Pilot Testing a Home-Based Rehabilitation Intervention Designed to Improve Outcomes of Frail Veterans Following Cardiothoracic Surgery

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1.0 * Study Name:
Home-based Rehabilitation Before Cardiothoracic Surgery (Pilot)

2.0 * Brief Description (using layman's terms) - 500 words or less:
Frail Veterans are at increased risk for poor surgical outcomes, and as the Veteran population grows older and more frail, there is a critical need to identify effective strategies for reducing surgical risks for these patients. Prior research shows that inter-disciplinary rehabilitation strategies deployed after surgery enhance recovery and improve outcomes by building strength and improving nutrition. We believe that similar improvements may be obtained by using similar interventions before surgery to "prehabilitate" patients' capacity to tolerate the stress of surgery. The proposed research will examine the feasibility of a novel, multifaceted, home-based prehabilitation intervention designed to improve functional capacity and postoperative outcomes for frail Veterans anticipating cardiothoracic surgery. Findings from the study will inform the design of a larger randomized controlled trial of the prehabilitation intervention. If proven effective, prehabilitation could benefit as many as 42,000 frail Veterans who are scheduled for major elective surgery each year.

* Abstract. Please provide a brief description of the study.

Background: Frail Veterans are at increased risk for poor surgical outcomes. Although surgical techniques have advanced to a level where surgery on very old adults is feasible, if a patient is also frail, the stress of surgery may overwhelm their adaptive capacities, placing them at increased risk of mortality, morbidity, and institutionalization even if surgery is technically successful. Frailty is a clinical syndrome that is commonly characterized by muscle atrophy, diminished strength and speed, decreased physical activity, and exhaustion. It is independent of any specific disease, but it increases with age and worsens disease prognoses by diminishing capacity to tolerate stressors. Thus, while surgery is often indicated for older patients, frail candidates are less likely than robust counterparts to tolerate the procedure and/or recover functional capacity. In fact, recent VA data demonstrate that frailty is a more powerful predictor of increased perioperative mortality, morbidity, length of stay, and cost than predictions based on age or comorbidity alone. As the Veteran and US populations grow older, frailty will increase, making it critically important to identify effective strategies for improving the surgical recovery and outcomes of frail patients.

"Prehabilitation" has the potential to improve surgical outcomes among the frail. Prior research demonstrates that inter-disciplinary rehabilitation strategies deployed after surgery enhance recovery and improve outcomes by building strength and improving nutrition. Based on this success, there is growing interest in "prehabilitation", which is a similar intervention deployed before surgery. By modifying physiological and environmental risks, prehabilitation aims to augment patients' capacity to compensate for the stress of surgery itself and the convalescent period thereafter. Frail patients may benefit disproportionately from prehabilitation because they have diminished capacity to endure the procedure and/or recovery. Preliminary evidence suggests that preoperative exercise interventions improve surgical outcomes. However, prehabilitation has not yet been studied in either Veteran or specifically frail populations, and no prior studies used home-based prehabilitation strategies to safely minimize travel-related barriers to participation.

Objectives: We will examine the feasibility of a novel, multifaceted, home-based prehabilitation intervention designed to improve functional capacity and postoperative outcomes for frail Veterans anticipating cardiothoracic surgery. Specific aims are to:

(1) Estimate rates of recruitment, retention, and adherence to the intervention; and evaluate participation barriers.

(2) Measure changes over time in frailty, physical function, pulmonary function, nutrition, and health-related quality of life at baseline, the day of surgery, and 30 and 90 days after surgery.

(3) Explore changes in postoperative mortality, major complications, length of hospital stay, and level of independent living using case-matched historical controls.

Methods: This single-arm pilot study will enroll a consecutive cohort of up to 50 Veterans identified as frail using a standardized frailty assessment and scheduled for major cardiothoracic surgery at the VA Pittsburgh Healthcare System. The 4 week long prehabilitation regimen will include: (a) aerobic conditioning, (b) strength and coordination training, (c) respiratory muscle training, and (d) nutritional coaching and supplementation. Pre- and post-prehabilitation assessments will include: (a) frailty; (b) physical function; (c) pulmonary function; (d) nutrition; and (e) health-related quality of life. Postoperative outcomes will include length of stay, mortality

Research Study Methods

View: 4 Research study methods

* Research Procedures/Interventions:

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C.1. Overview. In this single-arm pilot study, we will enroll a consecutive cohort of up to 50 Veterans identified as frail using a standardized frailty assessment and scheduled for major cardiothoracic surgery at the VA Pittsburgh Healthcare System. The 3-6 week long prehabilitation regimen will include: (a) aerobic conditioning, (b) strength and coordination training, (c) respiratory muscle training, and (d) nutritional coaching and supplementation. Pre- and post-prehabilitation assessments will include: (a) frailty; (b) physical function; (c) pulmonary function; (d) nutrition; and (e) health-related quality of life. Using physical performance tests, biomarkers, chart review, survey instruments, and patient logs, we will assess the feasibility of the recruitment, randomization, retention and assessment procedures, compensating patients for their time. Prehabilitation will not last more than 4 weeks for CABG patients. However, for non-cardiac thoracic patients, prehabilitation may be extended out to 6 weeks if the surgeon and patient so choose.

C.2. Eligibility criteria. We will recruit frail patients (i.e., RAI≥16 and Physician /Provider request for patient with RAI<16) scheduled for a CABG or Valve Surgery. Major non-cardiac thoracic surgery is defined according to VA Surgical Quality Improvement Program (VASQIP) criteria that include cases requiring general, epidural, or spinal anesthesia. It includes 193 unique CPT codes ranked by complexity (26 standard, 146 intermediate, and 21 complex) and excludes 58 low risk “minor” surgical procedures with limited morbidity (e.g., bronchoscopy, percutaneous lung biopsy). From these major surgeries, we will include those procedures that deliberately violate the visceral or parietal pleura with something larger than an 18 gauge needle. For example, we will include lung and esophagus resections of all kinds, but exclude thoracentesis. Exclusion criteria are designed to ensure participant safety in prehabilitation exercises (e.g., low-risk, stable cardiac disease without significant symptoms, arrhythmias, hemodynamic instability or critical coronary lesions). Based on historical data, we expect 2/3^{rds} of eligible

patients to exhibit mild frailty (RAI 16-25) with essentially intact independence and capacity for prehabilitation. Higher degrees of frailty may impose barriers to full participation, but characterizing those limitations is an important component of this pilot. We will stratify enrollment to ensure approximately equal enrollment of cardiac and non-cardiac thoracic patients.

C.3. Prehabilitation procedures. Prehabilitation will last 3-6 weeks—a time frame that does not delay surgery, corresponds to the typical lag for surgical scheduling, and strikes a pragmatic balance between improving physiologic reserve without unduly delaying definitive surgical therapy. Although the training intervention is only 3-6 weeks, studies repeatedly demonstrate neuromuscular strengthening,[9] diminished inflammation,[10] and respiratory improvements[8] within this time. Further, the program also fosters continuity between preoperative training and traditional postoperative rehabilitation, facilitating rapid mobilization and progressive exercise after surgery. Strategies like this enhance functional recovery and reduce the risks of subsequent episodes of disability (e.g., readmission or loss of independence).[58,78-81] If clinical contexts such as neoadjuvant chemotherapy or worsening angina require shorter (or permit longer) durations of training, we will examine these events in order to inform the optimal duration of prehabilitation for a larger clinical trial.

(a) Safety. Prehabilitation will begin in a telemetry-monitored, hospital-based setting to train patients in the home-based exercises and establish safe targets of exertion. If and as safety is established, exercise will shift to the home with weekly telephone/ VA Video Connect contact to ensure safety and reinforce technique. Remote telephone and VA Video Connect monitoring will be enhanced by the relationships, familiarity, and trust established during the hospital-based sessions. Although safety concerns will require some patients to complete all exercise in monitored, hospital-based settings, we anticipate that many patients will safely transition to home-based exercise after 1-4 hospital-based sessions. Study staff will initiate withdrawal procedures for patients who demonstrate insufficient cognitive or physical capacity to safely carry out the prescribed activities.

(b) Hospital-based training. Twice weekly 1-hour hospital sessions will be closely monitored and continue until participants demonstrate: (a) mastery of prehabilitation techniques; and (b) compliance with safe targets of exertion that do not induce cardiac symptoms. All patients will complete at least 1 sessions with telemetry to rule-out significant arrhythmia, but they will continue as long as needed to ensure that exercise can safely shift to the home. *Aerobic training* will focus on seated pedaling. Leg pedaling is preferred, but in cases of lower extremity disability, upper extremity exercise will be implemented. After a 3-5 minute warm-up at a low intensity of an 7-9 on the Borg Rating of Perceived Exertion (RPE) scale,[82] patients will be coached to reach 30 minutes of continuous (through bouts of 10 minutes or more to work up to the 30minutes), moderate exertion (RPE 11-13). If this exertion induces cardiac symptoms, the target will be adjusted down until a safe level is established. *Strength training* will use body weight and resistance bands (TheraBand™) at RPE 11-13 to focus on a spectrum of antagonist muscles to support the core abdominal and thoracic muscles impacted by surgery. *Coordination training* will involve exercises designed to strengthen the proper form of transitional movements required after surgery such as lying-to-side-lying, side lying-to-sitting, seated scooting, and sitting-to-standing. *Respiratory muscle training (RMT)* requires that subjects inspire and exhale through a mouthpiece at a comfortable rate using diaphragmatic breathing techniques while wearing a nose clip. The RMT device prohibits subjects from inhaling or exhaling until specific negative or positive pressures are achieved. Thresholds devices will be used and set at 40% of each patient's maximal inspiratory pressure (MIP) performed on the Pro2 device. Training will involve 5-20 breaths depending on patients capacity on the threshold device with resistance increased weekly based on RPE with a goal of moderate exertion (RPE 11-12) on both inhalation and exhalation.

(c) Home-based Training. Home-based training will increase gradually to reach the goal duration of 60 minutes allocated between strength training 3 days/week and aerobic, RMT and coordination training 5 days/week. Each session will begin with warm up before focused aerobic (pedal exerciser), strength, coordination, and RMT training, followed by cool down and stretching that matches the routines established during hospital-based training. Each patient will be given a portable, folding pedal exerciser that can be placed on the floor for leg pedaling or on a table for arm pedaling. Based on methods that successfully transition cardiac rehabilitation to the home,[7] exercise physiologists will use weekly, remote, telephone-based/ VA Video Connect calls to maintain relationship, answer questions, adjust goals and coach patients regarding their personally tailored prehabilitation regimens. Patients will record details of each training session in log books, and they may return to the hospital biweekly to assess progress in physical performance, or their biweekly session may be completed via VA Video Connect, at which time exercise physiologists will (a) adjust training goals and exercises, (b) remediate technique as needed; and (c) assess the safety of continued home exercise. Family members or other caregivers can assist patients in completing the log books if needed. Training regimens such as these have been shown to be both safe and effective among the frail elderly.[83]

(d) Nutritional Counseling. Standard or care consults with the VAPHS Nutrition Services will coincide with the initial IMPACT clinic visit. Staff nutritionists will administer the Subjective Global Assessment (SGA) of nutrition to identify nutritional needs and classify the patient as either normal or mildly, moderately or severely malnourished. All patients will receive best practice nutritional counseling focused on lean, high protein foods in preparation for surgery. Cardiac rehabilitation personnel/research staff will be trained to assess and reinforce progress on these dietary practices. In addition, standard of care nutritional supplementation will be prescribed to malnourished patients, including Impact® Advanced Recovery, an immunomodulating formula shown to improve outcomes after major surgery. Supplements will be delivered to patient's homes. Patients will also record their meals and supplements in log books, and cardiac rehab personnel/research staff will be trained to monitor and encourage consumption of the supplements as prescribed during the hospital-based coaching sessions. Family members or other caregivers can assist patients in completing the log books if needed.

(e) Occupational and Physical Therapy (OT/PT). We will arrange for a standard OT/PT consult to coincide with either the initial IMPACT clinic visit or the first scheduled visit to the Cardiac Rehabilitation facility. Staff therapists will perform routine, standardized assessments of the patient's home, environment and mobility, prescribing and supplying indicated durable medical equipment to aid mobility, exercise, and safe transition to independent living at home after the proposed surgery. As per their usual protocol, the PT/OT consult will consult with the Social Work services to adequately assess the home environment and supports in anticipation of postoperative discharge planning.

C.4. Assessment Schedule (Table1). As shown in Table 1, research staff will collect baseline data, including demographics, living location, physical performance, and nutrition, at the time of recruitment. Assessments will continue every 2 weeks up to and including the day of surgery, and then postoperatively at 30 and 90 days. Even among the robust, physical performance deteriorates immediately after surgery, but returns to baseline by 90 days.[31] Among the frail, the deterioration may endure, increasing the severity of frailty. Physical Performance Tests will be administered by exercise physiologists in the VAPHS Rehabilitation facility, located near the IMPACT clinic, and thus convenient for patients. Nutrition Assessments include serum prealbumin and c-reactive protein collected each time the participation is onsite for an assessment by a hospital phlebotomists, and the 7-point SGA administered by hospital nutritionists at baseline and again on the day of surgery. Patient Logs will assess patient adherence with the prehabilitation regimen and document progress. Family members or

other caregivers can assist patients in completing the log books if needed. Survey Instruments will be administered either face to face, by telephone/ VA Video Connect, or by mail, depending on patient preference. Responses will be entered directly into REDCap using a project utility distinct from the RAI measurement tool. For patients electing surveys by mail, we will send printed copies of the Redcap forms with a self-addressed, stamped envelope for return. Responses on returned surveys will be keyed into Redcap before storing the paper surveys in locked cabinets. Chart reviews will be completed by research staff to determine details of the surgical procedure, postoperative mortality, length of stay, and major complications. Patient Interviews will be conducted to evaluate barriers to prehabilitation and explore possible solutions. We will also track the time required to complete each measure to inform the design of the subsequent multi-center trial.

Assessments will end after the assessment planned for 90 days after the surgery. Ideally, patients will return to the hospital for this final visit to conduct measures of physical performance and nutrition along with the survey instruments. However, if they are unable to make the visit, we will conduct the surveys over the phone.

Minimizing the Burden of Assessments: Some participants in this study will be concurrently enrolled in a related study of frailty and preoperative palliative care consultation (Pro1840). Some of the outcome assessments planned for Pro 1840 are identical to those planned here. When a participant is enrolled in both studies (Pro1840 and Pro 2192) the study coordinators will work together to ensure that participants do not have to complete identical assessments twice. At any given time point when potentially duplicative assessments could occur, study staff will record the participant's singular response to a duplicative question simultaneously into the case report forms (CRFs) of each separate study. This could be accomplished by having a two separate study staff on the phone or in the room as the patient is interviewed. It could also be accomplished by having a single cross-listed staff member (e.g., listed on the staff form of both studies) administer the assessment and record the responses into the separate CRFs of each study at the same sitting. Additionally, some participants may be concurrently enrolled in a minimal risk study (PI James Ibinson MD; Pro1843) that has similar inclusion criteria. However participation in Pro1843 will not impact the outcomes of this protocol (2192).

To reduce patient burden due to travel once a patient has been determined to be safe to take part in home exercise they will have the option to complete an remote biweekly assessment via VA VideoConnect. Biweekly Assessments for patients that are unable to make it to the hospital will complete an remote, home-based biweekly assessment while on VA Video Connect with research staff members. VA Video Connect will be used in conjunction with Bluetooth connected peripheral monitors that record and transmit blood pressure, pulse, and oxygen saturation in real time. Single lead cardiac telemetry will also be used once this peripheral is made available (date pending). We will also monitor the patient visually through the video feed to ensure safety. The remote assessment will included the following items form the standard assessment: Five chair rises (standing and siting form a chair 5 times), two 4 meter walks at usual walking speed, assessment of breathing capacity on the threshold trainer (adjusted by RPE scale with goal of RPE 11-13), and if space allows a modified 6 minute walk test.

Table 1: Assessment Schedule					
	Baseline	Every other Week In-hospital	Day of surgery	30 Days post-op	90 Days post-op
Demographics					
Age, sex, race, ethnicity, etc	X				
Procedure-related variables	X			X	
Living Location	X		X	X	X
Physical Performance					
SPPB	X	X	X		x
MIP & MEP	X	X	X		x
6 Minute Walk Test	X	X	X		X
Frailty (multiple measures)	X	X	X		x
Nutrition					
Prealbumin (biweekly)	X	X	X		x
BMI	X	X	X		x
Subjective Global Assessment	X		X		x
Compliance					
Patient Logs		X	X		
Barrier Assessment	X	X	X	X	X
Outcomes					
Mortality				X	X
Length of Stay				X	
Major Complications (30 day)				X	
Quality of Life	X		X		X
Quality of Surgical Care (Pre)			X		
Quality of Surgical Care (Post)				X	
Measure of Flourishing	X		X		X
Measures of Decision Quality	x		x	X	x

C.5. Variables Assessed.

- Age, sex, race, ethnicity and socioeconomic status will be assessed by direct patient survey or chart review.
- Procedure-related variables will include the CPT codes of the initially planned operation as well as the operation actually performed. We will also abstract from the chart the type of anesthesia, the duration of the procedure, and the disposition of the patient at the end of surgery (e.g., discharge v. admission)
- Living Location is the environment where patients are living before and after the index operation (i.e., home, nursing home, etc). It will be assessed by direct patient survey or chart review and followed as an outcome.
- Short Physical Performance Battery (SPPB) is a test of balance, gait, strength, and endurance that combines gait speed, repeated chair stands and balance tests that together take less than 5 minutes to complete. Each of the 3 tests are scored on a scale from 0-4 with a combined score ranging from 0-12

with lower scores indicating worse performance.[26] Scores below 8 or 10 are interpreted as poor performance.[82] The SPPB accurately predicts adverse outcomes such as disability, hospitalization, nursing home admission, frailty and mortality, and is becoming the reference standard in rehabilitation literature.[82-86]

- 6 Minute Walk Test is a standard measure of physical performance that measures the total distance traversed in 6 minutes, measured in meters. Clinically significant differences can be quantified in as little as 30 meters. This is an exploratory measure that will only be administered if time allows. As a pilot study, we aim to determine what kinds of assessments are feasible in this group.
- Maximal Inspiratory & Expiratory Pressures (MIP & MEP) are the standard metrics of respiratory muscle strength[27] and will be measured using the TIRE device described above (D.6c). It has been shown that changes as small as 15 cm H_20 can significantly reduce postoperative pulmonary complications and length of stay.[78]
- Frailty will be assessed through several measures because no single measure of frailty captures the breadth of the syndrome. In addition to the RAI described above, we will quantify the Hopkins & Edmonton Frail Scales and independently analyze the gait speed and handgrip strength that is part of the Hopkins Frail Scale. We recently developed a streamlined approach to measuring all of these metrics simultaneously in a parsimonious exercise that takes <5 minutes to administer.[87]
- Hopkins Frail Scale encompasses slowness, weakness, weight loss, low physical activity, and exhaustion with ≥3/5 criteria required to distinguish frailty.[31,32] It is the most frequently cited tool shown to predict mortality and disability in large cohorts of community-dwelling elders and surgical patients.
- Edmonton Frail Scale is an 11-item survey that assesses 8 dimensions of frailty. Each item is scored 0, 1, or 2 with higher scores indicating greater frailty. The total score ranges from 0-17 with good inter-rater reliability (k = 0.77), moderate internal consistency (alpha=0.62), and strong correlation with a geriatrician's assessment of frailty (r=.64, p<.001).[88]
- Gait speed is one key measure of frailty[76,97,98] that has excellent inter-rater reliability (intraclass coefficient 0.88-0.96) and test-retest reliability (intraclass coefficient 0.86-0.91).
- Handgrip Strength has also been demonstrated to have key utility as an index of frailty.[32,89] A grip dynamometer will be used, averaging 2 serial assessments from the dominant hand.
- Prealbumin will be measured with standard serological testing. Changes can be detected in days, and it is the best available biomarker of nutrition.[90,91] However, because prealbumin can function as an acute phase reactant, we will also concurrently measure c-reactive protein as a measure of inflammation and interpret prealbumin as proposed by Jensen, et al.[92,93]
- Body Mass Index (BMI) will be calculated from height and weight assessed each week at the Cardiac Rehab facility, and is considered the most suitable, objective anthropometric indicator of nutritional status,[94] and changes in BMI have been shown to predict survival in the elderly.[95]
- Subjective Global Assessment of Nutrition (SGA) is the standard approach to nutritional assessment.[96] It evaluates multiple domains of nutrition and reliably categorizes patients into 1 of 4 categories: normal, mild-, moderate- and severely malnourished. We will use the 7-point SGA (See Appendix) because it is sensitive to 1-point changes in as little as 1 month and has excellent inter-rater reliability (k=.726).[28]
- Compliance with Prehabilitation. Each patient will receive a prehabilitation log book in which they will record details about their home-based regimen, including the date of training, duration and intensity of exercise, IMT repetitions and threshold pressures, nutritional supplements consumed, dietary intake, and pedometer data (e.g., step counts at the beginning and end of each training session). They will be coached in the use of this log at each hospital session. Data from the logbook will be collected from patients weekly and entered into the database for analysis. In addition, because the pedometer stores 7 days of data, and the exercise physiologists will record daily step counts as a measure of overall activity at each hospital session.

- Barrier Assessment will be conducted through face-to-face or telephone interviews with participants who encounter difficulty with recruitment to, retention in, or adherence with the training regimens. Barriers, including advanced frailty and cognitive deterioration will be described and participants will be asked to propose facilitators that might remove or minimize the barrier in future. Interviews will not be elaborate, but the questions are detailed in the case report forms. No formal qualitative analysis will be conducted, but responses will be collated and summarized by research staff. We will not record responses or attempt to create verbatim transcripts, but instead, the research staff conducting the interviews will summarize patient responses and record those summaries in the case report forms.
- Health-Related Quality of Life will be measured with the Assessment of Quality of Life (AQoL-6D) that includes 20 items on a Guttman scale assessing 6 domains: independent living, mental health, relationships, senses, pain and coping.[97] The utility score ranges from -.04 (state worse than death) to 1.0 (full health). It is sensitive to change with a minimum clinically important difference (MCID) of 0.06.[98]
- Quality of Surgical Care will be measured with the Surgical Care Survey (SCS) that includes subscales for quality of pre-surgical care (11 items), day of surgery (6 items), and postoperative care (12 items).[99]
- Flourishing will be measured by the "Secure Flourish" measure, which is 12 items assessing 6 domains: happiness & life satisfaction, mental & physical health, meaning & purpose, character & virtue, close social relationships, and financial & material stability. All items are scored from 0 to 10. This measure is calculating by summing the scores of all six domains.[96]
- Measures of Decision Quality include Decision Regret (5 items), Patient Centeredness of Care (12 items), Satisfaction with the Process of Decision Making (14 items), Satisfaction with the IMPACT clinic (8 items), Satisfaction with the frailty diagnosis (8 items), satisfaction with the palliative care consult (8 items), and Satisfaction with the surgeon (8 items).
- Mortality. Patients completing the 30- and 90-day surveys will be confirmed alive. For all others, chart review including telephone contact with identified surrogates will confirm vital status and date of death (if deceased).
- Length of Stay will be calculated from the date of surgery to the date of discharge or transfer from the hospital. We will also record the time spent in the intensive care unit. Intervals will be calculated in days.
- Major Complications will be abstracted from the chart according to VASQIP coding rules (Appendix). The presence or absence of each complication will be recorded separately, but analysis will focus on a dichotomous outcome indicating the occurrence of serious, Clavien-Dindo level IV complications.[100] These include deep wound infections, organ space infections, wound disruption, pneumonia, unplanned intubation, pulmonary embolism, mechanical ventilation for >48 hours, progressive renal insufficiency, acute renal failure, stroke, coma, cardiac arrest, myocardial infarction, bleeding in excess of 4 units, deep vein thrombosis, sepsis and C. difficile colitis. This approach to analyzing complications has been shown to correlate with frailty.[6] Co-I and Chief of Surgery Mark Wilson has authorized the VASQIP nurse abstractor to use standard VASQIP procedures to code the charts of participating patients.

Incidental Findings: If any of these tests generate an incidental finding of sufficient clinical significance to warrant review by the patient's primary care physician (PCP), we send the test results to the PCP and follow up with an encrypted email. We will also telephone the patient within a week to inform the patient of the finding and the planned PCP follow-up.

C.8. Data Analysis will focus on the feasibility of both the intervention and the outcome assessments.[1]

(a) General approach for quantitative data. We will first explore the data using descriptive statistics (e.g., means, standard deviations, percentiles, ranges) and graphical techniques (e.g., histograms,

scatter plots) to examine key variables to assess distributional assumptions, the existence of outliers and data sparseness. We will try to minimize the amount of data missing due to dropouts, but will use multiple imputation if indicated.

(b) Assess the feasibility of a novel prehabilitation intervention by estimating rates of recruitment, retention, and adherence to the intervention, and by evaluating barriers to participation [Aim 1]. We will summarize the total number of eligible patients approached, recruited, and retained through the completion of study procedures 90 days postoperatively, estimating proportions as well as associated confidence intervals (CIs).[95] We will then estimate rates of adherence to the prehabilitation intervention, computing overall and exercise-specific rates (and CIs) for the home and hospital portions of the regimen. Finally, we will qualitatively analyze reported barriers to participation with an eye to identifying potential solutions.

(c) Ascertain the feasibility of measuring changes over time in frailty, physical function, pulmonary function, nutrition, and health-related quality of life at baseline, the day of surgery, and 30 and 90 days after surgery [Aim 2]. We will summarize the time required to complete each assessment as well as the completeness of data, estimating completion rates with CIs. Graphical analyses will assess simple changes in frailty, physical performance, pulmonary function, nutrition and quality of life over the study period. Although sample size will limit model fit, we will prepare analyses for the larger trial by developing simple mixed models to explore changes over time (baseline and every other week up to the day of surgery, and then 30 and 90 days after). Separate models for each outcome will assess changes, including a fixed effect for time and a random effect for subject. The type of mixed model will depend on the outcome variable with linear mixed models for continuous variables (e.g., RAI, SPPB, 6MWT, MIP, MEP, etc) and generalized mixed models for ordinal/categorical variables (e.g., SGA, frailty phenotype). We will also explore dose-response relationships based on the actual duration of and adherence to the training regimen.

(d) Explore changes in postoperative mortality, major complications, length of hospital stay, and level of independent living using case-matched historical controls [Exploratory Aim]. We will match each participant to an historical control using local VASQIP data. VASQIP data include variables sufficient to calculate the RAI as well as details about the patient's procedure, comorbidities, outcomes, and a highly reliable prediction of postoperative 30-day mortality. Each historical control will be chosen from VAPHS VASQIP data from the 2 years prior to the study start and matched to the enrolled participant based on procedure, age, RAI score, and VASQIP predicted mortality. We will summarize separately the total number of deaths and major complications at 30 and 90 days for all patients, estimating proportions with associated CIs for the intervention and historical control groups. We will also compute summary statistics (mean, median, standard deviation, range) for length of hospital stay and return to independent living. We will then attempt to assess if differences exist between the groups with regard to these post-operative measures.

(e) Additional exploratory analyses. Two related pilot studies conducted by the PI use methods similar to those described here (e.g., Pro 1840 & Pro 1754). In particular, these studies collect identical patient reported survey measures and identical physical performance measures. Each study describes analyses of these data to generate reliable estimates of central tendency and dispersion for use in designing future studies. And in the case of this study and Pro 1754, they describe measuring change over time during the pre and post operative period. However, each study has struggled with recruitment leading to smaller than expected sample sizes. Therefore, we plan to transfer de-identified data from Pro 1840 and Pro 1754 into this study to augment the sample size and thereby increase the precision and power

of our estimates. We do not plan or expect data analysis of this augmented sample to differ in any way from that described in 1840 and 1754 and to which the participants gave consent; the only difference is that the value of each participant's data is augmented by joining it to other similar data.

Please provide a list of references *(Multi-site protocols: You may reference the page numbers in the original protocol):*

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