Multi-Component Prehabilitation Program for High-Risk Older Adults Undergoing Major Elective Surgery: A Pilot and Feasibility Study Protocol

Clinical Trial Registration: NCT05752474

Update History:

Version 1: 02/20/2023

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1. UPDATE HISTORY

Date	Summary
02/20/2023	Initial protocol completed

2. OVERVIEW

The purpose of this feasibility pilot study is to understand how a prehabilitation program for older adults with frailty can best be optimized to prepare at-risk patients for major surgery. As such, our program interventions target major risk factors that are modifiable yet rarely addressed in the pre-surgery period (physical function, nutrition, pain, sleep, anxiety, and cognition). We also aim to determine how these interventions can best be delivered for optimal participation.

Participants will receive 3 to 4 weeks of exercise training with a physical therapist, nutrition education with a registered dietitian, meditation with an experienced meditation teacher, and cognitive behavioral intervention to discuss goals, facilitators and barriers to program adherence with the goal to enhance motivation and promote self-efficacy. Two (2) follow-up assessments will additionally be performed at days 30 and 90. Further details of the intervention are provided below:

- Exercise training with home/virtual/in-center physical therapy will take place on average twice a week for 1 hour per session over 3-4 weeks. The participant will be encouraged to exercise on their own for 30 minutes per day for 4 or more days a week and track exercise in a diary (number of minutes achieved per day). They will also be asked to wear a physical activity tracking device (Fitbit Fitness tracker) to measure daily number of steps, active minutes, and heart rate. This device will also remind the participant to get up and move throughout the day.

- Nutrition class with a licensed nutritionist (registered dietitian) will take place on average once a week for 1 hour per session over 3-4 weeks. The participant will also be asked to drink/consume 1 high calorie, high protein nutritional supplement per day which will be provided to them by the study. They will be asked to write down their approximate daily food intake in a diary (3 days/week) – this will be an informal accounting of their intake with the primary focus being on protein-containing food items. This information will be used to measure their protein intake during their participation in the study.

- Meditation with a yoga/meditation teacher will take place once a week for 1 hour per session over 3-4 weeks. The participant will also be asked to practice meditation on their own for at least 12 minutes each day and track in a diary (number of minutes achieved each day).

- Weekly check-in calls will take place once a week for about 30 minutes per sssion over 3-4 weeks. During these calls the participant will talk about their goals, discuss personal motivation, and review their progress. They will be asked about any potential adverse events (such as sore muscles or falls).

- A 30 minute telephone interview will take place at the end of the intervention (in weeks 3 or 4). The participant will be asked to provide feedback discussing what parts of the

intervention worked well and what did not. We will use this information for protocol refinement.

The primary outcome is the feasibility of the prehabilitation protocol, defined as the *proportion of patients to whom we can deliver an adequate dose (≥50% of the planned sessions) of the 3 core interventions: physical therapy (≥4/8 sessions), nutrition (≥2/4 sessions), and meditation (≥2/4 sessions).* Secondary outcomes include 1) self-reported and objective measures of adherence; 2) patient-centered outcomes, measured using PROMIS physical, cognitive, depression, anxiety, and fatigue domains at baseline, following completion of the prehabilitation (before surgery), and on postoperative days 30 and 90; 3) clinical outcomes (3-D Confusion Assessment Method,[1] a composite complication score,[2] length of stay, and 30-day readmission and death); and 4) Postoperative Quality of Recovery Scale[3] to be obtained around postoperative day 3.

The proposed research will provide necessary information for a larger randomized controlled trial (RCT).

3. STUDY OBJECTIVES

The ***objective*** of this pilot study is to evaluate feasibility of a prehabilitation program in frail older adults undergoing major surgery. Our ***central hypothesis*** is that optimizing risk factors before surgery with a multicomponent prehabilitation protocol will improve postoperative outcomes in high-risk older adults undergoing major elective abdominal, gynecological oncologic, and urologic surgery. By utilizing a patient-centered multicomponent protocol, the most effective intervention strategies of the protocol can be refined for a larger scale randomized controlled trial. This research has four (4) intervention components: 1) physical therapy; 2), nutrition; 3) meditation; and 4) cognitive behavioral strategies will additionally be utilized to enhance motivation and support self-efficacy. We will accomplish the following two (2) ***specific aims***:

3.1 Objective/Aim 1. **To evaluate the feasibility of and adherence to the prehabilitation program.** We will estimate the duration of preoperative geriatric assessment screening; enrollment rate; feasibility of and adherence to the prehabilitation program; attrition rate; and extent of missing outcome data. We expect that *we will be able to deliver our prehabilitation program to ≥50% of patients*.

Feasibility is defined by proportions of enrollment, refusal, and adherence to intervention components as a whole and individually, potential barriers to adherence, and self-reported and objective measures of adherence including diaries, wearable sensors, and physical performance tests. As secondary outcomes, we will collect clinical outcomes (e.g., Postoperative Quality of Recovery Scale, surgical complications, and length of stay) and Patient-Reported Outcomes Measurement Information System (PROMIS) measures.

3.2 Objective/Aim 2. **To identify barriers and facilitators of prehabilitation program and refine protocol accordingly.** After the prehabilitation program, we will interview

patients and their caregivers to identify facilitators, barriers, and areas for improvement. After completing all qualitative interviews, we will refine the intervention components based on participant feedback. This information will inform the design of a future, larger RCT which will target frailty using the most effective intervention components.

By completing this research, we hope to generate evidence that rehabilitation interventions are feasible and effective for optimizing risk factors before surgery. Based on our review of literature, we concluded that the success of an RCT would depend on having a feasible and acceptable prehabilitation program in the preoperative period. Therefore, we chose to focus on intervention refinement to provide necessary information to design a large RCT to compare a multicomponent prehabilitation program versus usual care on clinical and patient-centered outcomes among high risk older adults undergoing major elective surgery.

4. BACKGROUND

Current practice of preoperative evaluation does not consider the intrinsic capacity of older adults to tolerate stress related to surgery**.** Frailty is a measure of intrinsic capacity.[4] Individuals with frailty have decreased physiologic reserve to tolerate stressors,[5] and thus they are more likely to experience poor surgical outcomes, such as complications, mortality, readmission, functional decline, and discharge to an institution.[6,7] While it is a reliable measure of surgical risk, frailty is not part of the preoperative assessment of older adults. Frailty assessment within the context of a comprehensive geriatric assessment—a multi-domain assessment of medical history, functional status, cognition, mood, physical performance, and nutritional status[8]—provides not only risk stratification but also opportunities to optimize modifiable risk factors to improve surgical outcomes.

Optimizing risk factors before surgery may improve outcomes. Interventions to increase reserve through physical activity and nutritional interventions before surgery are biologically plausible ways to improve surgical outcomes, but they are not routinely done in practice. To date, studies on prehabilitation have mostly been on gastrointestinal,[9-13] cardiothoracic,[10,14] and orthopedic surgeries[15] with physical activity and nutrition as single or dual interventions.[9-12,14] There are only a small number of RCTs on a multicomponent prehabilitation (≥3 interventions).[16-21] Some studies have shown that prehabilitation may decrease length of stay and postoperative complications, and improve function, while others did not show benefits.[9,11,12,14,22,23] Systematic reviews concluded insufficient evidence for prehabilitation for clinical use due to significant limitations of studies, including small sample sizes,[11,13,15,24,25] increased risk of bias (e.g., single-arm studies),[9-11,14,23,26] and lack of attention to adherence.[13,14,21,24,26] Little is known about facilitators of and barriers to adhering to prehabilitation interventions, particularly among frail patients.[27,28] Moreover, evidence as to which patients will most benefit from prehabilitation[10,29] and the effect of prehabilitation on patient-centered outcomes[14] are lacking.

The efficacy and potential mechani”ms o’ Interventions are supported by evidence (**Table 1**). Short duration (3-4 week) intensive exercise and protein-focused nutrition programs have also previously been shown to improve physical measures[30,31] and outcomes[18,19,32-34]; however, a robust RCT of a multi-component prehabilitation program addressing the aforementioned gaps is still needed.

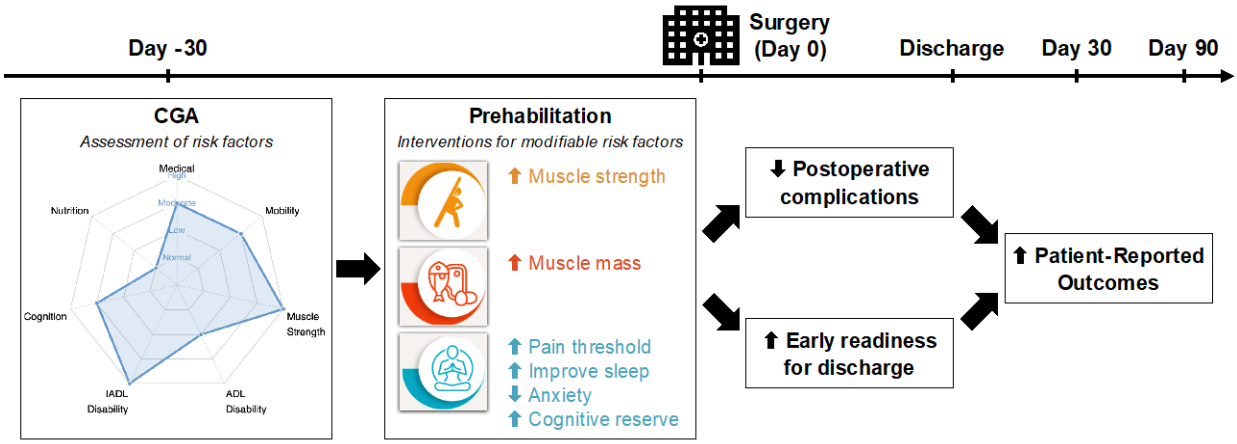
Table 1. Evidence and potential mechanisms for multi-component prehabilitation program

Intervention	Evidence	Mechanisms
Exercise	Meta-analysis of RCTs (Lau 2020)	• ⬆Anabolic effect on protein synthesis • ⬇Catabolic effect of inflammation on muscles
Nutrition	Meta-analysis of RCTs (Gillis 2018)	• Overcome age-related anabolic resistance • Meet increased need for protein due to inflammation
Mindfulness meditation	RCT (Hanley 2021) & single-arm study (Chavez 2020)	• Improve sleep by ⬆melatonin, ⬇GABA • Reduce pain and anxiety by thalamic deactivation and orbito-frontal activation; ⬇pain-related afferent processing; resetting expectations • Improve cognition by ⬆alpha-band power; ⬆BDNF;⬆network connectivity
Cognitive behavioral strategies	RCT (Latham 2014)	• Improve adherence to the intervention components as an adjunct intervention

BDRF, brain-derived neurotrophic factor; ONS, oral nutritional supplement; PROMIS, Patient-Reported Outcomes Measurement Information System

To accomplish this, we are planning to conduct an RCT of a multi-component prehabilitation program versus usual care on patient-centered outcomes in older adults undergoing major surgery (**Figure 1**).

Figure 1. Conceptual model for an RCT of prehabilitation program. Abbreviation: CGA, comprehensive geriatric assessment.



In this future RCT, we will identify candidates for prehabilitation based on the patient’s frailty level, which represents the physiologic reserve to tolerate stress from surgery and hospitalization. We will provide a multicomponent intervention which not only addresses the body but also the neurobehavioral aspect of a frail patient, given the link between frailty and cognition.[28] We will measure patient-centered outcomes using validated Patient-Reported Outcomes Measurement Information System (PROMIS) measures.[29] Therefore, we propose this pilot study to assess the feasibility of key steps of this ideal RCT and refine a multicomponent prehabilitation protocol to ensure its feasibility and adherence.

5. STUDY POPULATION

We will review schedules to identify patients who are 1) ≥65 years old; 2) scheduled for abdominal, gynecological oncologic, and urologic surgery; and 3) with a comprehensive geriatric assessment-based frailty index (range: 0-1; greater scores indicate more severe frailty) ≥0.25 (mild-to-severe frailty). A trained research assistant will perform preoperative geriatric assessment—which consists of 1) medical history (automated in EHR), 2) self-reported functional status (a questionnaire of 22 daily activities and physical tasks), 3) tests of cognitive function (MoCA test) and physical function (gait speed, chair stands, and grip strength), and 4) nutritional status (automated in EHR)—and calculate a frailty index using our EHR calculator. For those with a frailty index of ≥0.25, we will explain this to the patients and their surgeon and ask whether they are willing to participate in up to 4 weeks of prehabilitation. Remote or e-consent will be obtained. Screening of potential participants will take place during the surgeon's office visit. The assessment of eligibility will take place by telephone. Our target enrollment is 30 patients (2 patients per week for 15 weeks). See the detailed inclusion and exclusion criteria provided below:

5.1 Inclusion Criteria:

- Patient is ≥65 years old
- Patient is scheduled to have a gastrointestinal, gynecological oncologic, and urologic surgery
- Patient's frailty index is ≥0.25
- Patient provides an informed e-consent or remote consent

5.2 Exclusion Criteria:

- Surgery is scheduled less than 21 days from the expected start date of the prehabilitation intervention
- Patient is considered an inappropriate candidate per the surgeon's assessment.
- Non-English speaking
- Patient has a major cognitive impairment, which will be defined as telephone Montreal Cognitive Assessment (MoCA) <18.
- Patients with chronic kidney disease stage 4 or higher will be excluded from nutrition intervention of the prehabilitation intervention.

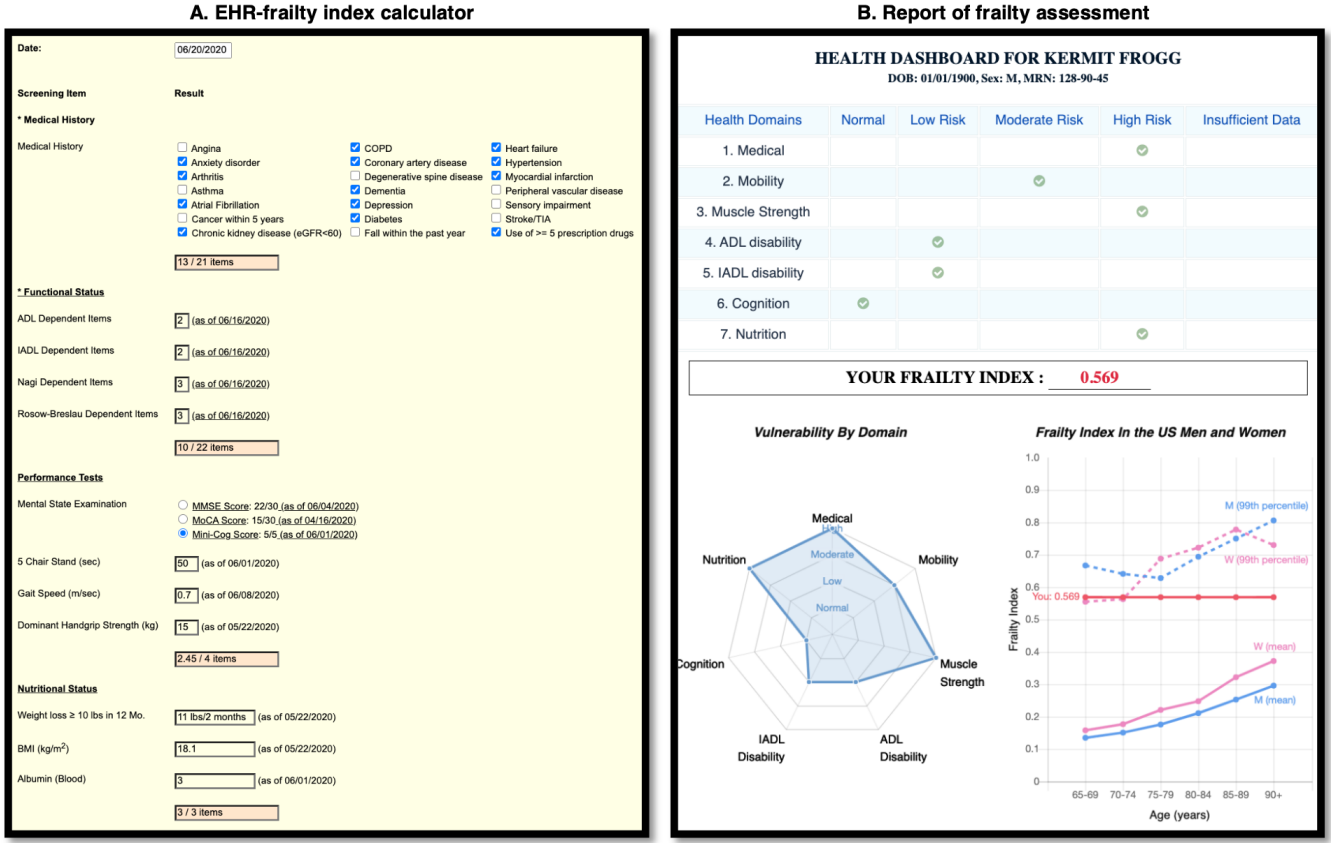
6. ENROLLMENT

As stated above, patients who are scheduled to undergo a gastrointestinal, gynecological oncologic, and urologic surgery, meet inclusion criteria, and have approval from their surgeon to participate will be contacted by a study clinician who will assess eligibility, including a telephone-based preoperative frailty assessment (only patients with frailty will be eligible). This assessment includes the following domains:

- Medical history
- Self-reported functional status (activities of daily living [ADL], instrumental activities of daily living [IADL], and physical tasks without another person's help)
- Tests of cognitive function (Telephone MoCA)
- Nutritional status (BMI and self-reported weight loss)

Most of these assessments are already available or routinely collected and entered in BIDMC Online Medical Record (OMR). The study clinician will verify the existing information in OMR with the patient and fill in any missing information if needed. The OMR frailty index calculator calculates the frailty index based on information available in OMR (Figure 2). The index ranges from 0 to 1; frailty is defined as ≥0.25.

Figure 2. Example report of OMR frailty index calculator and assessment report. The frailty index calculator (A) will use the latest information available in OMR to calculate a deficit-accumulation frailty index. The report shows the assessment domain-specific impairment and comparison of the frailty index against a reference population of Medicare beneficiaries.



6.1 Baseline Assessment

Once informed e-consent or remote consent is signed, trained research personnel will administer additional measurements that are not collected as part of preoperative assessment. These measurements (provided below) may be conducted 1) during the telephone call during which informed consent is obtained; 2) during a separate call (if requested by the patient or caregiver); 3) email survey; 4) during an in-person physical

therapy session (for gait speed, chair stands, and handgrip strength); or 5) a combination of these modalities.

- Usual walking speed from 4-meter walk (if not already measured)
- Time to complete 5 chair stands (if not already measured)
- Dominant handgrip strength: average of 3 measurements (if not already measured)
- 3-day diet recall (done by telephone)
- PROMIS Profile CAT v1.0 is a 29-item, computer adaptive, patient-reported outcome measure of social roles/activities, anxiety, depression, fatigue, pain interference/intensity, physical function, and sleep disturbance domains (may be done by telephone or email)
- PROMIS v2.0 Cognition CAT is a 12-item, computer adaptive, patient-reported outcome measure of cognitive function domain (may be done by telephone)

PROMIS (available at https://www.healthmeasures.net/index.php) is a publicly available, validated system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being for general population as well as people with chronic conditions. It is designed to enhance communications between clinicians and patients in diverse clinical and research settings. Computer adaptive test (CAT) allows accurate assessment with a limited number of questions from the PROMIS item bank, thereby reducing participant burden.

6.2 Medical Record Review:

Trained research personnel will obtain the following data from the OMR and record them in REDCap database:

- Demographic information: age, sex, race, ethnicity
- Chronic comorbidities
- Self-reported functional status: ADL, IADL, physical tasks by Nagi and Rosow-Breslau
- Cognitive function: telephone MOCA
- Physical function: gait speed, dominant handgrip strength, and chair stands
- Nutritional status: height, weight, BMI, weight loss in the past year, serum albumin level

7. STUDY INTERVENTION

All participants will be enrolled in a prehabilitation program that will start 3-4 weeks prior to the date of scheduled surgery. The intervention will target three principal components (physical activity, nutrition, and meditation) and deliver cognitive behavioral interventions (**Table 3**). Each intervention has 1) instructional or training components, delivered by our study team, and 2) self-directed components.

Table 3. Multicomponent prehabilitation program and measures of feasibility and adherence for each component

Target	Intervention	Measures of Feasibility or Adherence

Exercise: *increase muscle function*	• **Physical therapy (home, in-person, hybrid or virtual)**
	  • By physical therapists
	  • Average two 1-hour individual sessions per week (delivered in patient's home, in-person center, hybrid, or virtual)
	  • Goal: 6-8 total PT sessions
	  • Endurance, strengthening, flexibility
	• **Self-directed exercise**
	  • Goal: 30 mins/day x 4 days per week
		• **Number of sessions delivered (feasibility)**
		• Number of days with ≥30 min exercise per self-report diary
		• Step count from a wearable activity tracker (Fitbit Fitness tracker): provision of weekly feedback based on step count
		• Change in 5-chair stands and grip strength pre- and post- intervention

Nutrition: *Preserve lean body mass (Patients with CKD will be excluded)*	• **Nutrition counseling**
	  • By registered dietitian
	  • Average one 1-hour group session per week
	  • Goal: 3-4 total nutrition education sessions
	• **Self-directed protein consumption**
	  • Goal: 1-2 ONS (20 gram)/day x 4 days per week
		• **Number of sessions delivered (feasibility)**
		• Number of ONS consumed per self-report
		• Change in protein intake per 3-day dietary recall pre- and post- intervention
		• Change in quadriceps thickness by ultrasound pre- and post- intervention

Meditation: *Increase cognitive resilience*	• **Mindfulness meditation**
	  • By meditation teacher
	  • Average one 1-hour group session per week
	  • Goal: 3-4 total guided meditation sessions
	• **Self-directed meditation**
	  • Goal: 12 mins/day
		• **Number of sessions delivered (feasibility)**
		• Number of days with ≥12 min meditation per diary

Cognitive behavioral interventions: *Improve adherence to the above 3 core interventions*	• **Cognitive behavioral interventions**
	  • By research staff certified in cognitive behavioral therapeutic techniques
	  • Education about frailty, discussion about barriers, writing down individualized goals, and weekly progress review
	  • Average one 30-min individual session per week
	  • Goal: 3-4 total cognitive behavioral sessions
		• **Number of sessions delivered (feasibility)**

Abbreviation: CKD, chronic kidney disease; ONS, oral nutritional supplement; PROMIS, Patient-Reported Outcomes Measurement Information System. * Participants living within a 20-mile radius from HSL will be offered home in-person, center based, or hybrid physical therapy.

7.1 Component 1: Exercise

The instructional part will be delivered via average twice weekly, one-hour, in-person home, center-based, or virtual (via HSL's Zoom video-conferencing software) physical therapy sessions, depending on the patient's preference, familiarity with technology, availability of transportation, and other contingencies (e.g., COVID-19 based restrictions, incremental weather). Evidence suggests that virtual sessions offer similar benefits to in-person home sessions[30] or in-clinic sessions.[31] Although a twice-weekly schedule is aimed, the schedule will be adjusted flexibly to deliver a total of 6-8 sessions.

Exercises targeting flexibility, strength, and endurance will be adopted mainly, though not exclusively, from the NIA Go4Life guide (https://go4life.nia.nih.gov/). Sample exercises are shown in **Table 4**.

Before each in-person or virtual physical therapy session, the study physical therapist will review safe areas for exercise, safety techniques and warning signs (such as chest pain or pressure, severe dyspnea, left shoulder or arm pain, indigestion, heart palpitations, lightheadedness, dizziness, and headache). Participants will begin at a low level of effort and incrementally increase exercise intensity according to the therapist's guidance. For virtual sessions and self-directed exercise, we will ask caregivers, family members, or home health personnel to provide supervision for safety and development of adverse events, whenever possible. During the in-person session, blood pressure, heart rate, and blood oxygen level will be monitored by the physical therapist.

The self-directed part will include self-directed exercise (any types of exercise) at least 30 minutes per day for 4 or more days per week. Step count data from a wearable device (Fitbit Fitness Tracker) will monitor progress and provide feedback, which improves adherence in older adults. Fitbit Fitness tracker will either be provided at the pre-admission testing visit or mailed to the patient's home.

Table 4. Sample exercises for flexibility, strength, and endurance (source: *Go4Life*)

Flexibility (stretching)	Strength	Endurance
• Neck • Shoulder • Shoulder and upper arm • Upper body • Chest • Back • Ankle • Back of leg • Thigh • Hip • Calf	• Hand grip • Wrist curl • Arm raise • Arm curl • Seated row • Wall push-up • Elbow extension • Chair dip • Leg raise • Knee curl • Leg straightening • Chair stand • Toe stand	• Walking

7.2 Component 2: Nutrition

The instructional part will be delivered in once-weekly (on average), one-hour, virtual group sessions (via HSL Zoom software) by co-investigator/registered dietitian, Ms. Newmeyer, (the virtual sessions will be offered at three different days/times to accommodate participants' schedules). This nutrition counseling will focus on optimal protein intake (1.2 gram per kg of body weight) for lean body mass preservation (from food sources and oral nutritional supplements). Sessions will focus on nutrition for muscle gain and lean body mass preservation with topics including:

- *Session 1*: Good sources of protein and total needs (1.2 grams x weight in kg)
- *Session 2*: Protein intake timing: rule 15/30 (at least 15 grams within 30 minutes of exercise)

- *Session 3*: Protein for muscle gain
- *Session 4*: Tips to increase protein intake

The self-directed part will include consumption of oral nutritional supplements (20-30 grams of protein/day and between 150-350 calories/day, such as Think! High Protein Bar (20 grams protein, 22 grams carbohydrate, 150 calories) or Ensure Enlive (20 grams protein, 45 grams carbohydrate, 350 calories) , which will be provided by our study team. Oral nutrition supplements (ONS) will be ordered directly from the product manufacturer in bulk and mailed to the patient's home by a research assistant.. Due to ongoing supply chain shortages of popular nutrition supplements, we have identified multiple that meet the above macronutrient parameters. All supplements will be purchased in bulk for each participant with enough to last the entirety of the study. Supplements will not be changed unless the patient reports an adverse event such as GI distress (please see section *B5* for more detailed information). Protein supplements are shelf-stable and can be stored at room temperature until use by date when unopened. Once opened, product should be refrigerated within 4 hours. After opening, any remaining product should be discarded within 48 hours – though patients will be encouraged to consume product in its entirety within 24 hours per study protocol.

Patients with chronic kidney disease stage 3 or higher will not receive this intervention because high protein intake may accelerate kidney function decline. This will be determined by medical record review (medical history of chronic kidney disease or elevated creatinine value within the last 6 months) and/or lab results obtained before the start of the study intervention.

7.3 Component 3: Meditation

The instructional part will be delivered in once-weekly (on average), one-hour, virtual group sessions by a meditation teacher, Ms. Tulsi Chase, at BIDMC Sadhguru Center (the virtual sessions will be offered by BIDMC Zoom video-conferencing at three different days/times to accommodate participants' schedules). Classes will focus on breathing techniques, yoga, and mindful meditation practices.

The self-directed part will include practicing self-directed meditation for a minimum of 12 minutes daily.

7.4 Component 4: Cognitive Behavioral Interventions

A trained co-investigator will have (on average) once weekly 0.5-hour telephone-based sessions with individual patients to deliver cognitive behavioral strategies to increase adherence to the prehabilitation program. These strategies will include:

- Education about frailty and surgery
- Increase positive beliefs of the benefits of exercise and nutrition
- Discuss barriers

- Set individualized goals for surgery and recovery
- Develop a detailed exercise and nutrition plan (including logistics)
- Self-monitoring of progress using weekly exercise, diet, and meditation logs
- Enhance self-efficacy through the celebration of small wins

This co-investigator has completed the Professional Education Systems Cognitive Behavioral Therapy Intensive Training Course in preparation for this intervention. This course is designed for health professionals without formal cognitive therapy training.

8. STUDY ENDPOINTS/OUTCOMES

8.1 Primary Outcome For the *primary outcome* we will measure the following*:*

Feasibility of the prehabilitation program

- Measurement: proportion of patients to whom we can deliver an adequate dose (≥50% of the planned sessions) of the 3 core interventions: physical therapy (≥4/8 sessions), nutrition (≥2/3-4 sessions), and meditation (≥2/3-4 sessions).
- Range: 0-100% (higher values indicate higher feasibility).

8.2 Secondary Outcomes For *secondary outcomes*, we will measure the following*:*

- Change in 5-chair stand test (time)
  - Measurement: time to complete 5 chair stands (seconds), post-prehabilitation minus pre-prehabilitation
  - Range: -60 to 60 seconds (higher values indicate worsening performance)

- Change in dominant handgrip strength (kg)
  - Measurement: average of 3 measurements of dominant handgrip strength, post-prehabilitation minus pre-prehabilitation
  - Range: -50 to 50 kg (higher values indicate improved performance)

- Change in protein intake (grams)
  - Measurement: 3-day average protein intake from dietary recall, post-prehabilitation minus pre-prehabilitation
  - Range: -100 to 100 grams higher values indicate greater intake)

- Adherence to exercise
  - Measurement: proportion of days with ≥30 minutes of exercise out of 21-28 days per self-report
  - Range: 0-100% (higher values indicate better adherence)

- Adherence to protein intake
  - Measurement: proportion of oral nutritional supplement consumed over the total number of supplements provided per self-report

    - Range: 0-100% (higher values indicate better adherence)

- Adherence to meditation
    - Measurement: proportion of days with ≥12 minutes of meditation out of 21-28 days per self-report
    - Range: 0-100% (higher values indicate better adherence)

- Adverse events
    - Measurement: proportion of patients who experience any adverse events per self-report
    - Range: 0-100% (higher values indicate more adverse events)

- Change in PROMIS-CAT score in participation in social roles/activities (4 questions)
    - Measurement: self-reported measure of participation in social roles/activities
    - Range: 0-100 (higher values indicate higher participation)

- Change in PROMIS-CAT score in Anxiety (4 questions)
    - Measurement: self-reported measure of anxiety
    - Range: 0-100 (higher values indicate more anxiety)

- Change in PROMIS-CAT score in Depression (4 questions)
    - Measurement: self-reported measure of depression
    - Range: 0-100 (higher values indicate more depression)

- Change in PROMIS-CAT score in Fatigue (4 questions)
    - Measurement: self-reported measure of fatigue
    - Range: 0-100 (higher values indicate more fatigue)

- Change in PROMIS-CAT score in Pain interference (4 questions)
    - Measurement: self-reported measure of pain interference
    - Range: 0-100 (higher values indicate more interference)

- Change in PROMIS-CAT score in Pain intensity (1 question)
    - Measurement: self-reported measure of pain intensity
    - Range: 0-10 (higher values indicate more severe pain)

- Change in PROMIS-CAT score in Physical function (4 questions)
    - Measurement: self-reported measure of physical function
    - Range: 0-100 (higher values indicate better physical function)

- Change in PROMIS-CAT score in Sleep disturbance (4 questions)
    - Measurement: self-reported measure of sleep disturbance
    - Range: 0-100 (higher values indicate more sleep disturbance)

- Change in PROMIS-CAT score in Cognitive function (12 questions)
    - Measurement: self-reported measure of cognitive abilities
    - Range: 0-100 (higher values indicate better cognitive abilities)

8.3 Exploratory Outcomes For all *other outcomes,* we will measure the following*:*

- 3-D Confusion Assessment Method[34]
    - Measurement: proportion of patients who develop delirium according to 3-D Confusion Assessment Method, a clinically validated algorithm of delirium diagnosis, on any of the postoperative days 1 to 3.
    - Range: 0-100%

- Postoperative Quality of Recovery Scale[35]
    - Measurement: a clinically validated scale that includes physiologic, nociceptive, functional, cognitive, emotional recovery domains assessed as well as overall patient perspective on postoperative day 3.
    - Range: 40-200 (higher values indicate better recovery)

- Comprehensive complication index[36]
    - Measurement: a composite complication grading system by Clavien-Dindo Classification after an intervention
    - Range: 0-100 (higher values indicate more severe complications)

- Length of stay (time to readiness to discharge)
    - Measurement: number of hospital days from surgery until a patient becomes medically stable for discharge based on clinical notes
    - Range: ≥1 day

- 30-day readmission from all causes
    - Measurement: proportion of patients who were readmitted within 30 days of surgery
    - Range: 0-100%

- 30-day mortality from all causes
    - Measurement: proportion of patients who died within 30 days of surgery
    - Range: 0-100%

- 90-day mortality from all causes
    - Measurement: proportion of patients who died within 90 days of surgery
    - Range: 0-100%

The timing and modality of outcome measurements is shown in **Table 5**.

Baseline functional assessments with physical therapy staff from Hebrew SeniorLife's outpatient clinic and at the conclusion of the prehabilitation program (before surgery) will

be in-person assessments (though some baseline functional assessments may be done virtually via Zoom). In-hospital outcomes will be assessed via in-person interview or review of medical records. Postoperative assessment on post-op day 30±7 and 90±7 will be conducted via telephone interview, email survey, or medical record review.

Table 5. Timing of outcome measurement. Day 0 is defined as the date of surgery.

Outcome	Baseline functional assessment (In-person or may be done virtually)	Before surgery (In-person)	Hospitalization (In-person / medical record)	Postop Day 30±7 (Telephone / e-mail survey / medical record)	Postop Day 90±7 (Telephone / e-mail survey / medical record)
Feasibility		X			
Change in chair stands	X	X	X (if not done)*		
Change in handgrip strength	X	X	X (if not done)*		
Change in protein intake	X	X	X (if not done)*		
Adherence to exercise		X	X (if not done)*		
Adherence to protein intake		X	X (if not done)*		
Adherence to meditation		X	X (if not done)*		
Adverse events		X	X (if not done)*		
3-D CAM			X		
PQRS			X		
Surgical complications			X		
Length of stay			X		
Readmission				X	X
Death				X	X
PROMIS-CAT scores	X	X		X	X

Abbreviations: CAM, Confusion Assessment Method; PQRS, Postoperative Quality of Recovery Scale; PROMIS-CAT, Patient-Reported Outcomes Measurement Information System-Computer Assessment Test.
* We will try to measure these outcomes before surgery near the conclusion of the prehabilitation program; if not measured before surgery, we will measure them during the hospitalization.

9. QUALITATIVE INTERVIEWS

Near the end of the prehabilitation (from the last week of prehabilitation to hospital discharge), a trained co-investigator will conduct semi-structured qualitative interviews of patients and their caregivers (if they are involved in preoperative care).

An interview guide has been developed under qualitative expert consultant guidance. The questions have been grounded in the Behavioral Change Wheel framework to assess factors influencing capability (physical and psychological), opportunity (physical and social), and motivation (reflective and automatic).[36] The co-investigator will also ask participants about areas for improvement within our prehabilitation program.

Qualitative data analysis will seek to identify facilitators of and barriers to adhering to our prehabilitation program. We will conduct hybrid deductive and inductive thematic analysis based on the 3 components (capability, opportunity, and motivation) of the Behavioral Change Wheel framework, while also allowing new insights to emerge from the data. The interviews will be audio-recorded and transcribed verbatim. A coding framework to all transcripts will be applied via a collaborative approach through an iterative process. Codes and subsequently derived themes will be refined by the research team.

10. DATA AND SAFETY MONITORING

10.1 Adverse Events

Definition and Classification of Adverse Events

For this study, the following standard adverse event definitions are used:

- Adverse events: Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study intervention, regardless of whether it is considered related to the study intervention.
- Serious adverse event: Any adverse event that result in death, life-threatening experience, hospitalization or prolonged hospitalization, persistent or significant disability or incapacity.
- Unanticipated problems: Any experience that 1) is unexpected in terms of nature, severity, or frequency, given the research procedures described in the protocol document and the characteristics of the study population; 2) is related or possibly related to participation in the research; 3) suggests that the research places participants or others at a greater risk of harm than was previously recognized.

Adverse events are graded according to the following scale:

- Mild: An experience that is transient and requires no special treatment. The experience does not generally interfere with usual daily activities.
- Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.
- Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment, it becomes a severe adverse event.

The study uses the following adverse event attribution scale:

- Not related: The adverse event is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
- Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
- Definitively related: The adverse event is clearly related to the study procedures.

10.2 Adverse Event Monitoring

Monitoring adverse events will be primarily performed in two ways: 1) unsolicited report from study interventionists (physical therapist, dietitian, and meditation teacher); and 2) weekly assessments by telephone using a standardized checklist.

- Unsolicited reporting: Any adverse events that occur during the in-person or virtual sessions will be assessed for severity by the study interventionists (in conjunction

with PI or an MD co-investigator). In the event of a serious adverse event, the participant or caregiver will be instructed to contact emergency medical services to receive immediate medical attention. All adverse events will be reported to the PI.

- Standardized assessment: At the beginning of cognitive behavioral intervention telephone calls, co-investigator Ms. Newmeyer will assess adverse events using a standardized checklist that includes the following expected adverse events (see below).

Expected Adverse Events

- Exercise: fall or injury (expected risk is low); new or worsening musculoskeletal pain (expected risk is moderate); cardiovascular events including angina, arrhythmia, myocardial infarction, heart failure, or stroke (expected risk is very low); other symptoms including chest pain, dizziness/lightheadedness, dyspnea, palpitation, or syncope (expected risk is low).
- Nutrition: gastrointestinal distress such as diarrhea, nausea, constipation (expected risk is moderate); electrolyte imbalance or dehydration (expected risk is low), renal injury from increased renal solute load (expected risk is very low)[38] Meditation: psychological distress (expected risk is very low/rare)[39]
- Outcome measurement: possibility of incidental finding (such as suicidal ideation) through the Patient-Reported Outcomes Measurement Information System (PROMIS) surveys (expected risk is very low)

10.3 Interim Analysis

Since this is a pilot study, no interim analysis will be performed. Data analysis will be performed after study enrollment is complete.

10.4 Data Safety Monitoring Plan

The PI will assure that informed consent is obtained prior to performing any research procedures, that all participants meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Because this is a pilot study, a formal Data and Safety Monitoring Board will not be formed; instead, a safety officer will oversee and review adverse events during the study period. Please see below regarding the roles of the safety officer.

Frequency of Data and Safety Monitoring

Study data are accessible at all times for PI to review. The PI will review study progress weekly initially (bi-weekly once the study procedures are established), including the number of potential patients screened and provided informed consent, the number of drop-outs, protocol deviations, and adverse events. The PI will review serious adverse events in real-time and consult each other when needed for determination of the relatedness to the study interventions. The PI will ensure that all protocol deviations, adverse events, serious

adverse events, and unanticipated problems are reported to IRB. Serious adverse events and unanticipated problems that are definitively related to the study interventions will be reported to IRB within 48 hours from when we learn about the event.

Content of Data and Safety Monitoring Report

The content of the data and safety monitoring report will include accrual, baseline characteristics, efficacy data on primary and secondary outcomes, and adverse events.

DSMB/Safety Officer

A formal Data Safety Monitoring Board will not be established for this pilot study; however, a physician not directly involved in the study has been identified to fill the safety officer role: Dr. Sarah D. Berry, a geriatrician and clinical investigator at HSL Marcus Institute and Associate Professor of Medicine, HMS.

Conflict of Interest of DSMB/Safety Officer

The safety officer will have no direct involvement with the study investigators or intervention. The safety officer will sign a conflict-of-interest statement which includes current affiliations, if any, with pharmaceutical and biotechnology companies, and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to the study objectives.

DSMB/Safety Officer Responsibility

- Assess the research protocol, informed consent documents, and plans for data safety and monitoring
- Recommend initiation of subject recruitment after review of the protocol
- Evaluate trial progress quarterly, including recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcomes
- Consider factors external to the study when relevant, such as scientific or therapeutic developments that may impact the safety of the participants or the ethics of the trial
- Provide recommendations and assist in the resolution of problems reported by the PI
- Protect the safety of the study participants
- Provide recommendations to the PI regarding continuation, termination, or other study modifications based on the observed beneficial or adverse effects of the treatment under study
- Ensure the confidentiality of study data and monitoring results

11. ANALYSIS PLAN

11.1 Statistical Analysis for Feasibility

We will estimate the feasibility of the entire prehabilitation program and each component; mean time for preoperative geriatric assessment; proportion of participants who enroll in the prehabilitation program; proportion of participants who drop out; and rate of missing outcome data. No statistical testing will be performed.

Sample Size Justification: We anticipate that the 3 core components of our prehabilitation program would be completed for 70% of the eligible patients[9-15] (feasibility of ≥50% would be needed for a large RCT). Assuming a 20% margin of error and a lower bound of the 95% confidence interval of 0.50, we will need 30 patients.

11.2 Statistical Analysis for Qualitative Research

There is no statistical analysis for qualitative research.

Sample Size Justification: In most qualitative studies, interviews of 16-24 participants are needed to achieve thematic saturation of data.[40] Our target enrollment of 30 patients (2 patients per week for 15 weeks), ensures we meet that threshold, and our sample size is sufficient to reach thematic saturation to fully understand the "meaning" of the data.

12. HUMAN SUBJECT PROTECTION AND PROTECTION OF CONFIDENTIALTY

12.1 Risks to Human Subjects

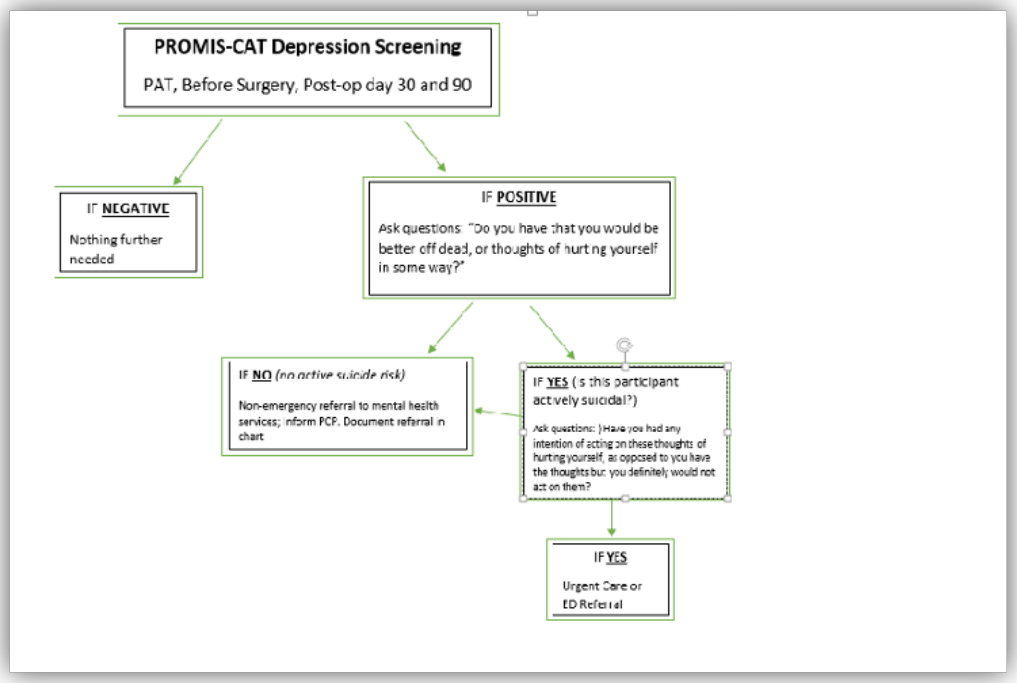
The potential risks to study participants include modest risk of physical harm, such as musculoskeletal pain, falls, cardiovascular or pulmonary events from low-intensity exercise; diarrhea, nausea, constipation, electrolyte imbalance, dehydration, or renal injury due to hyperosmolar content of some oral nutrition supplement formulations (Ensure Enlive). There is potential risk for increased anxiety or psychological distress from meditation. Lastly, while none of the PROMIS questions specifically ask about suicide, some of the possible questions through the computer-adaptive test may indicate that the patient is at risk. As such, there is potential risk to uncover suicidal ideation in patients. Loss of confidentiality is another potential risk. We do not anticipate any financial or legal risks.

12.2 Protection Against Risks

To minimize physical harm, the physical therapist will adapt the exercise program according to the participant's physical capacity, their level of confidence, and the home environment. Prior to participation in exercise, the therapist will encourage participants to express any concerns. Participants will be taught safe exercise techniques. To minimize gastrointestinal (GI) distress, only participants with clinically significant weight loss (>5%

x 1 month; >7.5 x 3 months; 10% x 6 months; 20% x 1 year)or who have a history of taking calorically-dense supplements without issue (confirmed by patient) will be provided the hyperosmolar protein supplemental shake (Ensure). All other participants will be provided with a high protein bar or powder (for patients with swallowing or chewing difficulty, powder can be mixed with a solid puree). Those receiving the shake will be instructed to consume no more than one high calorie, high protein supplement per day and to drink adequate fluids before and after taking supplement. In the event of gastrointestinal distress (nausea, diarrhea or constipation), patient will be instructed to consume supplement in divided doses (no more than 50% in one sitting) or to dilute formula 1:1 with water. If gastrointestinal distress continues, patient will be switched to the protein bar or powder. Due to the lower calorie content, those participants may be instructed to consume an additional high-calorie snack, if needed. . In the event that an incidental finding such as depression or suicidal ideation (SI), a specific protocol is outlined below in **Figure 3** to ensure patient safety:

Figure 3 - Incidental Finding: Depression and suicidal risk



In the case of adverse events, the physical therapist or the participant will be instructed to contact a study physician (for any adverse events) and emergency medical services (for serious adverse events). These procedures will prevent or mitigate the consequences of adverse events.

12.3 Potential Benefits to Human Subjects and Others

The proposed research will provide essential information for the future design of a large clinical trial that examines the impact of a multi-component prehabilitation program on post-operative outcomes in frail older adults undergoing major surgery. Under the current standard of care, frail patients continue to experience complications such as mortality,

readmission, functional decline, and discharge to an institution. The potential benefits to study participants include receiving our study intervention, which targets major risk factors that are modifiable yet rarely addressed in the preoperative period (physical function, nutrition, pain, sleep, anxiety, and cognition), at no cost. These interventions address 4 of the 8 target areas identified by the American College of Surgeons “Strong for Surgery” quality initiative to improve surgical outcomes. Moreover, each component of the intervention was studied to have some level of benefit based on biological plausibility and clinical findings. It is thus reasonably expected that the intervention will provide some benefits to the participants that are more likely to outweigh the modest risk of physical harms from exercise.

12.4 Importance of Knowledge to be gained

We will proceed with a large RCT if all of the progression criteria are met: 1) enrollment (we can enroll ≥1.5 patients per week); 2) feasibility (we can deliver an adequate dose of the core interventions to ≥50% of participants); 3) adherence (≥50% of participants adhere to the core interventions: ≥4 days with 30 minutes of exercise per week, ≥4 days with protein intake per week, and ≥4 days with 12 minutes of meditation per week); 4) follow-up (≥65% of surviving participants can complete PROMIS assessment on postoperative day 90). If these are not met, we will use information from qualitative interview to revise our study interventions before proceeding to an RCT. We will submit an NIH R01 application in 18 months.

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