Pilot Testing Prehabilitation services aimed at improving outcomes among frail Veterans following major abdominal surgery.

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*** 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 new, prehabilitation intervention aimed at improving postoperative surgical outcomes through preoperative exercise training and nutritional supplementation. 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 surgeons operate safely on even the oldest old, if the elder is also frail, the stress of surgery can result in significant mortality, morbidity, and institutionalization. Frailty is a clinical syndrome marked by muscle atrophy, diminished strength, decreased physical activity, and exhaustion. It is independent of any specific disease, but it increases with age, and 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 and more frail, it is critically important to identify effective strategies for improving the surgical outcomes of these 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, improving nutrition, and optimizing home supports. Based on this success, there is growing interest in deploying similar interventions before surgery in what some call "prehabilitation." By modifying physiological and environmental risks, prehabilitation aims to augment patients' capacity to compensate for the stress of both surgery and recovery. Frail patients will likely benefit disproportionately from prehabilitation because they have the most diminished capacity to adapt to the stress of surgery. However, prehabilitation has not yet been studied in either Veteran or specifically frail populations.

Objectives: We will examine the feasibility of a novel, multifaceted pre-habilitation intervention aimed at improving postoperative outcomes for frail Veterans undergoing major abdominal surgery. Specific aims are to:

(1) Estimate rates of recruitment, randomization, retention, and compliance with the prehabilitation intervention;

(2) Measure (a) physical performance, (b) pulmonary function, and (c) nutrition at baseline and 2-week intervals to estimate changes over time and explore the optimal duration of prehabilitation (2 vs. 4 vs. 6 weeks); and

(3) Estimate overall and treatment-specific summary statistics for postoperative outcomes in terms of 30- and 90-day (a) mortality, (b) major complications, (c) length of hospital stay, (d) health-related quality of life, (e) quality of surgical care, and (f) change in level of independent living.

Methods: This randomized pilot study will enroll a consecutive cohort of up to 50 Veterans identified as frail using a standardized frailty assessment and scheduled for major abdominal surgery on the general or urological surgery services at the VA Pittsburgh Healthcare System. We will randomize participants 1:1 to receive either: (1) standard preoperative optimization by the Interdisciplinary Medical Preoperative Assessment Consultation & Treatment Clinic (IMPACT), or (2) prehabilitation + standard IMPACT optimization. The 6-week long prehabilitation intervention

will include (1) strength and balance training; (2) inspiratory muscle training; and (3) nutritional coaching and supplementation. Assessments will include standard postoperative outcomes as well as the Short Physical Performance Battery to measure physical performance, Maximal Inspiratory Pressure to measure pulmonary function, and both prealbumin and the 7-point Subjective Global Assessment to measure nutrition. Outcomes will be assessed 30 or 90 days after surgery. Compliance with the prehabilitation regimen will be assessed through patient logs and pedometers. Analyses will inform the development of a larger randomized controlled trial testing the prehabilitation intervention. Findings will be relevant for the as many as 42,000 frail Veterans scheduled for major elective surgery each year.

*** Describe the study objectives. Please include primary aim and hypothesis, if applicable any secondary aims and hypotheses.**

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*** Provide a summary of the background of the study and explain how this research will contribute to existing knowledge. Describe previous studies that provides a basis to show that the proposed research can be carried out without undue risk to human subjects.**

A.1. What is frailty? Although frailty can be defined in many ways, an international panel of experts convened in 2011 agreed that it is a multidimensional construct consisting of 6 domains (physical performance, gait speed, mobility, nutritional status, mental health and cognition) that together indicate increased risk of death, disability and institutionalization.[30] Frailty goes beyond organ-specific comorbidities to characterize a broader state of global health that extends to both physical and cognitive attributes.[31-34] Frailty increases with age, but the elderly are not necessarily frail, and the young are not necessarily robust. As such, *frailty can be conceptualized as a measure of "physiologic reserve,"* defined as the critical threshold at which external stressors overwhelm the human body's multiple mechanisms for adaptation, resulting in decompensation (i.e., acute illness or injury).[1] Frailty is the consequence of a process whereby small deficits accumulate in multiple adaptive systems, any one of which might be clinically insignificant, but together they produce significant vulnerability to stress that can lead to catastrophic decompensation. Thus, a robust 80 year old might survive an operation that a frail 60 year old might not.

A.2. Frailty will increase as the US and Veteran populations age, constituting a growing vulnerable population. By 2040, the population over age 65 is expected to double and continue expanding thereafter.[35] Many aging Veterans will develop decreased physical and cognitive capacities,[36-38] making them vulnerable to impaired decision making,[39] loss of independence,[40] polypharmacy[41] and elder abuse.[42] The VA's Strategic Plan for 2014-2020 recognizes that "geriatric care will continue to be a significant portion of VA's health care,"[43] and the VA Office of Geriatrics and Extended Care includes treatment of the frail in its mandate.[44]

A.3. Frail Veterans frequently undergo major surgery with dramatically increased morbidity and mortality. Some form of frailty is present in half of all Veterans undergoing colorectal and cardiac surgery,[5] and one third of the US population is expected to undergo a major surgical procedure within the last year of life.[45] Some frail patients clearly benefit from surgery through improved symptom management and extended life. However, the high rate of surgical morbidity and mortality among the frail suggests that for many, surgery confers significant burdens for patients, families, and society at large.[4-9] For example, compared to robust patients, frail surgical patients are less likely to be discharged to home,[8] more likely to be readmitted within 30 days,[5,9] and have substantially increased rates of perioperative mortality and complications.[4,6,7,9] In fact, our preliminary analysis demonstrates similar patterns across 1,632 major abdominal operations performed at VAPHS from 2010 to 2014 where 192 (11.8%) Veterans with differing degrees of frailty suffered dramatically increased mortality, morbidity and length of stay. Even in the mildly frail, 30-day postoperative mortality was 10 times greater than among the robust (4% vs. 0.4%, p<.001), and increased dramatically with increasing frailty. *However, little is known about how to improve the surgical outcomes of frail patients.*

A.4. A recent expert panel of VA surgeons identified several potential targets for improving surgical care of Veterans before, during, and after surgery.[46] Targets included improved preoperative decision-making, optimized intraoperative anesthetic management, and postoperative prevention of frailty-associated complications like delirium. For example, the panel hypothesized that if patients and surgeons were accurately informed of frailty-associated risks, many would choose less invasive procedures or even non-surgical therapies, thereby avoiding predictable complications. In fact, our previous work provides preliminary support for this hypothesis: In one of the only prospective attempts to improve the surgical care of the frail, we demonstrated that pre-operative, palliative care consultation ordered by a surgeon to inform and clarify surgical decision-making was associated with a markedly reduced odds of dying, even after controlling for age, frailty, and whether or not Veterans had surgery (OR=0.27; 95% CI 0.11-0.68, p=.006).[47] Some of these Veterans opted out of surgery, but most proceeded to the operating room, *thus demonstrating the critically important need to identify effective strategies for mitigating frailty-associated risks of those choosing surgery.*

A.5. Prehabilitation is a promising, yet largely untested, strategy for mitigating surgical risk. The concept of prehabilitation *before* surgery is rooted in the demonstrated success of cardiac rehabilitation to advance activity, modify cardiac risk factors, and foster healthful lifestyles *after* surgery through a standardized, structured, exercise-educational-behavioral strategy.[10] The orientation of cardiac rehabilitation to surgical recovery evolved from its original function to first mobilize and then advance activity for patients who had survived what was usually a devastating myocardial infarction and/or who had undergone what was usually a severely debilitating coronary artery bypass procedure.[48] As demonstrated by several systematic reviews, similar strategies have proven successful not only for cardiac surgery,[10] but also for orthopedic,[11,13] lung,[14,49] and abdominal surgery.[12] However, rather than waiting until after the surgery to initiate these proven strategies, there is growing interest in deploying similar exercise-educational-behavioral strategies *before* surgery to mitigate perioperative risks by increasing patients' capacity to respond to intraoperative stress and accelerate postoperative recovery.[12,19,50] Several cohort and small randomized controlled trials (RCTs) have explored the feasibility and impact of prehabilitation for cardiac, orthopedic, and major abdominal operations.[16-18,20,21] *However, these studies focused on relatively high-functioning patients, and thus both the feasibility and effectiveness of prehabilitation among specifically frail populations remains uncertain*.

A.6. Prehabilitation is most promising among the frail. Although prehabilitation may benefit everyone, frail patients likely have the most to gain because they have the greatest deficits in physiologic reserve, and thus even modest improvements in strength, balance, and nutrition may prevent the physiologic decompensation that leads to poor outcomes.[51,52] However, it remains unclear if frail patients can fully comply with intensive physical therapy (PT), and even if they do, it is not clear if they will build strength, muscle mass, aerobic capacity, and nutrition demonstrated in more robust populations.[53] A recent review demonstrates preliminary feasibility, safety and effectiveness of PT programs focused on frail populations,[54] but because the most effective interventions lasted ≥5 months, it remains uncertain if clinically significant benefits can be achieved in the 4-6 weeks that typically elapse between diagnosis and surgery. To begin examining these questions, researchers in Canada are conducting a multi-site RCT of prehabilitation for *cardiac* surgery.[55] *However, further research is needed to demonstrate the feasibility and effectiveness of frailty-focused prehabilitation in the non-cardiac surgery that accounts for the majority of surgery conducted in US Veteran populations*.

A.7. We therefore developed a multifaceted prehabilitation intervention for frail patients scheduled for major abdominal surgery. We will leverage the existing standard of care at VAPHS through which all patients scheduled for surgery are routinely evaluated for frailty as part of a standard preoperative risk assessment (but not risk mitigation). For those identified as frail, we will offer prehabilitation focused on increasing physiological reserve through (a) strength and balance training to support the improved outcomes associated with early mobilization after abdominal surgery,[56] (b) inspiratory muscle training to reduce postoperative pulmonary complications[57] and (c) nutritional coaching and supplementation to enhance physical performance[58] and wound healing.[59] We will also arrange occupational and physical therapy consults to identify and supply needed durable medical equipment.

A.8. Conceptual model for prehabilitation. Our approach to prehabilitation is informed by a conceptual model adapted from Hoogeboom and colleagues[12] to illustrate how prehabilitation might improve postoperative outcomes by increasing physiological reserve at the time of surgery. As indicated by the solid lines, the decreased physiological reserves of frailty limit capacity to adapt to the stress of surgery, leading to worse outcomes. Prehabilitation aims to increase physiological reserve at the time of surgery by increasing physical and pulmonary function along with improved nutrition, thereby increasing adaptive capacity and improving outcomes including decreased mortality, complications length of stay and improved quality of life.

PRELIMINARY STUDIES

B.1. Our interdisciplinary research team has the expertise to accomplish this study. Dr. Hall is a general surgeon and former recipient of an HSR&D Career Development Award focused on improving the process of surgical informed consent. In 2014, he began collaborating with Dr. Johanning (Co-I) to validate the Risk Analysis Index (RAI) of frailty used in this study (B.2). He is a consultant on several quality improvement (QI) projects related to surgical frailty at the Omaha, Atlanta, Nashville and Pittsburgh VAMCs and the University of Pittsburgh. Dr. Forman is a geriatrician and cardiologist who directs the VAPHS Cardiac Rehabilitation Center. He has extensive experience with exercise physiology trials (B.3), including an ongoing RR&D I01 (F0834-R) aimed at understanding the effects of different types of exercise training on the functional capacity of heart failure patients. Dr. Johanning is a vascular surgeon and health system administrator with geriatric training who implemented the Frailty Screening Initiative at the Omaha VAMC (B.4), collaborated with Dr. Hall to validate the RAI, and serves as a consultant with similar initiatives at several VA and non-VA centers. Dr. Wilson, the Chief of Surgery at VAPHS, has expertise in surgical QI. With Dr. Hall, he implemented procedures at VAPHS to systematically

screen all preoperative patients for frailty, and will work closely with the team to implement the prehabilitation procedures proposed here. Dr. Cahalin brings key expertise as a leader in the field of inspiratory muscle training (IMT),[60-65] having developed a convenient and effect regimen for IMT (B.5). He is collaborating on Dr. Forman's RR&D I01 (B.3), and he will guide the IMT component of the present study.

B.2. Development, validation, and implementation of the Risk Analysis Index (RAI) of frailty. None of the existing tools for measuring frailty have proved suitable for widespread, prospective clinical screening. To fill this gap, Drs. Hall and Johanning developed, validated and refined the RAI that can be calculated retrospectively from VA Surgical Quality Improvement Program (VASQIP) data or prospectively from a 2-minute 14-item survey. Both versions of the RAI yield a continuous score that captures a full range of frailty from robust (0-15) to mild (16-25), moderate (26-35) and severe frailty (≥36). From July 2011 to September 2015, they used the 14-item survey to assess frailty in a consecutive cohort of 6,905 patients scheduled for surgery at the Omaha VAMC. In this cohort, the RAI has strong predictive power for 6-month mortality (c-statistic=0.772).[66] At a cutoff of ≥16, the RAI survey classified 12.5% of the cohort as frail with a sensitivity of 0.50 and specificity of 0.90. By linking this cohort to VASQIP data, they compared the RAI to the previously validated, retrospectively calculated modified Frailty Index (mFI)[67] in a sub-sample of 1,024 patients where the RAI survey (c=.797) performed on par with the mFI (c=.811), thus establishing preliminary convergent validity with the advantage of prospective assessment that can inform real-time clinical decisions. Based on these data, the RAI questionnaire was implemented as standard of care for pre-surgical risk stratification at the Omaha, Pittsburgh, Atlanta, Nashville and Phoenix VAMCs.

B.3. Effective implementation of exercise training programs in frail heart failure patients and recruiting subjects into training trials. Dr. Forman was Site PI for both the NHLBI aerobic training trial HF-ACTION[68] and the NCCAM Tai Chi Mind-Body Movement Therapy for Patients with Chronic Heart Failure.[69] He is skilled in the prehabilitation techniques planned for this investigation, reliably achieving both training effects and endpoints. For example, in a trial of older female patients, those randomized to a strength training program similar to that proposed here had significantly increased strength (43.4±8.8% vs.-1.7± 2.8% in controls, p= 0.001) and endurance (299±66% vs. 1±3%, p= 0.001).[70] Dr. Forman's RR&D I01 is currently randomizing 200 heart failure patients to regimens similar to those proposed here that focus on strength training and IMT.

B.4. The Omaha Frailty Screening Initiative (FSI) is the first feasible and effective facility-level intervention to improve postoperative survival among frail Veterans. While Chief of Surgery at the Omaha VA, Dr. Johanning began using the RAI to screen pre-surgical patients for frailty. Those identified as frail were subjected to an administrative review aimed at clarifying surgical decision-making through informal discussions with surgeons, anesthesiologists and palliative care physicians focused on each patient's frailty and frailty-associated risk.[47,71-73] By comparing outcomes after FSI implementation to historical controls, he and Dr. Hall found that 180-day survival among frail patients improved 7-fold after implementing the FSI (OR 7.50, 95% CI 4.08-13.79), reflecting a drop in 180-day mortality from 23.9% to 4.5% (p<.001).[74]

B.5. IMT improves pulmonary function in as little as 2 weeks. Dr. Cahalin's study of IMT in advanced heart failure patients found that dyspnea symptoms improved when maximal inspiratory pressure increased 24% (51±21 to 63±23 cm H_20, p=.0001) only 2 weeks after initiating an IMT regimen that was far more convenient and efficient than others which had been studied at that time.[62] A subsequent study also in heart failure patients showed that IMT significantly improved

gait speed and quality of life.[63] This experience informs both the methods presented here, as well those of Dr. Forman's RR&D I01.

*** Describe the overall significance of the research in terms of the problem to be studied and potential findings, as well as its relevance to the care of veterans, the VAPHS, and the VHA:**

C.1. The proposed research has potentially high impact because it addresses the needs of as many as 42,000 frail Veterans scheduled for major elective surgery each year.[29] These patients experience disproportionately poor outcomes and accrue markedly higher costs, thus representing a highly significant opportunity to improve the processes of surgical care through prehabilitation strategies to yield a practical, preventative strategy for improving both quality and quantity of life for vulnerable, frail Veterans.

C.2. Prehabilitation for the frail is innovative because it shifts established rehabilitation strategies to the preoperative period and focuses those strategies on the frail Veterans most likely to benefit. As such, it addresses a critical gap in the science of frailty research, and does so with a focused strategy to direct preventative resources to the limited population at greatest risk and thus most likely to benefit.

C.3. The proposed research is directly aligned with VA's operational imperatives. Our study "advances healthcare innovation" (Theme 3 of the VA's Strategic Plan[75]) by developing an innovative, preventative healthcare intervention that "anticipates and meets the unique needs of…[the] most vulnerable Veterans" (Blueprint Strategy 1). It also aligns with HSR&D Priority Areas A (access for vulnerable Veteran populations) and B (health equity) along with the Office of Geriatrics and Extended Care Service's focus on "optimizing the health and well-being of Veterans with multiple chronic conditions, life-limiting illness…and frailty."[44] Letters of support demonstrate that Assistant Deputy Under Secretary of Health for Clinical Operations and Management, Dr. Thomas Lynch, as well as the Director of Geriatrics and Extended Care Operations, Dr. Thomas Edes, are enthusiastic partners in the proposed research and are prepared to use study findings to guide future, system-wide initiatives to improve the quality of patient-centered surgical care throughout VHA. There is also significant interest from CMS Deputy Chief Medical Officer, Dr. Shari Ling, indicating that the VA can again lead the nation in developing high-value medical care.

Research study methods

Research Study Methods

Describe all study related procedures following enrollment of a subject in this study.

*** Research Procedures/Interventions:**

D.1. Overview. We will conduct a randomized pilot study of a prehabilitation intervention in a consecutive sample of up to 50 frail patients scheduled for elective major abdominal surgery at the VAPHS. Participants will be recruited from the mandatory preoperative IMPACT clinic where all patients are routinely screened for frailty. Frail patients agreeing to participate will be randomized 1:1 to (a) standard preoperative optimization by the IMPACT clinic or (b) prehabilitation + standard IMPACT optimization. The prehabilitation intervention will deploy existing cardiac rehabilitation resources to provide (a) strength and balance training, (b) respiratory muscle training, and (c) nutritional coaching and supplementation. 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.

D.4. Eligibility criteria. We will include all patients with RAI>16 scheduled for major abdominal surgery on the general or urological surgery services. Major surgery is defined according to VASQIP criteria to include cases requiring general, epidural, or spinal anesthesia.

For general and urological surgery, it includes 270 standard, 356 intermediate, and 34 complex procedures, but excludes 291 low risk, "minor" surgical procedures with limited morbidity (e.g., abscess drainage, lipomas, or hemorrhoids). From these major surgeries, we will include those abdominal procedures that deliberately violate the peritoneal or retroperitoneal spaces. For example, from the general surgery service we will include all bowel resections, biliary procedures, and abdominal wall reconstructions, but exclude open, anterior inguinal hernia repair. The list of included CPT codes (see Appendix) represents 56% and 35% of the general and urological surgery volume at VAPHS, respectively (Table 2 below). Given the burden of comorbidity among the frail, we anticipate that many eligible Veterans will have concurrent cognitive impairment or dependent living situations. These limitations need not preclude inclusion so long as the patient can provide first-person informed consent and participate in the prehabilitation regimen described below (D.6). No other exclusions are planned.

D.5. Randomization procedures and their rationale. Some patients may be reluctant to accept the possibility of randomization to control conditions, and if so, recruitment rates of a randomized trial would be diminished. We will therefore use the randomization feature in REDCap to randomize participants in a 1:1 ratio. As each patient enrolls, REDCap will assign the patient to intervention or control conditions as specified by a fixed allocation table. If patients refuse participation based on the risk of randomization, we will note this fact, but offer the opportunity to participate in the preferred arm (intervention or control). This approach will permit accurate estimates of randomization while accruing the largest possible sample size.

D.6. Prehabilitation Procedures.

(a) Overview. Prehabilitation will include hospital- and home-based components within an integrated intervention led by Dr. Forman. The hospital-based component will occur at the VAPHS Cardiac Rehabilitation facility and focus on supervised strength and balance training. One-hour sessions will be scheduled twice weekly for at least 4, but no more than 6 weeks before the operation. The home-based component will entail walking or seated pedaling on a home exerciser, as well as Respiratory Muscle Training (RMT), both of which are feasible and safe to do in a non-supervised setting. Nutritional supplementation will be linked to the composite training protocol. Compliance will be measured with exercise log books (See Appendix) and pedometers given to each participant. With the consent of the surgeon, operative dates will be scheduled to accommodate prehabilitation.

(b) Hospital-based Training will be scheduled twice weekly and include strength and balance training. All sessions will begin with an assessment of the subject's vital signs and a review of their progress with home-based training. Based on evaluation of the exercise log books and pedometer data, the exercise physiologist will reinforce the goals and techniques of the home-based regimen as needed. After the assessment phase, subjects will complete 5 minutes of warm-up with low-intensity walking or seated pedaling. Seated pedaling can be used to exercise the upper extremities in cases of lower extremity disability. Mode of exercise will depend on patient preference and safety, but the same mode of exercise will be used in both the hospital- and home-based regimens (see below). Subjects will then complete 10 minutes of balance training tailored to each subject's capacities and progressing as tolerated. Regimens will uniformly include elements of static, tandem and one-foot stands, weight shifts, side steps, crossovers, grape vines, backward walking, and stepping over objects. Balance training will be coupled with an additional 10 minutes of transitional movement training to enable and strengthen the proper form of movements required after surgery such as lying-to-sitting and sitting-to-standing. Next, subjects will complete 25 minutes of strength training (2 sets with 8-12 repetitions) focused on a spectrum of antagonist muscles for the core abdominal muscles impacted by surgery, including hip flexors and extensors, obliques, rhomboids, erectus spinous, and latissimus dorsi. In addition, to optimize mobility and daily function, we will target other muscle groups in the legs, arms, and hands (quads, hamstrings, calf, biceps, triceps, and hand groups). The hospital-based session will finish with full body stretching and reassessment of vital signs. During each session, the exercise physiologist will use a log book (Appendix) to

record completion of each component along with details about the duration and intensity of the aerobic training, balance, and weight training. Regimens such as this have been shown to be both safe and effective among the frail elderly,[76] and the improvements in strength and balance will likely facilitate early mobilization after surgery—an intervention shown to improve outcomes after surgery.[56]

(c) Home-based Training: Patients will be coached to complete home-based training at least 2-3 days a week and more as tolerated. Exercise will start with a 5 minute warm-up (i.e., slow paced walking or seated pedaling, consistent with the mode of exercise used in the hospital). The same exercise modality will then extend for an additional 30 minute aerobic training session. This phase will entail efforts at a comfortable speed with increasing duration. We will coach patients to reach 30 minutes of continuous, moderate exertion of 11-13 on the Borg Rating of Perceived Exertion (RPE) scale,[77] but it is expected that initially many subjects may only tolerate shorter intervals. In that case, 5-10 minute intervals of less intense (slower) walking or pedaling may then be combined with periods of rest, with the goal of repeating and elongating them as tolerated until 30 continuous minutes are achieved. If/when 30 minutes of continuous exercise is achieved (at RPE 11-13), the next step will be to progress the intensity (speed) with short periods of relatively greater speed (RPE 13-15) for 1-2 minutes, and alternate with slower intensity (speed) at RPE 11-13. Patients will record the duration and exertion of training in their log books along with step counts from their pedometer affixed to either the patient's waist (walking) or wrist/ankle (pedaling). Family members or other caregivers can assist patients in completing the log books if needed. After aerobic activity, home-based exercise will continue with 30 minutes of progressive RMT using a Threshold RMT device (Respironics™). Threshold RMT requires that subjects inspire and exhale through a mouthpiece at a comfortable rate using diaphragmatic breathing techniques. The Threshold IMT device prohibits the subject from inhaling or exhaling until a set negative pressure is achieved and overcome. This is accomplished through the use of weighted plungers or spring-loaded valves. It is inexpensive, convenient, and easy to administer at home. We will set each patient's threshold to 40% of maximal inspiratory and expiratory pressures (MIP & MEP) as measured by the Test of Incremental Respiratory Endurance (TIRE)[60] device, a breathing assessment tool that links a pneumotachometer to a computer tablet and can be used gauge inspiratory pressures. MIP & MEP are the peak pressures generated by respiratory muscles when patients forcibly inhale or exhale against resistance. It is analogous to a maximum weight lifted in the gym but measures the strength of the diaphragm and accessory breathing muscles. MIP & MEP will be defined as the average of 3 assessment breaths on a TIRE device. MIP & MEP will be measured at the first hospital-based session and bi-weekly thereafter, adjusting the Threshold RMT device to maintain a workload at 40% of MIP & MEP as respiratory muscle conditioning improves. Patients will again record the threshold and number of breaths completed in the 30-minute session in log books. Family members or other caregivers can assist patients in completing the log books if needed. Regimens such as this have been shown to increase MIP (15 cm H_20, 95% CI 9-21) and halve the risk of postoperative pulmonary complications following abdominal surgery (relative risk 0.48, 95% CI 0.26 to 0.8).[78]

(d) Nutritional Counseling. Malnutrition at hospital admission increases length of stay,[79] and nutritional supplementation has been shown to enhance both wound healing[59] and exercise-induced improvements in physical performance.[58] Based on patient preference and convenience, we will arrange for a standard consult with VAPHS Nutrition Services to coincide either with the initial IMPACT clinic visit or the first scheduled visit to the Cardiac Rehabilitation facility. Staff nutritionists (see letter) will administer the standardized Subjective Global Assessment (SGA) of nutrition (Appendix) 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 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.[80] Supplements will be delivered to patient's homes. Patients will also record their meals and supplements in log books (Appendix), and cardiac rehab personnel 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. Although the evidence is somewhat equivocal, approaches such as this have been shown to reduce postoperative complications (relative risk 0.67, 95% CI 0.53-0.84).[81]

(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 (see letter) 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.

D.7. Assessment Schedule. As shown in Table 1, research staff will collect baseline data at the time of recruitment regarding demographics, physical performance, and nutrition. We will monitor physical performance, nutrition and compliance every other week during in-hospital prehabilitation and on the day of surgery. Postoperative outcomes will be assessed 30 or 90 days after the surgery. Patient Survey Instruments will be administered either face to face, by telephone 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. Instruments assessing living location, quality of life, quality of surgical care, and decision quality are described in D.8. and in the Appendix. Chart reviews will be completed by the research assistant to determine details of the surgical procedure, including postoperative mortality, length of stay, and major complications. Physical Performance Tests will be administered by the exercise physiologist in the Cardiac Rehabilitation facility, located near the IMPACT clinic, and thus convenient for patients to visit on both the days of recruitment and surgery. Nutrition assessments include serum prealbumin and Body Mass Index (BMI) collected biweekly by hospital phlebotomists, and the 7-point Subjective Global Assessment (SGA-7)[28] administered by hospital nutritionists at baseline and again on the day of surgery. Patient Logs will assess patient compliance with the home-based prehabilitation regimen and document progress with aerobic training, IMT and nutritional supplementation. They will be collected weekly and on the day of surgery. *Those randomized to control conditions will not complete the patient logs or the weekly in-hospital assessments, but they will complete all other assessments.*

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.

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		
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	
Measures of Decision Quality	x		x	X	x

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 Pro1754 are identical to those planned here. When a participant is enrolled in both studies (Pro1840 and Pro1754) 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 (1754).

D.8. 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.
- 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]
- 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 (see letter) 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.

Research study methods: analysis Plan

* **Please describe the analysis plan for the study** *(it is acceptable to refer to the*

sponsor/multi-site protocol for section if applicable):

D.10. Data Analysis.

(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. For categorical variables, we will generate frequency and percentage distributions to identify data sparseness. In the event of data sparseness, categories with small frequencies will be merged when meaningful and appropriate. Continuous variables will be categorized into meaningful groups if the distributions are skewed. All analyses will be performed using Stata statistical software (StataCorp, 2013).

(b) Missing Data Strategies. We will attempt to minimize the amount of missing due to dropouts (withdrawals, lost to follow-up, or deaths) or individuals who missed at least one of the follow-up assessments (intermittent missing). In the event of missing data, we will use multiple imputation to impute the missing values.

(c) Estimate rates of recruitment, randomization, retention, and compliance with the prehabilitation intervention [Aim 1]. To assess the feasibility of recruitment, randomization, and retention, we will summarize the total number of eligible patients approached, recruited, randomized to intervention and control conditions, and retained through the completion of study procedures 90 days postoperatively, estimating rates as well as associated confidence intervals.[25] For those lost to follow up, we will estimate the proportion of planned in-hospital prehabilitation sessions completed before dropping out along with rates of 30-day outcome assessment (if available). For those randomized to the intervention condition, compliance with the hospital-based regimen will be measured as the number of scheduled sessions completed. If patients are able to comply with only a portion of the training regimen, this will be noted and the patient will be categorized as partially compliant. Compliance with the home-based regimen will be measured as the number of assigned activities documented in the patient logs. Overall compliance rates with confidence intervals (CIs) will be estimated for the home, hospital, and combined intervention. We will also compute rates (and CIs) of partial compliance as well as rates (and CIs) of intervention-specific task compliance.

(d) Measure (a) physical performance with the SPPB, (b) pulmonary function with MIP, and (c) nutrition with the SGA-7 and prealbumin at baseline and 2-week intervals to estimate changes over time and explore the optimal duration of prehabilitation (2 vs. 4 vs. 6 weeks) [Aim 2]. We will use graphical analyses to assess simple change in physical performance, pulmonary function and nutrition over the prehabilitation period. We will also use simple mixed models to explore changes over the multiple time points (baseline and 2, 4, and 6 weeks). Separate models for each outcome will assess the rate of change, including a fixed effect for time and a random effect for subject. The type of mixed model used will be dependent on the data type of the outcome with linear mixed model for continuous variables (SPPB, MIP, prealbumin, BMI and RAI) and generalized mixed models for categorical/ dichotomous (SGA). To the extent possible, the modelling of the rate of change in the outcomes over time will include an assessment of the shape of this relationship utilizing simple piecewise linear functions to explore any indication of the optimal duration of therapy. We anticipate that improvements in the outcome will grow logarithmically over time, and that the majority of the growth will be achieved between 3-6 weeks.

(e) Estimate overall and treatment-specific summary statistics for postoperative outcomes in terms of 30- and 90-day (a) mortality, (b) major complications, (c) length of hospital stay, (d) health-related quality of life, (e) quality of surgical care, and (f) change in level of independent living [Aim 3]. We will summarize separately the total number of deaths and major complications at 30 and 90 days for all patients, estimating rates (overall and by treatment-group) as well as associated CIs. Rates will be computed as the number of specific events (deaths or major complication), divided by the total accrued

person-time where person-time is defined as the amount of time a patient is followed from study start to either the end of study, death or loss to follow-up (whichever occurs first). We will also compute summary statistics (mean, median, standard deviation, range) for length of hospital stay, health-related quality of life, quality of surgical care and recovery to independent living. We will make assessments overall and by treatment group. While our emphasis is to assess feasibility, we will also attempt to assess if differences exist between the intervention and control conditions with regards to these post-operative measures.

D.11. Justification of Pilot sample size. Based on the historical surgical volume at VAPHS, the participating surgical services will treat 54 eligible patients who meet our inclusion criteria during a 7 month recruitment window (Table 3). We are not estimating the effect size between intervention and control conditions. Although there is a tradition of using pilot studies to do so, there is growing consensus that this approach is ill-founded because the small samples result in imprecision that makes power estimates unreliable.[23] Therefore, based on recruitment and retention rates estimated here (Aim 1), we will power our subsequent study based on "minimum clinically meaningful differences" defined for each outcome *a priori*.[24]

Table 3: Sample Size Estimates	General	Urology	Total
Total Surgical Cases/year	1488	610	2098
VASQIP Eligible Cases/year	748	298	1046
Proportion Abdominal	56.2%	35.3%	$\bar{x}$=50.2%
Proportion Frail	12.0%	10.3%	$\bar{x}$=11.5%
Eligible Cases/year	70.9	21.5	92.4
Eligible Cases/7 month recruitment	41.4	12.5	53.9

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