Cedars Sinai

CANCER

IIT2021-18-CHANG-PREHAB

A Supervised Prehabilitation Program for Patients with Pancreatic Cancer

Principal Investigator: **Philip Chang, DO**
Cedars-Sinai Medical Center
8700 Beverly Blvd, Los Angeles, CA 90048
310- 467- 4498
Philip.Chang@cshs.org

Sub-Investigator(s)	Department/Division
Arash Asher, MD	Department of Physical Medicine and Rehabilitation
Andrew Hendifar, MD	Department of Medical Oncology
Gillian Gresham, PhD	Cancer Research Center for Health Equity
Alix Sleight Warner, PhD	Department of Physical Medicine and Rehabilitation
Jun Gong, MD	Department of Medical Oncology
Arsen Osipov, MD	Department of Medical Oncology
Kamya Sankar, MD	Department of Medical Oncology
Jeremy Lorber, MD	Department of Medical Oncology
David Hoffman, MD	Department of Medical Oncology
Kevin Scher, MD	Department of Medical Oncology

Biostatistician: Shaowli Kabir, PhD

Funding Source: Cedars-Sinai Medical Center (CSMC)

ClincialTrials.gov Reg: Not Required

NCT Number: NCT05692323

ClincialTrials.gov Reporting: Not Required

Current Version: Protocol Version #4 Dated 23JAN2025

Initial version: Protocol Version #1 Dated 23MARCH2023

IIT2021-18-CHANG-PREHAB

Protocol Version #4: 23JAN2025

Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

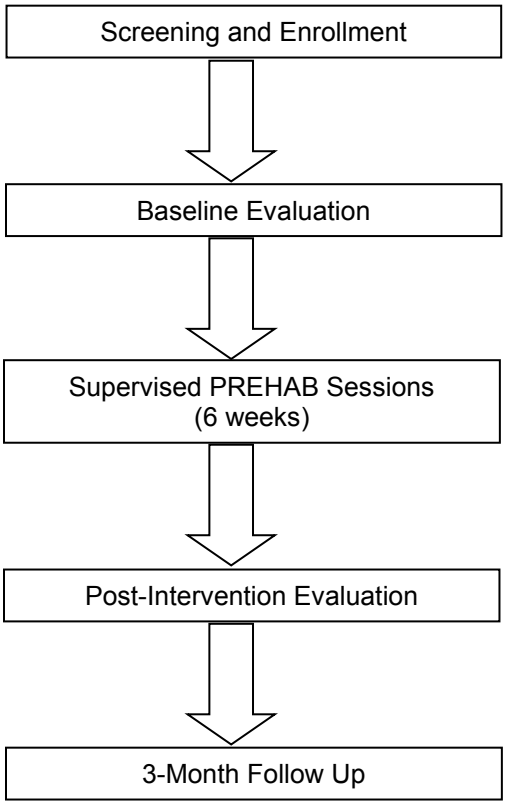
_____	_____
Principal Investigator (PI) Signature	**Date**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CRF	Case Report Forms
CCTO	Cancer Clinical Trials Office
CT	Computed Tomography
U.S CSMC	Cedars-Sinai Medical Center
DSMC	Data and Safety Monitoring Committee
FDA	U.S Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
PAR-Q	Physical Activity Readiness Questionnaire
PI	Principal Investigator
PREHAB	Prehabilitation
PROMIS-29	Patient-Reported Outcomes Measurement Information System
PROMIS Cancer Function	Patient-Reported Outcomes Measurement Information System Cancer Function
QMC	Quality Management Core
SOC	Standard of Care
SOCCI	Samuel Oschin Comprehensive Cancer Institute
UPIRSO	Unanticipated Problems Involving Risk to Subjects or Others

STUDY SCHEMA



Primary endpoint: Feasibility of a PREHAB program evaluated by attendance. The program will be considered feasible if at least 50% of participants attend at least 60% of exercise sessions.

PREHAB- Prehabilitation

STUDY SUMMARY

Title	A Supervised Prehabilitation Exercise Program for Patients with Pancreatic Cancer
Short Title	Exercise program for pancreatic cancer
Protocol Number	IIT2021-18-CHANG-PREHAB
Phase	Pilot
Methodology	Single Arm
Study Duration	12 Months
Study Center(s)	Single Center
Objectives	The primary objective is to test the feasibility of a supervised prehabilitation program for patients with pancreatic cancer.
Number of Subjects	16 subjects
Diagnosis and Main Inclusion Criteria	Main Inclusion Criteria: -Pancreatic cancer diagnosis (any stage) -Age ≥18 years -Independent ambulation and activities of daily living -Godin-Shephard Leisure-Time Physical Activity Questionnaire score of ≤ 23 -Physically able to participate in study assessments -Answers no to all questions on PAR-Q **OR** is cleared to participate by the study physician -Written informed consent obtained from subject and ability for subjects to comply with the requirements of the study
Study Product(s), Dose, Route, Regimen	Supervised exercise PREHAB program
Duration of administration	6 weeks
Reference therapy	None
Statistical Methodology	The primary analysis will test the hypothesis of feasibility using an one-sided exact Binomial test at 25% significance level. If 10 or more patients attend a minimum of 60% of exercise sessions during the initial 6-week period, then the study will be declared feasible.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

During 2022, there is estimated to be 62,000 new cases of pancreatic cancer, causing an estimated 49,000 deaths[1]. Individuals who develop pancreatic cancer tend to be older, with 70% of pancreatic diagnoses occurring in those ≥ 65 years[2]. As individuals age their risk of comorbidities such as sarcopenia and frailty increase[3]. Sarcopenia is the progressive loss of skeletal muscle mass, tone, quality and strength and has been reported to affect 65% of pancreatic cancer patients[4]. Results from a recent meta-analysis suggest sarcopenia is associated with decreased long-term survival and is an important prognostic factor in recurrent pancreatic cancer[4,5].

1.2 Study Background

1.2.1 Prehabilitation (PREHAB)

PREHAB is the process of improving the functional capability and psychological health of the individual to reduce the incidence and/or severity of future impairments[6]. While PREHAB has most commonly been described as occurring prior to neoadjuvant therapy and surgery it can also occur in nonsurgical patients and concurrently with neoadjuvant treatment[6,7]. The foundation of PREHAB is functional exercise yet can be multimodal in nature and can include additional components such as nutritional support, smoking cessation, and stress reduction[9]. PREHAB sessions are typically delivered through structured programs and have been shown to have a number of benefits such as improvements in functional activity and decreased postoperative complications[8].

1.2.2 Clinical Data

Multiple studies have reported the positive effects of PREHAB in cancer patients[9]. A recent systematic review reported improved functional activity and survival outcomes in a range of cancer types following moderate to vigorous intensity exercise participation[18]. In colorectal cancer patients, PREHAB programs have shown to improve VO2 max and functional activity (6 minute walk tests)[10,11]. In patients undergoing cystectomy, PREHAB has been shown to increase power output and performance with activities of daily living[12]. A recent review by Garcia et al, reported improved pulmonary function, less days spent in the hospital and reduced risk of postoperative complications in lung cancer patients following participation in a PREHAB program[13]. An additional Cochrane review of 167 patients with non-small cell lung cancer reported preoperative exercise training may reduce postoperative pulmonary complications, decrease postoperative hospital lengths of stay, and improved exercise capacity[14]. In a study by Ngo-Huang et al, 50 pancreatic cancer participants participated in a home-based multimodal program including at least 60 minutes moderate intensity aerobic exercise weekly and at least 60 minutes full body strengthening exercises weekly. The mean duration of the exercise program was 16 weeks and patients were found to have improved physical function and health related quality of life[15].

There is currently inconsistency surrounding PREHAB delivery method and use of additional nutritional dietary supplementation. In a recent systematic review of pancreatic cancer PREHAB studies (n=6) there was considerable variation seen in; when to initiate PREHAB, exercise programming duration, supervision of sessions, exercise types, dietary supplementation, and reporting of outcomes[8]. Favorable outcomes were reported in studies which started PREHAB prior to surgery, were ≥ 6-week in duration, included supervised sessions and included moderate intensity aerobic training combined with resistance training.

1.3 Rationale

PREHAB has previously been reported to significantly improve quality of life, physical function and decreased post-operative complications in several cancer populations. Given the positive benefits reported in both physical function and quality of life post participating in PREHAB sessions the purpose of this study is to demonstrate the feasibility of a multimodal supervised PREHAB program in pancreatic cancer patients. Secondary aims include assessing safety and exploring benefits in sarcopenia, quality of life and functional performance.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To assess the feasibility of a 6-week supervised PREHAB program for pancreatic cancer patients

2.2 Secondary Objective

2.2.1 To evaluate the safety of a 6-week supervised PREHAB program for pancreatic cancer patients

2.3 Exploratory Objectives

2.3.1 To assess the impact of a PREHAB program on sarcopenia

2.3.2 To assess the impact of a PREHAB program on health-related quality of life including domains of physical function, fatigue, and social participation

2.3.3 To assess the impact of a PREHAB program on functional performance including strength and endurance

2.3.4 To assess the association between a PREHAB program and healthcare utilization including number of hospitalizations and length of stay

2.3.5 To assess the impact of a PREHAB program on post-operative outcomes including length of stay and complication rates

2.3.6 To assess the impact of a PREHAB program on continuous activity and sleep patterns

2.3.7 To assess the impact of a validated, web-based, health self-management guide designed for individuals with chronic illnesses (www.painguide.com)

2.3.8 To assess the impact of a PREHAB program on weight and BMI

2.4 Endpoints

2.4.1 Primary Efficacy Endpoint

Feasibility – REHAB session feasibility is defined as at least 10 of the 16 participants attending at least 60% of scheduled sessions

2.4.2 Secondary Efficacy Endpoint

Safety - PREHAB program safety will be evaluated by monitoring unanticipated problems involving risk to subjects or others (UPIRSO). At each PREHAB session, the post intervention evaluation and the 3 month follow up visit the exercise physiologist or personal trainer will record any side effects or symptoms reported by the subject. Within a week the treating physician or Principal Investigator (PI) will review and classify all events. Any events meeting the definition of a UPIRSO will be documented on the UPIRSO log and/or to the IRB by the coordinator within 10 business days.

2.4.3 Exploratory Endpoints

2.4.3.1 Impact on sarcopenia we will be measured using changes in hand grip strength and the short physical performance battery measured at Baseline, Post-Intervention Evaluation and 3-month Follow Up. Changes in Muscle Mass measured at Baseline and 3-month Follow Up will also be utilized.

2.4.3.2 Health-related quality of life will be measured by changes in the PROMIS-29 and PROMIS Cancer Function 3D Profile[16] scores measured at Baseline, Post-Intervention Evaluation and 3-month Follow Up.

2.4.3.3 Functional Performance will be measured by changes in the 6-minute walk test and physical performance metrics scores measured at Baseline, Post-Intervention Evaluation and 3-month Follow Up.

2.4.3.4 Hospitalizations and length of stay will be recorded from medical record review and a telephone follow-up with the patient and their caregivers at the 3-month follow up. Only hospitalizations post Baseline will be recorded.

2.4.3.5 Post-operative outcomes will be recorded from medical record review and a telephone follow-up with the patient and their caregivers at the 3-month follow up. Only operations post Baseline will be recorded. Post-operative complications will be assessed by the investigator retrospectively using the Clavien-Dindo classification system[17,18].

2.4.3.6 Physical Activity and Sleep will be measured by continuous activity and sleep monitoring by the Fitbit wrist worn device. The Fitbit will be worn from Baseline through to the 3-month Follow Up.

2.4.3.7 Impact of the online Pain guide will be measured by the Patient Global Impression questionnaire administered at the Post Intervention Evaluation Visit.

2.4.3.8 Impact on weight and BMI will be measured using changes in weight and BMI measured at Baseline, Post-Intervention Evaluation and 3-month Follow Up.

3.0 STUDY DESIGN

This is single site, pilot study designed to test the feasibility of a 6-week PREHAB program in pancreatic patients. All patients will participate in a 6-week supervised PREHAB program with either an exercise physiologist or personal trainer. Each week, patients will undergo 3 x 1 hour supervised training sessions consisting of moderate intensity aerobic training and resistance training. In addition to the supervised sessions,

patients will be instructed to accumulate a total of 150 minutes per week of moderate aerobic training at home.
This study has been designed to assess the hypothesis that a supervised PREHAB program is feasible in pancreatic cancer patients.

3.1 Inclusion of Women and Underrepresented Minorities

The total number of subjects involved in the study will be 16. Of those, we estimate that approximately 20% will be cisgender women. The estimated racial/ethnic breakdown of the study may approximately be that 15% may be Black or African American, 5% may be Asian, and 1% may be Native Hawaiian-Pacific Islander. Approximately 15% of the subjects may be Hispanic. While this provides only an estimated breakdown of the study population, efforts should be made to ensure equitable recruitment of individuals that meet the above eligibility requirements.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Pancreatic cancer diagnosis (any stage)

4.1.2 Age ≥ 18 years

4.1.3 Independent ambulation and activities of daily living (Discretion of referring/ treating oncologist)

4.1.4 Godin-Shephard Leisure-Time Physical Activity Questionnaire score of ≤ 23

4.1.5 Physically able to complete functional assessments including 6-minute walk test, hand grip strength, short performance physical battery and performance metrics

4.1.6 Answers no to all questions on PAR-Q **OR** is cleared to participate by their treating oncologist

4.1.7 Written informed consent obtained from subject and ability for subjects to comply with the requirements of the study

Inclusion criteria for remote monitoring of physical activity (Fitbit) and online Pain portal only (failure to meet inclusion criterion 4.1.9 should not preclude subjects from participating in main study):

4.1.8 Access to a smart device capable of Fitbit syncing and accessing the online Pain portal (**www.painguide.com**)

4.2 Exclusion Criteria

4.2.1 Current pregnancy

Exclusion criteria for remote monitoring component of the study with Fitbit only (failure to meet exclusion criterion 4.2.3 should not preclude the subject from participating in main study):

4.2.2 Using a pacemaker, implantable cardiac defibrillator, neurostimulator, cochlear implants (removable hearing aids permitted), or other electronic medical equipment, unless the treating physician deems study participation safe.

5.0 INTERVENTION PLAN

This is a multimodal PREHAB program with the following elements:

5.1 PREHAB Components

5.1.1 Functional Exercise

Participants will attend 3 x weekly 1hr in-person supervised exercise sessions with a trained exercise physiologist or personal trainer for a 6-week period. Sessions will be scheduled around the participants and the trainer's availability. Sessions will be held in the hospital gym at Cedars-Sinai – 250N Robertson, Blvd, Beverly Hills. During these sessions patients will undergo aerobic and resistance training.

Missed Sessions: Patients will be strongly advised not to miss any sessions. Sessions missed due to cancellations from the study team or participant (due to sickness, holidays, etc.) will be made during an optional 7th week following the 6-week intervention. There will be up to three make-up sessions. Patients will not be required to attend these make-up sessions but if they do not attend it will count as a missed session.

5.1.2 Nutrition

If patients have not previously been referred to a hospital dietitian during their pancreatic cancer care, they will receive a referral prior to their first PREHAB session.

5.1.3 Self- Management

Participants will be provided with a wrist worn Fitbit device to wear continuously from the Baseline visit through to the 3 Month Follow Up Visit. The Fitbit will monitor daily physical activity, sleep, and heart rate.

Patients will be instructed to accumulate a total of 150 minutes per week of moderate aerobic training at home outside of the set sessions. This will be measured by Fitbit data. It is not a deviation if they do not complete this many minutes per week.

All patients will be given the option to access an online pain management portal. This website (www.painguide.com) from the University of Michigan provides information on the management and monitoring of symptoms and behaviors including sleep and physical activity. Participants will be provided training on how to use and interact with this online portal. Use of this platform is optional; however, participants will be encouraged to engage with the portal at least once weekly. Portal use will be assessed via self-report every two weeks.

Following completion of the 6-week intervention, patients will be given resistance bands to continue with resistance training at home. At home exercise following

the 6-week intervention is at the participants own discretion and will be monitored by Fitbit data.

5.1.4 Muscle Mass calculation

The SOC Abdomen CT scans will be reviewed for muscle mass. CT images will be analyzed via Analyze 14.0 software by the Cedars-Sinai Imaging Core or trained personal.

5.2 PREHAB intensity / injury

Patients will participate in specific PREHAB exercises as they are able. Aerobic activity will be adjusted per participant to a level of 4-6 on a modified Borg Scale. Level of resistance for each exercise will be adjusted by the exercise trainer/physiologist such that repetitions are being performed at ~75% of the one repetition maximum. Chest specific exercises including chest press, dips, and push-ups will be omitted for patients with ports. Any patients experiencing symptoms of dizziness, lightheadedness or dyspnea will be instructed to take a break until symptoms resolve. Patients with unresolving symptoms or more serious symptoms like chest pain will be referred to the cancer rehabilitation physician who will evaluate the patient and refer to acute services as indicated.

Patients who sustain injuries related to the PREHAB sessions may remain on the study as long as their injury does not prevent them from completing the exercise protocol.

5.3 Standard of Care (SOC) Procedures

As SOC, patients will undergo Computed Tomography (CT) scans periodically throughout their pancreatic cancer diagnosis and treatment. This study will review SOC Abdomen CT scans undertaken closest to both the Baseline and 3 month follow up visit.

Patients will also undergo SOC labs periodically throughout their pancreatic cancer diagnosis and treatment. This study will review SOC labs undertaken closest to each PREHAB session to determine safe physical activity participation.

5.4 Duration of Study Participation

The study duration per subject will be approximately 23 weeks, with up to 4 weeks of screening, up to 7 weeks on treatment, and 3 months of follow-up.

5.5 Removal of Patients from Protocol

Patients will be removed from the study when any of the criteria listed in *Section 6.6* apply. If any of these criteria are met the PI will be notified and the reason for study removal and the date the patient was removed will be recorded. The patient should be followed-up per protocol.

5.6 Subject Replacement

Subjects who withdraw from the study prior to their PREHAB session 1 will be replaced.

Subjects who attend at least the first session will be evaluable for both the primary and secondary endpoint analysis. To be evaluable for exploratory endpoints subjects will need to complete the 3 month follow up visit.

6.0 STUDY PROCEDURES

6.1 Screening Procedures (Within 28 days of Baseline)

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

6.1.1 Informed Consent

Informed consent will be obtained in accordance with the Institutional Review Board (IRB) policies and procedures as described in the IRB application. For non-English speaking patients, an interpreter will be used.

6.1.2 Medical history

Relevant medical history, including history of current disease and information regarding underlying diseases (Medical record review)

6.1.3 Demographics

Age, gender, race, ethnicity

Patients may be offered the Inclusive Demographics Questionnaire, which is a standard, non-study-specific document, available on the IRB Intranet. Study team to record responses in the subject's OnCore record. Completion is voluntary; patients may decline to complete the Inclusive Demographics Questionnaire.

6.1.4 Pregnancy status

Pregnancy status will be confirmed with patient and via medical record review.

6.1.5 Godin-Shephard Leisure-Time Physical Activity Questionnaire

For non-English speaking patients, an interpreter will be used for the questionnaire.

6.1.6 Physical Activity Readiness Questionnaire (PAR-Q)

Patients who answer no to all questions on the PAR-Q will not require physician clearance. Any patients who answer yes to a question may be cleared by either a) their treating/referring oncologist or b) one of the study physicians following an in-person visit or phone call with chart review.

For non-English speaking patients, an interpreter will be used for the questionnaire.

6.1.7 Physical Activity assessment

Ambulatory status, ability to complete functional assessments including 6-minute walk test, hand grip strength, short performance physical battery and performance metrics.

6.1.8 Review subject eligibility criteria

6.2 Baseline Procedures (within 14 days of first PREHAB session)

All baseline procedures will occur after the patient is deemed to be eligible by review of the eligibility criteria.

6.2.1 Physical Evaluation

- Vitals (Height, Weight, Body Mass Index (BMI))
- Six-minute walk test
- Hand grip strength
- Physical performance metrics
    - Strength is measured in reps within 60 seconds of leg press, bicep curls, heel raises, plank holds and lateral pull downs.
    - Functional testing includes the sit to stand test.
    - Balance testing includes static standing balance with the eyes open and closed on firm and foam surfaces. Balance is rated as poor, fair, good, or excellent.
- Short performance physical battery

6.2.2 Questionnaires

- Patient-Reported Outcomes Measurement Information System (PROMIS-29)
- Patient-Reported Outcomes Measurement Information System Cancer Function (PROMIS Cancer 3D Function)

For non-English speaking patients, an interpreter will be used for the questionnaires.

6.2.3 SOC Abdomen CT scan

- Document date of closest SOC Abdomen CT scan (ok if occurred prior to consent or greater than 14 days prior to first PREHAB session)

6.2.4 Review of SOC Lab Results

- Participants are anticipated to be undergoing neoadjuvant therapies concurrently with study participation. These therapies may impact the participants circulating cytokines, thus rendering them ineligible to participate in physical activity.
  Prior to each PREHAB session exercise physiologist or personal trainer will check the participants' medical records for the most recent SOC lab results.
  To participate all 3 thresholds must be met:
    - absolute neutrophils >0.5 $^{1000/UL}$
    - platelets > 50 $^{1000/UL}$
    - hemoglobin >8 g/dl

  If one or more of these thresholds are not met the PI will be notified and the participant will be unable to participate in the exercise session. Sessions will resume when all lab values have reached the required thresholds or at the PI's discretion.
  These thresholds were determined by the cancer rehabilitation physiatrists and referring pancreatic oncologists and are in line with other cancer activity recommendations[19,20].

6.2.5 Fitbit Training and Use

- Training will include how to wear, charge and sync Fitbit
- Participants will start wearing the Fitbit continuously from the Baseline session
- Subjects who are unable to meet eligibility criteria 4.1.9 or who do meet exclusion criteria 4.2.3 will be exempt from this study task.

6.2.6 Dietitian Referral

- Patients not previously referred to a hospital dietitian during their pancreatic cancer care will be referred

6.2.7 Online Pain Portal Training (first 8 participants only)

- Training will include how to use and interact with the validated online portal (www.painguide.com) created by the University of Michigan. The exercise physiologist/personal trainer staff will follow up with patients weekly to biweekly to record usage of the portal.
- Subjects who are unable to meet eligibility criteria 4.1.9 will be exempt from this study task.

6.3 Study Procedures

6.3.1 Week 1 – Week 6* (Within 14 days of Baseline)

- 3 x weekly 1 hour PREHAB session
- Continuous activity monitoring (Fitbit)
- Unanticipated Problem review
- Optional use of the Online Pain Portal. Self-Report portal interaction.
- SOC Lab review – **If labs do not meet criteria in Section 6.2.4, STOP and call the PI**
- 150 minutes of self-managed exercise per week at home (measured by Fitbit data)

*Up to 3 missed sessions will be made up in a 7th week

6.3.2 Post-Intervention Evaluation (Within 14 days following the last PREHAB session)

Can be on the same day as the last PREHAB session

- Vitals (Weight, BMI)
- Six-minute walk test
- Hand grip strength
- Physical performance metrics
- Short performance physical battery
- Unanticipated Problem review
- PROMIS-29 (for non-English speaking patients, an interpreter will be used for the questionnaire)
- PROMIS Cancer 3D Function Profile (for non-English speaking patients, an interpreter will be used for the questionnaire)
- Patient Global Impression of Change (Only those participants who used the Online Pain portal)
- Continuous activity monitoring (Fitbit)

6.4 Follow-up Procedures - Three Month Follow-Up (± 14 days)

6.4.1 Physical Evaluation

- Vitals (Weight, BMI)
- Six-minute walk test
- Hand grip strength
- Physical performance metrics
- Short performance physical battery
- Unanticipated Problem review
- Last day of Fitbit Use

6.4.2 Questionnaires

- PROMIS-29
- PROMIS Cancer 3D Function Profile

For non-English speaking patients, an interpreter will be used for the questionnaires.

6.4.3 SOC Abdomen CT scan

- Document date of closest SOC Abdomen CT scan (ok if occurs outside of the 3 month ± 14 days window)

6.4.4 Healthcare Utilization Assessment (May be assessed by chart review, in-person discussion at visit and/or phone call)

- Number of hospitalizations
- Reason for hospitalization
- Days hospitalized
- Disposition: continued therapy, hospice, death, other
- If underwent resection then evaluate post-op complications - Post-operative complications will be assessed using the Clavien-Dindo classification system[17,18]

6.5 Time and Events Table

	Screening (Within 28 days of Baseline)	**Baseline** (Within 14 days of first PREHAB session)	**Week 1 – Week 6**[1]	**Post-Intervention Evaluation** (Within 14 days of last PREHAB session)	**3 Month Follow-Up** (± 14 days)
Informed Consent	X				
Confirm Eligibility	X				
Medical History	X				
Demographics	X				
Pregnancy status[2]	X				
Godin Leisure-Time Exercise Questionnaire	X				
PAR-Q	X				
Physical Activity Assessment	X				
Vitals (Height, Weight, BMI)[3]		X		X	X
Six Minute Walk Test		X		X	X
Hand Grip Strength		X		X	X
Physical Performance Metrics		X		X	X
Short Performance Physical Battery		X		X	X
Unanticipated Problem review			X	X	X
PROMIS-29		X		X	X
PROMIS Cancer 3D Function Profile		X		X	X
SOC Abdomen CT Scan[4]		X			X
SOC Lab Test Review		X	X[5]		
Fitbit activity monitoring[6]		X	X	X	X
Dietitian referral[7]		X			
Online Pain platform[8] Training		X			
Online Pain platform use[8]			X		
Online Pain platform compliance			X[9]		
3 x Weekly 1HR PREHAB session			X		
Patient Global Impression of Change[10]				X	
Healthcare Utilization Assessment					X

BMI: Body Mass Index, CT: Computed Tomography, PAR-Q: Physical Activity Readiness Questionnaire

1. Up to 3 missed sessions will be made up in a 7th week
2. Pregnancy status confirmed with patient and via medical record review

3. Height will only be collected at Baseline
4. CT scans completed closest to baseline and 3-month follow-up will be used, even if they occurred outside of the relevant visit window.
5. SOC labs will be reviewed prior to each PREHAB session
6. Fitbit use is only required by those who met eligibility criteria 4.1.9 and do not meet exclusion criteria 4.2.3.
7. Only patients not previously referred to a Dietitian will be referred by the study team
8. Online Pain platform training and use is only required for those who met eligibility criteria 4.1.9 (First 8 participants only)
9. Online Pain platform compliance will be self-reported every 2 weeks (First 8 participants only)
10. Only completed by the participants who used the Online Pain Portal

6.6 Removal of Subjects from Study

Patients can be taken off the study intervention and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.6.1 Patient voluntarily withdraws (follow-up permitted);

6.6.2 Patient withdraws consent (termination of treatment and follow-up);

6.6.3 Patient is unable to comply with protocol requirements;

6.6.4 Treating physician determines continuation on the study would not be in the patient's best interest;

6.6.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

6.6.6 Lost to follow-up. If a research subject cannot be located to attend their 3-month follow up session subject may be considered "lost to follow-up." All attempts to contact the subject during the 3 months must be documented.

6.6.7 Patient displays aggression or hostility towards study staff.

7.0 UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS OR OTHERS (UPIRSO)

7.1 UPIRSO Collection and Reporting

As this trial intervention and the corresponding research procedures pose no known risk to subjects, unexpected/unanticipated problems will be reported in place of Adverse Event reporting. Treating investigator or PI will evaluate patients through medical record review or patient visit from PREHAB session 1 through to the 3 Month Follow-Up visit for any unanticipated problems.

7.1.1 Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB) approved

research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research).

7.2 Reporting Requirements for Unanticipated Problems

7.2.1 Reporting to the Principal Investigator (PI)

The PI must be notified by study staff or co-investigators within 24 hours of learning of any UPIRSO, , occurring during the study as specified in section

Phone Number for Expedited Reporting:
Philip Chang, MD,
Email: Philip.Chang@cshs.org Ph: (310) 467-4498

Alternate Phone Number for Expedited Reporting:
Arash Asher, MD,
Email: Arash.Asher@cshs.org Ph: (310) 423-1218

7.2.2 Reporting to Data and Safety Monitoring Committee (DSMC)

UPIRSOs deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) to be reported to the DSMC within 24 hours of awareness. Hardcopies or electronic versions of the UPIRSO, along with any other supporting documentation available, should be submitted to the DSMC Coordinator. The DSMC Coordinator will forward the information to the DSMC Chair, and/or medical monitor. The DSMC Chair will review all UPIRSOs upon receipt from the DSMC Coordinator and determination of whether the following actions are required: 1) takes action immediately, 2) convenes a special DSMC session (physical or electronic), or 3) defers the action until a regularly scheduled DSMC meeting. Reports are to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

7.2.3 Reporting to the Institutional Review Board (IRB)

The IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others.”

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the PI was unanticipated, involved risk to subjects or others, and has a reasonable possibility of relationship to the research.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the PI.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size and Randomization

We plan to enroll 16 patients to reach 80% power testing the hypothesis that the proportion of patients with attendance at least 60% of exercise sessions during the initial 6-week period is greater than 50% using an one-sided exact Binomial test at 25% significance level. The actual significance level is 22.7%.

8.2 Data Sets Analyzed

Data from all eligible subjects who have participated in a minimum of 60% of the exercise sessions will be analyzed.

8.3 Data Analyses/Study Endpoints

Primary Objective: The primary analysis will test the hypothesis of feasibility using an one-sided exact Binomial test at 25% significance level. If 10 or more patients attend a minimum of 60% of exercise sessions during the initial 6-week period, then the study will be declared feasible.

Secondary Endpoints: We will present descriptive measures for secondary endpoints with spaghetti and profile plots for repeated measures

8.3.1 Safety Analysis

All subjects entered into the study at Baseline will be included in the safety analysis. The frequencies of UPIRSOs by type, body system, severity and relationship to study intervention will be summarized.

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

9.2 IRB Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written approval of the study protocol and the informed consent form will be in the possession of the PI before the study is initiated and prior to the shipment of study supplies to participating sites, if applicable. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

In obtaining and documenting informed consent, the PI should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the U.S Food and Drug Administration (FDA) Regulations and local or state regulations. Once this essential information has been provided to the patient and the PI is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.3 Registration Procedures/Enrollment Procedures

All patients will be tracked following written informed consent. Those patients who are consented to participate in the clinical trial but do not meet one or more criteria required for participation during the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the PI. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study teams will track all subjects who sign consent using OnCore. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a three-digit numeric ID that follows the standard Samuel Oschin Comprehensive Cancer Institute (SOCCI) format (001, 002, etc.).

A) Eligibility Verification

Prior to registration, all subjects must undergo an eligibility verification by the study-specific research staff. Minimal risk studies are exempt from SOCCI Quality Management Core (QMC) central eligibility checklist review and eligibility verification. QMC central eligibility checklist review and eligibility verification for all subjects enrolled is performed only if requested by the PI at any time during the life of the study.

For patients requiring a protocol exception requestion and/or waiver due to eligibility concerns, refer to Section 9.7.2, Protocol Exceptions and Eligibility Waivers for instructions.

B) Registration

After eligibility is verified, each site will assign the subject a study number and site staff will then register the patient in OnCore®.

Registration is completed as follows:

- Assignment of a patient study number

- Enter the patient in OnCore
- Notify the treating physician that a subject has gone on study and the anticipated start date

Oversight by the PI is required throughout the entire registration process.

9.4 Data Management and Quality Control and Reporting

REDCap is the Cedars-Sinai Cancer institutional choice for the electronic data capture of case report forms (CRF) for SOCCI Investigator Initiated Trials. REDCap, a HIPAA-compliant database, will be used for electronic CRF in accordance with institutional requirements, as appropriate for the project. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

9.5 Data and Safety Monitoring

9.5.1 Safety Oversight

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group meetings (or equivalent). The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. It is the responsibility of the principal investigator to adher to the Data Safety Monitoring Plan throughout the life of the study.

In addition, safety oversight and efficacy data will be reviewed by the SOCC Data and Safety Monitoring Committee (DSMC). The DSMC will review this trial commensurate with the assigned risk class as categorized by the PRMC. The DSMC membership and responsibilities are governed by the committee charter. The DSMC findings and recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC outcome letters will be furnished to the FDA, as applicable. Refer to the DSMC Charter for details of the DSMC review.

9.5.2 Monitoring

The SOCC Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct internal monitoring visits and audits to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Refer to the DSMP for details pertaining to the type, frequency, and extent of monitoring that will be performed.

9.6 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, monitoring/auditing logs/letters, records of study drug receipt, dispensation,

destruction and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file in accordance with all applicable federal guidelines and local guidelines.

Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request.

9.7 Adherence to Protocol

It is the responsibility of the Investigator-sponsor to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at SOCCI are all performed as specified in the protocol. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the IRB of record, the study shall be conducted exactly as described in the approved protocol.

9.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 72 hours from the investigator's awareness of the event.

9.7.2 Protocol Exceptions and Eligibility Waivers

Minimal Risk
A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the CSMC IRB Policy*, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*. A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or impact an eligibility criterion, affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior IRB approval. The PI or their designee is responsible for submitting a protocol exception request and its supporting documents to the CSMC IRB if it meets the CSMC-IRB UPIRSO policy guidelines of a reportable exception/waiver. Study team should also refer to the IRB *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement* guidelines to determine which deviations and exception requests require IRB reporting. Once IRB approved, the deviation or exception can be implemented.

Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be submitted to the IRB for approval. Such requests for minimal risk studies do not require prior review by the CCTO Medical Director.

9.7.3 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the subject's research record or deviation log as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI CCTO's Standard Operating Procedure 12: *Deviation and Noncompliance Reporting* (or local policy, for multi-site studies). In this case, a Protocol Deviation report must be submitted in CSMC-IRB, per CSMC IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

9.7.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the PI. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

9.8 Obligations of Investigators

The PI is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP regulations and guidelines regarding clinical trials both during and after study completion.

The PI will be responsible for assuring that all the required data will be collected and entered onto the CRFs and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted, and the PI will provide access to their original records to permit verification of proper entry of data. At the completion of the study, all CRFs will be reviewed by the PI and will require their final signature to verify the accuracy of the data.

9.9 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor-investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

10.0 REFERENCES

1. Cancer of the Pancreas - Cancer Stat Facts. SEER. Accessed May 5, 2021. https://seer.cancer.gov/statfacts/html/pancreas.html

2. Pancreatic Cancer - Risk Factors. Cancer.Net. Published June 25, 2012. Accessed September 22, 2022. https://www.cancer.net/cancer-types/pancreatic-cancer/risk-factors

3. Cooper AB, Holmes HM, des Bordes JKA, et al. Role of neoadjuvant therapy in the multimodality treatment of older patients with pancreatic cancer. *J Am Coll Surg*. 2014;219(1):111-120. doi:10.1016/j.jamcollsurg.2014.02.023

4. Chan MY, Chok KSH. Sarcopenia in pancreatic cancer - effects on surgical outcomes and chemotherapy. *World J Gastrointest Oncol*. 2019;11(7):527-537. doi:10.4251/wjgo.v11.i7.527

5. Sakamoto T, Yagyu T, Uchinaka E, et al. Sarcopenia as a prognostic factor in patients with recurrent pancreatic cancer: a retrospective study. *World J Surg Oncol*. 2020;18(1):221. doi:10.1186/s12957-020-01981-x

6. Silver J. Cancer Prehabilitation in the Surgical Setting. In: *Cancer Rehabilitation*. 2nd ed. Springer Publishing Company; 2018:875-879.

7. Loewen I, Jeffery CC, Rieger J, Constantinescu G. Prehabilitation in head and neck cancer patients: a literature review. *J Otolaryngol Head Neck Surg*. 2021;50(1):2. doi:10.1186/s40463-020-00486-7

8. Bundred JR, Kamarajah SK, Hammond JS, Wilson CH, Prentis J, Pandanaboyana S. Prehabilitation prior to surgery for pancreatic cancer: A systematic review. *Pancreatology*. 2020;20(6):1243-1250. doi:10.1016/j.pan.2020.07.411

9. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. *World J Surg*. 2019;43(7):1661-1668. doi:10.1007/s00268-019-04950-y

10. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology*. 2014;121(5):937-947. doi:10.1097/ALN.0000000000000393

11. West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth*. 2015;114(2):244-251. doi:10.1093/bja/aeu318

12. Banerjee S, Manley K, Shaw B, et al. Vigorous intensity aerobic interval exercise in bladder cancer patients prior to radical cystectomy: a feasibility randomised controlled trial. *Support Care Cancer*. 2018;26(5):1515-1523. doi:10.1007/s00520-017-3991-2

13. Sebio Garcia R, Yáñez Brage MI, Giménez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2016;23(3):486-497. doi:10.1093/icvts/ivw152

14. Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev*. 2017;6:CD012020. doi:10.1002/14651858.CD012020.pub2

15. Ngo-Huang A, Parker NH, Bruera E, et al. Home-Based Exercise Prehabilitation During Preoperative Treatment for Pancreatic Cancer Is Associated With Improvement in Physical Function

and Quality of Life. *Integr Cancer Ther*. 2019;18:1534735419894061. doi:10.1177/1534735419894061

16. Smith SR, Vargo M, Zucker D, et al. Psychometric Characteristics and Validity of the PROMIS Cancer Function Brief 3D Profile. *Arch Phys Med Rehabil*. Published online February 4, 2021. doi:10.1016/j.apmr.2020.12.027

17. Ausania F, Senra P, Meléndez R, Caballeiro R, Ouviña R, Casal-Núñez E. Prehabilitation in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. *Rev Esp Enferm Dig*. 2019;111(8):603-608. doi:10.17235/reed.2019.6182/2019

18. Nakajima H, Yokoyama Y, Inoue T, et al. Clinical Benefit of Preoperative Exercise and Nutritional Therapy for Patients Undergoing Hepato-Pancreato-Biliary Surgeries for Malignancy. *Ann Surg Oncol*. 2019;26(1):264-272. doi:10.1245/s10434-018-6943-2

19. Vargo M. Precautions in Cancer Rehabilitation. In: *Cancer Rehabilitation*. 2nd ed. Springer Publishing Company; 2018:789-798.

20. Mohammed J, Aljurf M, Althumayri A, et al. Physical therapy pathway and protocol for patients undergoing hematopoietic stem cell transplantation: Recommendations from The Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) Group. *Hematol Oncol Stem Cell Ther*. 2019;12(3):127-132. doi:10.1016/j.hemonc.2018.12.003

11.0 APPENDIX

11.1 SUMMARY OF CHANGES

11.1.1 Protocol v2, 17JUL2023

1. Section 6.2.4, Review of SOC Lab Results: The absolute neutrophil count cut-off was reduced from 1.0 1000/uL to 0.5 1000/uL.
2. Section 6.2.7, Online Pain Portal Training (first 8 participants only): Removal of Dr. Warner; the exercise physiologist/personal trainer staff will follow up with patients weekly to biweekly to record usage of the portal.
3. Section 9.7.1, Emergency Modifications: Timeframe for IRB reporting changed from 10 days to 72 hours.

11.1.2 Protocol v3, 06AUG2024

1. Updated cover page with version # and date.
2. Updated biostatistician to Shaowli Kabir, PhD.
3. Updated study summary to remove “ability to read, write and understand English”
4. Removed inclusion criteria for “ability to read, write and understand English”
5. Section 6.1.1 Informed Consent, it was added that “for non-English speaking patients, an interpreter will be used”.
6. For sections 6.1.5, 6.1.6, 6.2.2, 6.3.2, 6.4.2, it was added that “for non-English speaking patients, an interpreter will be used for the questionnaires”.
7. Updated language in sections 9.3 and 9.5 to match boilerplate protocol language.

11.1.3 Protocol v3, 23JAN2025

1. Updated cover page with version # and date
2. Removed exclusion criteria 4.2.1 “has undergone or plans to undergo resection surgery prior to projected completion of PREHAB exercise intervention”.