of people living with frailty.

The primary objective of this study is to test the efficacy of home-based prehabilitation for older people with frailty having elective surgery with curative intent for intraabdominal or intrathoracic cancer, to improve postoperative function as measured by the 6-minute walk test (6-MWT) at their first postoperative clinic visit in a parallel-arm superiority trial with equal allocation between arms. Our secondary objective is to measure this intervention's efficacy in improving other important outcomes, including patient-reported and health system measures.

METHODS AND ANALYSIS

Study design and setting

We will conduct a single center, parallel arm randomized controlled trial of home-based prehabilitation vs. standard perioperative care in people living with frailty undergoing elective surgery for intraabdominal and intrathoracic known or suspected cancer at The Ottawa Hospital (TOH). This will be a superiority trial to test the hypothesis that home-based prehabilitation will result in improved postoperative functional outcomes compared to standard care plus a generic activity guide. This protocol is reported in keeping with the Standard Protocol Items: Recommendations for Intervention Trials guidelines.(14) TOH is a 900-bed tertiary care academic health sciences center serving a catchment area of 1.2 million people. TOH is the regional cancer referral center for the Eastern portion of the Canadian province of Ontario. On average, intraabdominal and intrathoracic cancer patients are seen 4 weeks prior to surgery (as

this is a provincial benchmark for cancer care). Research ethics board (REB) approval has been granted by the study center.

Eligibility criteria

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

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 people without frailty in less than 4 weeks before surgery (13,17) (see supplemental methods 1). Prehabilitation will consist of three 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. Intervention group patients will also be provided with standard nutritional advice. In addition to paper-based materials outlining the prehabilitation program, participants will have an individualized teaching session at the time of recruitment as well as being provided with a take

home video. Furthermore, activity logs and weekly phone calls will be used to encourage and measure compliance and to answer questions.

The strength training component consists of one set of 10 repetitions of 10 strength exercises. The exercises include; push ups, seated rows, chest fly, deltoid lift, bicep curls, triceps extensions, chair squats, hamstring curls, standing calf raises and abdominal crunches. The participants will be provided with an elastic band in order to complete these exercises at home. In addition, participants will be encouraged to modify the exercises based on ability. The aerobics component consists of the participants' choice of cardio (e.g. walking, biking, or swimming) for 20 minutes at moderate intensity. Lastly, the flexibility component consists of 6 stretches each to be held for 20 seconds, done for 2 repetitions. The stretches target the chest, arms, legs and truck.

Participants randomized to the control group will receive the World Health Organization (WHO) Global Recommendations for Physical Activity for Health for people 60 years and above pamphlet, as well as Canada's Food Guide. Both groups will receive pedometers to track their daily step-count before surgery.

All other pre-, intra- and postoperative care will be at the discretion of each patient's care team for both intervention and control arm participants. Specifically, intraoperative anesthesia interventions and intraoperative and postoperative surgical care will be at the discretion of treating physicians.

Outcomes

The primary outcome will be postoperative functional capacity, measured using the 6-MWT. The 6MWT will be administered at baseline and at the first postoperative clinic visit. The

6-MWT has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease (18). A clinically relevant difference in this outcome is a change of 25 meters walked over 6 minutes.(17,19) All patients will perform a standardized, self-paced 6-minute walk test in a 30-meter long corridor. They will be instructed to walk as far as possible for 6 minutes. Patients will be allowed to stop at any time, but will be encouraged to restart as soon as possible. Covered distance after 6 minutes will be measured to the nearest meter.

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

days after surgery. Disability free survival will be assessed at 90 days, based on an individual surviving to 90 days after surgery without developing a new disability.(29) Complications will be identified during the index hospitalization using the Postoperative Morbidity Survey (POMS).(30)

Healthcare resource utilization measures will include length of hospital stay, discharge to an institution, readmissions within 30 days of discharge, and total healthcare costs (using a validated algorithm in our administrative data (31)).

Patient experience with prehabilitation will be examined. The validated 10-item version of the positive and negative affect schedule (PANAS) will be used to measure participants' feelings and emotions after exercise (32). A subset of questions taken from the basic psychological needs in exercise scale (BPNES) will be used to measure participants' competence and autonomy felt in relation to their participation in the prehabilitation program (33). We will conduct semi-structured interviews using an interview guide informed by the Theoretical Domains Framework (TDF)(34) to provide insight into the barriers and facilitators to performing prehabilitation in this population. All participants will be asked how likely they would be to recommend the prehab program to a similar patient going for a similar surgery as themselves.

Sample size

To detect a clinically important 25 meter difference in the mean 6-MWT between study arms, using a two-sided two-sample equal-variance t-test at the 5% level of significance with 80% power, and assuming a standard deviation of 55 meters based on a previously published trial (13), we will require 77 patients per arm. This sample size calculation is conservative as it does not account for the increased efficiency due to adjustment for the baseline 6-MWT in an

ANCOVA. Assuming a conservative estimate of a 0.5 correlation with baseline 6-MWT, power to detect the minimum important difference increases to 90%. To account for up to 20% attrition we will enroll 100 patients per arm.

Recruitment

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

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 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 measured 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

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 ≥80% compliance based on activity logs (i.e. completion of ≥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

distributions, and frequency and proportion for categorical variables). Interview data will be transcribed and then coded in duplicate to identify responses relevant to the theoretical domains. The coded data will then be used to identify consistent belief statements, which represent an underlying theme that impacts behaviour. The frequency of each belief statement will be calculated.

ETHICS AND DISSEMINTATION

Ethics Approval

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

Confidentiality

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

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

of older adults living with frailty in the perioperative setting, and associated adverse outcomes, interventions tailored for, and tested in, this population are a priority.

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

Limitations

Exercise therapy is a complex intervention that we will test in a population of patients who tend to have low baseline activity levels; feasibility of the intervention in this population has not been evaluated previously. This could lead to issues with protocol compliance that could lead to underestimation of the efficacy of the intervention, although our study processes have been designed to minimize this risk through regular compliance and support calls to intervention arm

participants, and per protocol analyses. There is also the possibility that new introduction of increased activity in previously sedentary and functionally limited individuals could cause adverse effects such as falls or myocardial ischemia. However, in addition to monitoring for these potential adverse effects, exercise will be introduced in a graded fashion and supported by regular calls to advance activity as appropriate. Furthermore, participants will have already been deemed fit for major surgery, which typically involves tolerance of 4 metabolic equivalents (consistent with moderate intensity activity). Contamination could also occur between the control and intervention groups as physicians and nurses practicing at the site may be influenced by the research study and may incorporate exercise prescription as part of their practice. To mitigate the risk that knowledge of which arm a patient has been allocated to influence their behaviour, participants in both study arms will be told that they are being enrolled in an exercise trial and age-appropriate activity guidelines are being provided to control arm participants. While this could reduce the relative impact of the intervention through increasing activity levels in the control group, we believe that the reduction in the risks of bias from knowledge of their allocation status more than outweighs the concern about attenuation of the intervention effect. Furthermore, relative activity levels between study arms will be monitored though use of a pedometer in all study participants.

Conclusion

In summary, we propose to evaluate the efficacy of a home based prehabilitation program in frail elderly patients in preparation for cancer surgery to improve postoperative function. We plan to disseminate the results of this randomized clinical trial in peer reviewed journals and presentations at scientific meetings. The results of this study will inform current perioperative practice and will provide direction for future research.

REFERENCES

1. Etzioni D a, Liu JH, O'Connell JB, Maggard M a, Ko CY. Elderly patients in surgical workloads: a population-based analysis. Am Surg [Internet]. 2003 Nov;69(11):961–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14627256

2. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc [Internet]. 2005 Mar [cited 2013 Jan 17];53(3):424–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15743284

3. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg [Internet]. 2006 Dec [cited 2012 Nov 11];203(6):865–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17116555

4. Beggs T, Sepehri A, Szwajcer A, Tangri N, Arora RC. Frailty and perioperative outcomes: a narrative review. Can J Anesth Can d'anesthésie [Internet]. 2015 Feb 25;62(2):143–57. Available from: http://link.springer.com/10.1007/s12630-014-0273-z

5. Kim DH, Kim CA, Placide S, Lipsitz LA, Marcantonio ER. Preoperative Frailty Assessment and Outcomes at 6 Months or Later in Older Adults Undergoing Cardiac Surgical Procedures. Ann Intern Med [Internet]. 2016; Available from: http://annals.org/article.aspx?doi=10.7326/M16-0652

6. McIsaac DI, Jen T, Mookerji N, Patel A, Lalu MM. Interventions to improve the outcomes of frail people having surgery: A systematic review. Quinn TJ, editor. PLoS One [Internet]. 2017 Dec 29;12(12):e0190071. Available from: http://dx.plos.org/10.1371/journal.pone.0190071

7. Fried LP, Ferruci L, Darer J, Williamson J, Anderson G. Untangling the concepts of disability, frailty and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3):M255–63.

8. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ [Internet]. 2005 Aug 30 [cited 2014 Sep 16];173(5):489–95. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1188185&tool=pmcentrez&rendertype=abstract

9. McIsaac DI, Bryson G, Forster AJ, Taljaard M, Hamilton GM, Beaule PE, et al. Comparative assessment of two frailty instruments to predict patient-reported disability after elective noncardiac surgery. In: Canadian Anesthesiologists Society Annual Meeting. Niagara Falls, ON; 2017.

10. McIsaac DI, Bryson GL, van Walraven C. Association of Frailty and 1-Year Postoperative Mortality Following Major Elective Noncardiac Surgery. JAMA Surg [Internet]. 2016 Jan 20;online ahe. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2015.5085

11. de Labra C, Guimaraes-Pinheiro C, Maseda A, Lorenzo T, Millan-Calenti J. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. BMC Geriatr [Internet]. 2015 Dec 2;15(1):154. Available from: http://www.biomedcentral.com/1471-2318/15/154

12. Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, et al. The Effectiveness of Exercise Interventions for the Management of Frailty: A Systematic

Review. J Aging Res [Internet]. 2011;2011:1–19. Available from: http://www.hindawi.com/journals/jar/2011/569194/

13. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology [Internet]. 2014 Nov [cited 2015 Jan 11];121(5):937–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25076007

14. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med [Internet]. 2013 Feb 5;158(3):200. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-158-3-201302050-00583

15. Wallis SJ, Wall J, Biram RWS, Romero-Ortuno R. Association of the Clinical Frailty Scale (CFS) with hospital outcomes. QJM [Internet]. 2015; Available from: http://www.qjmed.oxfordjournals.org/cgi/doi/10.1093/qjmed/hcv066

16. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. C Can Med Assoc J [Internet]. 2014 Feb 4 [cited 2014 Feb 7];186(2):E95–102. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3903764&tool=pmcentrez&rendertype=abstract

17. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc [Internet]. 2013 Apr [cited 2015 Feb 17];27(4):1072–82. Available

from: http://www.ncbi.nlm.nih.gov/pubmed/23052535

18. American Thoracic Society. ATS Statement : Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med. 2002;166:111–7.

19. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg [Internet]. 2010 Aug [cited 2015 Feb 17];97(8):1187–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20602503

20. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. J Gerontol [Internet]. 1994 Mar 1;49(2):M85–94. Available from: http://geronj.oxfordjournals.org/cgi/doi/10.1093/geronj/49.2.M85

21. Freire AN, Guerra RO, Alvarado B, Guralnik JM, Zunzunegui MV. Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. J Aging Health [Internet]. 2012 Aug;24(5):863–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22422762

22. Volpato S, Cavalieri M, Sioulis F, Guerra G, Maraldi C, Zuliani G, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci [Internet]. 2011 Jan;66(1):89–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20861145

23. Bansback N, Tsuchiya A, Brazier J, Anis A. Canadian Valuation of EQ-5D Health States : Preliminary Value Set and Considerations for Future Valuation Studies. PLoS One.

2012;7(2).

24. Shulman MA, Wallace S, Ponsford J, Hons BA, Neuropsych MAC, Ph D. Measurement of Disability-free Survival after Surgery. 2015;(3):524–36.

25. Schlote A, Richter M, Wunderlich MT, Poppendick U, Möller C, Schwelm K, et al. WHODAS II with people after stroke and their relatives. Disabil Rehabil. 2009;31(11):855–64.

26. Wolf AC De, Tate RL, Lannin NA, Middleton J, Lane-brown A, Cameron ID. The World Health Organization Disability Assessment Scale , WHODAS II : reliability and validity in the measurement of activity and participation in a spinal cord injury population. J Rehabil Med. 2012;44(9):747–55.

27. Soberg HL, Finset A, Roise O. The Trajectory of Physical and Mental Health From Injury to 5 Years After Multiple Trauma : A Prospective , Longitudinal. Arch Phys Med Rehabil. 2012;93(5):765–74.

28. Garin O, Ayuso-mateos JL, Almansa J, Nieto M, Chatterji S, Vilagut G, et al. Validation of the " World Health Organization Disability Assessment Schedule , WHODAS-2 " in patients with chronic diseases. Health Qual Life Outcomes. 2010;8(1):51.

29. Shulman MA, Myles PS, Chan MT V., McIlroy DR, Wallace S, Ponsford J. Measurement of Disability-free Survival after Surgery. Anesthesiology [Internet]. 2015 Mar;122(3):524–36. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000542-201503000-00014

30. Grocott MPW, Browne JP, Van der Meulen J, Matejowsky C, Mutch M, Hamilton M a., et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. J Clin Epidemiol. 2007;60(9):919–28.

31. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on Person-Level Costing Using Administrative Databases in Ontario [Internet]. Toronto, ON; 2013. Available from: http://www.hsprn.ca/uploads/files/Guidelines_on_PersonLevel_Costing_May_2013.pdf

32. Mackinnon A, Jorm AF, Christensen H, Korten AE, Jacomb PA, Rodgers B. A short form of the Positive and Negative Affect Schedule: Evaluation of factorial validity and invariance across demographic variables in a community sample. Pers Individ Dif. 1999;27(3):405–16.

33. Vlachopoulos SP, Michailidou S. Development and Initial Validation of a Measure of Autonomy, Competence, and Relatedness in Exercise: The Basic Psychological Needs in Exercise Scale. Meas Phys Educ Exerc Sci. 2006;10(3):179–201.

34. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):1–18.

35. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The Prevention and Treatment of Missing Data in Clinical Trials. N Engl J Med [Internet]. 2012 Oct 4;367(14):1355–60. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMsr1203730

Author's Contributions: DM is the Principal Investigator. DM was involved in the conception and design of the study and initial draft of the protocol. CS contributed to the draft of the protocol. CS and EH participated in the implementation of the study (submissions to ethics committee, daily management of the trial) and EH critically reviewed the protocol and its contents. JN provided her expertise in kinesiology and contributed to the knowledge needed for the prehabilitation program. HM, LL, ML, GB, AH, and SG provided their experience in epidemiology, quality improvement, and clinical practice to the study design and procedures, and writing of the protocol. BP provided her knowledge for the care of aging patients and provided insight into the intervention design. AF contributed heavily to the study design and methodology. CSB contributed to the study design and the details of the intervention and control groups. CVW was involved in the study methodology and provided his expertise on data linkage. MT developed the analysis plan. CM provided mentorship oversight and helped draft the protocol. All authors have read and approved the final protocol.

Acknowledgements: We would like to acknowledge Kristin Dorrance for her insight into the patient experience component of the protocol.

Funding Statement: This work was supported by the International Anesthesia Research Society and the University of Ottawa Anesthesiology Research Grant.

Competing Interests Statement: All authors have completed the ICMJE disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). LTL reports grants from Sanofi, personal fees from Sanofi and Ferring, outside the submitted work. CJLM reports other from Teleflex Medical, outside the submitted work. DIM, CS, EH, JN, HM, ML, GLB, AH, SG, BP, AJF, CSB, CVW, MT, have nothing to disclose.

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.

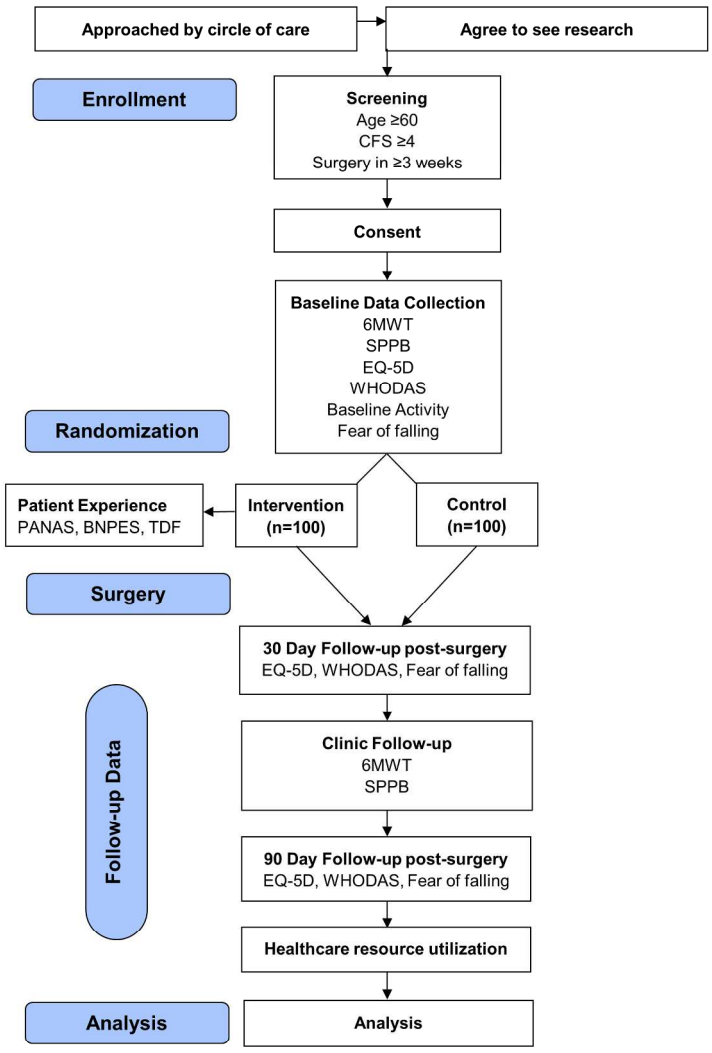

Figure 1: Study flow

*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 orknee 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 truck stretches, with each stretch to be held for 20 seconds, done for 2 repetitions.

The Ottawa Hospital | L'Hôpital d'Ottawa

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

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

WHAT IS EXPECTED OF ME?

Before Your Surgery

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

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

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

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

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

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.

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

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

POTENTIAL BENEFITS

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

VOLUNTARY PARTICIPATION & WITHDRAWAL

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

NEW INFORMATION

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

COMPENSATION

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

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

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

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 Ottawa Hospital | L'Hôpital d'Ottawa

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

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

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
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

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
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
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_
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	25
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__supplemental__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022057.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Apr-2018
Complete List of Authors:	McIsaac, Daniel; The Ottawa Hospital, Anesthesiology and Pain Medicine Saunders, Chelsey; The Ottawa Hospital Research Institute , Anesthesiology and Pain Medicine Hladkowicz , Emily ; The Ottawa Hospital Research Institute , Anesthesiology and Pain Medicine Bryson, Gregory; The Ottawa Hospital, Anesthesiology and Pain Medicine; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Forster, Alan; The Ottawa Hospital , Internal Medicine ; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Gagne , Sylvain; The Ottawa Hospital, Anesthesiology and Pain Medicine Huang, Allen; The Ottawa Hospital, Geriatric Medicine; The Ottawa Hospital Research Institute , Clinical Epidemiology Lalu, Manoj; The Ottawa Hospital, Anesthesiology and Pain Medicine; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Lavallee, Luke; The Ottawa Hospital, Surgical Oncology ; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Moloo, Husein; The Ottawa Hospital, Surgical Oncology; The Ottawa Hospital Research Institute , Clinical Epidemiology Program Nantel, Julie; University of Ottawa, Health Sciences Power , Barbara; The Ottawa Hospital, Geriatric Medicine; The Ottawa Hospital Research Institute, Clinical Epidemiology Program Scheede-Bergdahl, Celena; McGill University , Kinesiology and Physical Education Taljaard, Monica; Ottawa Hospital Research Institute, Clinical Epidemiology Program van Walraven, Carl; Ottawa Hospital Research Institute, Clinical Epidemiology; Institute for Clinical Evaluative Sciences, McCartney, Colin; University of Ottawa Faculty of Medicine, Anesthesiology
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Geriatric medicine
Keywords:	Geriatrics, Exercise, Functional outcomes, Frailty, SURGERY

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

Corresponding Author: Daniel I McIsaac MD, MPH, FRCPC
Assistant Professor of Anesthesiology and Pain Medicine, University of Ottawa; Associate Scientist, Ottawa Hospital Research Institute
Email: dmcisaac@toh.ca
Phone-613-761-4940/Fax-613-761-5209
Department of Anesthesiology, The Ottawa Hospital Civic Campus
Room B311, 1053 Carling Ave
Ottawa, ON K1Y 4E9

Authors: Daniel I. McIsaac[1,2], Chelsey Saunders[3], Emily Hladkowicz[4], Gregory L. Bryson[2,5], Alan J. Forster[6,7], Sylvain Gagne[5], Allen Huang[8,9], Manoj Lalu[1,2], Luke T. Lavallée[2,11], Husein Moloo[2,12], Julie Nantel[13], Barbara Power[9,10], Celena Scheede-Bergdahl[14], Monica Taljaard[7,15], Carl van Walraven[7,16,17], Colin J.L. McCartney[18,19]

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.

Affiliations:

1 Staff Anesthesiologist and Assistant Professor; Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

2 Associate Scientist; Clinical Epidemiology Program; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

3 Research Assistant; Department of Anesthesiology and Pain Medicine, the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

4 Research Coordinator; Department of Anesthesiology and Pain Medicine, the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

5 Staff Anesthesiologist and Associate Professor; Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

6 Staff General Internist and Full Professor; Division of General Internal Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

7 Senior Scientist; Clinical Epidemiology Program; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

8 Division Head and Associate Professor; Division of Geriatric Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

9 Clinician Investigator; Clinical Epidemiology Program; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

10 Chief; Division of Geriatric Medicine; The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

11 Staff Surgical Oncologist and Assistant Professor; Division of Urology, The Ottawa Hospital, University of Ottawa, 501 Smyth Rd, Ottawa, ON, Canada, K1H 8L6

12 Staff Surgical Oncologist and Associate Professor, Division of General Surgery, The Ottawa Hospital, University of Ottawa, 737 Parkdale Ave, Ottawa, ON, K1Y IJ8

13 Associate Professor; School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, 125 University, ON, Canada, K1N 6N5

14 Faculty Lecturer, Department of Kinesiology and Physical Education, McGill University, 475 Pine Ave West, Montreal, QC, Canada, H2W 1S4

15 Associate Professor, School of Epidemiology, Population Health and Preventative Medicine, University of Ottawa, 125 University, ON, Canada, K1N 6N5

16 Staff Physician and Professor; Department of Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K17 4E9

17 Site Director; Institute for Clinical Evaluative Sciences @uOttawa, ASB 1st Floor, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

18 Department Head and Full Professor; Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

19 Scientist; the Ottawa Hospital Research Institute, 1053 Carling Ave, Ottawa, ON, Canada, K1Y 4E9

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 prehabilitaion 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

(preoperative exercise training) of people without frailty having colorectal surgery improves postoperative function when compared to postoperative exercise alone(14), an effect that may be especially pronounced in people who are older or who have multimorbidity. A recent randomized trial of personalized prehabilitation in high-risk older people having abdominal surgery reduced complications by 50%.(15) Therefore, we hypothesize that exercise prehabilitation may be an appropriate intervention to improve the postoperative outcomes of people living with frailty.

The primary objective of this study is to test the efficacy of home-based exercise prehabilitation for older people with frailty having elective surgery with curative intent for intraabdominal or intrathoracic cancer, to improve postoperative function as measured by the 6-minute walk test (6-MWT) at their first postoperative clinic visit in a parallel-arm superiority trial with equal allocation between arms. Our secondary objective is to measure this intervention's efficacy in improving other important outcomes, including patient-reported and health system measures.

METHODS AND ANALYSIS

Study design and setting

We will conduct a single center, parallel arm randomized controlled trial of home-based exercise prehabilitation vs. standard perioperative care in people living with frailty undergoing elective surgery for intraabdominal and intrathoracic known or suspected cancer at The Ottawa Hospital (TOH). This will be a superiority trial to test the hypothesis that home-based exercise prehabilitation will result in improved postoperative functional outcomes compared to standard care plus a generic activity guide. This protocol is reported in keeping with the Standard Protocol

Items: Recommendations for Intervention Trials guidelines.(16) TOH is a 900-bed tertiary care academic health sciences center serving a catchment area of 1.2 million people. TOH is the regional cancer referral center for the Eastern portion of the Canadian province of Ontario. On average, intraabdominal and intrathoracic cancer patients are seen 4 weeks prior to surgery (as this is a provincial benchmark for cancer care). Research ethics board (REB) approval has been granted by the study center.

Eligibility criteria

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

Intervention

The intervention will be a home-based total-body exercise training program (exercise prehabilitation), based on a protocol with proven efficacy in improving the function of people without frailty in less than 4 weeks before surgery (14,19) (see supplemental methods 1). All

intervention group participants will be exposed to at least 3 weeks of exercise, as previous use of this exercise protocol was shown to be efficacious with a median of 24 days participation,(14) and because provincial benchmarks require less than 4 weeks from diagnosis to cancer surgery. However, because some individuals will undergo neoadjuvant chemotherapy, diagnosis to surgery timeframes may vary. Therefore, we will take a pragmatic approach and allow for variable exposure periods for the intervention. Exercise prehabilitation will consist of three components: 1) strength training; 2) aerobic exercise and 3) flexibility. Exercise prehabilitation will be prescribed as 1-hour sessions performed a minimum of 3 times per week. Intervention group patients will also be provided with standard nutritional advice. In addition to paper-based materials outlining the exercise prehabilitation program, participants will have an individualized teaching session at the time of recruitment as well as being provided with a take home video. Furthermore, activity logs and weekly phone calls will be used to encourage and measure compliance and to answer questions.

The strength training component consists of one set of 10 repetitions of 10 exercises. The exercises include; push ups, seated rows, chest fly, deltoid lift, bicep curls, triceps extensions, chair squats, hamstring curls, standing calf raises and abdominal crunches. The participants will be provided with an elastic band in order to complete these exercises at home. In addition, participants will be encouraged to modify the exercises based on ability. The aerobics component consists of the participants' choice of cardio (e.g. walking, biking, or swimming) for 20 minutes at moderate intensity. Lastly, the flexibility component consists of 6 stretches each to be held for 20 seconds, done for 2 repetitions. The stretches target the chest, arms, legs and truck.

Participants randomized to the control group will receive the World Health Organization (WHO) Global Recommendations for Physical Activity for Health for people 60 years and above

pamphlet, as well as Canada's Food Guide. Both groups will receive pedometers to track their daily step-count before surgery.

All other pre-, intra- and postoperative care will be at the discretion of each patient's care team for both intervention and control arm participants. Specifically, intraoperative anesthesia interventions and intraoperative and postoperative surgical care will be at the discretion of treating physicians.

Outcomes

The primary outcome will be postoperative functional capacity, measured using the 6-MWT. The 6-MWT will be administered at baseline and at the first postoperative clinic visit. The 6-MWT has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease (20). A clinically relevant difference in this outcome is a change of 25 meters walked over 6 minutes.(19,21) All patients will perform a standardized, self-paced 6-MWT test in a 30-meter long corridor. They will be instructed to walk as far as possible for 6 minutes. Patients will be allowed to stop at any time but will be encouraged to restart as soon as possible. Covered distance after 6 minutes will be measured to the nearest meter.

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 exercise 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 evaluates lower extremity functioning in older individuals

through assessment of balance, gait speed and lower limb functional strength (22–24). Individuals unable to complete a task, receive a score of 0.

Patient-reported Health Related Quality of Life using the EQ-5D(25) (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 (26), a 12-item, 30-day look-back multidimensional disability scale that is validated in a variety of disease states, including surgery (27)(28)(29)(30)(26). Disability scores will be measured at baseline, first clinic follow-up and 90 days after surgery. Disability free survival will be assessed at 90 days, based on an individual surviving to 90 days after surgery without developing a new disability.(31) Complications will be identified during the index hospitalization using the Postoperative Morbidity Survey (POMS).(32)

Healthcare resource utilization measures will include length of hospital stay, discharge to an institution, readmissions within 30 days of discharge, and total healthcare costs (using a validated algorithm in our administrative data (33)).

Patient experience with exercise prehabilitation will be examined. The validated 10-item version of the positive and negative affect schedule (PANAS) will be used to measure participants' feelings and emotions after exercise (34). A subset of questions taken from the basic psychological needs in exercise scale (BPNES) will be used to measure participants' competence and autonomy felt in relation to their participation in the exercise prehabilitation program (35). We will conduct semi-structured interviews using an interview guide informed by

the Theoretical Domains Framework (TDF)(36) to provide insight into the barriers and facilitators to performing exercise prehabilitation in this population. All participants will be asked how likely they would be to recommend the prehab program to a similar patient going for a similar surgery as themselves.

Sample size

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

Recruitment

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

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 measured 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

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 ≥80% compliance based on activity logs (i.e. completion of ≥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

distributions, and frequency and proportion for categorical variables). Interview data will be transcribed and then coded in duplicate to identify responses relevant to the theoretical domains. The coded data will then be used to identify consistent belief statements, which represent an underlying theme that impacts behaviour. The frequency of each belief statement will be calculated.

ETHICS AND DISSEMINTATION

Ethics Approval

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

Confidentiality

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

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 exercise 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 as soon as possible. Local protocols mandate that reporting occur within 7 days if the study-related serious adverse event is unexpected and involves greater risk. 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 of older adults living with frailty in the perioperative setting, and associated adverse outcomes, interventions tailored for, and tested in, this population are a priority.

Several studies have demonstrated that exercise prehabilitation in patients going for abdominal or cancer surgery may reduce adverse events and improve postoperative function(14,15) However, to our knowledge, no studies have measured the impact of exercise prehabilitation on postoperative outcomes in surgical patients living with frailty. Furthermore, studies that have evaluated the impact of exercise prehabilitation on outcomes in any surgical patients have typically been underpowered for many important outcomes (median sample size 54 participants), and at significant risk of several biases (16). Additionally, most studies have focused on younger and relatively well patients (mean age 63 years), populations who may be less likely to derive benefit from exercise prehabilitation.(40–42) In several studies of surgical patients with an average age <65 years, function and health related quality of life were not consistently improved (41–43). In contrast, a recent study of high risk older people (mean age 71 years) demonstrated improvements in postoperative function and a decreased rate of complications.(15) In keeping with these findings, our study focuses on individuals with lower baseline functional capacity (i.e. frailty). Such individuals, we hypothesize, may have the most to gain from preoperative exercise. Our study is also adequately powered to detect an important difference in a patient-centered outcome and has been designed to be at low risk of bias through

use of robust methods of allocation concealment, blinding, and outcome adjudication. Furthermore, collection of our more distal patient-reported secondary outcome measures (disability, HRQoL) will allow for accurate sample size estimations for future, multi-center studies of exercise prehabilitation in older people living with frailty.

Limitations

Exercise therapy is a complex intervention that we will test in a population of patients who tend to have low baseline activity levels; feasibility of the intervention in this population has not been evaluated previously. This could lead to issues with protocol compliance that could lead to underestimation of the efficacy of the intervention, although our study processes have been designed to minimize this risk through regular compliance and support calls to intervention arm participants, and per protocol analyses. There is also the possibility that new introduction of increased activity in previously sedentary and functionally limited individuals could cause adverse effects such as falls or myocardial ischemia. However, in addition to monitoring for these potential adverse effects, exercise will be introduced in a graded fashion and supported by regular calls to advance activity as appropriate. Furthermore, participants will have already been deemed fit for major surgery, which typically involves tolerance of 4 metabolic equivalents (consistent with moderate intensity activity).(44) Contamination could also occur between the control and intervention groups as physicians and nurses practicing at the site may be influenced by the research study and may incorporate exercise prescription as part of their practice. To mitigate the risk that knowledge of which arm a patient has been allocated to influence their behaviour, participants in both study arms will be told that they are being enrolled in an exercise trial and age-appropriate activity guidelines are being provided to control arm participants. While

this could reduce the relative impact of the intervention through increasing activity levels in the control group, we believe that the reduction in the risks of bias from knowledge of their allocation status more than outweighs the concern about attenuation of the intervention effect. Furthermore, relative activity levels between study arms will be monitored though use of a pedometer in all study participants.

Conclusion

In summary, we propose to evaluate the efficacy of a home based exercise prehabilitation program in frail elderly patients in preparation for cancer surgery to improve postoperative function. We plan to disseminate the results of this randomized clinical trial in peer reviewed journals and presentations at scientific meetings. The results of this study will inform current perioperative practice and will provide direction for future research.

REFERENCES

1. Etzioni D a, Liu JH, O'Connell JB, Maggard M a, Ko CY. Elderly patients in surgical workloads: a population-based analysis. Am Surg [Internet]. 2003 Nov;69(11):961–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14627256

2. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc [Internet]. 2005 Mar [cited 2013 Jan 17];53(3):424–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15743284

3. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg [Internet]. 2006 Dec [cited 2012 Nov 11];203(6):865–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17116555

4. Beggs T, Sepehri A, Szwajcer A, Tangri N, Arora RC. Frailty and perioperative outcomes: a narrative review. Can J Anesth Can d'anesthésie [Internet]. 2015 Feb 25;62(2):143–57. Available from: http://link.springer.com/10.1007/s12630-014-0273-z

5. Kim DH, Kim CA, Placide S, Lipsitz LA, Marcantonio ER. Preoperative Frailty Assessment and Outcomes at 6 Months or Later in Older Adults Undergoing Cardiac Surgical Procedures. Ann Intern Med [Internet]. 2016; Available from: http://annals.org/article.aspx?doi=10.7326/M16-0652

6. McIsaac DI, Jen T, Mookerji N, Patel A, Lalu MM. Interventions to improve the outcomes of frail people having surgery: A systematic review. Quinn TJ, editor. PLoS One [Internet]. 2017 Dec 29;12(12):e0190071. Available from: http://dx.plos.org/10.1371/journal.pone.0190071

7. Fried LP, Ferruci L, Darer J, Williamson J, Anderson G. Untangling the concepts of disability, frailty and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59(3):M255–63.

8. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ [Internet]. 2005 Aug 30 [cited 2014 Sep 16];173(5):489–95. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1188185&tool=pmcentrez&rendertype=abstract

9. McIsaac DI, Bryson G, Forster AJ, Taljaard M, Hamilton GM, Beaule PE, et al. Comparative assessment of two frailty instruments to predict patient-reported disability after elective noncardiac surgery. In: Canadian Anesthesiologists Society Annual Meeting.

Niagara Falls, ON; 2017.

10. McIsaac DI, Bryson GL, van Walraven C. Association of Frailty and 1-Year Postoperative Mortality Following Major Elective Noncardiac Surgery. JAMA Surg [Internet]. 2016 Jan 20;online ahe. Available from: http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2015.5085

11. de Labra C, Guimaraes-Pinheiro C, Maseda A, Lorenzo T, Millan-Calenti J. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. BMC Geriatr [Internet]. 2015 Dec 2;15(1):154. Available from: http://www.biomedcentral.com/1471-2318/15/154

12. Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. J Aging Res [Internet]. 2011 Apr 4;2011:569194. Available from: http://www.hindawi.com/journals/jar/2011/569194/

13. Tarazona-Santabalbina FJ, Gómez-Cabrera MC, Pérez-Ros P, Martínez-Arnau FM, Cabo H, Tsaparas K, et al. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. J Am Med Dir Assoc [Internet]. 2016 May 1;17(5):426–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26947059

14. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology [Internet]. 2014 Nov [cited 2015 Jan 11];121(5):937–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25076007

15. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery : A Randomized Blinded Controlled Trial. Ann Surg. 2018;267(1):50–6.

16. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med [Internet]. 2013 Feb 5;158(3):200. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-158-3-201302050-00583

17. Wallis SJ, Wall J, Biram RWS, Romero-Ortuno R. Association of the Clinical Frailty Scale (CFS) with hospital outcomes. QJM [Internet]. 2015; Available from: http://www.qjmed.oxfordjournals.org/cgi/doi/10.1093/qjmed/hcv066

18. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. C Can Med Assoc J [Internet]. 2014 Feb 4 [cited 2014 Feb 7];186(2):E95–102. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3903764&tool=pmcentrez&rendertype=abstract

19. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc [Internet]. 2013 Apr [cited 2015 Feb 17];27(4):1072–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23052535

20. American Thoracic Society. ATS Statement : Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med. 2002;166:111–7.

21. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg [Internet]. 2010 Aug [cited 2015 Feb 17];97(8):1187–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20602503

22. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. J Gerontol [Internet]. 1994 Mar 1;49(2):M85–94. Available from: http://geronj.oxfordjournals.org/cgi/doi/10.1093/geronj/49.2.M85

23. Freire AN, Guerra RO, Alvarado B, Guralnik JM, Zunzunegui MV. Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. J Aging Health [Internet]. 2012 Aug;24(5):863–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22422762

24. Volpato S, Cavalieri M, Sioulis F, Guerra G, Maraldi C, Zuliani G, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci [Internet]. 2011 Jan;66(1):89–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20861145

25. Bansback N, Tsuchiya A, Brazier J, Anis A. Canadian Valuation of EQ-5D Health States : Preliminary Value Set and Considerations for Future Valuation Studies. PLoS One. 2012;7(2).

26. Shulman MA, Wallace S, Ponsford J, Hons BA, Neuropsych MAC, Ph D. Measurement of Disability-free Survival after Surgery. 2015;(3):524–36.

27. Schlote A, Richter M, Wunderlich MT, Poppendick U, Möller C, Schwelm K, et al. WHODAS II with people after stroke and their relatives. Disabil Rehabil. 2009;31(11):855–64.

28. Wolf AC De, Tate RL, Lannin NA, Middleton J, Lane-brown A, Cameron ID. The World Health Organization Disability Assessment Scale , WHODAS II : reliability and validity in the measurement of activity and participation in a spinal cord injury population. J Rehabil Med. 2012;44(9):747–55.

29. Soberg HL, Finset A, Roise O. The Trajectory of Physical and Mental Health From Injury to 5 Years After Multiple Trauma : A Prospective , Longitudinal. Arch Phys Med Rehabil. 2012;93(5):765–74.

30. Garin O, Ayuso-mateos JL, Almansa J, Nieto M, Chatterji S, Vilagut G, et al. Validation of the " World Health Organization Disability Assessment Schedule , WHODAS-2 " in patients with chronic diseases. Health Qual Life Outcomes. 2010;8(1):51.

31. Shulman MA, Myles PS, Chan MT V., McIlroy DR, Wallace S, Ponsford J. Measurement of Disability-free Survival after Surgery. Anesthesiology [Internet]. 2015 Mar;122(3):524–36. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000542-201503000-00014

32. Grocott MPW, Browne JP, Van der Meulen J, Matejowsky C, Mutch M, Hamilton M a., et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. J Clin Epidemiol. 2007;60(9):919–28.

33. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on Person-Level

Costing Using Administrative Databases in Ontario [Internet]. Toronto, ON; 2013. Available from: http://www.hsprn.ca/uploads/files/Guidelines_on_PersonLevel_Costing_May_2013.pdf

34. Mackinnon A, Jorm AF, Christensen H, Korten AE, Jacomb PA, Rodgers B. A short form of the Positive and Negative Affect Schedule: Evaluation of factorial validity and invariance across demographic variables in a community sample. Pers Individ Dif. 1999;27(3):405–16.

35. Vlachopoulos SP, Michailidou S. Development and Initial Validation of a Measure of Autonomy, Competence, and Relatedness in Exercise: The Basic Psychological Needs in Exercise Scale. Meas Phys Educ Exerc Sci. 2006;10(3):179–201.

36. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):1–18.

37. The Anaesthesia and Perioperative Care Priority Setting Partnership [Internet]. 2015 [cited 2015 Aug 27]. Available from: http://niaa.org.uk/Results#pt

38. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med [Internet]. 2002 Apr 4;346(14):1061–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11932474

39. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The Prevention and Treatment of Missing Data in Clinical Trials. N Engl J Med [Internet]. 2012 Oct 4;367(14):1355–60. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMsr1203730

40. Marmelo F, Rocha V, Gonçalves D. The impact of prehabilitation on post-surgical complications in patients undergoing non-urgent cardiovascular surgical intervention: Systematic review and meta-analysis. Eur J Prev Cardiol [Internet]. 2018 Jan 17;204748731775237. Available from: http://journals.sagepub.com/doi/10.1177/2047487317752373

41. Ferrara PE, Rabini A, Maggi L, Piazzini DB, Logroscino G, Magliocchetti G, et al. Effect of pre-operative physiotherapy in patients with end-stage osteoarthritis undergoing hip arthroplasty. Clin Rehabil [Internet]. 22(10–11):977–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18955429

42. D'Lima DD, Colwell CW, Morris BA, Hardwick ME, Kozin F. The effect of preoperative exercise on total knee replacement outcomes. Clin Orthop Relat Res [Internet]. 1996 May;(326):174–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8620638

43. Bäck M, Wennerblom B, Wittboldt S, Cider A. Effects of high frequency exercise in patients before and after elective percutaneous coronary intervention. Eur J Cardiovasc Nurs [Internet]. 2008 Dec;7(4):307–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18372218

44. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise. Anesth Analg [Internet]. 2008 Mar [cited 2013 Jan 17];106(3):685–712. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18292406

Author's Contributions: DM is the Principal Investigator. DM was involved in the conception and design of the study and initial draft of the protocol. CS contributed to the draft of the protocol. CS and EH participated in the implementation of the study (submissions to ethics committee, daily management of the trial) and EH critically reviewed the protocol and its contents. JN provided her expertise in kinesiology and contributed to the knowledge needed for the prehabilitation program. HM, LL, ML, GB, AH, and SG provided their experience in epidemiology, quality improvement, and clinical practice to the study design and procedures, and writing of the protocol. BP provided her knowledge for the care of aging patients and provided insight into the intervention design. AF contributed heavily to the study design and methodology. CSB contributed to the study design and the details of the intervention and control groups. CVW was involved in the study methodology and provided his expertise on data linkage. MT developed the analysis plan. CM provided mentorship oversight and helped draft the protocol. All authors have read and approved the final protocol.

Acknowledgements: We would like to acknowledge Kristin Dorrance for her insight into the patient experience component of the protocol.

Funding Statement: This work was supported by the International Anesthesia Research Society and the University of Ottawa Anesthesiology Research Grant.

Competing Interests Statement: All authors have completed the ICMJE disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). LTL reports grants from Sanofi, personal fees from Sanofi and Ferring, outside the submitted work.

CJLM reports other from Teleflex Medical, outside the submitted work. DIM, CS, EH, JN, HM, ML, GLB, AH, SG, BP, AJF, CSB, CVW, MT, have nothing to disclose.

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.

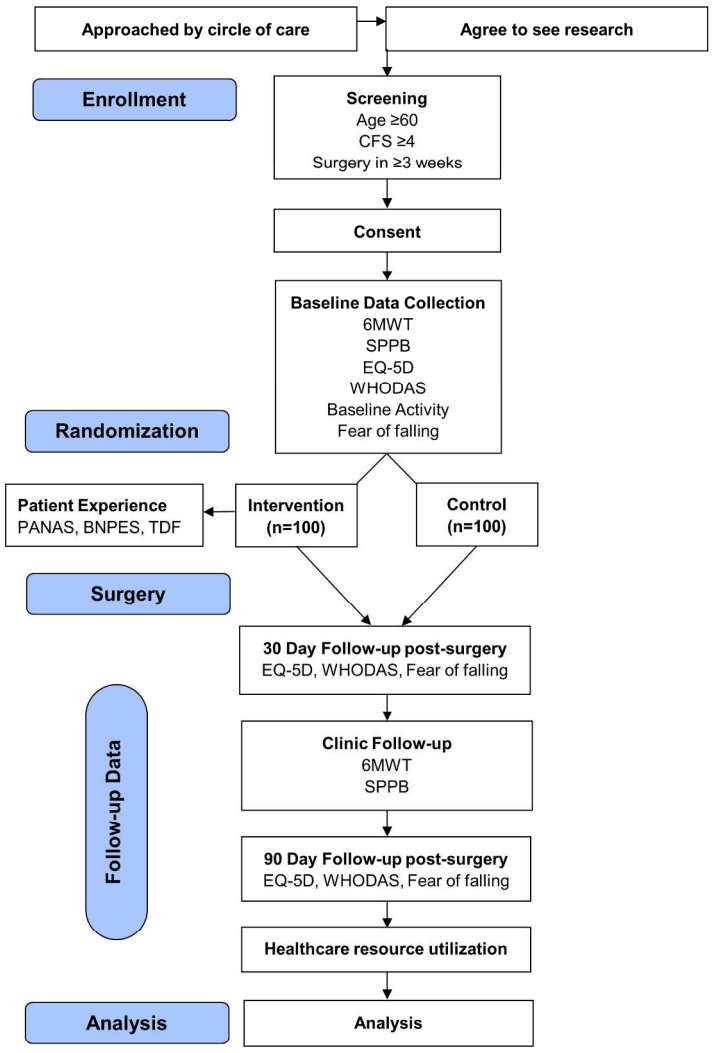

Figure 1: Study flow
*CFS: Clinical Frailty Scale; 6 MWT: 6-Minute Walk Test; SPPB: Short Physical Performance Battery; EQ-5D: Health Related Quality of Life Measure; WHODAS: WHO Disability Assessment Schedule measuring Disability Free Survival; Baseline Activity Questionnaire; Fear of Falling Questionnaire; 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 orknee 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 truck stretches, with each stretch to be held for 20 seconds, done for 2 repetitions.

The Ottawa Hospital | L'Hôpital d'Ottawa

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

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

WHAT IS EXPECTED OF ME?

Before Your Surgery

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

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

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

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

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

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.

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

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

POTENTIAL BENEFITS

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

VOLUNTARY PARTICIPATION & WITHDRAWAL

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

NEW INFORMATION

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

COMPENSATION

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

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

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

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 Ottawa Hospital | L'Hôpital d'Ottawa

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

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 (≥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____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
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)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
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
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_
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	27
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__supplemental__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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