PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Precision-Exercise-Prescription in Lung Cancer Patients Undergoing Surgery: Rationale and Design of the PEP Study Trial
AUTHORS	Ulrich, Cornelia; Himbert, Caroline; Boucher, Kenneth; Wetter, David W; Hess, Rachel; Kim, Jaewhan; Lundberg, Kelly; Ligibel, Jennifer; BARNES, CHRISTOPHER Alan; Rushton, Bailee; Marcus, Robin; Finlayson, Samuel R.G.; LaStayo, Paul; Varghese, Thomas

VERSION 1 – REVIEW

REVIEWER	AM May Julius Center, University Medical Center Utrecht,Utrecht University, The Netherlands
REVIEW RETURNED	02-Jul-2018

GENERAL COMMENTS	The study prescribed in the current design paper is already ongoing, so no large methodological changes can be made anymore. Taking this into account, I reviewed the paper and provided my comments below. - Randomization: Why is a fixed block size chosen, a random block size is more unpredictable and therefore preferred. - Has the AM-PAC score already been used to personalize exercise or is this the first time? Did it have added value during the pilot phase? - PEP intervention: Could you provide more information about the intervention, so that others would be able to repeat the intervention? E.g. what resistance exercises will be applied, how are bouts defined and how are exercises progressed? How is the intensity of resistance exercises determined? Is the use of the patients' AM PAC mobility stage the only measure of personalization or are there more measured that determine personalized exercise? - How will the Fitbit be used to motivate and self-monitor? Are the Fitbit data shared with the physiotherapists or the researcher? - Control patients will be encouraged to increase walking. How is this monitored? By the 7-day PA recall phone interview, or do the control patients also get the exercise diaries? This is not totally clear.

- The description of the secondary endpoints is very short. In Table 3 follow-up questionnaires are mentioned – could you define these questionnaires?
It is not mentioned in the text that saliva samples are taken – for what? Only to assess smoking status? Why is this not done at baseline?

- Statistics: Only statistics for the primary endpoint are described. How will the repeated measurements be analyzed – using mixed effects models?
Using ANCOVA in RCTs, missing data on the outcome do not need to be imputed necessarily. See: Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol. 2012;175:210–217. doi: 10.1093/aje/kwr302.

- On page 14, the authors mentioned that a pilot study has been performed, but they provide no feasibility results (in the study protocol they do). The protocol paper would definitely profit from providing results on feasibility, intervention uptake and also experiences with the AM-PAC stratification.

Very minor:
- Page 5, line 29: delete 'a'; and Page 8, line 26: delete '.'

REVIEWER	Brian C Focht, PhD FACSM, CSCS
	The Ohio State University USA
REVIEW RETURNED	04-Jul-2018

GENERAL COMMENTS	This protocol paper discusses the rationale and design of the Precision-Exercise-Prescription (PEP) in Lung Cancer Patients Undergoing Surgery randomized clinical trial. This study is proposed as a phase III clinical trial designed to test the clinical effectiveness and feasibility of a personalized exercise intervention in lung cancer patients undergoing surgery. With the vast impact of lung cancer-related morbidity and mortality and the need for more theory-based, effective and feasible physical activity interventions in the lung cancer patient population, this protocol would certainly be of interest to the readership of BMJ Open. There are notable strengths of the study rationale and design. The potential significance of the study is discussed including details of how results from the study may potentially impact current clinical standard-of-care practices. The study design includes both objective and patient reported measures of mobility and physical performance. In addition, the protocol employs evidence-based psychological constructs and behavioral strategies which have been successfully used to promote exercise adoption and adherence. Overall, the authors have developed a pragmatic and conceptually-sound approach which acknowledges the importance of individualized tailoring of exercise, is aligned with the extant evidence supporting a multi-disciplinary approach to improving cancer rehabilitation and survivorship, and aims to evaluate the cost-effectiveness of delivering such an intervention. However, there are a few methodological concerns which detract from the potential impact of the paper. While most concerns reflect issues which simply require clarification, other select concerns necessitate more detailed justification or reinterpretation.
	1. Including a more detailed and specific description of the primary hypothesis in the introduction. For example, I suggest including the

hypothesis text in section 4, would enhance the clarity to the rationale.

2. The description of the exercise resources available to participants and their associated monetary cost should be more clearly articulated. For example, will all participants have equal access to the wellness center? For those engaging in home exercise, what equipment will be provided and will there be an associated monetary burden on participants? Explicitly addressing in each of these aspects will be particular instructive with regard to the comparability of the exercise arms and their respective cost-effectiveness.

3. A more detailed description of the exercise intervention/prescription is warranted. The types of exercises performed by the participants should be more clearly articulated. The description of the exercises is quite general. Added specificity of these descriptions would add clarity to the range of exercises performed and the modalities utilized to perform the exercises based on individual functionality of each participant.

4. The procedures for using the exercise diary/calendar mechanisms available to participants need to be more clearly articulated. Although each participant will have a general exercise guideline as determined by AM-PAC score and therapist prescription, will they be required to record daily frequency, duration, sets, repetitions, or intensity of exercise? How will feelings of well-being be recorded such as perceived exertion and pain associated with exercise?

5. Self-efficacy is mentioned as a secondary endpoint to be explored. However, given the multi-dimensional, behavior specific nature of self-efficacy measures, more detailed description of the measures are warranted. I urge the authors to clarify the type of self-efficacy being measured (i.e. task, barrier, self-regulatory self-efficacy), the rationale for including this assessment, as well as the psychometric properties of the measure.

6. How will participant compliance to the constructs of the cognitive-behavioral portion of the intervention will be assessed? Promotion of self-monitoring, goal-setting, barrier problem-solving, and mastery experiences are listed as key elements of the MAPS method. Aside from the audio-recordings of the weekly telephone calls, are there any procedures in-place to evaluate each participant's level of mastery and successful development of these skills?

7. Inclusion of the proposed statistical analyses associated with the primary and secondary endpoints would add necessary detail to the statistical considerations section. Furthermore, explicitly addressing how missing data, attrition, and/or lack of adherence will be addressed in the analysis will also be particularly informative.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Reviewer Name: AM May
Institution and Country: Julius Center, University Medical Center Utrecht, Utrecht University,
The Netherlands Please state any competing interests or state 'None declared': None declared

The study prescribed in the current design paper is already ongoing, so no large methodological changes can be made anymore. Taking this into account, I reviewed the paper and provided my comments below.

1. Randomization: Why is a fixed block size chosen, a random block size is more unpredictable and therefore preferred.

   We agree that random block size is preferred and apologize for the misleading text. In fact, the software used for the randomization produced random block sizes of up to 8. We have revised the manuscript as follows:

   Page 8: Participants are randomized using a uniform 1:1 allocation ratio with random block sizes of 8 individuals to either (1) Intervention Group […]

2. Has the AM-PAC score already been used to personalize exercise or is this the first time? Did it have added value during the pilot phase?

   To our knowledge, the AM-PAC mobility score has not been used to personalize exercise. The positive findings from the pilot regarding physical function with the use of AM-PAC and a personalized exercise program suggest the AM-PAC is value-added. We are using the level of mobility stemming from the AM-PAC, to provide generalized guidelines for mode and dose of exercise. Importantly, the AM-PAC is easily administered in a busy clinical environment so it is completed at each time-point. Therefore, the modes and dosages of exercise are amenable to change at each time point. We have added information on the pilot study. Please refer to comment 11. We have further added information on the AM-PAC mobility score as follows:

   Page 17: To our knowledge, the AM-PAC mobility score has not been used to personalize exercise interventions and this is a well-validated and highly standardized instrument.

3. PEP intervention: Could you provide more information about the intervention, so that others would be able to repeat the intervention? E.g. what resistance exercises will be applied, how are bouts defined and how are exercises progressed? How is the intensity of resistance exercises determined?

   We thank the reviewer for the suggestion. We would like to highlight the challenge of developing a clinically pragmatic framework for personalized exercise from a strict detailed exercise protocol. The lung cancer survivors' level of physical function varies considerably, and can vary within-individuals across time points. Therefore, we are using the level of mobility stemming from the AM-PAC to provide generalized guidelines for mode and dose of exercise. Importantly, the AM-PAC is easily administered in a busy clinical environment so it is completed at each time-point. Therefore, the modes and dosages of exercise are amenable to change at each time point, and exercise modes and dosages are nimble and personalized to individuals over time. This clinically-pragmatic, patient-centered approach to exercise prescription does not lend itself to easy description, as each patient receives a prescription tailored to their specific goals and circumstances.

   However, we have added more information on the exercise intervention as follows:

   Page 9-10: 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.

4. Is the use of the patients' AM PAC mobility stage the only measure of personalization or are there more measured that determine personalized exercise?

The AM-PAC mobility stage is the only measure of personalization. However, the exercise mode and dosage indicated by a participant's AM-PAC mobility stage may be further modified by a study physical therapist in response to presenting physical impairments: e.g., fatigue, muscle weakness, pain, and shortness of breath. Guidelines may also be modified to encourage exercise adherence, and address psychosocial barriers such as time and space constraints, and low participant motivation. We have added this information in the revised manuscript as follows:

Page 9: 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.

5. How will the Fitbit be used to motivate and self-monitor? Are the Fitbit data shared with the physiotherapists or the researcher?

   Self-monitoring of behavior, such as that provided by counting steps with a Fitbit, is a fundamental component of most behavior change strategies, and has also been a central component of successful exercise interventions among individual living with or recovering from cancer (Bourke L. et. al. Interventions for promoting habitual exercise in people living with and beyond cancer. *Cochrane Database Syst Rev.* 2013). As such, it is provided to all participants in the study and is not a component of the PEP intervention that is specifically being evaluated (i.e., participants in both treatment groups receive Fitbits). Fitbit data are not shared with the team of investigators. We have added clarifying text to the revised manuscript as follows:

   Page 11: 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.[62]

6. Control patients will be encouraged to increase walking. How is this monitored? By the 7-day PA recall phone interview, or do the control patients also get the exercise diaries? This is not totally clear.

   The encouragement for more walking is part of HCI's usual care. This is not part of the intervention and not monitored. However, physical activity levels across both groups will be measured by using the 7-day physical activity recall phone interview. We elaborate this information as follows:

   Page 13: 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.

   Page 14: […] 7-day physical activity recall phone interview to monitor and compare physical activity levels across study arms […]

7. The description of the secondary endpoints is very short. In Table 3 follow-up questionnaires are mentioned – could you define these questionnaires?

   To address this comment, we have revised the paragraph on secondary endpoints. When the name of the instrument is not self-explanatory, we provide more details on the measured domain. The revised paragraph reads now as follows:

   Page 14: 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) 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);[68] the Functional Assessment of Cancer Therapy-Lung (FACT-L),[69] 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),[70][71] and 7-day physical activity recall phone interview to monitor and compare physical activity levels across study arms,[72] Diet History Questionnaire II (DHQII) to collect information on dietary lifestyle factors,[73] self-efficacy by Sallis JF,[74] Modified Differential Emotion Scale (mDES) to capture emotional experiences;[75] Social support for exercise by Sallis JF,[76] Subjective Social Status Ladders,[77] and financial strain [78] to assess social status, loneliness by Cacioppo;[79] 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[80] at 2 to 6 month follow-up. We will test former smokers to assess smoking recidivism by collecting and analyzing saliva samples. Given that patients are required to quit smoking before they are eligible to undergo surgery, saliva samples will only be taken at the 6 month clinic visit. Smoking history will be assessed prior to undergoing surgery using standardized questionnaires.

We have further reviewed table 3 and refer to the revised Section 3 for more information on questionnaire instruments that are used in the follow-up questionnaires.
Table 3:
Follow-up questionnaires (for details on questionnaire instruments please refer to section 3)

8. It is not mentioned in the text that saliva samples are taken – for what? Only to assess smoking status? Why is this not done at baseline?

   We agree that this information has to be added in the text. Details on the saliva sample collection are included in the revised manuscript as follows:

   Page 15: 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.

9. Statistics: Only statistics for the primary endpoint are described. How will the repeated measurements be analyzed – using mixed effects models?

   We thank the reviewer for the advice to add this information in the manuscript. We have revised the section on the statistics as follows:

   Page 15: Mixed effects models with random intercept will be used for analysis of repeated measurements.

10. Using ANCOVA in RCTs, missing data on the outcome do not need to be imputed necessarily. See: Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol. 2012;175:210–217. doi: 10.1093/aje/kwr302.

    We thank the reviewer for the reference. Our experience has been that journals have required an intent to treat analysis of all randomized participants for the primary analysis of randomized clinical trials. For this reason we proposed to use multiple imputation in the study design.

11. On page 14, the authors mentioned that a pilot study has been performed, but they provide no feasibility results (in the study protocol they do). The protocol paper would definitely profit from

providing results on feasibility, intervention uptake and also experiences with the AM-PAC stratification.

We thank the reviewer for the positive feedback. We have added more detailed information on the pilot study as follows:

Page: 16: 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 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.

Very minor:

12. Page 5, line 29: delete 'a'; and Page 8, line 26: delete '.'

> **We have addressed this comment accordingly.**

Reviewer 2
Reviewer Name: Brian C Focht, PhD FACSM, CSCS Institution and Country: The Ohio State University, USA Please state any competing interests or state 'None declared': N/A

This protocol paper discusses the rationale and design of the Precision-Exercise-Prescription (PEP) in Lung Cancer Patients Undergoing Surgery randomized clinical trial. This study is proposed as a phase III clinical trial designed to test the clinical effectiveness and feasibility of a personalized exercise intervention in lung cancer patients undergoing surgery. With the vast impact of lung cancer-related morbidity and mortality and the need for more theory-based, effective and feasible physical activity interventions in the lung cancer patient population, this protocol would certainly be of interest to the readership of BMJ Open. There are notable strengths of the study rationale and design. The potential significance of the study is discussed including details of how results from the study may potentially impact current clinical standard-of-care practices. The study design includes both objective and patient reported measures of mobility and physical performance. In addition, the protocol employs evidence-based psychological constructs and behavioral strategies which have been successfully used to promote exercise adoption and adherence. Overall, the authors have developed a pragmatic and conceptually-sound approach which acknowledges the importance of individualized tailoring of exercise, is aligned with the extant evidence supporting a multi-disciplinary approach to improving cancer rehabilitation and survivorship, and aims to evaluate the cost-effectiveness of delivering such an intervention. However, there are a few methodological concerns which detract from the potential impact of the paper. While most concerns reflect issues which simply require clarification, other select concerns necessitate more detailed justification or reinterpretation.

1. Including a more detailed and specific description of the primary hypothesis in the introduction. For example, I suggest including the hypothesis text in section 4, would enhance the clarity to the rationale.

We thank the reviewer for the positive feedback. In order to clarify the primary hypothesis, we have improved the text in the revised manuscript. The introduction reads now as follows:

Page 6: We hypothesize that lung cancer patients undergoing surgical resection will improve their physical function from 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.

2. The description of the exercise resources available to participants and their associated monetary cost should be more clearly articulated. For example, will all participants have equal access to the wellness center? For those engaging in home exercise, what equipment will be provided and will there be an associated monetary burden on participants? Explicitly addressing in each of these aspects will be particular instructive with regard to the comparability of the exercise arms and their respective cost-effectiveness.

We thank the reviewer for this great advice. We agree that differences in accessibility to exercise across the study groups need to be more clearly stated. The information has been added to the revised manuscript as follows:

Page 12: 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.

3. A more detailed description of the exercise intervention/prescription is warranted. The types of exercises performed by the participants should be more clearly articulated. The description of the exercises is quite general. Added specificity of these descriptions would add clarity to the range of exercises performed and the modalities utilized to perform the exercises based on individual functionality of each participant.

Please refer to reviewer 1 comment 3.

4. The procedures for using the exercise diary/calendar mechanisms available to participants need to be more clearly articulated. Although each participant will have a general exercise guideline as determined by AM-PAC score and therapist prescription, will they be required to record daily frequency, duration, sets, repetitions, or intensity of exercise? How will feelings of well-being be recorded such as perceived exertion and pain associated with exercise?

We have added the following:

Page 10: 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 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.

5. Self-efficacy is mentioned as a secondary endpoint to be explored. However, given the multi-dimensional, behavior specific nature of self-efficacy measures, more detailed description of the measures are warranted. I urge the authors to clarify the type of self-efficacy being measured (i.e. task, barrier, self-regulatory self-efficacy), the rationale for including this assessment, as well as the psychometric properties of the measure.

The current study uses the Self-Efficacy and Exercise Habits Survey (Sallis JF et. al. The development of self-efficacy scales for health-related diet and exercise behaviors. *Health Education Research.* 1988), one of the most widely utilized Self-Efficacy scales in the world

(e.g., cited 747 times). The scale includes two subscales: 1) "resisting relapse/sticking to it", and 2) "making time to exercise". These subscales would be likely be classified as "self-regulatory" and "barrier" measures. Both subscales are reliable and valid. Test-retest reliability and coefficient alpha are 0.68 and 0.85 for resisting relapse/sticking to it, and 0.68 and 0.83 for making time to exercise. The revised manuscript reads now as follows:

Page 14: […] self-efficacy by Sallis JS (the scale includes two subscales: 1)"resting relapse/sticking to it", and 2)"making time to exercise"), […]

6. How will participant compliance to the constructs of the cognitive-behavioral portion of the intervention will be assessed? Promotion of self-monitoring, goal-setting, barrier problem-solving, and mastery experiences are listed as key elements of the MAPS method. Aside from the audio-recordings of the weekly telephone calls, are there any procedures in-place to evaluate each participant's level of mastery and successful development of these skills?

   We have added the following to the manuscript:

   Page 12: 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.

7. Inclusion of the proposed statistical analyses associated with the primary and secondary endpoints would add necessary detail to the statistical considerations section. Furthermore, explicitly addressing how missing data, attrition, and/or lack of adherence will be addressed in the analysis will also be particularly informative.

   We have added this information in the revised manuscript as follows:

   Page 16: Missing data will be handled by multiple imputation via chained equations, as implemented by the R package MICE.

VERSION 2 – REVIEW

REVIEWER	Anne May UMC Utrecht, NL
REVIEW RETURNED	11-Sep-2018

GENERAL COMMENTS	My comments have been well addressed. I have no further comments.

REVIEWER	Brian C. Focht, PhD The Ohio State University, USA
REVIEW RETURNED	25-Sep-2018

GENERAL COMMENTS	The revised manuscript has satisfactorily addressed all the concerns raised in the review of the initial version of the paper. I commend the authors for their efforts in revising the manuscript. I have no further revisions/comments at this time