



STUDY PROTOCOL

Prehabilitation during a pandemic: preoperative exercise to improve fitness in patients undergoing complex surgery for cancer of the lung or oesophagus, the PRE-HIIT trial: an updated study protocol [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Pre-operative fitness is an established predictor of postoperative outcome; accordingly, targeting pre-operative fitness through exercise prehabilitation has logical appeal. Exercise prehabilitation for patients with cancer of the lung or oesophagus is challenging to implement due to the short opportunity for intervention between diagnosis and surgery. In addition, there are now additional challenges to providing prehabilitation during the coronavirus disease 2019 (COVID-19) pandemic due to concerns about social distancing and minimising patient contact. The PRE-HIIT project will examine the influence of virtually delivered exercise prehabilitation on physiological outcomes and postoperative recovery. **Methods:** The PRE-HIIT randomised controlled trial (RCT) will compare a 2-week high intensity interval training programme to standard preoperative care in a cohort of patients with thoracic and oesophageal cancers. A protocol for this study has been published

Open Peer Review

Reviewer Status ? ✓

	Invited Reviewers	
	1	2
version 1	?	✓
07 Jan 2021	report	report
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previously. As a result of the COVID-19 pandemic, changes to the study assessment battery and the mode of intervention delivery have been made. The PRE-HIIT programme will now be a home-based intervention. Both the exercise intervention and standard care will be delivered via telehealth. The recruitment target for the study remains 78 participants. There is no change to the primary outcome of the study; cardiorespiratory fitness. Secondary outcomes include measures of pulmonary and physical function, quality of life and post-operative morbidity. Outcomes will be measured at baseline and post-intervention. The impact of PRE-HIIT on well-being will be examined qualitatively with interviews post-intervention (T1). This revised protocol will also explore participant's satisfaction with delivery of prehabilitation via telehealth. The healthcare costs associated with the PRE-HITT programme will also be examined.

Discussion: The overall aim of this RCT is to examine the effect of tailored, individually prescribed high intensity interval training on pre-operative fitness and postoperative recovery for patients undergoing complex surgical resections.

Trial registration: ClinicalTrials.Gov [NCT03978325](https://clinicaltrials.gov/ct2/show/study/NCT03978325) 07/06/2019

Keywords

Telehealth, multidisciplinary rehabilitation, exercise, diet, education

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Any reports and responses or comments on the
article can be found at the end of the article.

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Introduction

An Update on the Pre-HIIT Trial

This update relates to the PRE-HIIT study protocol, a randomized clinical trial examining the effect of a pre-operative high intensity interval training (HIIT) programme on cardiorespiratory fitness in patients scheduled for oesophagectomy and major lung resections. This update should be read in conjunction with the original protocol publication¹.

Cancer prehabilitation aims to reduce post-treatment morbidity and improve pre-treatment health status to increase treatment options. There are now multiple opportunities for prehabilitation in oncology care which require further exploration². However, due to the outbreak of the global Coronavirus disease 2019 (COVID-19) virus, there is a need to explore how to deliver safe and effective preparation for surgery during a pandemic. The original PRE-HIIT study involved the face to face delivery of hospital-based exercise training for patients awaiting major thoracic oncological resections. However, the current delivery of exercise based prehabilitation must balance minimising the risk of nosocomial spread of COVID-19 against optimising care for acute surgical conditions³.

It continues to be crucial to develop prehabilitation strategies which target modifiable risk factors, such as pre-operative fitness, which may have an impact on postoperative outcomes⁴. For patients in which social distancing recommendations or a COVID-19 infection resulted in them performing less physical activity than their usual baseline, an increase in physiologic operative stress related to cardiopulmonary deconditioning is expected. Decreased physical activity levels may present along with changes in other behaviours that are well documented to be associated with increased surgical risk, such as poor nutrition⁵. Therefore, it is as important as ever to optimise patient's preparation for surgery through delivering virtual prehabilitation exercise programmes when it is not permissible for participants to attend regular face to face exercise training sessions. The PRE-HIIT protocol has been updated to ensure investigation continues into how strategies, such as HIIT, can be used to optimise patients' post-operative outcomes during a global pandemic.

Study aims

The overall aim of this work remains unchanged from the original published protocol¹: to examine the impact of a pre-operative HIIT programme on the cardiorespiratory fitness of patients scheduled for major thoracic surgery (transthoracic oesophagectomy or major lung resection).

As per the original protocol, secondary aims will explore the impact of the intervention on physical fitness levels post chemo(radio) therapy, post-operative complications, post-operative physical recovery, and post-operative health care costs. Participants' experiences of prehabilitation will also be explored. In addition to these existing aims, this revised protocol will also explore participant's satisfaction with delivery of prehabilitation via telehealth.

Methods

Study design

As previously described¹, the PRE-HIIT trial will take the form of a two-armed randomised control trial (RCT); an intervention group who in addition to standard care will undertake a 2-week HIIT exercise programme (PRE-HIIT programme) in advance of their surgery, and a control group who receive standard care only which includes a moderate intensity physiotherapy led exercise programme. The PRE-HIIT programme will now be delivered as a home-based intervention. Both the exercise intervention and standard care will be delivered via telehealth. The study assessments will continue to take place in the Wellcome Trust-Health Research Board (HRB) Clinical Research Facility (CRF) at St James's Hospital (SJH), Dublin. Approval for this updated protocol has been granted from the Tallaght University Hospital (TUH)/St James's Hospital (SJH) Ethics Committee. The study will be performed according to the Declaration of Helsinki. The flow of participants through the study is depicted in [Figure 1](#).

Study participants

Inclusion and exclusion criteria are detailed elsewhere¹. In brief, participants must have a confirmed diagnosis of oesophageal or lung cancer, be scheduled for either a transthoracic oesophagectomy or major lung resection, be ≥ 2 weeks from their date of surgery at the baseline assessment, have medical approval to participate, successfully complete a cardiopulmonary exercise test (CPET), and be free from any contraindication for safe exercise prescription. To facilitate remote delivery of prehabilitation participants must also have high speed internet access suitable for video calling.

Recruitment and screening

Participant recruitment and screening procedures will take place in SJH, Dublin, Ireland and will be conducted as per the original protocol¹.

The recruitment target for the study remains 78 participants (39 per study arm). Potentially eligible patients will be informed about the study by a member of the research team (SJH) and will receive a participant information leaflet. Initial eligibility screening will be completed by the research team. In light of the current pandemic participants will give initial consent verbally over the telephone. A participant screening assessment will then be completed over the telephone and, if eligible, participants will be scheduled for an appointment in the Clinical Research Facility in St James's Hospital. In order to minimise face-to-face contact, where possible, assessment data will be collected via telephone/videocall (e.g. demographic data, dietary interview etc). Questionnaires will be provided to participants to complete before or after their face to face assessment. Written informed consent will then be obtained during the participants first face to face assessment (see extended data⁶).

Randomisation, allocation, concealment and blinding

Randomisation, allocation, concealment and blinding of participants will be conducted as per the original protocol¹.

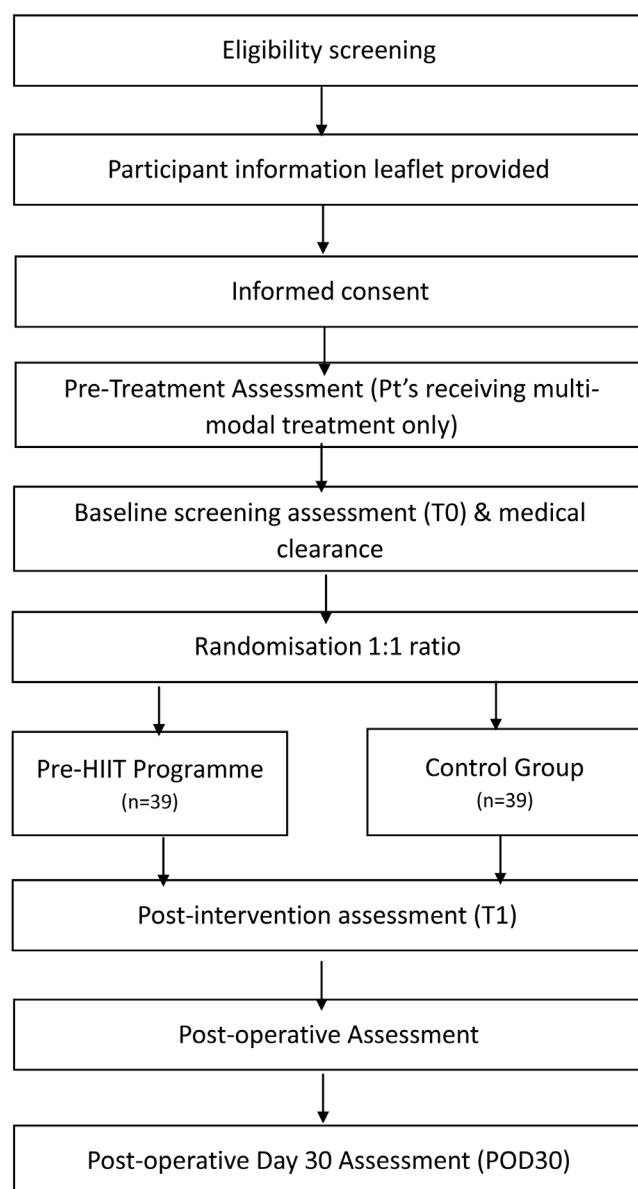


Figure 1. The PRE-HIIT trial outline.

In brief, participants will be randomised in a 1:1 ratio to the intervention or control arm by computer-generated randomisation. Study assessments will be performed by an assessor blinded to treatment allocation.

Intervention

PRE-HIIT intervention. The PRE-HIIT intervention prescription has been previously described¹. In summary the programme is a pre-operative HIIT training programme which is delivered for at least two weeks, five days per week in advance of surgery. Due to the COVID-19 pandemic, public health guidelines in Ireland now advise patients to self-isolate for two weeks in advance of their surgery. Accordingly, it is not appropriate to deliver

the intervention as per the original protocol which would involve participants attending the multiple hospital-based exercise sessions within that two-week preoperative period. As a result, participants assigned to the HIIT programme will complete the exercise intervention in their homes. All participants will be provided with a programmable bike on loan for the duration of their intervention. Participants will complete their first home exercise session under in-person supervision from a physiotherapist with experience in exercise prescription and exercise oncology. During the first session, the research team will set up the bike and familiarise the participant with the exercise protocol. All subsequent home exercise sessions will be supervised by a physiotherapist via video call. Exercise intensity will be monitored via Polar heart rate monitors (Polar M200) with information available remotely to the research team.

Maintenance of nutritional adequacy. As described previously, participants randomised to the intervention will receive an additional tailored dietetic assessment with the exercise programme to ensure nutritional adequacy is maintained throughout the duration of the intervention¹. Weight and height will be measured and BMI will be calculated. Dietary intake will be assessed using tailored dietary interview strategies (incorporating 24-hour recalls and qualitative information such as meal pattern and eating strategies). Moreover, gastrointestinal symptoms and dietary complications will be assessed and recorded. The dietetic assessment will now be carried out remotely via video call/telephone by a registered dietitian with experience working with surgical oncology patients.

Standard survivorship care group. The standard care control group will continue to receive standard medical care and nutrition support. This group will not be given specific advice regarding exercise beyond that considered usual medical care. This group will continue to receive standard pre-operative exercise advice and prescription of a moderate intensity exercise programme; now delivered via telehealth.

Outcomes

The updated PRE-HIIT study outcomes are listed in [Table 1](#). The main assessment battery will be performed at: diagnosis (Dx), baseline (T0), and post-intervention (T1). In addition, follow-up data will be collected post-surgery (T2).

In light of the current COVID-19 pandemic, face to face interaction time during assessments will be minimised with trial participants in order to protect participants and research staff whilst the pandemic continues. Where possible data will be collected via telephone/ videocall (e.g. demographic data, dietary interview etc.), and questionnaires will be provided to participants to complete before or after their face to face assessment.

Primary outcome – The primary outcome for the trial remains cardiopulmonary fitness, measured by a maximal cardiopulmonary exercise test. Testing will be carried out as previously described¹.

Table 1. Updated Pre-HIIT outcomes.

Outcome	Instrument	Diagnosis	Baseline	Post-intervention	Post-operatively
		Dx	T0	T1	T2
Primary outcome					
Cardiorespiratory fitness	Cardiopulmonary Exercise Test (CPET)	X	X	X	
Secondary outcomes					
<i>Pulmonary and Physical Performance</i>					
Functional performance	Short Physical Performance Battery (SPPB)	X	X	X	
Muscle Strength	Leg Press 1-RM	X	X	X	
Physical activity	International Physical Activity Questionnaire	X	X	X	
Pulmonary Function*	Spirometry				
Maximum Inspiratory Pressure*	PowerBreathe K-series				
Nutritional Status	Dietary interview	X	X	X	
Quality of Life	EORTC-QLQ-C30	X	X	X	X
Cancer specific quality of Life	EORTC-QLQ-OG25 (oesophago-gastric cancer)	X	X	X	X
	EORTC-QLQ-LC 13 (lung cancer)	X	X	X	X
Qualitative approach	Semi-structured interviews (1:1 via telephone)			X	
Cost analyses	EQ5D				X
	Service Use Inventory				X
Programme Acceptability	Acceptability Survey			X	
Post-operative Morbidity					
Post-operative outcomes	Self-reported Functional Recovery				X
	Postoperative Morbidity Survey*				X
	Clavien Dindo Score				X
	Comprehensive Complications Index				X
Other					
Adherence	Record in case report form/ exercise diary			X	
Sociodemographic details	Participant self-report		X		
Body composition	Anthropometry		X	X	
Cancer/Surgery history	Medical records		X		
Adverse events	Reports of patients/research personnel			X	

POD: Post-operative day, diagnosis (Dx), baseline (T0), and post-intervention (T1), post-surgery (T2).

*These measures will not be completed while the COVID-19 pandemic is ongoing

Secondary outcomes

Secondary outcome 1: Postoperative morbidity

No changes have been made to the measurement of postoperative morbidity. A suite of validated instruments will be used to collect data; the Clavien-Dindo Scale, the Postoperative Morbidity index (POMS) and the Comprehensive Complications Index (CCI).

Secondary outcome 2: Pulmonary and physical performance

Measures of pulmonary and physical performance include pulmonary function, ventilatory and peripheral muscle strength, functional capacity and self-reported functional recovery.

Secondary measures of pulmonary function and maximal inspiratory pressure (P_{Imax}) will not be completed with participants while the COVID-19 pandemic remains a concern due to the risk associated with aerosol generating procedures.

No changes will be made to measures of peripheral muscle strength (measured by 1 repetition max), self-reported physical activity (measured by the IPAQ), functional performance (measured by the short physical performance battery) or self-reported functional recovery.

Secondary outcome 3: Quality of life (QOL)

As per the original protocol, QOL will be measured using EORTC QLQ-C30 and relevant subsets at Dx, T0, T1 and on POD30. Disease specific modules such as the oesophageal EORTC QLQ-OES18 and QLQ-OES25 and the lung EORTC QLQ-LC 13 will be used in conjunction with the main questionnaire to monitor disease specific symptoms. QOL will be further measured using the EuroQol (EQ) EQ-5D-5L to analyse cost effectiveness of the intervention.

Secondary outcome 4: Programme acceptability

Patients will be asked to complete a self-administered survey to evaluate the acceptability of the PRE-HIIT programme delivered via telehealth⁷.

Qualitative approach

At the pre-surgery assessment (T1) a sub-cohort of the study's participants will take part in a semi-structured interview⁷. This interview will collect feedback on how the PRE-HIIT study has impacted on their preparation for surgery and participant satisfaction with the delivery of PRE-HIIT via telehealth. Interviews will be held via telephone/videocall with approximately the first 20 participants enrolled on the trial or until data saturation is reached.

Adherence

Adherence to the exercise component of PRE-HIIT will be measured with traditional adherence variables, i.e. completion of supervised home-based sessions, and monitoring of compliance to the prescribed exercise protocol. Compliance to the aerobic component will be documented by the achieved heart rates on the Polar heart rate monitors, and the duration of aerobic exercise. During the supervised home sessions compliance will be monitored by the supervising physiotherapist. During unsupervised homebased sessions participants will record their compliance in a home exercise diary. In addition to these traditional measures of adherence, PRE-HIIT will implement a series of drug trial adapted adherence outcomes as described by Nilsen *et al.*⁸. These additional adherence variables will include permanent treatment discontinuation, treatment interruption, dose modification, early session termination, and pre-treatment intensity modification. Updated adherence variables are described fully in [Table 2](#).

Safety

As previously described, prior to baseline testing, all participants will require written medical approval confirming their suitability for participation¹. Patients will only be formally enrolled in the study after successfully completing a CPET with electrocardiogram (ECG) monitoring. All CPET will be medically supervised. All incidents will be recorded, and serious incidents will be reported to the research ethics committees. An antibacterial/antiviral filter will be installed in the CPET circuit to minimise infection risk by reducing the amount of droplet

Table 2. Updated Pre-HIIT Adherence Variables.

Variable	Definition
Total number of supervised sessions attended	Total number of supervised sessions completed by the patient at home
Total number of compliant sessions completed	Total number of supervised aerobic sessions where target exercise intensity was achieved
Permanent treatment discontinuation	Permanent discontinuation of the PRE-HIIT programme
Treatment interruption	Missing at least two consecutive supervised PRE-HIIT sessions
Early session termination	Number of sessions requiring early session termination
Pre-treatment intensity modification	Number of sessions requiring modification because of a pre-exercise screening indication.

aerosol dispersion in the air mitigating the contamination of the environment during testing.

In response to the COVID-19 pandemic, all research staff will wear appropriate levels of PPE and will maintain physical distancing from participants where possible during all assessments and supervised exercise sessions. In line with infection control operating procedures, participants will be screened for symptoms of COVID-19 the day before their assessment/supervised home exercise session via telephone. Participants will be re-screened on arrival at the Clinical Research Facility for their assessment. Participants will be required to sanitise their hands on arrival and wear a surgical face mask. After each appointment the research team will remove all PPE in assessment area. The research team will wipe down all used surfaces with detergent wipes and perform hand hygiene.

Statistical considerations

Sample size calculation. As outlined previously, the primary response is the change in VO_{2peak} from baseline (T0) to post-intervention (T1). On the basis of estimates calculated from our pilot study, a sample of size 64 (32 in each arm) is needed in order to detect a mean difference in VO_{2peak} of 1ml/kg/min between the control and intervention groups.

Statistical analysis, data monitoring, dissemination, public and patient involvement. Information on the study Statistical Analysis, Data Monitoring, Dissemination, Public and patient involvement is described previously¹. A brief overview of each section is provided here:

Statistical analysis

Quantitative data analysis will be performed using R IBM SPSS software. Summary statistics for continuous variables and categorical will be presented. A linear mixed model will be used to model the longitudinal change in the primary response between the groups, allowing for missing data and allowing for within subject correlations in the repeated measures across time. The model will adjust for the baseline response variable and other covariates as necessary.

Qualitative data will be digitally audio-recorded and transcribed verbatim for data analysis. Braun and Clarke's 6 stage approach to thematic analysis will be used to analyse all data collected. A team of researchers will analyse all transcripts following an agreed process using nVivo 12 (QSR International, Australia).

Data monitoring

Data monitoring will be provided by the trial steering committee, including overall project supervision, progress monitoring, advice on scientific credibility and ensuring the integrity and appropriate running of the project. The research team will make quarterly reports to the trial steering committee.

Data management

The Data Management Plan⁷ will outline how research data will be handled during and after the project. The data management plan is a live document and will be reviewed regularly throughout the study. Source documents for this study will include hospital records, procedure reports and data collection forms. Outcome assessments will be recorded in a paper-based case report form. Data from the case report form will then be entered into a password protected computer data repository. Data validation will be used to avoid erroneous data entry. All participants will be allocated a unique study code. The key to the study code will be stored securely and separately. All paper records will be stored in locked filing cabinets, in a locked office in a restricted access building with swipe access. Electronic records will be stored on password protected encrypted devices. Upon completion of the trial an anonymised data set will be deposited on a secure online repository in line with open access publication requirements.

Public and patient involvement (PPI)

PRE-HIIT will involve a number of PPI initiatives. We will seek feedback on participant documentation, particularly the participant information leaflet and consent form, to ensure readability and clarity. In addition, a patient representative will be invited to speak at the education symposium in the final year of the project.

Dissemination of information

Findings of PRE-HIIT will be disseminated via peer reviewed publications and conference presentations. Aggregate study results will be presented to participants and their families at an education symposium upon study completion. Anonymised data will be made available on an open access repository.

Study status

Recruitment will begin in January 2021.

Discussion

The in-hospital delivery of prehabilitation is no longer a feasible approach to service delivery due to public health and patient safety concerns arising from the COVID-19 pandemic⁹. Prehabilitation delivered via telehealth presents an accessible means of providing home based exercise interventions for patients, while promoting patient safety and respecting governmental guidelines in view of the current and future pandemics¹⁰. HIIT exercise training stimulates great improvements in cardiopulmonary fitness over short periods compared to continuous aerobic training and therefore may be ideally suited to exercise prehabilitation¹. Adapting the PRE-HIIT trial to a virtually delivered exercise prehabilitation will allow further investigation into how exercise can attenuate postoperative risk and improve postoperative recovery, thus improving patient quality of life as well as having considerable economic benefits for the healthcare system.

Ethical statement

Ethical approval has been granted by the Tallaght University Hospital/St James's Hospital Research Ethics Committee (REC: 2020–02 List 7).

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: Prehabilitation during a pandemic: Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus, the PRE-HIIT trial: An Updated Study Protocol. <https://doi.org/10.17605/OSF.IO/9SEVW>⁶

This project contains the following extended data:

- 190329 APPENDIX I Pre-HIIT_Consent_Form_(PIL A+B) Version 1.0.docx

- 200715 PRE-HIIT Interview Guide Version 2.docx (Focus group/ interview guide)
- 201028 PRE-HIIT Data Management Plan (DMP) Version 4.pdf

Reporting guidelines

Open Science Framework: SPIRIT checklist for Prehabilitation during a pandemic: Preoperative Exercise to Improve Fitness in Patients Undergoing Complex Surgery for Cancer of the Lung or Oesophagus, the PRE-HIIT trial: An Updated Study Protocol. <https://doi.org/10.17605/OSF.IO/9SEVW>⁶

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Acknowledgments

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Open Peer Review

Current Peer Review Status:



Version 1

Reviewer Report 29 July 2021

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Thank you for inviting me to review this updated study protocol. I read the original protocol cited and this updated protocol in response to the pandemic with great interest. This article concisely describes how the research team has adapted their original randomised controlled trial protocol in order to deliver the study intervention remotely, in place of the face to face, hospital based intervention in the original protocol. The research team has designed an interesting and important study that should contribute valuable knowledge in the areas of prehabilitation and telehealth.

Please consider the following comments:

Abstract:

Methods:

Lines 4-5 *"The PRE-HIIT programme will now be a home-based intervention. Both the exercise intervention and standard care will be delivered via telehealth."*

This does not indicate to the reader that the exercise will be supervised. It would be helpful to specify in the abstract that the exercise sessions will be carried out at home and will be supervised, remotely via telehealth.

Line 8 *"Outcomes will be measured at baseline and post-intervention"*

A number of the measures - including QOL and post-op outcomes - are described in the main text/table as being measured post surgery (T2). State this in the abstract also.

Main Text:

Methods:

Study Design Lines 4-5: specify that the exercise intervention will be supervised.

Study Participants Lines 5-6:

Recruitment and screening Lines 6-7: Are any other factors, other than internet access, to be considered or recorded during screening to assess if participants are suitable or willing to enrol in a study of exercise under remote supervision? For example, considerations regarding availability of appropriate device, technology literacy, acceptability of and/or space for exercise equipment within home.

Recruitment and screening Lines 9-10: *"Questionnaires will be provided to participants to complete before or after their face to face assessment."*

Specify how questionnaires will be administered and returned.

Intervention - PRE-HIIT intervention: Line 7-13: More information is required to consider reproducibility of home based remote HIIT session using the bike.

Will the home based bike be of similar or different specifications to the equipment in the original lab based environment?

It would be helpful to provide equipment details such as manufacturer and bike model. Specify how the bike will be programmed - e.g. to deliver the %PPO intervals as detailed in the original protocol or otherwise. Will the bike outputs (resistance, cadence) be monitored remotely by the physiotherapist or self-reported by participants?

Detail how, via what platform/software/method, the heart rate monitor and bike output information is monitored remotely by the study team.

Intervention - Standard survivorship care group: Line 3-4: More detail regarding the moderate intensity programme prescribed to the standard care group is required. Is this a one-off session or continued input, is it individualised or generic advice?

Outcomes: Lines 6-9: *"Where possible data will be collected via telephone/videocall (e.g. demographic data, dietary interview etc.), and questionnaires will be provided to participants to complete before or after their face to face assessment."*

Specify how questionnaires will be administered and returned - in paper or electronic format, provided in person or via post/email? It is not clear *when* these questionnaires will be completed, will it be on the same day as the face to face assessment or within a timeframe either side of face to face assessment? If posted/emailed how will you ensure these are completed and returned?

Have you considered the validity of administering the instruments remotely or electronically, if required?

Qualitative approach: Line 2: ? incorrect citation

Adherence: Line 5-6 *"During the supervised home sessions compliance will be monitored by the supervising physiotherapist."*

The remote monitoring of heart rate and exercise output is not described. As above - will readings be visible to the physiotherapist during the video call or relayed remotely via a system/app/platform?

The use of additional adherence variables as per Nilsen et al. is an interesting approach which will provide a valuable addition to the process evaluation of the trial.

Safety:

There is no mention of the safety considerations of changing from a face to face, hospital/lab based exercise intervention to a remotely supervised home-based intervention. Will the delivery of the intervention sessions remotely require any additional procedures to mitigate, or respond to, any potential incidents or adverse events? If the research team have considered or identified any differences in risk between the original intervention and the remote intervention then how they will be managed should be described.

I will look forward to seeing the results of this trial.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exercise oncology, physiotherapy, physical activity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 26 January 2021

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Lisa Loughney

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Roisin Tully 

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Thank you for inviting me to review this interesting and important study.

Well done to the authors on adapting the protocol to continue research during the pandemic. Home-based exercise programmes and telehealth are important to investigate as it allows for

ease of access to those who live outside of Dublin.

We have some minor comments and suggestions outlined below:

Abstract

Methods

L 3-13

Suggest rephrasing L 3 – 13 as I believe pulmonary function and maximal inspiratory pressure will not be measured in the new protocol. Additionally, describe the standard care group. Suggested rephrasing is provided below:

The PRE-HIIT randomised controlled trial (RCT) will compare a 2-week high intensity interval training programme to standard preoperative care in a cohort of patients with thoracic and oesophageal cancers. A protocol for this study has been published previously. The recruitment target for the study remains 78 participants. Outcomes will be measured at baseline and post-intervention. There is no change to the primary outcome of the study which is cardiorespiratory fitness. Secondary outcomes include measures of physical function, quality of life and post-operative morbidity (pulmonary function and maximal inspiratory pressure will not be measured). As per previous protocol, the impact of PRE-HIIT on well-being will be examined qualitatively with interviews post-intervention (T1) and the healthcare costs associated with the PRE-HITT programme will also be examined. However, as a result of the COVID-19 pandemic, the new protocol includes that some assessments to be conducted over phone/videocall to minimise patient contact time. Additionally, the PRE-HIIT programme will now be a home-based intervention and supervised via telehealth. The standard care will receive x x x and will also be delivered via telehealth. Furthermore, participant's satisfaction with delivery of prehabilitation via telehealth will be explored.

Main Text

Introduction

Paragraph 3, L2-3 Suggest rephrasing to read as:

However, at present, there is a need to explore how to deliver safe and effective pre-operative interventions to prepare patients for surgery during the outbreak of the global Coronavirus disease 2019 (COVID-19) virus.

Paragraph 3, L5-6 Suggest rephrasing to read as:

The current delivery of the exercise prehabilitation intervention however allows us to minimise the risk of nosocomial spread of COVID-19 and at the same time optimise care for acute surgical conditions³.

Paragraph 3, L1-2 Suggest rephrasing to read as:

Targeting modifiable risk factors such as pre-operative fitness is crucial and it may have an impact on postoperative outcomes⁴.

Paragraph 3, L3-6 Suggest rephrasing to read as:

It is possible that social distancing recommendations (including lockdowns) and acquiring a COVID-19 infection may result in reduced physical activity levels which in turn may increase physiologic operative stress due to cardiopulmonary deconditioning.

Paragraph 3, L 9-11 Suggest rephrasing to read as:

The PRE-HIIT protocol has been updated to ensure investigation continues into how strategies, such as HIIT, can be used to optimise post-operative outcomes during a global pandemic.

Methods

Study Design, L5-6

Both the exercise intervention and standard care will be delivered via telehealth.

- More information is required regarding the standard care group.

Study participants

To facilitate remote delivery of prehabilitation participants must also have high speed internet access suitable for video calling.

- How will you manage patient disappointment if those eligible don't have high speed internet? This will impact recruitment as many of this patient group may not have access to high-speed internet.
- More information on what standard care is in your hospital may answer this.

Intervention, Line 5-6

Participants will complete their first home exercise session under in-person supervision from a physiotherapist with experience in exercise prescription and exercise oncology. During the first session, the research team will set up the bike and familiarise the participant with the exercise protocol. All subsequent home exercise sessions will be supervised by a physiotherapist via video call. Exercise intensity will be monitored via Polar heart rate monitors (Polar M200) with information available remotely to the research team.

- How will you manage this under Level 5 lockdowns? More information is required on protective factors to ensure there is not transmission of infection. Could the participant possibly have a brief familiarisation session whilst on site for their CPET to avoid home visits? This needs to be elaborated on.

L 13-14

Exercise intensity will be monitored via Polar heart rate monitors (Polar M200) with information available remotely to the research team.

- Could you describe this further as this is really important component and one of interest.
- Although not part of the protocol, could the research team consider including resistance exercises given the strong evidence base that both aerobic and resistance exercise combined have positive benefits. If funding allows purchasing some dumbbells for participants would be a beneficial addition to the protocol. If funding precludes this, the research team would explore using body weight exercises or using household items (ACSM Guidelines for Exercise and Cancer 2019).

Maintenance of nutritional adequacy. L3-4

Weight and height will be measured and BMI will be calculated.

- Please add in when and by whom?

L5-6

Dietary intake will be assessed using tailored dietary interview strategies (incorporating 24-hour recalls and qualitative information such as meal pattern and eating strategies).

- Can you describe this further.

Standard survivorship care group. The standard care control group will continue to receive standard medical care and nutrition support. This group will not be given specific advice regarding exercise beyond that considered usual medical care. This group will continue to receive standard pre-operative exercise advice and prescription of a moderate intensity exercise programme; now delivered via telehealth.

- Can you describe this further as more information around the standard survivorship care group is important. Keep the terminology consistent throughout (standard care control group/standard survivorship care group). Also please address this in the abstract.

Outcomes

Paragraph 2, L1 Suggest rephrase to read as follows:

The duration of face-to-face assessments will be minimised to protect participants and research staff whilst the pandemic continues. Where possible data will be collected via telephone/videocall (e.g. demographic data, dietary interview etc.), and questionnaires will be provided to participants to complete before or after their face to face assessment.

- Where will participants fill out their questionnaires? Are they being posted out before/after face to face assessments?

Secondary outcomes

Secondary outcome 2: Pulmonary and physical performance

No changes will be made to measures of peripheral muscle strength (measured by 1 repetition max), self-reported physical activity (measured by the IPAQ), functional performance (measured by the short physical performance battery) or self-reported functional recovery.

- For IPAQ, would it be possible to measure PA using objective measurements such as PA monitoring. Many studies report that people with cancer over report their daily PA using IPAQ when compared to PA monitoring. If funding is not possible to assess this on all participants, a sub-study including IPAQ and PA monitoring would be interesting.

Secondary outcome 4: Programme Acceptability

Patients will be asked to complete a self-administered survey to evaluate the acceptability of the PRE-HIIT programme delivered via telehealth⁷.

- Will those receiving usual standard care complete this survey as they will also undertake a moderate intensity programme delivered via telehealth?

Adherence, L3-4

During unsupervised homebased sessions participants will record their compliance in a home exercise diary.

- Will participants be advised to exercise outside the supervised session? This needs to be described further.

In addition to these traditional measures of adherence, PRE-HIIT will implement a series of drug trial adapted adherence outcomes as described by Nilsen *et al.* These additional adherence variables will include permanent treatment discontinuation, treatment interruption, dose modification, early session termination, and pre-treatment intensity modification. Updated adherence variables are described fully in Table 2.

- This is a very impressive approach to reporting adherence. Is this a new addition also? If so add to abstract. Please can you further describe each as this is an important component of exercise interventions. I know it is outlined in the Table but more information should be provided in the main text.

Public and patient involvement (PPI)

PRE-HIIT will involve a number of PPI initiatives. We will seek feedback on participant

documentation, particularly the participant information leaflet and consent form, to ensure readability and clarity. In addition, a patient representative will be invited to speak at the education symposium in the final year of the project.

- You may have already done this but PPI should assist in final trial protocol including design and processes. If you have done this add to the new protocol and if not the research team should consult PPI on the new protocol.

Discussion, L1 Suggest rephrasing to read as follows:

The in-hospital delivery of prehabilitation is no longer a feasible approach due to public health and patient safety concerns arising from the COVID-19 pandemic⁹.

L3-4

Prehabilitation delivered via telehealth presents an accessible means of providing home based exercise interventions for patients, while promoting patient safety and respecting governmental guidelines in view of the current and future pandemics.

- Do you mean current and future lockdowns?
- As the health care costs will be examined, could you give details on what effect this might have on future planning of service delivery both in the context of during and after the COVID 19 pandemic?

Other:

Will COVID 19 status be recorded pre- or post-operatively?

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dr Lisa Loughney – Clinical Exercise Physiology, Cancer Prehabilitation. Dr Roisin Tully – Surgery, Cancer Prehabilitation.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.
