BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024672
Article Type:	Protocol
Date Submitted by the Author:	13-Jun-2018
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Keywords:	Non-small lung cancer, exercise, clinical trial, Thoracic surgery < SURGERY, physical activity

Precision-Exercise-Prescription in Lung Cancer Patients Undergoing Surgery: Rationale and Design of the PEP Study Trial

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Running title: The PEP study

Word count: 2649
Tables: 3
Figures: 2

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ABSTRACT

INTRODUCTION: Lung cancer is a significant burden on societies worldwide, and the most common cause of death in cancer patients overall. Exercise intervention studies in lung cancer patients have consistently shown benefits with respect to physical and emotional functioning. However, to date, exercise training has not been consistently implemented into clinical practice given that interventions have been costly and not aligned with clinical care.

METHODS/DESIGN: The Precision-Exercise-Prescription (PEP) study is a prospective randomized-controlled trial comparing the effectiveness and feasibility of a personalized intervention exercise program among lung cancer patients undergoing surgery. Two-hundred patients who are diagnosed with stage primary or secondary lung cancer, and are eligible to undergo surgical treatment at HCI, comprise the target population. Patients are randomized to either (1) outpatient precision-exercise intervention group, or (2) delayed intervention group. The intervention approach utilizes Motivation And Problem-Solving (MAPS), a hybrid behavioral treatment based on motivational interviewing and practical problem-solving. The dosage of the exercise intervention is personalized based on the individual's Activity Measure for Post-Acute-Care™ outpatient basic mobility (AM-PAC) score, and incorporates four exercise modes: mobility, calisthenics, aerobic, and resistance. Exercise is implemented by physical therapists at study visits from pre-surgery until 6 months post-surgery. The primary endpoint is the level of physical function assessed by 6-minute walk distance at 2 months post-surgery. Secondary outcomes include patient-reported outcomes (e.g., QoL, fatigue, and self-efficacy); and other clinical outcomes, including length of stay, complications, readmission, pulmonary function, and treatment-related costs up to 6 months post-surgery.

ETHICS/DISSEMINATION: The PEP study will test the clinical effectiveness and feasibility of a personalized exercise intervention in lung cancer patients undergoing surgery. Outcomes of this clinical trial will be presented at national and international conferences and symposia and will be published in international, peer-reviewed journals. Ethics approval was obtained at the University of Utah (IRB 00104671).

TRIAL REGISTRATION: ClinicalTrials.gov, ID: NCT03306992

KEY WORDS: Non-small lung cancer, exercise, clinical trial, thoracic surgery, physical activity

BOX 1. Strenghts and Limitations

- This is the first RCT to examine a personalized exercise program for both, primary and secondary lung cancer patients
- This is an innovative approach designed be aligned and easily translatable into the clinical workflow.
- The intervention spans the entire continuum of care from the pre-surgery to post-surgery period including impacting lung cancer survivorship
- The intervention is designed so that it can successfully be translated into different populations, including rural and fontier populatios that are encounter challenges due to the distance to health care providers.
- The results will yield important health care cost information using the Value-Driven-Outcomes tool.
- The cost of the behavioral intervention delivered by a physical therapist for weekly phone calls during the outpatients period, may still be too high for future implementation in health care settings.

INTRODUCTION

Lung cancer—both primary and secondary—is a significant source of morbidity and mortality worldwide.[1 2] Primary lung cancer is the leading cause of cancer death in both men and women, causing more deaths than the next three cancers (breast, prostate, colon) combined.[2] Lung metastases (secondary lung cancer) are identified in 30 to 50% of all cancer patients.[1] The cost of cancer care for lung cancer patients is significant and expected to exceed $14.7 billion by 2020 (out of a total expense of cancer care of $157.7 billion).[3]

Surgical intervention in localized primary non-small cell lung cancer (NSCLC) improves survival outcomes.[4] Additionally, resection of isolated secondary lung cancer has led to increased progression free and overall survival in patients with certain cancers such as sarcoma and colon cancer.[5-10] Although surgery can improve outcomes in patients with early and, at times, later stage malignancies, surgical procedures a lead to significant morbidity in cancer patients. Surgical patients suffer decreased pulmonary and physical function, reduced quality of life, chronic pain and reduced activity levels following surgery.[11 12] These effects can be ameliorated by exercise. Studies have shown that exercise training positively affects QoL, physical capacity and fatigue in cancer patients, irrespective of the tumor type.[13-15] Initial exercise studies among lung cancer patients during the pre-and post-operative settings demonstrate improvement in physical performance, cardiorespiratory fitness, and hospital length-of stay.[16-21] The consistency of these findings is compelling.[16-41]

Despite promising findings for exercise, translation to the clinic has not been achieved in large part because the interventions tested to date are cumbersome, expensive, and not easy to implement in a busy clinical practice. For translation to succeed, an exercise regimen needs to be identified that can be easily integrated into the clinical workflow, and achieved with a limited,

yet effective, scope of financial resources and personnel. Such a regimen would be most effective if it used clinic contact points both prior to surgery and post-surgery. The Precision Exercise Prescription (PEP) Study (National Cancer Institute [NCI] R01 CA211705) is a randomized phase III clinical trial (n=200 patients) that will investigate the effect of a personalized exercise program on physical function, as measured by the 6-Minute Walk Test, in NSCLC patients (stage I, II, IIIa) and secondary lung cancer patients who are undergoing surgical treatment at the Huntsman Cancer Institute (HCI). Secondary aims including evaluating the impact of the intervention on other measures of physical function (short physical performance battery (SPPB)), patient-reported outcomes (PROs) (QoL, fatigue, pain, sleep, and self-efficacy), clinical outcomes (length of stay, complications, readmission, and pulmonary function), and treatment-related cost.

We hypothesize that lung cancer patients undergoing surgical resection will benefit from a precision exercise prescription that is tailored to their mobility level, motivation, and other behavioral and environment factors as they progress (or regress) through the multiple phases of the pre- and post-surgery periods. The PEP Study will test an intervention that we expect will help lung cancer patients undergoing surgery to maintain, regain, and improve their physical function during the continuum from surgery to lung cancer survivorship.

METHODS

1. Study Design

1.1. Screening Eligibility and Baseline Data Collection

We will conduct a single-center, prospective, two-armed, phase III randomized controlled trial at HCI in Salt Lake City, Utah. The PEP study has been approved by the Institutional Review Board of the University of Utah (IRB 00104671) and all participants are required to provide written informed consent. NSCLC patients stage I, II, or IIIa, or secondary lung cancer patients over 18 years old, who undergo surgical lung resection at HCI are recruited. Detailed eligibility criteria are listed in **Table 1**. Eligibility criteria for this study primarily focus on whether a patient is eligible for surgery or not.

{Insert Table 1}

The primary outcome measure of physical function, the 6MW test, is obtained by the licensed study physical therapist, or trained study staff. Additional measurements are also obtained, including height, weight, waist and hip circumferences, systolic and diastolic blood pressure, resting one-minute pulse, and patient-reported mobility status (Activity Measure-Post Acute Care™ outpatient basic mobility (AM-PAC) score). Patients receive a baseline questionnaire to either (1) complete in clinic or (2) take home to complete and return either by mail or at their pre-surgery appointment two weeks later. After randomization (**Section1.3**) and completion of all baseline testing, patients start their intervention or control activities.

1.2.Study Participant Schedule

Figure 1 shows the proposed participant flow through the trial. Potential participants are approached during their first clinical visit prior to surgery (about 2-4 weeks pre-surgery).

Consenting participants undergo required baseline assessments, which are presented for each study time point in **Table 2**. Both groups are seen at the following study time points: pre-surgery (1 day before surgery), discharge (first visit after discharge from the hospital, ~ 1 week post-discharge), 2 and 6 months post-surgery.

{Insert Figure 1}

{Insert Table 2}

1.3. AM-PAC score for exercise tailoring

The AM-PAC basic mobility assessment **(Table 3)** is completed on each day that the study participant is seen by a physical therapist. The AM-PAC Outpatient Basic Mobility Short Form (18 questions) takes about 2 minutes to complete and is used to precisely guide the exercise prescription for each patient in a personalized manner.. The AM-PAC has high test-retest and subject-proxy reliability in outpatient settings (0.97 and 0.86, respectively), and with inpatients the AM-PAC has a high intraclass correlation coefficient (0.85) when administered by clinicians.[42-45] Scores on the AM-PAC correlate with well-established physical function subscales, e.g. Functional Independence Measure (r=0.65). A standardized response mean of 1.06 and a minimal detectable change with 90% confidence of 4.72 has been delineated with AM-PAC.[44]

{Insert Table 3}

1.4 Randomization

Consenting participants are stratified by their AM-PAC mobility stage (low mobility: stages 1, 2, and 3 vs. high mobility: stages 4 and 5), and cancer type (primary vs. secondary). Participants are randomized using a uniform 1:1 allocation ratio with block sizes of 8 individuals to either (1) Intervention Group: PEP intervention, or (2) Delayed Intervention Group: standard

of care for six months with PEP intervention session after study completion. The allocation sequence is produced via computer-generated random numbers and concealed from clinical trials office staff.

2. Study Arms

2.1. Intervention Group

The PEP intervention is 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) at: the pre-surgery visit with the surgeon; the discharge visit (about 1 week post-discharge from the hospital); and the 2 month post-surgery follow-up appointment with the surgeon. The intervention uses existing resources in the clinical setting and as such, is pragmatic and more generalizable than other exercise programs. An exercise education manual is used by the physical therapist to educate the patients on all aspects of starting and maintaining the exercise intervention. The Intervention Group is given access to exercise tools (e.g., light weights and external resistance bands) as needed, tracking diary/calendar, and activity tracker for the home-based exercise program (see below). The study physical therapist goes over (verbally and in writing) the individual exercise modes and dosages to be performed at home. Although individually-prescribed, the exercise mode and dosage is standardized with respect to the patient's AM-PAC mobility stage (**Figure 2)**. For example, a patient in AM-PAC mobility stage 3 will perform aerobic exercise similar in intensity to 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. Additionally, this patient will also perform a resistance exercise, such as standing squats, at the same perceived exertion for short bouts that add up to 5 minutes per day. These

aerobic and resistance exercises will increase to 20 minutes and 10 minutes per day respectively as the participant progresses to AM-PAC mobility stage 4.

The outpatient exercises are performed at home, the HCI Wellness Center, or a recreational center. The exercise modes include basic mobility exercises, calisthenics, aerobic, and resistance exercises, and are performed in various postures (supine, sitting, standing and walking) with variable challenges (e.g., level walking, bending, incline walking, stair walking, and squatting). Instructional exercise sheets demonstrating exercise modes and doses are handed out after each exercise intervention adjustment.

Telephone calls between the participant and the study staff (including the physical therapists and clinical research coordinator,) take place weekly to answer questions and optimize patient engagement. Ongoing monitoring of attitudes and barriers to exercise occurs, and strategies for encouraging uptake of the exercise intervention are individually tailored. A consumer wearable device (e.g., Fitbit Flex II Wireless Activity Tracker) is used as a pragmatic motivational and self-monitoring tool to improve participant exercise efficacy and home exercise program adherence.[62]

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)[46] 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 (**Figure 2**).

{Insert Figure 2}

Motivation And Problem-Solving (MAPS) is the hallmark behavioral intervention utilized in parallel with the exercise intervention. MAPS is a holistic, dynamic approach to facilitating behavior change that utilizes a combined motivational enhancement and problem-solving approach based on motivational interviewing (MI) and social cognitive theory.[47] The behavioral intervention utilizes an overarching conceptual basis of the intervention is the social cognitive model [48-50] which posits that high levels of both motivation and self-efficacy are necessary for behavior change.[68] Thus, 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.[46 48 51] 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. MAPS or its precursors have been demonstrated to be effective in four randomized controlled trials with respect to: 1) increasing treatment utilization,[52] 2) enhancing behavior change success rates,[53] 3) reducing relapse,[54] and 4) addressing multiple risk behavior change.[55]

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/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.[56-60] As such, we believe the PEP intervention is an innovative combination of motivational enhancement and social cognitive intervention techniques.

2.1. Delayed Intervention Group (Control Group)

The Delayed Intervention Group will receive standard therapy for their lung cancer. Although all patients, independent of group assignment are encouraged by clinical staff to increase walking both in the pre-surgery and post-surgery period, there is no formalized pre- or post-surgery exercise program. Patients will undergo assessments timed to coincide with regularly scheduled cancer care: the first post-discharge clinic visit is scheduled at 1 week after discharge from the hospital, with the second clinic visit at 2 months. Upon study completion (at the 6 month post-surgery follow-up visit) the Delayed Intervention Group is offered a PEP-Intervention session with precision exercise counseling, and receives a free activity tracker.

3. Primary and Secondary Endpoints

Endpoint assessments are presented in **Table 3**. The primary endpoint is a physical function mobility performance assessment of the distance walked in 6 minutes (6MW test) that will be assessed at the pre-operative baseline and the three post-surgery time points. The 6MW test is the most pragmatic, non-laboratory test to measure mobility physical functioning in individuals with chronic lung disease (including lung cancer).[61] In accordance with the American Thoracic Society recommendations,[62] the 6MW test is a self-paced walking test with standardized instructions and encouragement that measures the distance (m) the patient can walk indoors on a 25m level, smooth-surfaced track over six minutes. A number of studies have demonstrated the criterion predictive validity of the 6MW test in lung cancer with some demonstrating positive relationships between 6MW distance and post-surgery outcomes including QoL, survival, function and physical activity levels.[63-66] The minimally clinically important difference of the 6MW distance in patients with lung cancer is 22-42m.[66]

Secondary endpoints include: the short physical performance battery (SPPB), which captures domains of strength, endurance, and balance and is highly predictive of disability;[67] patient-reported outcomes (PROs) measured by using generic-, as well as disease-specific instruments, such as data from the NIH Patient Reported Outcomes Measurement Information System (PROMIS),[68] the Functional Assessment of Cancer Therapy-Lung (FACT-L),[69] Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue), the Pittsburgh Sleep Quality Index (PSQI), Behavioral Regulation in Exercise Questionnaire 3 (BREQ-3),[70 71] 7-day physical activity recall phone interview,[72] Diet History Questionnaire II (DHQII),[73] self-efficacy by Sallis JF,[74] Modified Differential Emotion Scale (mDES),[75] Social support for exercise by Sallis JF,[76] Subjective Social Status Ladders,[77] financial strain,[78] loneliness by Cacioppo,[79] pain (1-10 scale), shortness of breath (1-10 scale), living condition, clinical endpoints, such as length of stay post-surgical resection, complications; and health care costs, including inpatient hospitalization and outpatient follow-up, using the University of Utah Value Driven Outcomes (VDO) cost database[80] at 2 to 6 month follow-up.

4. Statistical Considerations and Primary Endpoint Analysis

The trial analysis will follow the intention-to-treat principle, which implies all participants who will be randomized (n=200) will be included in the analysis regardless of their adherence to the study. We hypothesize that the difference in the 6MW distance between the study arms (Intervention/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 m increase in the 6MW distance in NSCLC patients.[74] Consistent with Arbane,[21] we assume SD=100 m and correlation=0.5 between repeated 6MW test measurements on the same subject. Power to detect the treatment

effect was estimated by simulation 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. For our primary endpoint, with at least 150 evaluable subjects (accounting for a 25% dropout rate) the estimated power is greater than or equal to 80% at two sided type I error equal 0.05.

A sensitivity analysis will be performed with additional adjustment variables (gender, age, baseline smoking status, primary or secondary lung cancer, neoadjuvant treatment, tumor stage, baseline level of outcome, pain, and sleep). Missing data will be handled using multiple imputation.[75]

As of April 30, 2018 n=24 patients have been recruited into the PEP study, with recruitment anticipated to continue through July 2020. To date, only one patient has withdrawn.

5. Patient and Public Involvement

A pilot study of 40 lung cancer patients had been performed in the development of this trial. As part of the pilot study we performed formal quality control interviews with patients to inform and refine the trial interventions and processes. The data from the pilot trial as well as the close work with the Clinical Trials Office (CTO) at Huntsman Cancer Institute (HCI) have been used to ensure that the study protocol engages participants in a respectful, ethical and impactful way, while performing the PEP Study intervention. The CTO and other HCI resources further provides assistance with the ethical standards of the trial, as well as the translation and disseminations of the research findings to community members, patients, and cancer support groups. In addition, the study is conducted by an interdisciplinary team with long-standing expertise in exercise, behavioral interventions, and surgery. Involved clinicians and researchers

work with the target population on a daily bases and used these experiences to help inform the development of the research question, outcome measures, and performance of the intervention.

DISCUSSION

The primary results from the PEP study will test the clinical effectiveness and feasibility of a personalized exercise intervention in lung cancer patients undergoing surgery. This trial fills the gap in knowledge precisely, by testing an exercise intervention that can be readily integrated into the clinic and by obtaining data on functional efficacy and patient-reported-outcomes.

The feasibility of the PEP study was tested in a successful pilot study and builds on studies that have been previously performed by the interdisciplinary investigator team.[81-98] The behavioral intervention approach builds on prior work using MAPS,[90] a holistic and dynamic approach to assisting individuals to make positive behavioral changes.

In a recent opinion piece, Alfano et al. argued that *"it is time to revitalize the link between cancer survivorship and rehabilitation and investigate a new model of comprehensive cancer rehabilitation involving a multidisciplinary team of providers."*[99] PEP will be responsive to this call for action- it will integrate a team of surgeons and physical therapists. The study will being at the initial pre-surgery clinic visit and continue during the inpatient and outpatient post-surgery periods, thus helping lung cancer patients undergoing surgery to maintain, regain, and improve their physical function during the continuum from surgery to lung cancer survivorship.

ACKOWLEDGEMENTS

We thank our collaborators involved in the PEP study patient recruitment, data entry, and regulatory organization, specifically the clinical staff of the cardiothoracic surgery clinic 1A, the Clinical Trials Office (CTO), Biorepository and Molecular Pathology Bank (BMP), Research informatics, and the data management team at HCI.

FUNDING

The PEP study is funded by the National Institutes of Health (NIH)/National Cancer Institute (NCI) R01 CA211705 and Huntsman Cancer Foundation. Some authors were supported by grants from the NIH/NCI (R01 CA189184, R01 CA207371, U01 CA206110), and P30CA042014.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

CONTROBUTORSHIP STATEMENT

All authors contributed to the design and development of the PEP Study protocol. Specifically, CMU, PL, and TKV are the Principal Investigators of the trial. CH assisted with the design, implementation of a pilot study and implementation of the PEP Study. CH drafted the manuscript and the study protocol. KB provided statistical input, guidance, and all calculations used in the design of the clinical trial. RH oversees the assessments of patient-reported outcomes as part of the PROMIS score. DWW and KL designed and conduct the behavioral support elements of the study intervention. JK is responsible for cost effectiveness analyses and respective protocols. JAL, RM, and SRGM provided significant input with respect to the design

and performance of the trial. CAB is the study physical therapist and assisted in the design of the personalized exercise intervention. BR assisted with the optimization and implementation of the study protocol. CMU, CH, KB, DWW, RH, JK, KL, JAL, CAB, BR, RM, SRGF, PL, and TKV contributed to writing, editing, review, and approval of the study protocol, meeting the International Committee of Medical Journal Editors (ICMJE) recommendations for authorship. All authors reviewed and agreed the final manuscript.

REFERENCES

1. Schwartz D. Secondary Lung Tumors. 2014 December 08. http://emedicine.medscape.com/article/426820-overview (accessed 10.28.2016).
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;**66**(1):7-30.
3. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. Journal of the National Cancer Institute 2011;**103**(2):117-28.
4. Network NCC. NCCN guidelines--non-small cell lung cancer. Secondary NCCN guidelines--non-small cell lung cancer 2016. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
5. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;**113**(1):37-49.
6. Hornbech K, Ravn J, Steinbruchel DA. Outcome after pulmonary metastasectomy: analysis of 5 years consecutive surgical resections 2002-2006. J Thorac Oncol 2011;**6**(10):1733-40.
7. Younes RN, Fares AL, Gross JL. Pulmonary metastasectomy: a multivariate analysis of 440 patients undergoing complete resection. Interact Cardiovasc Thorac Surg 2012;**14**(2):156-61.
8. Larsen KR, Svendsen UG, Milman N, et al. Cardiopulmonary function at rest and during exercise after resection for bronchial carcinoma. Ann Thorac Surg 1997;**64**(4):960-4.
9. Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". J Thorac Oncol 2011;**6**(8):1373-8.
10. Baser S, Shannon VR, Eapen GA, et al. Pulmonary dysfunction as a major cause of inoperability among patients with non-small-cell lung cancer. Clin Lung Cancer 2006;**7**(5):344-9.
11. Pompili C, Brunelli A, Xiume F, et al. Predictors of postoperative decline in quality of life after major lung resections. Eur J Cardiothorac Surg 2011;**39**(5):732-7.
12. Wildgaard K, Ravn J, Nikolajsen L, et al. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011;**55**(1):60-8.
13. Kuehr L, Wiskemann J, Abel U, et al. Exercise in patients with non-small cell lung cancer. Med Sci Sports Exerc 2014;**46**(4):656-63.

14. Lakoski SG, Eves ND, Douglas PS, et al. Exercise rehabilitation in patients with cancer. Nat Rev Clin Oncol 2012;**9**(5):288-96.
15. Mock V, Pickett M, Ropka ME, et al. Fatigue and quality of life outcomes of exercise during cancer treatment. Cancer Pract 2001;**9**(3):119-27.
16. Hoffman AJ, Brintnall RA, Brown JK, et al. Too sick not to exercise: using a 6-week, home-based exercise intervention for cancer-related fatigue self-management for postsurgical non-small cell lung cancer patients. Cancer Nurs 2013;**36**(3):175-88.
17. Jones LW, Eves ND, Peterson BL, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer 2008;**113**(12):3430-9.
18. Jones LW, Eves ND, Peddle CJ, et al. Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. Appl Physiol Nutr Metab 2009;**34**(2):197-202.
19. Peddle CJ, Jones LW, Eves ND, et al. Effects of presurgical exercise training on quality of life in patients undergoing lung resection for suspected malignancy: a pilot study. Cancer Nurs 2009;**32**(2):158-65.
20. Arbane G, Tropman D, Jackson D, et al. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 2011;**71**(2):229-34.
21. Sebio Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, et al. 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):486-97.
22. Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. Lung Cancer 2011;**74**(3):441-5.
23. Bobbio A, Chetta A, Ampollini L, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg 2008;**33**(1):95-8.
24. Cesario A, Ferri L, Galetta D, et al. Pre-operative pulmonary rehabilitation and surgery for lung cancer. Lung Cancer 2007;**57**(1):118-9.
25. Cesario A, Ferri L, Galetta D, et al. Post-operative respiratory rehabilitation after lung resection for non-small cell lung cancer. Lung Cancer 2007;**57**(2):175-80.

26. Coats V, Maltais F, Simard S, et al. Feasibility and effectiveness of a home-based exercise training program before lung resection surgery. Can Respir J 2013;**20**(2):e10-6.
27. Divisi D, Di Francesco C, Di Leonardo G, et al. Preoperative pulmonary rehabilitation in patients with lung cancer and chronic obstructive pulmonary disease. Eur J Cardiothorac Surg 2013;**43**(2):293-6.
28. Granger CL, Chao C, McDonald CF, et al. Safety and feasibility of an exercise intervention for patients following lung resection: a pilot randomized controlled trial. Integr Cancer Ther 2013;**12**(3):213-24.
29. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 2007;**110**(3):590-8.
30. Peddle-McIntyre CJ, Bell G, Fenton D, et al. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. Lung Cancer 2012;**75**(1):126-32.
31. Pehlivan E, Turna A, Gurses A, et al. The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. Ann Thorac Cardiovasc Surg 2011;**17**(5):461-8.
32. Riesenberg H, Lubbe AS. In-patient rehabilitation of lung cancer patients--a prospective study. Support Care Cancer 2010;**18**(7):877-82.
33. Sekine Y, Chiyo M, Iwata T, et al. Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg 2005;**53**(5):237-43.
34. Spruit MA, Janssen PP, Willemsen SC, et al. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. Lung Cancer 2006;**52**(2):257-60.
35. Stigt JA, Uil SM, van Riesen SJ, et al. A randomized controlled trial of postthoracotomy pulmonary rehabilitation in patients with resectable lung cancer. J Thorac Oncol 2013;**8**(2):214-21.
36. Wall LM. Changes in hope and power in lung cancer patients who exercise. Nurs Sci Q 2000;**13**(3):234-42.

37. Gao K, Yu PM, Su JH, et al. Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: A study for 342 cases. Thorac Cancer 2015;**6**(4):443-9.
38. Pouwels S, Fiddelaers J, Teijink JA, et al. Preoperative exercise therapy in lung surgery patients: a systematic review. Respir Med 2015.
39. Chang NW, Lin KC, Lee SC, et al. Effects of an early postoperative walking exercise programme on health status in lung cancer patients recovering from lung lobectomy. J Clin Nurs 2014;**23**(23-24):3391-402.
40. Edvardsen E, Skjonsberg OH, Holme I, et al. High-intensity training following lung cancer surgery: a randomised controlled trial. Thorax 2015;**70**(3):244-50.
41. Chen HM, Tsai CM, Wu YC, et al. Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. Br J Cancer 2015;**112**(3):438-45.
42. Jette DU, Stilphen M, Ranganathan VK, et al. Interrater Reliability of AM-PAC "6-Clicks" Basic Mobility and Daily Activity Short Forms. Phys Ther 2015;**95**(5):758-66.
43. Jette DU, Stilphen M, Ranganathan VK, et al. AM-PAC "6-Clicks" functional assessment scores predict acute care hospital discharge destination. Phys Ther 2014;**94**(9):1252-61.
44. Jette DU, Stilphen M, Ranganathan VK, et al. Validity of the AM-PAC "6-Clicks" inpatient daily activity and basic mobility short forms. Phys Ther 2014;**94**(3):379-91.
45. Andres PL, Haley SM, Ni PS. Is patient-reported function reliable for monitoring postacute outcomes? Am J Phys Med Rehabil 2003;**82**(8):614-21.
46. Miller W, Rollnick S. *Motivational Interviewing. Third Edition. Helping People Change*. New York. NY: Guilford Press, 2014.
47. Vidrine JI, Reitzel LR, Figueroa P, et al. Motivation and Problem Solving (MAPS): Motivationally-based skills training for treating substance abuse. Cognitive Behavioral Practice EPub 2011.
48. Marlatt GA, Donovan DM. *Relapse prevention: maintanance strategies in the treatment of addictive behaviors*. New York, NY: Guliford Press, 2005.
49. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;**31**(2):143-64.

50. Marlatt GA, Gordon JR. *Relapse prevention: maintenance strategies in the treatment of addictive behaviors.* . New York, NY: Guilford Press, 1985.
51. Rollnick S, Miller W. What is motivational interviewing? Behavioral and Cognitive Psychotherapy 1995;**23**.
52. McClure JB, Westbrook E, Curry SJ, et al. Proactive, motivationally enhanced smoking cessation counseling among women with elevated cervical cancer risk. Nicotine Tob Res 2005;**7**(6):881-9.
53. Wetter DW, Mazas C, Daza P, et al. Reaching and treating Spanish-speaking smokers through the National Cancer Institute's Cancer Information Service. A randomized controlled trial. Cancer 2007;**109**(2 Suppl):406-13.
54. Reitzel LR, Vidrine JI, Businelle MS, et al. Preventing postpartum smoking relapse among diverse low-income women: a randomized clinical trial. Nicotine Tob Res 2010;**12**(4):326-35.
55. Correa-Fernandez V, Diaz-Toro EC, Reitzel LR, et al. Combined treatment for at-risk drinking and smoking cessation among Puerto Ricans: A randomized clinical trial. Addictive behaviors 2017;**65**:185-92.
56. Rubak S, Sandbaek A, Lauritzen T, et al. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract 2005;**55**(513):305-12.
57. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. J Consult Clin Psychol 2003;**71**(5):843-61.
58. Martins RK, McNeil DW. Review of Motivational Interviewing in promoting health behaviors. Clin Psychol Rev 2009;**29**(4):283-93.
59. Spencer JC, Wheeler SB. A systematic review of Motivational Interviewing interventions in cancer patients and survivors. Patient Educ Couns 2016;**99**(7):1099-105.
60. Stacey FG, James EL, Chapman K, et al. A systematic review and meta-analysis of social cognitive theory-based physical activity and/or nutrition behavior change interventions for cancer survivors. J Cancer Surviv 2015;**9**(2):305-38.
61. Granger CL, McDonald CF, Berney S, et al. Exercise intervention to improve exercise capacity and health related quality of life for patients with non-small cell lung cancer: a systematic review. Lung Cancer 2011;**72**(2):139-53.

62. Society AT. 98th International Conference of the American Thoracic Society. Atlanta, Georgia, 2002.
63. Jones LW, Hornsby WE, Goetzinger A, et al. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. Lung Cancer 2012;**76**(2):248-52.
64. Saad IA, Botega NJ, Toro IF. Predictors of quality-of-life improvement following pulmonary resection due to lung cancer. Sao Paulo Med J 2007;**125**(1):46-9.
65. Kasymjanova G, Correa JA, Kreisman H, et al. Prognostic value of the six-minute walk in advanced non-small cell lung cancer. J Thorac Oncol 2009;**4**(5):602-7.
66. Granger CL, Holland AE, Gordon IR, et al. Minimal important difference of the 6-minute walk distance in lung cancer. Chron Respir Dis 2015;**12**(2):146-54.
67. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;**49**(2):M85-94.
68. PROMIS. PROMIS-Dynamic Tools to Measure Health Outcomes from the Patient Perspective. 2011.
69. Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;**12**(3):199-220.
70. Markland D, Tobin V. A modification to the behavioural regulation in exercise questionnaire to include an assessment of amotivation. Journal of Sport and Exercise Psychology 2004;**2**(26):191-6.
71. Wilson PM, Blanchard CM, Nehl E, et al. Predicting physical activity and outcome expectations in cancer survivors: an application of Self-Determination Theory. Psychooncology 2006;**15**(7):567-78.
72. Sallis JF, Buono MJ, Roby JJ, et al. Seven-day recall and other physical activity self-reports in children and adolescents. Med Sci Sports Exerc 1993;**25**(1):99-108.
73. Beasley JM, Davis A, Riley WT. Evaluation of a web-based, pictorial diet history questionnaire. Public Health Nutr 2009;**12**(5):651-9.
74. Sallis JF, Pinski RB, Grossman RM, et al. The development of self-efficacy scales for healthrelated diet and exercise behaviors. Health Education Research 1988;**3**(3):283-92.

75. Fredrickson BL, Tugade MM, Waugh CE, et al. What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. Journal of personality and social psychology 2003;**84**(2):365-76.
76. Sallis JF, Grossman RM, Pinski RB, et al. The development of scales to measure social support for diet and exercise behaviors. Prev Med 1987;**16**(6):825-36.
77. Adler NE, Epel ES, Castellazzo G, et al. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000;**19**(6):586-92.
78. de Souza JA, Yap BJ, Hlubocky FJ, et al. The development of a financial toxicity patient-reported outcome in cancer: The COST measure. Cancer 2014;**120**(20):3245-53.
79. Hughes ME, Waite LJ, Hawkley LC, et al. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. Res Aging 2004;**26**(6):655-72.
80. Kawamoto K, Martin CJ, Williams K, et al. Value Driven Outcomes (VDO): a pragmatic, modular, and extensible software framework for understanding and improving health care costs and outcomes. J Am Med Inform Assoc 2015;**22**(1):223-35.
81. Farjah F, Flum DR, Varghese TK, Jr., et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg 2009;**87**(4):995-1004; discussion 05-6.
82. Farjah F, Backhus L, Cheng A, et al. Failure to rescue and pulmonary resection for lung cancer. J Thorac Cardiovasc Surg 2015;**149**(5):1365-71; discussion 71-3.e3.
83. Varghese TK. Comparative effectiveness issues in lung cancer. Cancer Treat Res 2015;**164**:101-19.
84. LaStayo PC, Marcus RL, Dibble LE, et al. Eccentric exercise versus usual-care with older cancer survivors: the impact on muscle and mobility--an exploratory pilot study. BMC Geriatr 2011;**11**:5.
85. Campo RA, Agarwal N, LaStayo PC, et al. Levels of fatigue and distress in senior prostate cancer survivors enrolled in a 12-week randomized controlled trial of Qigong. J Cancer Surviv 2014;**8**(1):60-9.
86. Jacobs JL, Marcus RL, Morrell G, et al. Resistance exercise with older fallers: its impact on intermuscular adipose tissue. Biomed Res Int 2014;**2014**:398960.

87. Wetter DW, McClure JB, Cofta-Woerpel L, et al. A randomized clinical trial of a palmtop computer-delivered treatment for smoking relapse prevention among women. Psychol Addict Behav 2011;**25**(2):365-71.
88. Reitzel LR, McClure JB, Cofta-Woerpel L, et al. The efficacy of computer-delivered treatment for smoking cessation. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2011;**20**(7):1555-7.
89. Vidrine JI, Shete S, Cao Y, et al. Ask-Advise-Connect: a new approach to smoking treatment delivery in health care settings. JAMA internal medicine 2013;**173**(6):458-64.
90. Vidrine JI, Reitzel LR, Figueroa PY, et al. Motivation and Problem Solving (MAPS): motivationally based skills training for treating substance use. Cognitive and Behavioral Practice 2013;**20**(4):501-16.
91. Nickman NA, Haak SW, Kim J. Cost minimization analysis of different growth hormone pen devices based on time-and-motion simulations. BMC Nurs 2010;**9**:6.
92. Hanmer J, Feeny D, Fischhoff B, et al. The PROMIS of QALYs. Health Qual Life Outcomes 2015;**13**:122.
93. Akerley W, Boucher KM, Bentz JS, et al. A phase II study of erlotinib as initial treatment for patients with stage IIIB-IV non-small cell lung cancer. J Thorac Oncol 2009;**4**(2):214-9.
94. Wiskemann J, Kuehl R, Dreger P, et al. Efficacy of exercise training in SCT patients-who benefits most? Bone Marrow Transplant 2013.
95. Ungar N, Sieverding M, Ulrich CM, et al. What explains the intention to be physically active in cancer patients? Different determinants for active and insufficiently active patients. J Psychosoc Oncol 2015;**33**(1):15-33.
96. Schmidt ME, Meynkohn A, Habermann N, et al. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. Int J Radiat Oncol Biol Phys 2016;**94**(2):329-37.
97. Ligibel JA, Giobbie-Hurder A, Olenczuk D, et al. Impact of a mixed strength and endurance exercise intervention on levels of adiponectin, high molecular weight adiponectin and leptin in breast cancer survivors. Cancer Causes Control 2009;**20**(8):1523-8.

98. Ligibel JA, Partridge A, Giobbie-Hurder A, et al. Physical and psychological outcomes among women in a telephone-based exercise intervention during adjuvant therapy for early stage breast cancer. J Womens Health (Larchmt) 2010;**19**(8):1553-9.
99. Alfano CM, Ganz PA, Rowland JH, et al. Cancer survivorship and cancer rehabilitation: revitalizing the link. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;**30**(9):904-6.

Table 1: Study inclusion and exclusion criteria
Inclusion criteria
Patient diagnosed with primary lung cancer stage I, II or IIIa or secondary lung cancer undergoing surgery at HCI
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 Delayed Intervention Group.
Exclusion criteria:
Deemed ineligible for surgery by the enrolling physician
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 will be assessed by the NCN Distress Thermometer. Any value higher than 7 will trigger further intervention, but ultimately enrollment into the clinical trial will be determined by the enrolling physician.

Table 2: AM-PAC Stages according to Arbane	
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.

Table 3: Baseline, discharge assessment, 2 months and 6 months measurements

Measure	Bsl[1]	Dis[2]	2Mo[3]	6Mo[4]
Eligibility and baseline questionnaire (medical history, medication use, exercise habits, health habits)	X			
AM-PAC mobility score	X	X	X	X
6 minute walk (6MW) distance	X	X	X	X
Short Physical Performance Battery (SPPB)	X	X	X	X
Patient reported outcomes (PRO)	X	X	X	X
Exercise Diary provided/reviewed	X	X	X	X
Follow-up questionnaires		X	X	X
Length of stay post-surgical resection		X		
Cost data from VDO		X	X	X
Smoking assessment (saliva)				X

[1] Baseline: first clinic visit
[2] Discharge visit: about 1 week after discharge from the hospital
[3] 2 months post-surgery
[4] 6 months post-surgery

Figure 1: Participant flow chart for the PEP study

Figure 2: AM-PAC Stage: Exercise Mode and Dose

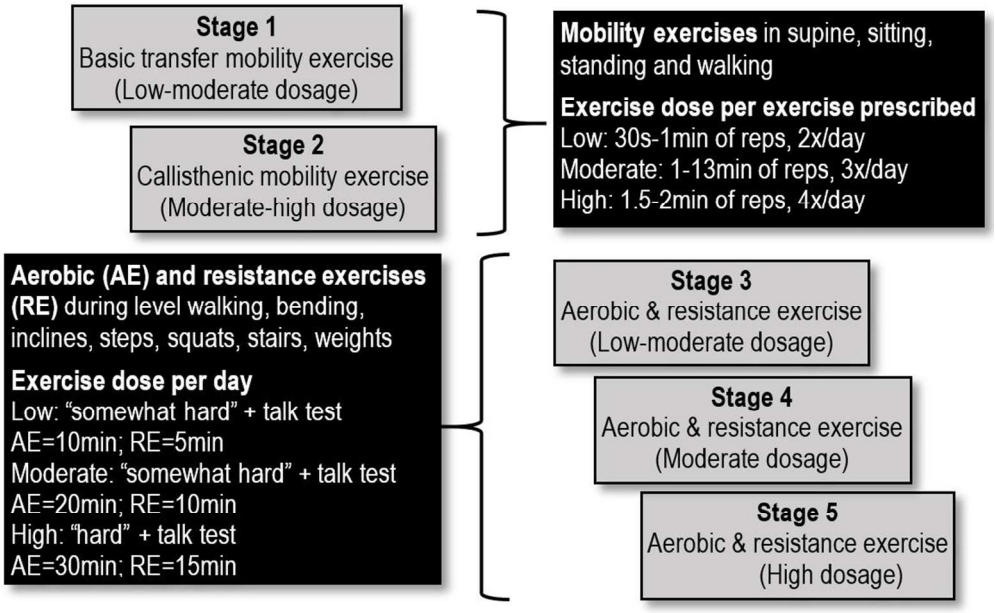

Figure 1: Participant flow chart for the PEP study

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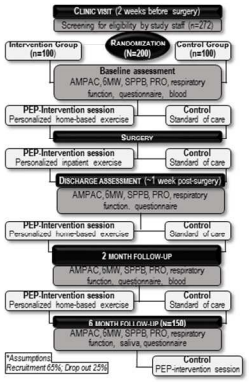

Figure 2: AM-PAC Stage: Exercise Mode and Dose

338x190mm (96 x 96 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	13-14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8-9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8-9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8-9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8-9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13/14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13/14
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	4
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-15
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Precision-Exercise-Prescription in Lung Cancer Patients Undergoing Surgery: Rationale and Design of the PEP Study Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024672.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Sep-2018
Complete List of Authors:	Ulrich, Cornelia; Huntsman Cancer Institute, Population Sciences Himbert, Caroline; Huntsman Cancer Institute, Population Sciences Boucher, Kenneth; Huntsman Cancer Institute, Population Sciences Wetter, David; Huntsman Cancer Institute, Population Sciences Hess, Rachel; University of Utah Schools of the Health Sciences, Health System Innovation and Research Kim, Jaewhan; Huntsman Cancer Institute, Population Sciences Lundberg, Kelly; University of Utah Department of Psychiatry Ligibel, Jennifer; Harvard University Dana-Farber Harvard Cancer Center BARNES, CHRISTOPHER; University of Utah, Physical Therapy and Athletic Training Rushton, Bailee; Huntsman Cancer Institute, Population Sciences Marcus, Robin; University of Utah, Physical Therapy and Athletic Training Finlayson, Samuel ; University of Utah Department of Surgery LaStayo, Paul; University of Utah, Physical Therapy and Athletic Training Varghese, Thomas; University of Utah Department of Surgery
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology, Patient-centred medicine, Rehabilitation medicine, Sports and exercise medicine, Surgery
Keywords:	Non-small lung cancer, exercise, clinical trial, Thoracic surgery < SURGERY, physical activity

Precision-Exercise-Prescription in Lung Cancer Patients Undergoing Surgery: Rationale and Design of the PEP Study Trial

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Running title: The PEP study

Word count: 3585
Tables: 3
Figures: 2

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ABSTRACT

INTRODUCTION: Lung cancer is a significant burden on societies worldwide, and the most common cause of death in cancer patients overall. Exercise intervention studies in lung cancer patients have consistently shown benefits with respect to physical and emotional functioning. However, to date, exercise training has not been consistently implemented into clinical practice given that interventions have been costly and not aligned with clinical care.

METHODS/DESIGN: The Precision-Exercise-Prescription (PEP) study is a prospective randomized-controlled trial comparing the effectiveness and feasibility of a personalized intervention exercise program among lung cancer patients undergoing surgery. Two-hundred patients who are diagnosed with stage primary or secondary lung cancer, and are eligible to undergo surgical treatment at HCI, comprise the target population. Patients are randomized to either (1) outpatient precision-exercise intervention group, or (2) delayed intervention group. The intervention approach utilizes Motivation And Problem-Solving (MAPS), a hybrid behavioral treatment based on motivational interviewing and practical problem-solving. The dosage of the exercise intervention is personalized based on the individual's Activity Measure for Post-Acute-Care™ outpatient basic mobility (AM-PAC) score, and incorporates four exercise modes: mobility, calisthenics, aerobic, and resistance. Exercise is implemented by physical therapists at study visits from pre-surgery until 6 months post-surgery. The primary endpoint is the level of physical function assessed by 6-minute walk distance at 2 months post-surgery. Secondary outcomes include patient-reported outcomes (e.g., QoL, fatigue, and self-efficacy); and other clinical outcomes, including length of stay, complications, readmission, pulmonary function, and treatment-related costs up to 6 months post-surgery.

ETHICS/DISSEMINATION: The PEP study will test the clinical effectiveness and feasibility of a personalized exercise intervention in lung cancer patients undergoing surgery. Outcomes of this clinical trial will be presented at national and international conferences and symposia and will be published in international, peer-reviewed journals. Ethics approval was obtained at the University of Utah (IRB 00104671).

TRIAL REGISTRATION: ClinicalTrials.gov, ID: NCT03306992

KEY WORDS: Non-small lung cancer, exercise, clinical trial, thoracic surgery, physical activity

BOX 1. Strenghts and Limitations

- This is the first RCT to examine a personalized exercise program for both, primary and secondary lung cancer patients
- This is an innovative approach designed be aligned and easily translatable into the clinical workflow.
- The intervention spans the entire continuum of care from the pre-surgery to post-surgery period including impacting lung cancer survivorship
- The intervention is designed so that it can successfully be translated into different populations, including rural and fontier populatios that are encounter challenges due to the distance to health care providers.
- The results will yield important health care cost information using the Value-Driven-Outcomes tool.
- The cost of the behavioral intervention delivered by a physical therapist for weekly phone calls during the outpatients period, may still be too high for future implementation in health care settings.

INTRODUCTION

Lung cancer—both primary and secondary—is a significant source of morbidity and mortality worldwide.[1 2] Primary lung cancer is the leading cause of cancer death in both men and women, causing more deaths than the next three cancers (breast, prostate, colon) combined.[2] Lung metastases (secondary lung cancer) are identified in 30 to 50% of all cancer patients.[1] The cost of cancer care for lung cancer patients is significant and expected to exceed $14.7 billion by 2020 (out of a total expense of cancer care of $157.7 billion).[3]

Surgical intervention in localized primary non-small cell lung cancer (NSCLC) improves survival outcomes.[4] Additionally, resection of isolated secondary lung cancer has led to increased progression free and overall survival in patients with certain cancers such as sarcoma and colon cancer.[5-10] Although surgery can improve outcomes in patients with early and, at times, later stage malignancies, surgical procedures a lead to significant morbidity in cancer patients. Surgical patients suffer decreased pulmonary and physical function, reduced quality of life, chronic pain and reduced activity levels following surgery.[11 12] These effects can be ameliorated by exercise. Studies have shown that exercise training positively affects QoL, physical capacity and fatigue in cancer patients, irrespective of the tumor type.[13-15] Initial exercise studies among lung cancer patients during the pre-and post-operative settings demonstrate improvement in physical performance, cardiorespiratory fitness, and hospital length-of stay.[16-21] The consistency of these findings is compelling.[16-41]

Despite promising findings for exercise, translation to the clinic has not been achieved in large part because the interventions tested to date are cumbersome, expensive, and not easy to implement in a busy clinical practice. For translation to succeed, an exercise regimen needs to be identified that can be easily integrated into the clinical workflow, and achieved with limited, yet

effective, scope of financial resources and personnel. Such a regimen would be most effective if it used clinic contact points both prior to surgery and post-surgery. The Precision Exercise Prescription (PEP) Study (National Cancer Institute [NCI] R01 CA211705) is a randomized phase III clinical trial (n=200 patients) that will investigate the effect of a personalized exercise program on physical function, as measured by the 6-Minute Walk Test, in NSCLC patients (stage I, II, IIIa) and secondary lung cancer patients who are undergoing surgical treatment at the Huntsman Cancer Institute (HCI). Secondary aims including evaluating the impact of the intervention on other measures of physical function (short physical performance battery (SPPB)), patient-reported outcomes (PROs) (QoL, fatigue, pain, sleep, and self-efficacy), clinical outcomes (length of stay, complications, readmission, and pulmonary function), and treatment-related cost.

We hypothesize that lung cancer patients undergoing surgical resection will improve their physical function by participating in a precision exercise prescription that is tailored to their mobility level, motivation, and other behavioral and environment factors as they progress (or regress) through the multiple phases of the pre- and post-surgery periods. The PEP Study will test an intervention that we expect will help lung cancer patients undergoing surgery to maintain, regain, and improve their physical function during the continuum from surgery to lung cancer survivorship.

METHODS

1. Study Design

1.1. Screening Eligibility and Baseline Data Collection

We will conduct a single-center, prospective, two-armed, phase III randomized controlled trial at HCI in Salt Lake City, Utah. The PEP study has been approved by the Institutional Review Board of the University of Utah (IRB 00104671) and all participants are required to provide written informed consent. NSCLC patients stage I, II, or IIIa, or secondary lung cancer patients over 18 years old, who undergo surgical lung resection at HCI are recruited. Detailed eligibility criteria are listed in **Table 1**. Eligibility criteria for this study primarily focus on whether a patient is eligible for surgery or not.

{Insert Table 1}

The primary outcome measure of physical function, the 6MW test, is obtained by the licensed study physical therapist, or trained study staff. Additional measurements are also obtained, including height, weight, waist and hip circumferences, systolic and diastolic blood pressure, resting one-minute pulse, and patient-reported mobility status (Activity Measure-Post Acute Care™ outpatient basic mobility (AM-PAC) score). Patients receive a baseline questionnaire to either (1) complete in clinic or (2) take home to complete and return either by mail or at their pre-surgery appointment two weeks later. After randomization (**Section1.3**) and completion of all baseline testing, patients start their intervention or control activities.

1.2. Study Participant Schedule

Figure 1 shows the proposed participant flow through the trial. Potential participants are approached during their first clinical visit prior to surgery (about 2-4 weeks pre-surgery).

Consenting participants undergo required baseline assessments, which are presented for each study time point in **Table 2**. Both groups are seen at the following study time points: pre-surgery (1 day before surgery), discharge (first visit after discharge from the hospital, ~ 1 week post-discharge), 2 and 6 months post-surgery.

{Insert Figure 1}

{Insert Table 2}

1.3. AM-PAC score for exercise tailoring

The AM-PAC basic mobility assessment **(Table 3)** is completed on each day that the study participant is seen by a physical therapist. The AM-PAC Outpatient Basic Mobility Short Form (18 questions) takes about 2 minutes to complete and is used to precisely guide the exercise prescription for each patient in a personalized manner. The AM-PAC has high test-retest and subject-proxy reliability in outpatient settings (0.97 and 0.86, respectively), and with inpatients the AM-PAC has a high intraclass correlation coefficient (0.85) when administered by clinicians.[42-45] Scores on the AM-PAC correlate with well-established physical function subscales, e.g. Functional Independence Measure (r=0.65). A standardized response mean of 1.06 and a minimal detectable change with 90% confidence of 4.72 has been delineated with AM-PAC.[44]

{Insert Table 3}

1.4 Randomization

Consenting participants are stratified by their AM-PAC mobility stage (low mobility: stages 1, 2, and 3 vs. high mobility: stages 4 and 5), and cancer type (primary vs. secondary). Participants are randomized using a uniform 1:1 allocation ratio with random block sizes of 8 individuals to either (1) Intervention Group: PEP intervention, or (2) Delayed Intervention

Group: standard of care for six months with PEP intervention session after study completion. The allocation sequence is produced via computer-generated random numbers and concealed from clinical trials office staff.

2. Study Arms

2.1. Intervention Group

The PEP intervention is 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) at: the pre-surgery visit with the surgeon; the discharge visit (about 1 week post-discharge from the hospital); and the 2 month post-surgery follow-up appointment with the surgeon. The intervention uses existing resources in the clinical setting and as such, is pragmatic and more generalizable than other exercise programs. An exercise education manual is used by the physical therapist to educate the patients on all aspects of starting and maintaining the exercise intervention. The Intervention Group is given access to exercise tools (e.g., light weights and external resistance bands) as needed, tracking exercise diary/calendar, and activity tracker for the home-based exercise program (see below) at no cost. The study physical therapist goes over (verbally and in writing) the individual exercise modes and dosages to be performed at home. The exercise mode and dosage is standardized with respect to the patient's AM-PAC mobility stage (**Figure 2)**. The exercise mode and dosage may be further modified by the study physical therapist in response to physical impairments such as fatigue, muscle weakness, pain, and shortness of breath. Modification of the intervention may also take place in order to encourage exercise adherence, and to address psychosocial barriers. Resistance exercises, using body weight or exercise band resistance, are prescribed for the upper and lower body though

more exercises are focused on the lower extremities than the upper extremities. For all exercises, including calisthenics and aerobic modes, bouts are defined by duration ranging from 5 to 30 minutes, and intensity ranging from moderate to high intensity. Exercise intensity is determined by perceived exertion, with moderate-high intensity defined as activity that allows the participant to talk but not sing while exercising. For example, a patient in AM-PAC mobility stage 3 will perform aerobic exercise similar in intensity to 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. Additionally, this patient will also perform a resistance exercise, such as standing squats, at the same perceived exertion for short bouts that add up to 5 minutes per day. These aerobic and resistance exercises will increase to 20 minutes and 10 minutes per day respectively as the participant progresses to AM-PAC mobility stage 4.

Participants are encouraged to record the duration of each bout of exercise in their diaries, in accordance with the use of duration and intensity in the dosing of exercises, rather than counting sets and repetitions. With every exercise prescription or adjustment, participants are advised to maintain the level of exercise intensity appropriate to their AM-PAC stage. This is reinforced in interactions with PEP staff during weekly phone calls. Well-being, perceived exertion, pain, fatigue, and other participant's responses to exercise are recorded in logs of weekly Motivational and Problem-solving (MAPS) phone calls. Any issues with exercise that require PT attention are referred to the study PT for intervention face-to-face in clinic, or by phone at home. We may not achieve full completion rates given the severity of the disease of the study participants and disease-related comorbidities.

The outpatient exercises are performed at home, the HCI Wellness Center, or a recreational center. The exercise modes include basic mobility exercises, calisthenics, aerobic, and resistance

exercises, and are performed in various postures (supine, sitting, standing and walking) with variable challenges (e.g., level walking, bending, incline walking, stair walking, and squatting). Instructional exercise sheets demonstrating exercise modes and doses are handed out after each exercise intervention adjustment.

Telephone calls between the participant and the study staff (including the physical therapists and clinical research coordinator,) take place weekly to answer questions and optimize patient engagement. Ongoing monitoring of attitudes and barriers to exercise occurs, and strategies for encouraging uptake of the exercise intervention are individually tailored. A consumer wearable device (e.g., Fitbit Flex II Wireless Activity Tracker) is used as a fundamental component to support behavior change. This pragmatic motivational and self-monitoring tool is used to improve participant exercise efficacy and home exercise program adherence.[46]

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)[47] 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 (**Figure 2**).

{Insert Figure 2}

Motivation And Problem-Solving (MAPS) is the hallmark behavioral intervention utilized in parallel with the exercise intervention. MAPS is a holistic, dynamic approach to facilitating behavior change that utilizes a combined motivational enhancement and problem-solving

approach based on motivational interviewing (MI) and social cognitive theory.[48] The behavioral intervention utilizes an overarching conceptual basis of the intervention is the social cognitive model [49-51] which posits that high levels of both motivation and self-efficacy are necessary for behavior change. Thus, 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.[47 49 52] 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. MAPS or its precursors have been demonstrated to be effective in four randomized controlled trials with respect to: 1) increasing treatment utilization,[53] 2) enhancing behavior change success rates,[54] 3) reducing relapse,[55] and 4) addressing multiple risk behavior change.[56] Interactions between patients and interventionists are coded and evaluated with respect to the quality of the interaction utilizing a modified version of the Motivational Interviewing Treatment Integrity (MITI), including the ability to shift between motivational interviewing strategies and more cognitive-behavioral or practical problem-solving skills. It is hypothesized that participants who received the MAPS intervention will have improved psychosocial and emotional outcomes, measured by study questionnaires, improved exercise adherence, as indicated by exercise diaries and 7-day physical activity recall interviews, and, most importantly, improved physical function as measured by six-minute walk and other performance-based outcomes.

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/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.[57-61]

As such, we believe the PEP intervention is an innovative combination of motivational enhancement and social cognitive intervention techniques.

2.2. Delayed Intervention Group (Control Group)

The Delayed Intervention Group will receive standard therapy for their lung cancer. Although all patients, independent of group assignment are encouraged by clinical staff to increase walking both in the pre-surgery and post-surgery period (as part of HCI's usual clinical care), there is no formalized pre- or post-surgery exercise program. All patients will have equal access to the HCI Wellness Center, as well as equal opportunity for referral to non-study physical therapists and other exercise professionals.

Patients will undergo assessments timed to coincide with regularly scheduled cancer care: the first post-discharge clinic visit is scheduled at 1 week after discharge from the hospital, with the second clinic visit at 2 months. Upon study completion (at the 6 month post-surgery follow-up visit) the Delayed Intervention Group is offered a PEP-Intervention session with precision exercise counseling, and receives a free activity tracker.

3. Primary and Secondary Endpoints

Endpoint assessments are presented in **Table 3**. The primary endpoint is a physical function mobility performance assessment of the distance walked in 6 minutes (6MW test) that will be assessed at the pre-operative baseline and the three post-surgery time points. The 6MW test is the most pragmatic, non-laboratory test to measure mobility physical functioning in individuals with chronic lung disease (including lung cancer).[62] In accordance with the American Thoracic Society recommendations,[63] the 6MW test is a self-paced walking test with standardized

instructions and encouragement that measures the distance (m) the patient can walk indoors on a 25m level, smooth-surfaced track over six minutes. A number of studies have demonstrated the criterion predictive validity of the 6MW test in lung cancer with some demonstrating positive relationships between 6MW distance and post-surgery outcomes including QoL, survival, function and physical activity levels.[64-67] The minimally clinically important difference of the 6MW distance in patients with lung cancer is 22-42m.[67]

Secondary endpoints include: the short physical performance battery (SPPB), which captures domains of strength, endurance, and balance and is highly predictive of disability;[68] patient-reported outcomes (PROs) on physical, mental, and social well-being measured by using generic-, as well as disease-specific instruments, such as data from the NIH Patient Reported Outcomes Measurement Information System (PROMIS);[69] the Functional Assessment of Cancer Therapy-Lung (FACT-L),[70] and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) to measure fatigue; the Pittsburgh Sleep Quality Index (PSQI) to assess the patients' sleep habits and quality; Behavioral Regulation in Exercise Questionnaire 3 (BREQ-3),[71 72] and 7-day physical activity recall phone interview to monitor and compare physical activity levels across study arms,[73] Diet History Questionnaire II (DHQII) to collect information on dietary lifestyle factors,[74] self-efficacy by Sallis JF (the scale includes two subscales: 1)"resting relapse/sticking to it", and 2)"making time to exercise"),[75] Modified Differential Emotion Scale (mDES) to capture emotional experiences;[76] Social support for exercise by Sallis JF,[77] Subjective Social Status Ladders,[78] and financial strain [79] to assess social status, loneliness by Cacioppo;[80] symptoms, such as pain (1-10 scale), and shortness of breath (1-10 scale), living condition, clinical endpoints, such as length of stay post-surgical resection, complications; and health care costs, including inpatient hospitalization and outpatient follow-up, using the

University of Utah Value Driven Outcomes (VDO) cost database[81] at 2 to 6 month follow-up. We will test former smokers to assess smoking recidivism at the 6 month clinic visit by collecting and analyzing saliva samples. Patients are required to quit smoking before they are eligible to undergo surgery, thus no saliva is collected at baseline. Smoking history will be assessed prior to undergoing surgery using standardized questionnaires.

4. Statistical Considerations and Primary Endpoint Analysis

The trial analysis will follow the intention-to-treat principle, which implies all participants who will be randomized (n=200) will be included in the analysis regardless of their adherence to the study. We hypothesize that the difference in the 6MW distance between the study arms (Intervention/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 m increase in the 6MW distance in NSCLC patients.[74] Consistent with Arbane,[21] we assume SD=100 m and correlation=0.5 between repeated 6MW test measurements on the same subject. Power to detect the treatment effect was estimated by simulation 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. For our primary endpoint, with at least 150 evaluable subjects (accounting for a 25% dropout rate) the estimated power is greater than or equal to 80% at two sided type I error equal 0.05.

Mixed effects models with random intercept will be used for analysis of repeated measurements. A sensitivity analysis will be performed with additional adjustment variables (gender, age, baseline smoking status, primary or secondary lung cancer, neoadjuvant treatment,

tumor stage, baseline level of outcome, pain, and sleep). Missing data will be handled using multiple imputation via chained equations, as implemented by the R package MICE.[75]

As of April 30, 2018 n=24 patients have been recruited into the PEP study, with recruitment anticipated to continue through July 2020. To date, only one patient has withdrawn.

5. Patient and Public Involvement

A pilot study of 40 lung cancer patients had been performed in the development of this trial. Every eligible patient was approached, and all patients approached (100%) agreed to participate in the intervention. The 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. The intervention included individually-prescribed exercise modes (mobility, flexibility, calisthenic, aerobic and resistance) and dosages (low, moderate, high) tailored to the patient's AM-PAC mobility stage. To our knowledge, the AM-PAC mobility staging used to personalize exercise interventions was unique and facilitated the successful implementation of the intervention into clinical workflow using existing space in the clinic of Thoracic Surgery. 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. We have subsequently optimized our design and materials through the conduct of this pilot study. Our preliminary data reinforces that our pragmatic mobility screen (i.e., AM-PAC score/staging) is the key determinant of physical function (independent of age, sex, cancer stage, etc.) and that exercise modes and dosages can be successfully aligned to the AM-PAC score.

As part of the pilot study we performed formal quality control interviews with patients to inform and refine the trial interventions and processes. The data from the pilot trial as well as the close work with the Clinical Trials Office (CTO) at Huntsman Cancer Institute (HCI) have been used to ensure that the study protocol engages participants in a respectful, ethical and impactful way, while performing the PEP Study intervention. The CTO and other HCI resources further provides assistance with the ethical standards of the trial, as well as the translation and disseminations of the research findings to community members, patients, and cancer support groups. In addition, the study is conducted by an interdisciplinary team with long-standing expertise in exercise, behavioral interventions, and surgery. Involved clinicians and researchers work with the target population on a daily bases and used these experiences to help inform the development of the research question, outcome measures, and performance of the intervention.

DISCUSSION

The primary results from the PEP study will test the clinical effectiveness and feasibility of a personalized exercise intervention in lung cancer patients undergoing surgery. This trial fills the gap in knowledge precisely, by testing an exercise intervention that can be readily integrated into the clinic and by obtaining data on functional efficacy and patient-reported-outcomes.

The feasibility of the PEP study was tested in a successful pilot study and builds on studies that have been previously performed by the interdisciplinary investigator team.[82-99] grated into the clinic and by obtaining data on functional efficacy and patient-reported-outcomes. To our knowledge, the AM-PAC mobility score has not been used to personalize exercise and this is a well-validated and highly standardized instrument. The behavioral intervention approach builds

on prior work using MAPS,[91] a holistic and dynamic approach to assisting individuals to make positive behavioral changes.

In a recent opinion piece, Alfano et al. argued that *"it is time to revitalize the link between cancer survivorship and rehabilitation and investigate a new model of comprehensive cancer rehabilitation involving a multidisciplinary team of providers."*[100] PEP will be responsive to this call for action- it will integrate a team of surgeons and physical therapists. The study will being at the initial pre-surgery clinic visit and continue during the inpatient and outpatient post-surgery periods, thus helping lung cancer patients undergoing surgery to maintain, regain, and improve their physical function during the continuum from surgery to lung cancer survivorship.

ACKOWLEDGEMENTS

We thank our collaborators involved in the PEP study patient recruitment, data entry, and regulatory organization, specifically the clinical staff of the cardiothoracic surgery clinic 1A, the Clinical Trials Office (CTO), Biorepository and Molecular Pathology Bank (BMP), Research informatics, and the data management team at HCI.

FUNDING

The PEP study is funded by the National Institutes of Health (NIH)/National Cancer Institute (NCI) R01 CA211705 and Huntsman Cancer Foundation. Some authors were supported by grants from the NIH/NCI (R01 CA189184, R01 CA207371, U01 CA206110), and P30CA042014.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

CONTROBUTORSHIP STATEMENT

All authors contributed to the design and development of the PEP Study protocol. Specifically, CMU, PL, and TKV are the Principal Investigators of the trial. CH assisted with the design, implementation of a pilot study and implementation of the PEP Study. CH drafted the manuscript and the study protocol. KB provided statistical input, guidance, and all calculations used in the design of the clinical trial. RH oversees the assessments of patient-reported outcomes as part of the PROMIS score. DWW and KL designed and conduct the behavioral support elements of the study intervention. JK is responsible for cost effectiveness analyses and respective protocols. JAL, RM, and SRGF provided significant input with respect to the design

and performance of the trial. CAB is the study physical therapist and assisted in the design of the personalized exercise intervention. BR assisted with the optimization and implementation of the study protocol. CMU, CH, KB, DWW, RH, JK, KL, JAL, CAB, BR, RM, SRGF, PL, and TKV contributed to writing, editing, review, and approval of the study protocol, meeting the International Committee of Medical Journal Editors (ICMJE) recommendations for authorship. All authors reviewed and agreed the final manuscript.

REFERENCES

1. Schwartz D. Secondary Lung Tumors. 2014 December 08. http://emedicine.medscape.com/article/426820-overview (accessed 10.28.2016).
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;**66**(1):7-30.
3. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. Journal of the National Cancer Institute 2011;**103**(2):117-28.
4. Network NCC. NCCN guidelines--non-small cell lung cancer. Secondary NCCN guidelines--non-small cell lung cancer 2016. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
5. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;**113**(1):37-49.
6. Hornbech K, Ravn J, Steinbruchel DA. Outcome after pulmonary metastasectomy: analysis of 5 years consecutive surgical resections 2002-2006. J Thorac Oncol 2011;**6**(10):1733-40.
7. Younes RN, Fares AL, Gross JL. Pulmonary metastasectomy: a multivariate analysis of 440 patients undergoing complete resection. Interact Cardiovasc Thorac Surg 2012;**14**(2):156-61.
8. Larsen KR, Svendsen UG, Milman N, et al. Cardiopulmonary function at rest and during exercise after resection for bronchial carcinoma. Ann Thorac Surg 1997;**64**(4):960-4.
9. Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". J Thorac Oncol 2011;**6**(8):1373-8.
10. Baser S, Shannon VR, Eapen GA, et al. Pulmonary dysfunction as a major cause of inoperability among patients with non-small-cell lung cancer. Clin Lung Cancer 2006;**7**(5):344-9.

11. Pompili C, Brunelli A, Xiume F, et al. Predictors of postoperative decline in quality of life after major lung resections. Eur J Cardiothorac Surg 2011;**39**(5):732-7.
12. Wildgaard K, Ravn J, Nikolajsen L, et al. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011;**55**(1):60-8.
13. Kuehr L, Wiskemann J, Abel U, et al. Exercise in patients with non-small cell lung cancer. Medicine and science in sports and exercise 2014;**46**(4):656-63.
14. Lakoski SG, Eves ND, Douglas PS, et al. Exercise rehabilitation in patients with cancer. Nat Rev Clin Oncol 2012;**9**(5):288-96.
15. Mock V, Pickett M, Ropka ME, et al. Fatigue and quality of life outcomes of exercise during cancer treatment. Cancer Pract 2001;**9**(3):119-27.
16. Hoffman AJ, Brintnall RA, Brown JK, et al. Too sick not to exercise: using a 6-week, home-based exercise intervention for cancer-related fatigue self-management for postsurgical non-small cell lung cancer patients. Cancer Nurs 2013;**36**(3):175-88.
17. Jones LW, Eves ND, Peterson BL, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer 2008;**113**(12):3430-9.
18. Jones LW, Eves ND, Peddle CJ, et al. Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. Appl Physiol Nutr Metab 2009;**34**(2):197-202.
19. Peddle CJ, Jones LW, Eves ND, et al. Effects of presurgical exercise training on quality of life in patients undergoing lung resection for suspected malignancy: a pilot study. Cancer Nurs 2009;**32**(2):158-65.

20. Arbane G, Tropman D, Jackson D, et al. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 2011;**71**(2):229-34.
21. Sebio Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, et al. 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):486-97.
22. Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. Lung Cancer 2011;**74**(3):441-5.
23. Bobbio A, Chetta A, Ampollini L, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg 2008;**33**(1):95-8.
24. Cesario A, Ferri L, Galetta D, et al. Pre-operative pulmonary rehabilitation and surgery for lung cancer. Lung Cancer 2007;**57**(1):118-9.
25. Cesario A, Ferri L, Galetta D, et al. Post-operative respiratory rehabilitation after lung resection for non-small cell lung cancer. Lung Cancer 2007;**57**(2):175-80.
26. Coats V, Maltais F, Simard S, et al. Feasibility and effectiveness of a home-based exercise training program before lung resection surgery. Can Respir J 2013;**20**(2):e10-6.
27. Divisi D, Di Francesco C, Di Leonardo G, et al. Preoperative pulmonary rehabilitation in patients with lung cancer and chronic obstructive pulmonary disease. Eur J Cardiothorac Surg 2013;**43**(2):293-6.
28. Granger CL, Chao C, McDonald CF, et al. Safety and feasibility of an exercise intervention for patients following lung resection: a pilot randomized controlled trial. Integr Cancer Ther 2013;**12**(3):213-24.

29. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 2007;**110**(3):590-8.

30. Peddle-McIntyre CJ, Bell G, Fenton D, et al. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. Lung Cancer 2012;**75**(1):126-32.

31. Pehlivan E, Turna A, Gurses A, et al. The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. Ann Thorac Cardiovasc Surg 2011;**17**(5):461-8.

32. Riesenberg H, Lubbe AS. In-patient rehabilitation of lung cancer patients--a prospective study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2010;**18**(7):877-82.

33. Sekine Y, Chiyo M, Iwata T, et al. Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg 2005;**53**(5):237-43.

34. Spruit MA, Janssen PP, Willemsen SC, et al. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. Lung Cancer 2006;**52**(2):257-60.

35. Stigt JA, Uil SM, van Riesen SJ, et al. A randomized controlled trial of postthoracotomy pulmonary rehabilitation in patients with resectable lung cancer. J Thorac Oncol 2013;**8**(2):214-21.

36. Wall LM. Changes in hope and power in lung cancer patients who exercise. Nurs Sci Q 2000;**13**(3):234-42.

37. Gao K, Yu PM, Su JH, et al. Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: A study for 342 cases. Thorac Cancer 2015;**6**(4):443-9.

38. Pouwels S, Fiddelaers J, Teijink JA, et al. Preoperative exercise therapy in lung surgery patients: a systematic review. Respir Med 2015.

39. Chang NW, Lin KC, Lee SC, et al. Effects of an early postoperative walking exercise programme on health status in lung cancer patients recovering from lung lobectomy. J Clin Nurs 2014;**23**(23-24):3391-402.

40. Edvardsen E, Skjonsberg OH, Holme I, et al. High-intensity training following lung cancer surgery: a randomised controlled trial. Thorax 2015;**70**(3):244-50.

41. Chen HM, Tsai CM, Wu YC, et al. Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. Br J Cancer 2015;**112**(3):438-45.

42. Jette DU, Stilphen M, Ranganathan VK, et al. Interrater Reliability of AM-PAC "6-Clicks" Basic Mobility and Daily Activity Short Forms. Phys Ther 2015;**95**(5):758-66.

43. Jette DU, Stilphen M, Ranganathan VK, et al. AM-PAC "6-Clicks" functional assessment scores predict acute care hospital discharge destination. Phys Ther 2014;**94**(9):1252-61.

44. Jette DU, Stilphen M, Ranganathan VK, et al. Validity of the AM-PAC "6-Clicks" inpatient daily activity and basic mobility short forms. Phys Ther 2014;**94**(3):379-91.

45. Andres PL, Haley SM, Ni PS. Is patient-reported function reliable for monitoring postacute outcomes? Am J Phys Med Rehabil 2003;**82**(8):614-21.

46. Bourke L, Homer KE, Thaha MA, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. The Cochrane database of systematic reviews 2013(9):Cd010192.

47. Miller W, Rollnick S. *Motivational Interviewing. Third Edition. Helping People Change*. New York. NY: Guilford Press, 2014.

48. Vidrine JI, Reitzel LR, Figueroa P, et al. Motivation and Problem Solving (MAPS): Motivationally-based skills training for treating substance abuse. Cognitive Behavioral Practice EPub 2011.

49. Marlatt GA, Donovan DM. *Relapse prevention: maintanance strategies in the treatment of addictive behaviors*. New York, NY: Guliford Press, 2005.

50. Bandura A. Health promotion by social cognitive means. Health Educ Behav 2004;**31**(2):143-64.

51. Marlatt GA, Gordon JR. *Relapse prevention: maintenance strategies in the treatment of addictive behaviors.* . New York, NY: Guilford Press, 1985.

52. Rollnick S, Miller W. What is motivational interviewing? Behavioral and Cognitive Psychotherapy 1995;**23**.

53. McClure JB, Westbrook E, Curry SJ, et al. Proactive, motivationally enhanced smoking cessation counseling among women with elevated cervical cancer risk. Nicotine Tob Res 2005;**7**(6):881-9.

54. Wetter DW, Mazas C, Daza P, et al. Reaching and treating Spanish-speaking smokers through the National Cancer Institute's Cancer Information Service. A randomized controlled trial. Cancer 2007;**109**(2 Suppl):406-13.

55. Reitzel LR, Vidrine JI, Businelle MS, et al. Preventing postpartum smoking relapse among diverse low-income women: a randomized clinical trial. Nicotine Tob Res 2010;**12**(4):326-35.

56. Correa-Fernandez V, Diaz-Toro EC, Reitzel LR, et al. Combined treatment for at-risk drinking and smoking cessation among Puerto Ricans: A randomized clinical trial. Addictive behaviors 2017;**65**:185-92.

57. Rubak S, Sandbaek A, Lauritzen T, et al. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract 2005;**55**(513):305-12.

58. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. J Consult Clin Psychol 2003;**71**(5):843-61.

59. Martins RK, McNeil DW. Review of Motivational Interviewing in promoting health behaviors. Clin Psychol Rev 2009;**29**(4):283-93.

60. Spencer JC, Wheeler SB. A systematic review of Motivational Interviewing interventions in cancer patients and survivors. Patient Educ Couns 2016;**99**(7):1099-105.

61. Stacey FG, James EL, Chapman K, et al. A systematic review and meta-analysis of social cognitive theory-based physical activity and/or nutrition behavior change interventions for cancer survivors. J Cancer Surviv 2015;**9**(2):305-38.

62. Granger CL, McDonald CF, Berney S, et al. Exercise intervention to improve exercise capacity and health related quality of life for patients with non-small cell lung cancer: a systematic review. Lung Cancer 2011;**72**(2):139-53.

63. Society AT. 98th International Conference of the American Thoracic Society. Atlanta, Georgia, 2002.

64. Jones LW, Hornsby WE, Goetzinger A, et al. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. Lung Cancer 2012;**76**(2):248-52.

65. Saad IA, Botega NJ, Toro IF. Predictors of quality-of-life improvement following pulmonary resection due to lung cancer. Sao Paulo Med J 2007;**125**(1):46-9.

66. Kasymjanova G, Correa JA, Kreisman H, et al. Prognostic value of the six-minute walk in advanced non-small cell lung cancer. J Thorac Oncol 2009;**4**(5):602-7.

67. Granger CL, Holland AE, Gordon IR, et al. Minimal important difference of the 6-minute walk distance in lung cancer. Chron Respir Dis 2015;**12**(2):146-54.

68. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;**49**(2):M85-94.

69. PROMIS. PROMIS-Dynamic Tools to Measure Health Outcomes from the Patient Perspective. 2011.

70. Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;**12**(3):199-220.

71. Markland D, Tobin V. A modification to the behavioural regulation in exercise questionnaire to include an assessment of amotivation. Journal of Sport and Exercise Psychology 2004;**2**(26):191-6.

72. Wilson PM, Blanchard CM, Nehl E, et al. Predicting physical activity and outcome expectations in cancer survivors: an application of Self-Determination Theory. Psychooncology 2006;**15**(7):567-78.

73. Sallis JF, Buono MJ, Roby JJ, et al. Seven-day recall and other physical activity self-reports in children and adolescents. Medicine and science in sports and exercise 1993;**25**(1):99-108.

74. Beasley JM, Davis A, Riley WT. Evaluation of a web-based, pictorial diet history questionnaire. Public Health Nutr 2009;**12**(5):651-9.

75. Sallis JF, Pinski RB, Grossman RM, et al. The development of self-efficacy scales for healthrelated diet and exercise behaviors. Health Education Research 1988;**3**(3):283-92.

76. Fredrickson BL, Tugade MM, Waugh CE, et al. What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. Journal of personality and social psychology 2003;**84**(2):365-76.

77. Sallis JF, Grossman RM, Pinski RB, et al. The development of scales to measure social support for diet and exercise behaviors. Prev Med 1987;**16**(6):825-36.

78. Adler NE, Epel ES, Castellazzo G, et al. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000;**19**(6):586-92.

79. de Souza JA, Yap BJ, Hlubocky FJ, et al. The development of a financial toxicity patient-reported outcome in cancer: The COST measure. Cancer 2014;**120**(20):3245-53.

80. Hughes ME, Waite LJ, Hawkley LC, et al. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. Res Aging 2004;**26**(6):655-72.

81. Kawamoto K, Martin CJ, Williams K, et al. Value Driven Outcomes (VDO): a pragmatic, modular, and extensible software framework for understanding and improving health care costs and outcomes. J Am Med Inform Assoc 2015;**22**(1):223-35.

82. Farjah F, Flum DR, Varghese TK, Jr., et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg 2009;**87**(4):995-1004; discussion 05-6.

83. Farjah F, Backhus L, Cheng A, et al. Failure to rescue and pulmonary resection for lung cancer. J Thorac Cardiovasc Surg 2015;**149**(5):1365-71; discussion 71-3.e3.

84. Varghese TK. Comparative effectiveness issues in lung cancer. Cancer Treat Res 2015;**164**:101-19.

85. LaStayo PC, Marcus RL, Dibble LE, et al. Eccentric exercise versus usual-care with older cancer survivors: the impact on muscle and mobility--an exploratory pilot study. BMC Geriatr 2011;**11**:5.

86. Campo RA, Agarwal N, LaStayo PC, et al. Levels of fatigue and distress in senior prostate cancer survivors enrolled in a 12-week randomized controlled trial of Qigong. J Cancer Surviv 2014;**8**(1):60-9.

87. Jacobs JL, Marcus RL, Morrell G, et al. Resistance exercise with older fallers: its impact on intermuscular adipose tissue. Biomed Res Int 2014;**2014**:398960.

88. Wetter DW, McClure JB, Cofta-Woerpel L, et al. A randomized clinical trial of a palmtop computer-delivered treatment for smoking relapse prevention among women. Psychol Addict Behav 2011;**25**(2):365-71.

89. Reitzel LR, McClure JB, Cofta-Woerpel L, et al. The efficacy of computer-delivered treatment for smoking cessation. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2011;**20**(7):1555-7.

90. Vidrine JI, Shete S, Cao Y, et al. Ask-Advise-Connect: a new approach to smoking treatment delivery in health care settings. JAMA internal medicine 2013;**173**(6):458-64.

91. Vidrine JI, Reitzel LR, Figueroa PY, et al. Motivation and Problem Solving (MAPS): motivationally based skills training for treating substance use. Cognitive and Behavioral Practice 2013;**20**(4):501-16.

92. Nickman NA, Haak SW, Kim J. Cost minimization analysis of different growth hormone pen devices based on time-and-motion simulations. BMC Nurs 2010;**9**:6.

93. Hanmer J, Feeny D, Fischhoff B, et al. The PROMIS of QALYs. Health Qual Life Outcomes 2015;**13**:122.

94. Akerley W, Boucher KM, Bentz JS, et al. A phase II study of erlotinib as initial treatment for patients with stage IIIB-IV non-small cell lung cancer. J Thorac Oncol 2009;**4**(2):214-9.

95. Wiskemann J, Kuehl R, Dreger P, et al. Efficacy of exercise training in SCT patients-who benefits most? Bone Marrow Transplant 2013.

96. Ungar N, Sieverding M, Ulrich CM, et al. What explains the intention to be physically active in cancer patients? Different determinants for active and insufficiently active patients. J Psychosoc Oncol 2015;**33**(1):15-33.

97. Schmidt ME, Meynkohn A, Habermann N, et al. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. Int J Radiat Oncol Biol Phys 2016;**94**(2):329-37.

98. Ligibel JA, Giobbie-Hurder A, Olenczuk D, et al. Impact of a mixed strength and endurance exercise intervention on levels of adiponectin, high molecular weight adiponectin and leptin in breast cancer survivors. Cancer causes & control : CCC 2009;**20**(8):1523-8.

99. Ligibel JA, Partridge A, Giobbie-Hurder A, et al. Physical and psychological outcomes among women in a telephone-based exercise intervention during adjuvant therapy for early stage breast cancer. J Womens Health (Larchmt) 2010;**19**(8):1553-9.

100. Alfano CM, Ganz PA, Rowland JH, et al. Cancer survivorship and cancer rehabilitation: revitalizing the link. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;**30**(9):904-6.

Table 1: Study inclusion and exclusion criteria
Inclusion criteria
Patient diagnosed with primary lung cancer stage I, II or IIIa or secondary lung cancer undergoing surgery at HCI
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 Delayed Intervention Group.
Exclusion criteria:
Deemed ineligible for surgery by the enrolling physician
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 will be assessed by the NCN Distress Thermometer. Any value higher than 7 will trigger further intervention, but ultimately enrollment into the clinical trial will be determined by the enrolling physician.

Table 2: AM-PAC Stages according to Arbane	
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.

Table 3. PEP Study schedule of enrolment, interventions, and assessments.

	STUDY PERIOD				
	Enrolment	Surgery	Post-allocation		Close-out
TIMEPOINT	*Baseline*[1]	0	*Discharge*[2]	*2 Months*[3]	*6 Months*[4]
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation	X				
INTERVENTIONS:					
Group 1	←	—	—	—	→
Group 2					X (Delayed intervention)
ASSESSMENTS:					
AM-PAC mobility score	X		X	X	X
6 Minute walk distance	X		X	X	X
Short Physical Performance Battery	X		X	X	X
Patient reported outcomes	X		X	X	X
Exercise diary provided/reviewed	X	X	X	X	X
Follow-up questionnaires			X	X	X
Length of stay post-surgery			X		
Cost Data			X	X	X
Smoking assessment (saliva)					X

[1] Baseline: first clinic visit with surgeon
[2] Discharge visit: about 1 week after discharge from the hospital
[3] 2 months post-surgery
[4] 6 months post-surgery

Figure 1: Participant flow chart for the PEP study

Figure 2: AM-PAC Stage: Exercise Mode and Dose

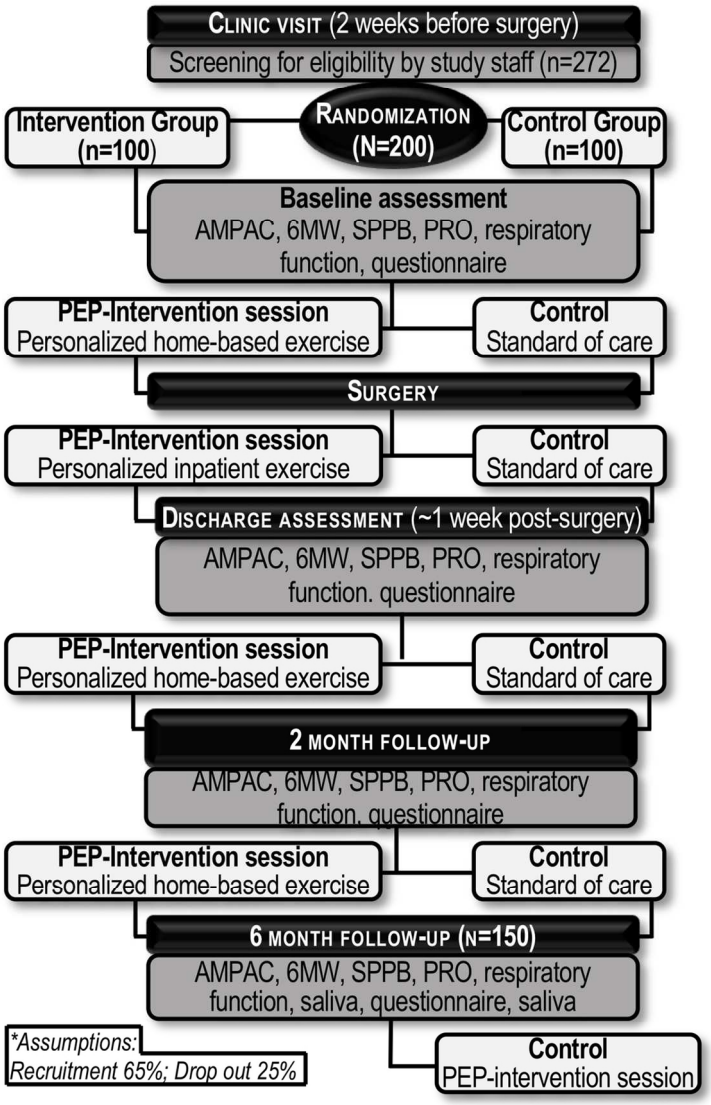

Figure 1: Participant flow chart for the PEP study

102x155mm (300 x 300 DPI)

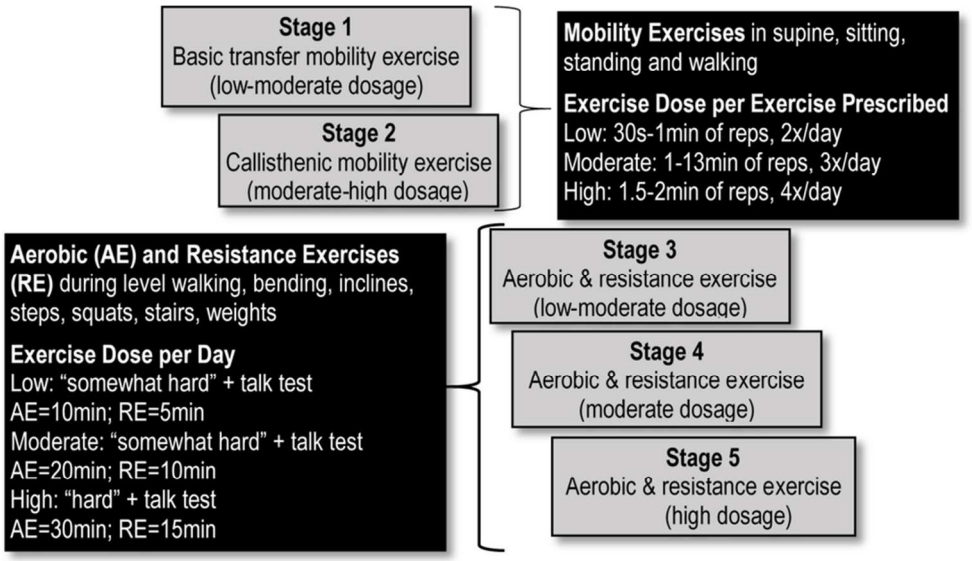

Figure 2: AM-PAC Stage: Exercise Mode and Dose

88x53mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry - Page 3
	2b	All items from the World Health Organization Trial Registration Data Set - N/A
Protocol version	3	Date and version identifier - Protocol (Appendix)
Funding	4	Sources and types of financial, material, and other support - Page 19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - Page 1 and 19-20
	5b	Name and contact information for the trial sponsor - Page 19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities - N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) - Appendix (Protocol)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - Page 1-2
	6b	Explanation for choice of comparators - Page 6
Objectives	7	Specific objectives or hypotheses - Page 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) - Page 6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained - Page 7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - Page 9-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) - Page 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) - Page 13-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial - N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - Page 13- 15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) - Table 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations - Page 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size - Page 7-8

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions - Page 8-9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned - Page 8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions - Page 7-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial - N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol - Page 13-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols - Protocol (Appendix)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol - Protocol (Appendix)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol - Page 15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) - Page 15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) - Page 15-16
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed - Protocol (Appendix)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial - Protocol (Appendix)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct - Protocol (Appendix)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor - Protocol (Appendix)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval - Page 3 and 7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) - Protocol (Appendix)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) - Page 7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable - N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial - Protocol (Appendix)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site - Page 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators - Protocol (Appendix)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation - N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - Protocol (Appendix)
	31b	Authorship eligibility guidelines and any intended use of professional writers - Protocol (Appendix)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - Protocol (Appendix)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates - Protocol (Appendix)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable - Page 14

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.