A Phase III Randomized Study Comparing the Effects of a Personalized Exercise Program (PEP) Against No Intervention in Patients with Stage I-IIIa Primary Non-Small Cell Lung Cancer or Secondary Lung Cancer Undergoing Surgical Resection

Trial ID: HCI104671/IRB# 104671

NCT # TBD

HCI-17-PopSci-15

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Historical Protocol Versions

Version 1: 9/11/2017

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
6MW	Six Minute Walk
AE	Adverse Event OR Aerobic Exercise *(contextual)*
AM-PAC	Boston University Activity Measure for Post-Acute Care
BMI	Body Mass Index
BP	Blood Pressure
BREQ-3	Behavioral Regulation in Exercise Questionnaire 3
COPD	Chronic Obstructive Pulmonary Disease
CRC	Clinical Research Coordinator
CRF	Case report form
CTCAE	Common Toxicity Criteria for Adverse Events
eCRF	Electronic case report form
ERV	Expiratory Reserve Volume
FACT-L	Functional Assessment of Cancer Therapy-Lung
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
HAPA	Health Action Process Approach
HR	Heart rate
hr	Hour or hours
i.e.	Id est (that is)
IND	Investigational New Drug
IRB	Institutional Review Board
IRV	Inspiratory Reserve Volume
LOC	Locus of Control
MFI	Multidimensional Fatigue Inventory
MI	Motivational Interviewing
NCCN	National Comprehensive Cancer Network
NSCLC	Non-Small Cell Lung Cancer
PEF	Peak Expiratory Flow
PEP	Personalized Exercise Program

Abbreviation or Term[1]	Definition/Explanation
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
PT	Physical Therapy / Therapist *(contextual)*
RCT	Randomized Clinical Trial
RE	Resistance Exercises
SAE	Serious Adverse Event
SD	Standard deviation
SPPB	Short Physical Performance Battery
SOC	Standard Of Care
UUHS	U of Utah Healthcare system
VC	Vital capacity
VDO	Value Driven Outcomes

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

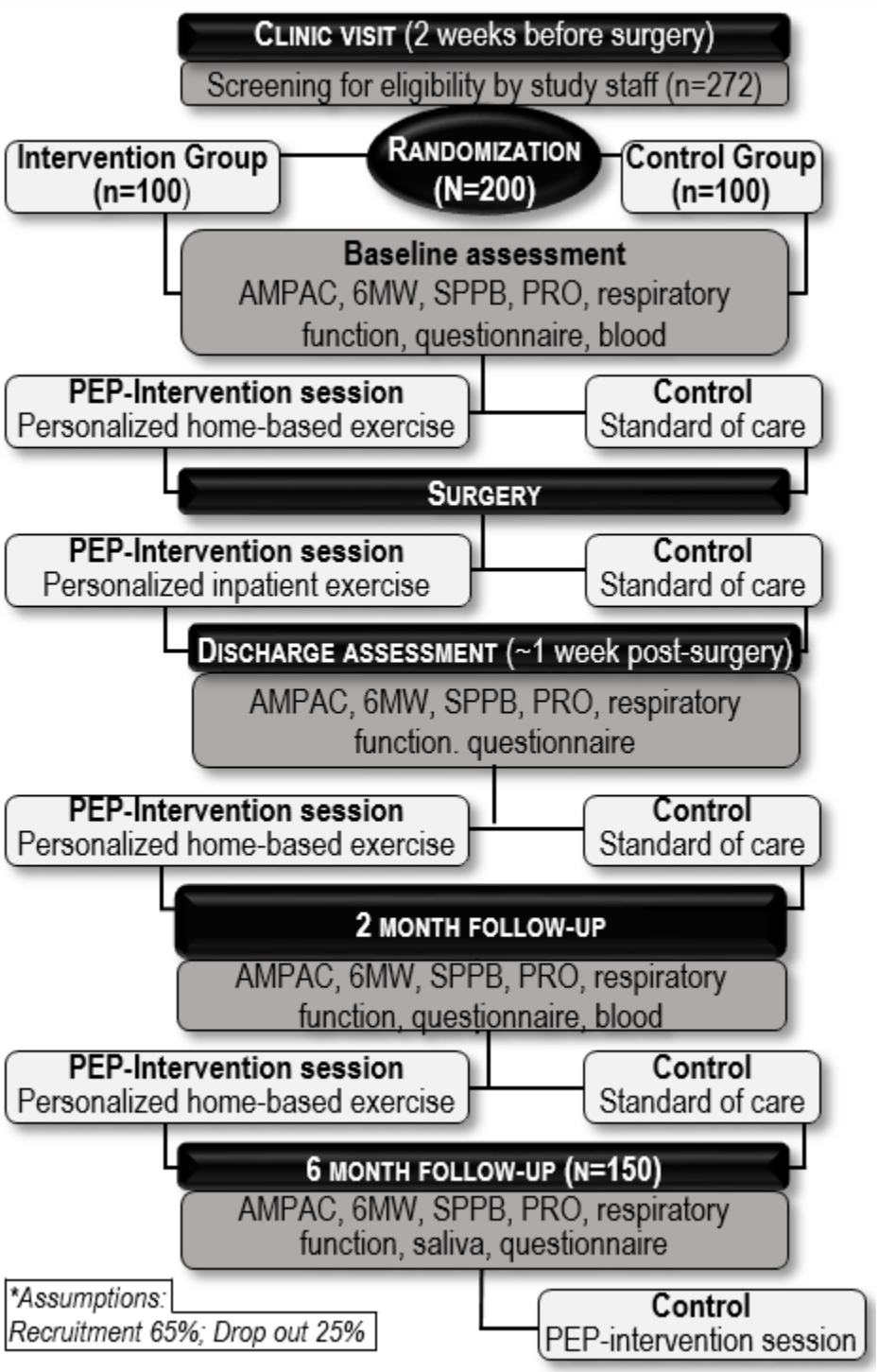
Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	A Phase III Randomized Study Comparing the Effects of a Personalized Exercise Program (PEP) Against Standard of Care (No Intervention) in Patients with Stage I-IIIa Non-Small Cell Primary Lung or Secondary Lung Cancer Undergoing Surgical Resection
Short Title	PEP Intervention Study Randomized Clinical Trial
Protocol Number	104671
IND	IND exempt
NCT number	TBD
Phase	3
Design	Randomized two-arm clinical trial comparing a personalized exercise program (Intervention Arm – Group 1) to the standard of care (Control Arm – Group 2: no exercise program) in patients with lung cancer (primary stage I-IIIa or secondary)
Study Duration	4 years
Study Center(s)	Single center - Huntsman Cancer Institute
Objectives	**Primary:** Evaluate the improvement in mobility performance via the 6 Minute Walk (6MW) test **Secondary:** 1. Evaluate the improvement in strength, endurance, and balance via the Short Physical Performance Battery (SPPB) test. 2. Evaluate the improvement in respiratory function status via spirometry measurements. 3. Gather patient-reported outcomes regarding disease specific symptoms, multidimensional fatigue, common mental health issues, and hypothesized treatment mechanisms, via questionnaires
Number of Subjects	Randomized clinical trial: 200 (approximately 106 men and 94 women), and 300 approached (anticipated recruitment rate 65%)
Diagnosis and Main Eligibility Criteria	**Inclusion:** • Male or female subject aged ≥ 18 years. • Diagnosis of primary lung cancer stage I, II, or IIIa OR secondary lung cancer. • Disease amenable to surgical resection to be performed at the Huntsman Cancer Hospital in the opinion of the treating surgeon. • Patients must be able to follow directions and complete questionnaires and exercise diaries in English. • Patients must agree to be randomly assigned to either Intervention or Control Group.

	Exclusion: • Contraindications for entry into an exercise training program (unstable angina, uncontrolled hypertension [systolic > 200, diastolic > 100], orthostatic hypotension [> 20 mm fall in systolic], moderate or serve aortic stenosis, uncontrolled arrhythmia, uncontrolled congestive heart failure, third degree heart block, pericarditis, myocarditis, pulmonary/systemic embolism within the past 6 months, thrombophlebitis, ST displacement > 3 mm at rest, history of cardiac arrest. • Patient is morbidly obese (BMI > 40 kg/m^2) or anorexic (BMI < 17.5 kg/m^2). • Abnormalities on screening physical exam judged by study physicians or physical therapist to contra-indicate participation in exercise program compliance. • Alcohol or drug abuse as judged by study physicians. • Significant mental or emotional problems that would interfere with study participation (assessed by NCCN Distress Thermometer).
Study Product, Dose, Route, Regimen and Duration	A personalized exercise regimen based on a patient's AM-PAC score and performed in the outpatient setting starting 2 to 4 weeks pre-surgery, inpatient for the duration of the hospital stay, and outpatient 6 months post-surgery.
Statistical Methodology	**Primary analysis** Power calculations are based on the group effect in an analysis of covariance for the 6MW test at 8 weeks, with baseline 6MW test as covariate. The planned sample size (n = 200) allows for a 25% dropout rate leaving at least 150 subjects evaluable for the primary endpoint. The hypothesis is that the difference in the 6MW distance between the study arms (Intervention vs. Control) will be ≥ 39.95 m. This effect size stems from a meta-analysis where 4 weeks of post-surgery exercise training provided a 39.95 increase in the 6MW distance in NSCLC patients. Consistent with Arbane, SD = 100 m and correlation = 0.5 between repeated 6MW test measurements on the same subject are assumed. Power to detect the treatment effect was estimated by simulation (in R) of an analysis of covariance model with 6MW test at 2 months post-surgery as outcome, treatment group as primary predictor and pretreatment 6MW test as covariate. Pre and post 6MW test was assumed to be bivariate normally distributed. **Secondary analyses** See section 10 for details.

SCHEMA


CLINIC VISIT (2 weeks before surgery)
Screening for eligibility by study staff (n=272)
Intervention Group (n=100)
RANDOMIZATION (N=200)
Control Group (n=100)
Baseline assessment
AMPAC, 6MW, SPPB, PRO, respiratory function, questionnaire, blood
PEP-Intervention session
Personalized home-based exercise
Control
Standard of care
SURGERY
PEP-Intervention session
Personalized inpatient exercise
Control
Standard of care
DISCHARGE ASSESSMENT (~1 week post-surgery)
AMPAC, 6MW, SPPB, PRO, respiratory function. questionnaire
PEP-Intervention session
Personalized home-based exercise
Control
Standard of care
2 MONTH FOLLOW-UP
AMPAC, 6MW, SPPB, PRO, respiratory function, questionnaire, blood
PEP-Intervention session
Personalized home-based exercise
Control
Standard of care
6 MONTH FOLLOW-UP (N=150)
AMPAC, 6MW, SPPB, PRO, respiratory function, saliva, questionnaire
*Assumptions:
Recruitment 65%; Drop out 25%
Control
PEP-intervention session

1 OBJECTIVES

This study is designed to establish whether participation in a personalized exercise program during the pre- and post-operative setting can positively affect physical performance, cardiorespiratory fitness, quality of life, clinical outcomes (hospital length-of stay and readmission rate, complications), and treatment related costs in patients undergoing surgery for the treatment of stage I-IIIa NSCLC as well as secondary lung cancer when compared to the current standard of care (no exercise program).

1.1 Primary Objective

1.1.1 Evaluate the improvement in mobility performance.

Primary Endpoint: Six Minute Walk (6MW) distance.

1.2 Secondary Objectives

1.2.1 Evaluate the improvement in strength, endurance, and balance.

Secondary Endpoint #1: Short Physical Performance Battery (SPPB) test scores

1.2.2 Gather patient-reported outcomes regarding disease specific symptoms, multidimensional fatigue, common mental health issues, and hypothesized treatment mechanisms and evaluate differences between arms.

Secondary Endpoint #2: results from PROMIS, FACT-L (Functional Assessment of Cancer Therapy-Lung), FACIT-F (Chronic Illness Fatigue Scale), PSQI (Pittsburgh Sleep Quality Index), and BREQ-3 (Behavioral Regulation in Exercise Questionnaire 3) questionnaires.

1.2.3 Evaluate the improvement in respiratory function status.

Secondary Endpoint #3: spirometry measurements (FEV1, PEF, VC, IRV, ERV).

Further secondary endpoints to be explored include self-efficacy, social support, disease-related symptoms (e.g., pain shortness of breath), activities of daily life, personal habits, emotions, demographics, background information, and living conditions.

1.3 Exploratory Objectives

1.3.1 Evaluate changes in biomarker levels.

Exploratory Endpoint #1: potential prognostic or mechanistic biomarkers, such as inflammatory biomarkers, in serum, plasma, and buffy coat.

1.3.2 Evaluate the rate of complications.

Exploratory Endpoint #2: rate of occurrence of pulmonary, cardiac, and other complications requiring treatment (e.g., liver dysfunction, gastric ulcer,

wound infection, colitis, depression), readmissions and deaths within the first 30 days after discharge.

1.3.3 Measure the length of stay post-surgical resection.

Exploratory Endpoint #3: time from surgery to discharge obtained from clinical databases.

1.3.4 Evaluate costs and utilization from admission to discharge, from discharge to 2 months follow-up, and from 2 to 6 months follow-up.

Exploratory Endpoint #4: total cost of care and utilization for each of the three periods collected through the UUHS VDO, the Utah APCD, daily electronic diaries, and time-line follow-back.

2 BACKGROUND

2.1 Lung Cancer: A Major Public Health and Clinical Challenge

The incidence and prevalence of lung cancer has risen dramatically. In 1953, primary lung cancer became the most common cause of cancer death in men, while the same occurred for women in 1985 in the United States.[1] Worldwide, lung cancer is one of the most commonly diagnosed cancer types and also the leading cause of death in men.[1] Among the most aggressive cancers, lung cancer causes more deaths than the next three most lethal common cancers combined.[1] The lungs are the most common site for metastatic disease (secondary lung cancers), which are identified in 30-55% of metastatic cancer patients.[2]

Non-small cell lung cancer (NSCLC) accounts for the majority of primary lung cancer (~ 85%). Stage I disease (small lesion, no spread in lymph nodes) and stage II disease (larger lesion, no spread in lymph nodes and involvement of structures such as the chest wall or diaphragm, or involvement of hilar lymph nodes) make up about a third of patients with NSCLC.[1] Treatment options for lung cancer depend on histology, stage, and patient-specific factors. Randomized clinical trials have established surgical resection of a single lobe of the lung, or lobectomy, as the treatment of choice for operable lung cancer patients in stage I and II,[1] improving survival to up to 75%.[1,2] For those patients with stage IIIa disease (involvement of ipsilateral mediastinal lymph nodes), surgical resection plays a role after chemoradiation therapy, provided no further spread of disease has occurred, and patients remain medically operable. The lung is also a common site for metastatic spread from other primary cancers (most common: breast, colon, sarcoma and melanoma). Experience with surgical resection of secondary lung cancers (pulmonary metastasectomy), once the primary cancer has been controlled, has confirmed that resection can substantially prolong survival and potentially cure some patients.[3-8] In 2015, lung cancer accounted for $13.4 billion in costs out of a total expense of cancer care of $147.5 billion.[9] Lung cancer patients often experience multidimensional impairments affecting quality-of-life (QoL) during their course of disease.[10] Impairments result from both symptoms of the disease and comorbidities, as well as side effects of treatment. Interventions aimed at minimizing morbidity would have a significant impact on public and population health.

2.2 Functional Outcomes after Surgery

Surgical resection is the treatment of choice for primary lung cancer patients with stage I to IIIa lung cancer, as it offers the best chance for cure. The goal of surgical resection for lung cancer patients is excision of one or more lobes of the lung that are affected by cancer. For secondary lung cancers, this goal is complete removal of the lesion with adequate margins. Lung cancer patients suffer substantial functional decline and reduced activity levels following surgical lung resection.[11-13] There is a significant deterioration in six minute walk (6MW) distance at five days post-operatively compared with pre-operatively (average of 337m vs. 467m).[11] Lung resection is associated with an immediate 12% reduction in exercise tolerance and 18% reduction in pulmonary function.[12] Lung resection also has an impact on post-surgery health-related QoL[14-16] and causes persistent pain following surgical treatment for up to 33% of patients.[17] The postsurgical period is associated with a 20-40% reduction in physiological and functional capacity, particularly in the elderly with comorbidities, who may never return to pre-surgery levels of function.[18-20] Additionally, poor pre-surgery physical performance has been shown to increase the risk of mortality,[21] post-surgery complications, and prolonged functional recovery.[22] Thus, the pre-operative and post-operative periods are ideal periods to intervene. Enhancing functional capacity 2-4 weeks prior to a lung resection is feasible and motivates the patient to continue with physical activities and exercises post-operatively, which is essential for optimizing outcomes

2.3 Exercise Training in Oncological Patients

Exercise intervention studies prior to, during and after cancer treatment consistently show beneficial effects for various physical and psychosocial outcomes.[23-33] The American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors concluded that exercise training is safe during and after cancer treatments and results in improved physical function, QoL, and cancer-related fatigue in multiple cancer survivor groups.[24] It has been shown that exercise interventions can ameliorate or reverse cancer treatment-induced impairment of physical function and QoL, such as cancer-related fatigue and pain.[24-37]

Several non-randomized intervention studies and ten randomized controlled trials have demonstrated positive effects of pre- or post-surgical exercise intervention in lung cancer patients.[11,38-59] In a review, Crandall et al. concluded that compared to usual care, exercise interventions among lung cancer patients both pre- and post-surgery are associated with improved cardiopulmonary exercise capacity and muscle strength, and reduced fatigue, post-operative complications and hospital length of stay.[60] Despite this consistent and convincing evidence, implementation of exercise programs in clinical practice for patients with lung cancer is still low, perhaps due to unacceptable financial and resource demands on the patient and the health care system (e.g., center-based exercise). There are further gaps in the evidence base: Although the majority of exercise studies have demonstrated positive impact, only a small Turkish trial has covered the continuum from pre-surgery to the survivorship period,[49] and none have used a highly standardized, yet patient-tailored approach. Most of the exercise studies in lung cancer patients have been developed outside of the United States, and there are currently only two American trials recruiting patients, both of which differ substantially

in their design. One trial tests a 16-week exercise intervention that starts at least one year following the completion of therapy and requires participants to attend three supervised sessions per week (NCT 01068210). The other trial provides mindfulness-based pulmonary rehabilitation prior to surgery for both lung cancer and COPD patients (NCT 01682850). There is clearly a need for testing innovative exercise interventions in lung cancer patients that can be translated into clinical practice across the entire continuum of care.

2.4 Physical Functioning (AM-PAC Scores) Among Lung Cancer Patients at HCI

The AM-PAC mobility score[61] was implemented as the inpatient mobility assessment tool in June of 2014 within the University of Utah Health Care system (UUHS) and has become a standard mobility measure collected by physical therapists in the University's acute hospitals (see Appendices 1-3). The PEP Study team plans to extend assessments to pre-surgery visits for the standardized precision exercise program. As part of a pilot study, n = 63 AM-PAC scores were collected at Dr. Varghese's clinic from lung cancer patients during their pre-operative outpatient clinic visit. The average score was 54 ± 13. Patients were 54% female, with mean age of 61 ± 15 years. Overall 44% of patients were categorized as AM-PAC stage 3, indicating that they had difficulty with community mobility. Eighteen % had stage 2, indicating that they had difficulty with mobility within the home. Patients ranging across mobility stages 2-4 are generally capable of performing exercise that will have the greatest likelihood in resulting in positive outcomes. The level of physical function of patients in the clinic can vary widely, reinforcing the PEP concept of an exercise intervention that is tailored for the mobility stage of each patient. No correlations between the AM-PAC score and age, sex or cancer stage (all $p > 0.05$; $|r| < 0.30$); some 75 year olds had better function than 50 year old patients. This suggests that the AM-PAC score is well-suited and sufficient to assess physical function, and should be evaluated for appropriate tailoring of exercise interventions.

2.5 Rationale for Conducting the Study

Studies that have investigated the effect of exercise in lung cancer patients undergoing surgery have been center-based and resource intensive, and consequently have not been implemented in the clinical setting.[65-67] Pre-operatively, effective exercise programs lasting 6-12 weeks are not feasible since patients with lung cancer do not want to delay surgery. In fact, one randomized controlled trial (RCT)[38] was prematurely discontinued because neither patients nor providers were willing to delay surgery longer than 4 weeks. Post-surgery, home-based exercise strategies capable of improving mobility and fatigue levels of patients following surgery for lung cancer and colorectal cancer [45] have been prohibitively expensive because they required supervised visits by a nurse.[32] In addition, these programs have been "one size fits all," lacking a personalized approach to optimize adherence and efficacy.[65-68]

To date, no attempt has been made to test a pragmatic and personalized exercise intervention (i.e., face to face visits at clinical contacts, telephone counseling in the home, and personalized exercise prescriptions) before and following surgery for

patients with lung cancer. Unfortunately, the application of personalized principles of exercise in randomized controlled trials with cancer survivors (specifically non-breast cancer survivors) is incomplete and inconsistent.[69] To establish consistency in the exercise prescription while accommodating the exercise to match the patient's level of mobility, a validated basic mobility assessment tool to create modes and dosages of exercise that can be implemented across the continuum of the pre- and post-operative surgical experience in lung cancer patients. The Activity Measure-Post Acute Care™ (AM-PAC) (described in Figure 2) will be used as the basic mobility assessment tool that prompts the prescribed exercise mode and dose for the patient. The AM-PAC has been developed as a pragmatic measurement system that can be used across care settings and a very broad range of impairments, limitations and diagnoses.[70] The PEP Study's approach with the use of AM-PAC will address a gap in the care of lung cancer patients, i.e., the underutilization of exercise because it is clinically not pragmatic and it is not known how and when to implement exercise.[71]

2.6 Rationale for the PEP Intervention Design

Dr. Ulrich's previous work with the empirically validated MotivAction intervention will serve as the foundation for the PEP intervention, which will be adapted for lung cancer patients. The Health Action Process Approach (HAPA) describes a general framework for self-regulation and behavior change among individuals with chronic illness.[72-78] The overarching conceptual basis is the social cognitive model [74-76] which posits that high levels of both motivation and self-efficacy are necessary for behavior change.[29] Thus, in the HAPA model, a key element for lasting behavior change is a motivational shift that instigates a decision and commitment to change. In the absence of such a shift, skill training is viewed as premature.[74,79,80] As such, the PEP intervention focuses on both enhancing the motivation to achieve and maintain change, as well as developing the self-efficacy and skills necessary to do so. Many interventions focus largely on either motivation or problem-solving/skills training despite the strong theoretical and empirical bases for doing both. When motivation is addressed, the focus is typically on initiating a change attempt, with little attention given to the motivation to maintain change. Specific components of the PEP intervention include: individualized tailoring of the exercise prescription; individualized tailoring of the counseling based on motivation and self-efficacy to engage in exercise including the use of simple motivational interviewing (MI) [79] techniques (e.g., reflective listening, avoiding argumentation; developing discrepancy); identifying barriers to exercising and problem-solving solutions; use of goal setting and self-monitoring (including via the activity tracker); and, implementing specific strategies for improving self-efficacy (e.g., building a series of small achievable goals; practicing specific exercises during the face to face visits to increase mastery (see Figure 1).

In sum, the PEP intervention is a directive but patient-centered approach designed to enhance motivation for change, and increase self-efficacy in a non-confrontational manner. Several meta-analyses and systematic reviews have supported the efficacy of both social cognitive and MI-based interventions for behavior change in general and with respect to cancer patients specifically.[81-85]

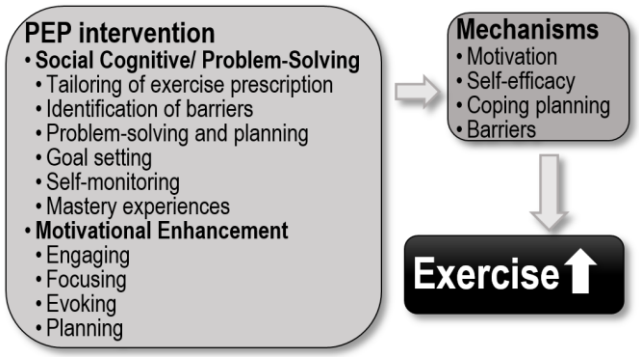


Figure 1: PEP interventions strategies and mechanisms

2.7 PEP Study Pilot

In order to test the feasibility of patient recruitment and study implementation, a pilot study was conducted (IRB 91478, The PEP Study: Precision Exercise Prescription among lung cancer patients, approved 7/3/2016).

Between 7/7/2016 and 10/11/2016, n=18 lung cancer patients were recruited into the intervention program at their pre-surgery consult with Dr. Varghese. Every eligible patient was approached, and all patients approached (100%) agreed to participate in the intervention. Their physical function was assessed with 6MW test, SPPB, and AM-PAC score. The testing and precise exercise prescription was implemented within normal clinic workflow and clinic space by a trained physical therapist (Dr. Barnes) using existing space in the clinic of Thoracic Surgery. The intervention included individually-prescribed exercise modes (mobility, flexibility, callisthenic, aerobic and resistance) and dosages (low, moderate, high) tailored to the patient's AM-PAC mobility stage.

The baseline observed 6MW distance varied from 209-679m with a mean distance of 467±119m. Normal 6MW distance for healthy 60-69 year olds is 572m for men and 538m for women. For ten patients, post-operative 6MW distances were obtained prior to 10/15 (max. follow-up time 20 post-operative days within the pilot). Compared to comparable control patients (for whom 6MW distances at comparable pre- and post-time points were available) PEP patients maintained their physical function and experienced a lesser reduction in 6MW distance (median 6.8% decline in PEP and 18.7% in controls, see Figure 1). Although this comparison is not based on a randomized study, it is notable that the decrease (47m) in 6MW distance in the controls exceeded the minimal clinically important distance, despite the time points achieved at this point being very early in the intervention process. To date, only one patient has dropped out (5.5% drop-out rate).

A follow-up phone evaluation of the PEP intervention showed that patients planned to exercise an average of 4.7 days per week and 93% agreed (86% strongly) that exercise should be part of their cancer treatment; 86% also strongly agreed with the statement that they believe that the exercise program will have a positive effect on their cancer treatment. Several patients noted that they loved being in the program and the effort of our team. They emphasized that the exercise intervention helped them immensely with recovery from surgery.

In conclusion, these preliminary results demonstrate that: (1) our team has successfully worked together on the PEP study intervention, generated pilot data, and two scientific abstracts;[90,91] (2) lung cancer patients differ dramatically in their functional status, independent of age, sex and stage, requiring individualized interventions; (3) the PEP intervention was feasible within the existing workflow of a high-volume surgical clinic, with only the addition of a physical therapist to manage the intervention; (4) the PEP intervention is welcomed by patients and appears to show early efficacy; and (5) our assumptions for anticipated patient recruitment (65%) and drop-out rates (15%) are conservative. Overall, this pilot work sets the base for a successful clinical trial.

3 STUDY DESIGN

3.1 Description

This is a Phase 3 study aimed at investigating the effects of a personalized exercise program (PEP) in NSCLC patients (stage I, II, IIIa) and secondary lung cancer patients undergoing surgical treatment at the University of Utah and comparing the intervention to the current standard of care (no exercise program).

Eligible patients will be randomized between two arms (1:1 ratio) prior to the surgery and will be followed for 6 months post-surgery:

- An Intervention Arm (referred to in materials as Group 1) which features pre- and post-surgery PEP interventions.
- A Control Arm (referred to in materials as Group 2) which does not include a personalized exercise program (the standard of care). Patients randomized to the Control Arm will be given the opportunity to participate in a PEP-intervention session providing exercise counseling after the 6 month assessment and will receive a free activity tracker for their participation.

3.2 Number of Patients

The target enrollment for the randomized clinical trial is 200 patients (approximately 106 men and 94 women). It is estimated that 300 patients will be approached about the study which will achieve a conservative recruitment rate of 65%.

3.3 Number of Study Centers

This study will open at a single center at the Huntsman Cancer Institute.

3.4 Duration

Participants will be recruited over the course of 33 months. The estimated total duration of the study from the first enrollment to the end of the last 6-months follow-up is 4 years.

4 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with investigator's signature in the patient research chart.

Patient No. _____

Patient's Initials: (L, F, M) _____

4.1 Inclusion Criteria
Yes/No (Response of "no" = patient ineligible)

4.1.1 _____ Male or female subject aged ≥ 18 years.

4.1.2 _____ Diagnosis of primary lung cancer stage I, II, or IIIa OR secondary lung cancer.

4.1.3 _____ Disease amenable to surgical resection in the opinion of the treating surgeon.

4.1.4 _____ Patients must be able to follow directions and complete questionnaires and exercise diaries in English.

4.1.5 _____ Patients must agree to be randomly assigned to either Intervention or Control Group.

4.2 Exclusion Criteria
Yes/No (Response of "yes" = patient ineligible)

4.2.1 _____Contraindications for entry into an exercise training program including, but not limited to: unstable angina, uncontrolled hypertension (systolic > 200 mm Hg, diastolic > 100 mm Hg), orthostatic hypotension (> 20 mm Hg fall in systolic), moderate or serve aortic stenosis, uncontrolled arrhythmia, uncontrolled congestive heart failure, third degree heart block, pericarditis, myocarditis, pulmonary/systemic embolism within the past 6 months, thrombophlebitis, ST displacement > 3 mm at rest, history of cardiac arrest.

4.2.2 _____ Patient is morbidly obese (BMI > 40 kg/m^2) or anorexic (BMI < 17.5 kg/m^2).

4.2.3 _____ Abnormalities on screening physical exam judged by study physicians or supervising physical therapist to contraindicate participation in exercise program compliance.

4.2.4 _____ Alcohol or drug abuse as judged by study physicians.

4.2.5 _____ Significant mental or emotional problems that would interfere with study participation (assessed by NCCN Distress Thermometer).

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____ _____ _____

Investigator Signature **Date** **Time**

5 INTERVENTION

5.1 Control Group

Patients randomized to the Control Group (Group 2) will not experience any changes in the standard of care for lung cancer patients according to their cancer stage. Although patients are encouraged to increase walking both in the pre-surgery and post-surgery period, there is no formalized pre-surgery exercise program. Upon study completion (at the 6 month post-surgery follow-up visit), participants in the Control Group will be offered a PEP-intervention session with precision exercise counseling and receive a free activity tracker.

5.2 Intervention Group

The PEP intervention involves a combination of home-based exercise as well as in-patient exercise. The exercise modes will include basic transfer and calisthenics mobility, aerobic and resistance exercises and will be performed in various postures (supine, sitting, standing and walking) with variable challenges (level walking, bending, inclines, steps and squatting).

For patients randomized to the Intervention Group (Group 1), the PEP intervention will be personalized, implemented, and modified (based on the patients AM-PAC mobility stage) by a licensed physical therapist in face-to-face meetings (~30-40 minutes). An exercise education manual, specifically developed for this study, will be used by the physical therapist to educate the patients on all aspects of starting and maintaining the exercise intervention.

5.2.1 Inpatient Sessions

The post-surgery inpatient PEP intervention will be performed under the supervision of the physical therapist in accordance with the exercise education manual and the patient's AM-PAC mobility stage.

5.2.2 Home-Based Exercise

The outpatient exercises will be performed both pre- and post-surgery and will be done at home, the HCI Wellness Center, or a recreational center.

The study physical therapist will go over (verbally and in writing) the individual exercise modes and dosages to be performed at home. Although individually-prescribed, the exercise mode and dosage will be standardized with respect to the patient's AM-PAC mobility stage (as shown in Figure 2). For example, a patient in AM-PAC mobility stage 3 will progress from walking on level surfaces for 10 minutes per day at a "somewhat hard" perceived exertion with the ability to talk but not sing during walking. The rate of steps/minute will be ~100. Additionally, this patient will also perform squatting exercise at the same perceived exertion for short bouts that add up to 5 minutes per day. These aerobic and resistance exercises will be progressed to 20 minutes and 10 minutes per day respectively as they progress to AM-PAC mobility stage 4.

Patients will be given access to instruction sheets demonstrating exercise modes along with exercise tools (e.g., light weights and external resistance bands), tracking diary/calendar and activity tracker (see note below) for the home-based exercise program.

Telephone calls or TeleHealth interactions between the participant and the physical therapist will take place weekly to answer questions, optimize patient engagement, and adjust exercise prescriptions remotely as needed.

Ongoing monitoring of attitudes and barriers to exercise will occur and strategies for encouraging uptake of the exercise intervention will be individually tailored. U of Utah TeleHealth capabilities, including video chat, will be used to augment telephone communications.

Note: the activity tracker, a consumer wearable device (e.g., Fitbit Zip Wireless Activity Tracker), will be used as a pragmatic motivational and self-monitoring tool to improve participant exercise efficacy and home exercise program adherence.[86]

Stage (score) function	
1	(0-34) Limited in bed, basic, transfers.
2	(35-52) Limited mobility inside of a building, unable to do bending/ reaching activities.
3	(53-66) Little difficulty in moving inside a building but limited in going outdoors.
4	(67-84) Walks independently inside and outside, some difficulty in doing moderate or strenuous activities.
5	(85-100) Moves inside or outside independently and participants in strenuous sports.

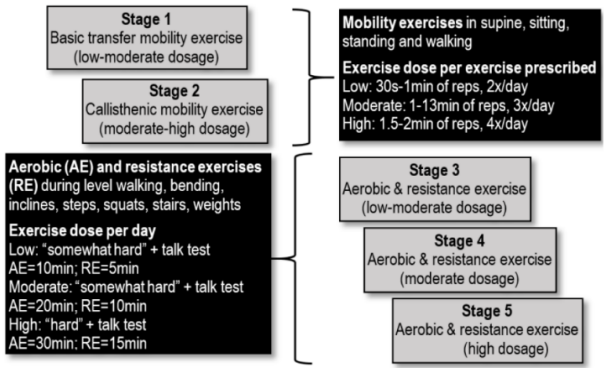


Figure 2: AM-PAC stages (according to Arbane) and corresponding exercise modes and dosages.

5.2.3 Interruption and Discontinuation

The PEP intervention is already personalized, implemented, and modified based on an individual's patient characteristics. However, if, at any time during the study a participant develops an illness that contraindicates exercise in the opinion of the enrolling physician (including but not limited to those described in exclusion criterion 4.2.1), the patient's primary care physician will be consulted regarding whether and when it would be safe to re-start the exercise program.

Should any participant develop any condition that would limit their ability to fully participate in the prescribed protocol, the participant would be temporarily, or if necessary permanently, withdrawn from the study.

6 SCHEDULE OF EVENTS

PROCEDURES	Pre-surgery visit 2-4 weeks pre-surgery	Before surgery	Pre-anesthesia visit	While inpatient 6 to 10 days	Discharge visit	During follow-up	Post-surgery outpatient visit 2 month post-surgery	Post-surgery outpatient visit 6 months post-surgery
Informed consent	X							
Body measurements[1]	X							
Baseline questionnaires[7]	X							
Eligibility review	X							
Randomization	X							
Follow-up questionnaires[7]					X		X[8]	X[8]
AM-PAC outpatient form	X				X		X	X
6MW test	X				X		X	X
Short Physical Performance Battery	X				X		X	X
Correlative blood collection			X				X	
Saliva sample								X
Respiratory function test	X[2]		(X)[2]		X		X	X
† PEP materials distribution[3]	X				X		(X[6])	(X[6])
† PEP intervention (with PT)	X						X	X
† PEP intervention (home based)		Daily				Daily between visits		
† PT assessment + activity review	X[4]			X[5]	X[6]		X[6]	X[6]
† PT phone call + activity review[7]		Weekly				Weekly[6]		

† **Only due for patients participating in the PEP intervention**

1. Body measurements will include height, weight, waist and hips measurements.

2. Respiratory function test is a standard of care procedure which can be completed at the pre-surgery visit OR the pre-anesthesia visit.
3. Materials include an exercise packet (with exercise tool), diary/calendar, and activity tracker at baseline and new tracking diary/calendars at the follow-up visits.
4. There will be no activity review at baseline (no activity started) and during the inpatient stay or at discharge (since the PEP intervention is on hold).
5. While inpatient the physical therapist will assess the patient (including AM-PAC scoring) as needed depending on the patient's condition.
6. Activity review + AM-PAC scoring *could* lead to an adjustment in exercise mode / dosage as well as the patient being given a new version of the tracking diary.
7. See details in Section 7.
8. Not yet included. Will be submitted as an amendment

7 QUESTIONNAIRES

Concept/ Instruments	# of Items	Baseline pre-surgery visit	Discharge
1. Exercise			
2. Behavioral Regulation in Exercise Questionnaire (BREQ-3)	24		24
3. Self-Efficacy (Sallis) James F. Sallis et al; The development of self-efficacy scales for healthrelated diet and exercise behaviors, *Health Education Research*, Volume 3, Issue 3, 1 September 1988, Pages 283–292	12		12
4. Social Support for Exercise (Sallis) Sallis JF et al. The development of scales to measure social support for diet and exercise behaviors. Prev Med. 1987;16(6):825-36. Epub 1987/11/01. PubMed PMID: 3432232.	13		13
5. Your health and well-being			
6. FACT-L	37	37	37
7. Pain scale (1-10)	2	2	2
8. FACIT-F, chronic illness fatigue scale	13	13	13
9. Your sleep habits			
10. PSQI (Pittsburgh sleep quality index)	10	10	10

11. Activities of daily life			
12. Activities of daily life – from WHI form 155; https://www.whi.org/researchers/studydoc/WHI%20Forms/F155%20v1.pdf (bottom, page 5)	7	7	
13. Your Personal Habits			
14. Weight change – from WHI form 34 https://www.whi.org/researchers/studydoc/WHI%20Forms/F034%20v2.pdf (Form F34, WHI, page 4)	2	2	
15. Physical activity/ exercise, asks about the usual physical activity and exercise – from WHI form 155 https://www.whi.org/researchers/studydoc/WHI%20Forms/F155%20v1.pdf (Form F155, WHI, page 4-5)	3	3	
16. Tobacco history – from David Wetter	11	11	
17. Your thoughts and feelings			
18. Modified Differential Emotion Scale (mDES), Emotion experience during the past 24 hours	20		20
19. WHI Emotions during past week – from WHI form 155 https://www.whi.org/researchers/studydoc/WHI%20Forms/F034%20v2.pdf (Form F155, WHI, page 14)	12	12	
20 Loneliness (Cacioppo) Hughes, M. E. et al. (2004). A short scale for measuring loneliness in large surveys: Results from two population-based studies. *Research on Aging*, *26*(6), 655-672. DOI: 10.1177/0164027504268574	3		3
21 Your background			
22 Birthday – ColoCare Questionnaire	1	1	
23 Sex – ColoCare Questionnaire	1	1	
24 Ethnicity – ColoCare Questionnaire	3	3	

25 Education – ColoCare Questionnaire	1	1	
26 Marital Status – ColoCare Questionnaire	1	1	
27 Income – ColoCare Questionnaire	2	2	
28 Weight – ColoCare Questionnaire	2	2	
29 Height – ColoCare Questionnaire	1	1	
30 Subjective Social Status Ladders – from David Wetter	2	2	
31 Your financial situation			
32 Financial Strain– COST Questionnaire	8	8	
33 Living condition (nursing home, relationship etc.)			
34 Living conditions – from WHI questionnaire form 155 https://www.whi.org/researchers/studydoc/WHI%20Forms/F155%20v1.pdf (Form 34, page 6)	3	2	
35 Others			
36 PROMIS Score (Dimensions)	CAT	Part of every clinical visit	

8 STUDY PROCEDURES

8.1 Pre-Surgery Clinic Visit

During their pre-surgery clinic visit (which typically takes place 2-4 weeks prior to surgery), all lung cancer patients who are surgical candidates (as determined by the surgeon) will be approached about the PEP study. Patients who are interested and potentially eligible will undergo the following procedures:

- Informed consent.
- Verification of the patient's eligibility for the study.
- Randomization.
- Baseline assessments by physical therapist including:
  - Body measurements (height, weight, waist and hips measurements).
  - Medical history, medication use.
  - AM-PAC mobility score (via the 18 questions AM-PAC outpatient form).
  - 6 Minute Walk Test (6MW) and Short Physical Performance Battery (SPPB).
- Respiratory function tests (spirometry: FEV1, PEF, VC, IRV, ERV).
- Baseline questionnaires (all patients – details in Section 7).

Patients randomized to the Intervention arm will also receive the following:

- Exercise packet (with exercise tool), instruction for access to supplementary instructional video, tracking diary/calendar, and activity tracker for the home-based pre-surgical exercise program.
- Individual instruction by physical therapist (verbal and written) about the individual exercise modes and dosages to be performed at home and first PEP intervention.

8.2 In the Weeks Leading to Surgery (Outpatient)

During the 2 to 4 weeks before the surgery, patients randomized to the Intervention arm will complete a daily PEP intervention as instructed by the physical therapist and record their activity on the tracking diary/calendar.

Weekly telephone calls or TeleHealth interactions (including video chat) between the patient and the physical therapist will take place to answer questions and optimize patient engagement. Ongoing monitoring of attitudes and barriers to exercise will occur and strategies for encouraging uptake of the exercise intervention will be individually tailored.

8.3 Pre-Anesthesia Visit

At the time of the pre-anesthesia visits the following procedures will be done for all patients:

- Respiratory function tests (spirometry: FEV1, PEF, VC, IRV, ERV) only if they were not performed at the pre-surgery visit.

- Correlative blood samples collection.

8.4 Inpatient Stay

The inpatient stay post-surgery is expected to last from 5 to 10 days and will include assessments by the physical therapist for all patients. The frequency of the assessments will follow standard of care guidelines and is dependent on the patient's condition.

8.5 Hospital Discharge Visit

The following procedures will be completed at the discharge visit:

- Assessment by physical therapist including:
  - AM-PAC mobility score (18 questions outpatient form).
  - Education on acute and sub-acute post-operative mobility limitations.
- 6 Minute Walk test (6MWT) and Short Physical Performance Battery (SPPB).
- Follow-up questionnaires (see section 6 for details).
- Distribution of tracking diary/calendar.

Patients randomized to the Intervention arm will also receive the following:

- Review of home exercises and, if needed, adjustments to the mode/dose of the exercise regimen (for patients randomized to the Intervention arm only).
- Patients randomized to the Intervention arm will also receive the following:

8.6 During the Follow-Up (Outpatient)

For patients randomized to the Intervention arm, weekly telephone calls or TeleHealth interactions between the participant and the physical therapist will continue as described in section 8.3.

8.7 Follow-Up Clinic Visits (2 and 6 Months Post-Surgery).

The following procedures will be completed at the follow-up visits scheduled 2 and 6 months after surgery:

- Assessment by physical therapist including AM-PAC mobility score (18 questions outpatient form).
- 6 Minute Walk test (6MW) and Short Physical Performance Battery (SPPB)
- Respiratory function tests (spirometry: FEV1, PEF, VC, IRV, ERV)
- Follow-up questionnaires
- Distribution of tracking diary/calendar
- Correlative blood samples collection (2 months follow-up only)
- Saliva samples (6 months follow-up only).

Patients randomized to the Intervention arm will also receive the following:

- Review of tracking diary/calendar
- If needed, adjustments to the mode/dose of the exercise regimen

9 CRITERIA FOR EVALUATION OF ENDPOINTS

9.1 Physical Function Performance

The primary endpoint associated with the evaluation of improvement in mobility performance is the result of the 6MW test (6MW distance). The distance patients can walk indoors on a 25 meters level smooth-surfaced track over the course of 6 minutes will be measured at baseline as well as at the time of discharge and at the 2 and 6 months follow-up. Median distances will be computed for each arm at the various time points and the expected post-surgery decline and recovery during follow-up will be compared between arms.

A secondary endpoint associated with the evaluation of improvement in physical performance is the result of the short physical performance battery test. The SPPB score (ranging from 1 to 12) will be obtained for each patient at the time points described above. Medians will be obtained and compared for each arm.

9.2 Patient Reported Outcomes

Questionnaires aimed at measuring disease specific symptoms, multidimensional fatigue, common mental health issues (i.e., depression, anxiety, and alcohol use), and hypothesized treatment mechanisms will be obtained on this study at baseline, at discharge, and at the 2 and 6 months follow-up. The effect of the PEP intervention on patient reported outcomes will be evaluated by comparison between each arm of the study.

9.3 Respiratory Function Status

The effect of the PEP intervention on respiratory functional status will be evaluated by comparison of the following parameters between each arm of the study: FEV1, PEF, VC, IRV, and ERV. These will be measured at baseline, discharge, and at the 2 and 6 months follow-up.

9.4 Exploratory Objectives

Data gathered from all patients who received the PEP intervention and pertaining to the quality of the intervention, participation in the intervention, and attitudes toward exercise (obtained via questionnaires) will be analyzed.

Additionally, the effects of the PEP intervention on the following will be evaluated by comparison between each arm of the study:

- Rate of complications (pulmonary and cardiac events, other complications requiring treatment [e.g., liver dysfunction, gastric ulcer, wound infection, colitis, depression], readmissions, and deaths within the first 30 days after discharge).
- Length of stay post-surgical intervention.

Finally, the effects of the PEP intervention on the following will be evaluated by comparison between each arm of the study:

- Total cost of care and utilization (obtained through the UUHS VDO, the Utah APCD, daily electronic diaries, and time-line follow-back)
- Levels of potential prognostic or mechanistic biomarkers such as inflammatory biomarkers, in serum, plasma, and buffy coat.

10 STATISTICAL CONSIDERATIONS

10.1 Randomization

Randomization will have a uniform 1:1 allocation ratio with block sizes of 8. The random allocation sequence will be stratified by pre-treatment AM-PAC stage only; based on primary data (as described in section 2.4), the AM-PAC stage is sufficient to assess physical function.

10.2 Outcomes, Power, and Sample Size Considerations

Objectives and endpoints are described in Section 1. Covariates used in sensitivity or mediation analysis of the objectives will be age, gender, baseline smoking status, primary or secondary lung cancer, neoadjuvant treatment, tumor stage, baseline level of outcome, pain, sleep.

Power calculations are based on the group effect in an analysis of covariance for the 6MW test at 8 weeks, with baseline 6MW test as covariate. The planned sample size (n = 200) allows for a 25% dropout rate (the main reasons for drop outs observed during the pilot study was found to be complications or poor health status preventing follow-up visits as well as distance to study site), leaving at least 150 subjects evaluable for the primary endpoint. The hypothesis is that the difference in the 6MW distance between the study arms (Intervention vs. Control) will be $\geq$ 39.95 m. This effect size stems from a meta-analysis where 4 weeks of post-surgery exercise training provided a 39.95 increase in the 6MW distance in NSCLC patients.[87] Consistent with Arbane,[11] SD = 100 m and correlation = 0.5 between repeated 6MW test measurements on the same subject are assumed. Power to detect the treatment effect was estimated by simulation (in R) of an analysis of covariance model with 6MW test at 2 months post-surgery as outcome, treatment group as primary predictor and pretreatment 6MW test as covariate. Pre and post 6MW test was assumed to be bivariate normally distributed.

10.3 Primary Endpoint Analysis

Analyses will include all patients that are evaluable for our primary endpoint (expected at least n=150). The primary outcome will be the group effect for an analysis of covariance model with 6MW test at 2 months post-surgery as outcome and pretreatment 6MW test as covariate, tested at the nominal two-sided 0.05 significance level. A sensitivity analysis will be performed with additional adjustment variables (listed as covariates in Section 10.1). Missing data will be handled using multivariate imputation by chained equations [88] as implemented in the R package "mice".

10.4 Other Endpoint Analyses

The approach to testing for group differences for each continuous outcome (e.g., quality of life and fatigue summary scales, pulmonary function, length of stay after surgical

resection, cost) will be to test for the group effect in an analysis of covariance model with adjustment for covariates listed in Section 10.1 as well as baseline values of the outcome variable when available.

The proportion of patients who continue to smoke post-surgery is expected to be too small to include as a reliable adjustment variable or outcome (~ 5%).[89] Former smokers will be tested at the 6 month clinic visit to assess smoking recidivism (saliva). A separate descriptive analysis will be performed in the subset of smokers.

An analogous approach will be used for endpoints coded as binary variables (complications, readmission) using logistic regression models instead of analysis of covariance models. If diagnostics plots show significant deviation from model assumptions, then a separate sensitivity analysis will be performed using appropriate robust regression methods such as those available in the "robustbase" package in R.

The study design provides 96% power to detect a 10 point increase in FACT-L in the Intervention Group compared to the Control Group, similar to the effect of aerobic training on FACT-L reported in Jones.[46]

For estimation of mediation, mixed effects regression analysis will be performed with random slope and intercept for each participant and unstructured covariance matrix. The direct and indirect effects of the intervention will be examined. Indirect effects analysis can provide important information about underlying mechanisms (e.g. treatments could achieve the same outcome via different mechanisms). Particular attention will be paid to the potential mediating/moderating effects of pain and self-efficacy. For indirect effects analyses, sensitivity analyses will be conducted to examine the robustness of effects under different assumptions regarding missing data. Gender-specific effects of the intervention will also be investigated.

11 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must not have any study procedures or begin protocol treatment prior to registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

Randomization to the Intervention or Control Arm will be done at the time of enrollment by the enrolling coordinator using OnCore (the Clinical Trials Office's electronic clinical research management system).

12 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) for this study are a set of electronic forms for each patient that provides a record of the data generated according to the protocol. CRFs should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. Data capture should be restricted to endpoints and relevant

patient information required for planned manuscripts. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

13 SPECIAL INSTRUCTIONS

13.1 Correlative Studies

13.1.1 Blood

Correlative blood samples will be taken at the pre-operative visit as well as at the 2 months post-surgery visit.

One 10mL red top tube and one 10mL EDTA tube will be collected at each visit. Serum, plasma and buffy coat will be stored for future analysis.

13.1.2 Saliva

Patients will be asked to collect a saliva sample at 6 months follow-up.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Informed Consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

14.2 Institutional Review

This study will be approved by the Institutional Review Board of University of Utah.

14.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled in Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the

issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

14.4 Adverse Events / Serious Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting the PEP regimen. Abnormal test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

For this low-risk study, information about a subset of adverse events of interest will be collected, recorded and followed as appropriate. This subset includes **all injuries, events, and conditions which could be related to the PEP intervention and require medical attention.**

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. Its severity grade based on CTCAE v.4 (grade 1-5).
2. Its relationship to the PEP intervention (definite, probable, possible, unlikely, not related).
3. Its duration (start and end dates or if continuing at final exam).
4. Action taken (no action taken; PEP intervention adjusted, temporarily interrupted, permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization).
5. Whether it constitutes an SAE.

All adverse events will be treated appropriately. Such treatment may include changes in the intervention (as described in Figure 2). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the PEP regimen, the interventions required to treat it, and the outcome.

14.5 SAE Reporting Requirements

SAEs must be reported to the DSMC as well as the IRB and the FDA (when applicable) according to the requirements described below:

The Investigator (or a properly delegated study team member) must complete a MedWatch 3500A form and submit it to the Research Compliance Office (compliance@hci.utah.edu) as soon as possible, but no later than 10 business days of first knowledge or notification of the event (5 business days for fatal or life threatening event).

14.5.1 DSMC Notifications

Upon receipt of the MedWatch 3500A, an HCI Ressearch Compliance Officer will process and submit the form to the proper DSMC member as necessary for this study.

The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

14.5.2 IRB Notifications

Events meeting the University of Utah IRB reporting requirements (described at (https://irb.utah.edu) will be submitted by the Investigator (or a properly delegated study team member) through the IRB's electronic reporting system (ERICA) within 10 working days.

14.5.3 FDA Notifications

Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:

- Serious
- Unexpected
- Definitely, probably, or possibly related to the intervention

Fatal or life-threatening events which meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.

All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.

Prior to submission to the FDA, the RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements. The MedWatch report will then be submitted to the FDA through the voluntary reporting method by the Regulatory Coordinator.

14.6 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

14.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant, or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

14.8 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

14.9 Clinical Trials Data Bank

The study will be registered on http://clinicaltrials.gov and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

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APPENDIX 1 - AM-PAC Basic Mobility Outpatient Form and Conversion Table

Precision Exercise Prescription

Precision Exercise Prescription

PEP-Study

Boston University AM-PAC™

Generic Basic Mobility Outpatient Short Form

Please check the box that reflects your best answer to each question.

How much difficulty do you currently have ...	Unable	A Lot	A Little	None
1. Bending over from a standing position to pick up a piece of clothing from the floor without holding onto anything?	1	2	3	4
2. Standing up from a low, soft couch?	1	2	3	4
3. Taking a 1-mile brisk walk, without stopping to rest?	1	2	3	4
4. Running for 5 minutes on even surfaces?	1	2	3	4
5. Walking several blocks?	1	2	3	4
6. Walking up and down steep unpaved inclines (e.g., steep gravel driveway)?	1	2	3	4
7. Running a short distance, such as to catch a bus?	1	2	3	4
8. Carrying something in both arms while climbing a flight of stairs (e.g., laundry)?	1	2	3	4
9. Going up and down a flight of stairs outside, without using a handrail	1	2	3	4
10. Making sharp turns when running fast?	1	2	3	4
11. Taking part in strenuous activities (e.g., running 3 miles, swimming half mile, etc.)	1	2	3	4
12. Standing up from an armless straight chair (e.g., dining room chair)?	1	2	3	4
13. Walking on an uneven surface (e.g., grass, dirt road or sidewalk, brick walkways, sidewalks with curb and driveways cuts)?	1	2	3	4
14. Walking around one floor of their home, taking into consideration thresholds, doors, furniture, and a variety of floor coverings?	1	2	3	4
15. Doing light housework (e.g., dusting, minor sweeping)?	1	2	3	4
16. Moving up in bed (e.g., reposition self)?	1	2	3	4
17. Getting into and out of a car/taxi (sedan)?	1	2	3	4
18. Cleaning up spills on the floor with a mop?	1	2	3	4

Raw Score: _____ CMS 0-100% Score: _____

Standardized Score: _____ CMS Modifier: _____

AM-PAC Short Form Manual (v. 4)

Precision Exercise Prescription

PEP-Study

Boston University AM-PAC™

Generic Basic Mobility Outpatient Short Form Score Conversion Table*

AM-PAC Raw Score	AM-PAC t-scale Score	Scale Score Standard Error	CMS 0-100% Score	CMS 'G Code' Modifier
18	29.41	5.21	100%	CN
19	32.18	4.57	94.56%	CM
20	34.18	4.11	90.63%	CM
21	36.16	3.62	86.74%	CM
22	37.89	3.24	83.34%	CM
23	39.36	2.97	80.45%	CM
24	40.66	2.79	77.89%	CL
25	41.85	2.68	75.56%	CL
26	42.95	2.60	73.39%	CL
27	44.00	2.54	71.33%	CL
28	44.99	2.49	69.38%	CL
29	45.94	2.44	67.52%	CL
30	46.85	2.38	65.73%	CL
31	47.72	2.32	64.02%	CL
32	48.57	2.25	62.35%	CL
33	49.39	2.17	60.74%	CL
34	50.18	2.10	59.19%	CK
35	50.95	2.03	57.67%	CK
36	51.68	1.96	56.24%	CK
37	52.38	1.91	54.86%	CK
38	53.05	1.86	53.55%	CK
39	53.70	1.82	52.27%	CK
40	54.33	1.79	51.03%	CK
41	54.95	1.76	49.81%	CK
42	55.57	1.74	48.60%	CK
43	56.17	1.73	47.42%	CK
44	56.78	1.72	46.22%	CK
45	57.38	1.71	45.04%	CK
46	57.98	1.70	43.86%	CK
47	58.57	1.69	42.70%	CK
48	59.16	1.69	41.54%	CK
49	59.76	1.68	40.36%	CK
50	60.35	1.68	39.20%	CJ
51	60.94	1.68	38.04%	CJ
52	61.53	1.69	36.88%	CJ
53	62.12	1.69	35.72%	CJ

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Precision Exercise Prescription

Precision Exercise Prescription

PEP-Study

AM-PAC Raw Score	AM-PAC t-scale Score	Scale Score Standard Error	CMS 0-100% score	CMS 'G Code' Modifier
54	62.72	1.71	34.55%	CJ
55	63.31	1.72	33.39%	CJ
56	63.92	1.74	32.19%	CJ
57	64.53	1.77	30.99%	CJ
58	65.15	1.80	29.77%	CJ
59	65.78	1.84	28.53%	CJ
60	66.43	1.88	27.25%	CJ
61	67.09	1.93	25.96%	CJ
62	67.78	1.99	24.60%	CJ
63	68.51	2.06	23.17%	CJ
64	69.29	2.15	21.63%	CJ
65	70.14	2.27	19.96%	CI
66	71.07	2.42	18.14%	CI
67	72.13	2.61	16.05%	CI
68	73.36	2.87	13.64%	CI
69	74.72	3.17	10.96%	CI
70	76.19	3.49	8.08%	CI
71	78.20	3.86	4.13%	CI
72	80.30	4.09	0.00%	CH

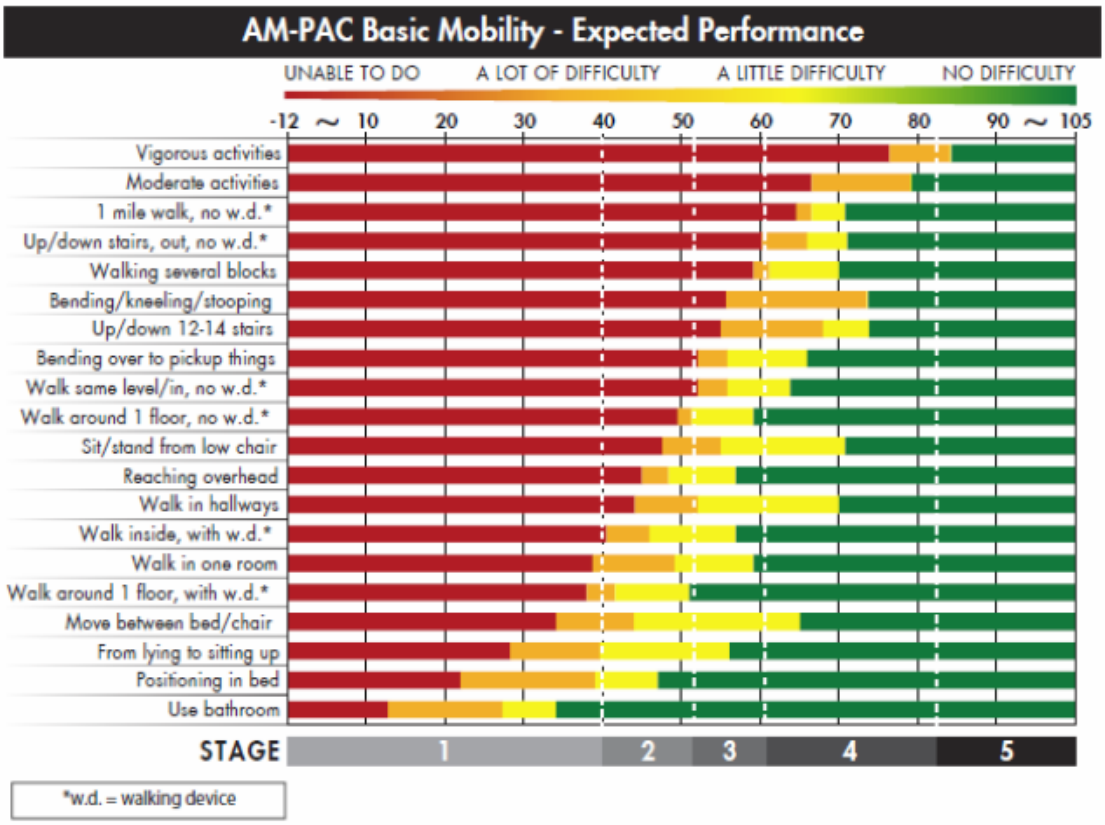
*Use this form to convert AM-PAC Generic Basic Mobility Outpatient RawScores.

AM-PAC Generic Outpatient Basic Mobility Short Form Scoring Example

1. Add the number values associated with the response to each item. For example, items totals yield a Raw Score of 55.
2. Match the raw score to the t-Scale scores (t-Scale score = 63.31, SE =1.72).
3. Find the associated CMS % (CMS % = 33.39%).
4. Locate the correct CMS Functional Modifier Code, or 'G Code' (G code = CJ)

NOTE: Each AM-PAC Short Form has a separate conversion table. Make sure that you use the correct conversion table.

APPENDIX 2 - AM-PAC Basic Mobility Staging and Expected Performance



Stage 5: 84 – 104.9 Strenuous Recreation/Sports

Your score suggests a high level of independence in moving about both at home and in the community. You may be able to participate in most physical activities without much difficulty.

Stage 4: 66 – 83 Moving Around Outdoors

Your score suggests that you are able to walk inside your home and other buildings without any difficulty. You may be able to move about outdoors without any limitations. You should be able to bend over and pick up things without much difficulty. Activities that might be difficult to manage without assistance include climbing a full flight of stairs, bending, kneeling or stooping. Vigorous activities such as playing sports or walking several miles may be very difficult to complete.

Stage 3: 52 – 65 Moving Around Indoors

Your score suggests that you may be able to move about on the ground floor of your home where you are familiar with the environment. Activities that might be difficult to manage without assistance include sitting and standing from a low chair, climbing stairs, bending, kneeling or stooping. You may have some difficulty moving about outdoors and in the community.

Stage 2: 34 – 51 Limited Mobility Indoors

Your score suggests significant difficulty in moving about independently and the need for assistance. You may be able to move about in a small area of your home that has been adapted to eliminate safety hazards. You may have difficulty moving from a sitting to standing position, climbing stairs and you may have a great deal of difficulty moving about outdoors and in the community.

Stage 1: -11.95 – 33 Limited Movement

Your score suggests you may have a lot of difficulty or are unable to get out of your bed, to stand for several minutes and/or to walk short distances. You might have some difficulty completing the most basic mobility tasks including repositioning yourself in bed.