



PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma

O'Connor, D., Brown, M., Bowdery, R., Eatock, M., Hulme, C., Maraveyas, A., Robinson, R., Turkington, R. C., Vince, R., Wadsley, J., & Prue, G. (2020). PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma. *AMRC Open Research*, 2(22), 1-17. <https://doi.org/10.12688/amrcopenres.12907.1>

[Link to publication record in Ulster University Research Portal](#)

Publication Status:

Published (in print/issue): 08/06/2020

DOI:

[10.12688/amrcopenres.12907.1](https://doi.org/10.12688/amrcopenres.12907.1)

Document Version

Publisher's PDF, also known as Version of record

Document Licence:

CC BY

General rights

The copyright and moral rights to the output are retained by the output author(s), unless otherwise stated by the document licence.

Unless otherwise stated, users are permitted to download a copy of the output for personal study or non-commercial research and are permitted to freely distribute the URL of the output. They are not permitted to alter, reproduce, distribute or make any commercial use of the output without obtaining the permission of the author(s).

If the document is licenced under Creative Commons, the rights of users of the documents can be found at <https://creativecommons.org/share-your-work/ccllicenses/>.




Take down policy

The Research Portal is Ulster University's institutional repository that provides access to Ulster's research outputs. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact pure-support@ulster.ac.uk



STUDY PROTOCOL

REVISED **PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma [version 2; peer review: 1 approved, 1 approved with reservations]**

Dominic O'Connor ¹, Malcolm Brown¹, Roy Bowdery ², Martin Eatock³, Claire Hulme⁴, Anthony Maraveyas⁵, Rebecca Robinson⁶, Richard C. Turkington^{3,7}, Rebecca Vince⁸, Jonathan Wadsley⁹, Gillian Prue ¹

¹School of Nursing and Midwifery, Queens University, Belfast, Northern Ireland, UK

²Patient and Public Involvement (PPI) representative, Pancreatic Cancer UK, London, UK

³The Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, Belfast, Northern Ireland, UK

⁴Institute of Health Research, University of Exeter Medical School, Exeter, UK

⁵Joint Centre for Cancer Studies, The Hull York Medical School, Faculty of Health Sciences, Castle Hill Hospital, Hull, UK

⁶English Institute of Sport, Sheffield, UK

⁷The Patrick G Johnston Centre for Cancer Research, Queens University, Belfast, Northern Ireland, UK

⁸Department of Sport, Health and Exercise Science, University of Exeter, Hull, UK

⁹Weston Park Cancer Centre, Weston Park Hospital, Sheffield, UK

V2 First published: 08 Jun 2020, 2:22
<https://doi.org/10.12688/amrcopenres.12907.1>

Latest published: 17 Aug 2020, 2:22
<https://doi.org/10.12688/amrcopenres.12907.2>





Abstract

Background: Patients with resectable pancreatic ductal adenocarcinoma (PDAC), undergoing adjuvant chemotherapy can experience an array of complications including fatigue, pain and the loss of physical function. Accumulating evidence from largely early stage breast cancer studies supports exercise as an adjunct therapy to help mitigate treatment complications. However, there is a lack of evidence of its feasibility in pancreatic cancer. The purpose of this study is to explore the initial feasibility of delivering a supervised, individualized, and progressive concurrent exercise intervention to individuals with resectable PDAC who are undergoing adjuvant therapy.


Methodology: Ten patients with resectable PDAC undergoing adjuvant chemotherapy will be recruited. Clinical care teams will screen patients against inclusion criteria to determine eligibility. All enrolled participants will complete a 16-week, supervised, tailored, moderate intensity exercise intervention consisting of aerobic and muscle strengthening activities. The primary outcome will be feasibility of delivering a supervised exercise intervention. Secondary outcomes will include measures of physical fitness, fatigue, and

Open Peer Review

Approval Status  

	1	2
version 2		
(revision)		
17 Aug 2020	view	view
		
version 1		
08 Jun 2020	view	

1. **Emer Guinan**, University of Dublin, Dublin, Ireland

2. **Nathan H Parker** , The University of Texas MD Anderson Cancer Center, Houston, USA

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

quality of life. Outcomes will be measured at baseline (T1), 16 weeks (T2) and 3 months post intervention (T3). The feasibility, acceptability and potential utility of the supervised exercise intervention will be explored qualitatively through semi-structured interviews with key stakeholders (e.g. active participants, eligible participants that declined participation and the research staff including exercise physiologists and recruiting clinicians). The use of health and social care services, medications and personal expenses incurred during the trial will also be used to determine cost-effectiveness of this intervention and a potential further RCT in PDAC.

Discussion: The overall aim of this study is to determine the utility of a supervised, tailored, moderate intensity exercise intervention in PDAC patients undergoing adjuvant chemotherapy. This feasibility study will help inform the design of future randomised controlled trials to determine the efficacy of the exercise intervention in PDAC.

Keywords

supervised exercise, pancreatic cancer, aerobic, strength, feasibility



This article is included in the [Pancreatic Cancer UK gateway](#).

Corresponding author: Dominic O'Connor (dominic.oconnor@qub.ac.uk)

Author roles: **O'Connor D:** Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation; **Brown M:** Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Bowdery R:** Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Eatock M:** Conceptualization, Methodology, Resources, Writing – Review & Editing; **Hulme C:** Methodology, Resources, Writing – Review & Editing; **Maraveyas A:** Conceptualization, Funding Acquisition, Writing – Review & Editing; **Robinson R:** Conceptualization, Funding Acquisition, Writing – Review & Editing; **Turkington RC:** Conceptualization, Funding Acquisition, Methodology, Resources, Writing – Review & Editing; **Vince R:** Funding Acquisition, Methodology, Writing – Review & Editing; **Wadsley J:** Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Prue G:** Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by Pancreatic Cancer UK [grant reference: 2018RIF_12].
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2020 O'Connor D *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: O'Connor D, Brown M, Bowdery R *et al.* **PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma [version 2; peer review: 1 approved, 1 approved with reservations]** Health Open Research 2020, 2:22 <https://doi.org/10.12688/amrcopenres.12907.2>

First published: 08 Jun 2020, 2:22 <https://doi.org/10.12688/amrcopenres.12907.1>

REVISED Amendments from Version 1

This version includes an updated introduction which considers the impact of covid-19 on supervised exercise delivery. Further details have been included in the methodology around the exercise prescription and an exercise intervention outline has been provided. This gives the reader a greater understanding of the tailoring of the interventions to each individual. An amendment to include home-based exercise under restrictions imposed by covid-19 has been included. As it was incorrect in the published version 1, author Rebecca Vince's affiliation has now been corrected to "Department of Sport, Health and Exercise Science, University of Hull, Hull, UK".

Any further responses from the reviewers can be found at the end of the article

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas, representing 90% of all pancreatic neoplasms¹. PDAC accounted for approximately 458,000 new cases and 432,000 mortalities in 2018, making it the 14th most common and 7th deadliest cancer worldwide². However, epidemiological evidence suggests that age standardized incidence rates have been steadily increasing with figures between 1974–2014 estimating a 1.03% annual rise³. As such, current data from the United States predicts PDAC will surpass breast, prostate and colorectal cancer to become the 2nd most common cause of cancer related mortality by 2030⁴. The late presentation of symptoms and a lack of effective screening methods, means a large proportion (80–90%) are diagnosed with unresectable advanced disease, contributing to an unfavorable prognosis and dismal 5-year survival rate of ~5%⁵. For those suitable for potentially curative resection, followed by adjuvant chemotherapy, patient survival is improved⁶, although 3-year and 5-year survival rates stand at 63.4% and 28.8%, respectively^{7,8}.

Intensive cancer treatments (i.e. surgery and chemotherapy) have debilitating complications including fatigue, pain and impaired physical function⁹. Following surgical resection, measures of aerobic fitness (VO_{2peak}) using cardiopulmonary exercise testing and muscular strength, via handheld dynamometry, in PDAC patients can be significantly lower than healthy normative values (VO_{2peak} : 18–24%; strength: 12–15%)¹⁰. When combined with common complications in pancreatic cancer such as a high prevalence of unintentional weight loss (seen in ~90% at diagnosis) and psychological distress¹¹, these can have a significant impact on quality of life. Therefore, the maintenance of physical function and quality of life are seen as primary treatment goals for pancreatic patients, particularly during adjuvant therapy¹². Taken together, the evidence presents a strong case for the implementation of supportive care interventions to help alleviate disease and treatment related complications and improve quality of life.

Exercise training is emerging as an accepted component of patient care and evidence suggests regular exercise may induce an

array of physiological and psychosocial benefits¹³. Observational data indicates that consistent exercise participation can significantly reduce pancreatic cancer risk by 26% (RR= 0.74, 95 % CI 0.61–0.90)¹⁴. For those with a cancer diagnosis, current exercise guidelines recommend moderate intensity aerobic (3x/week for at least 30 minutes) and resistance exercise (2x/week), as well as avoiding prolonged inactivity, to help address health-related/clinically-relevant outcomes including fatigue, physical function and quality of life¹³. However, data underlying these guidelines was predominantly obtained from breast cancer trials, due to their high prevalence and survival estimates¹⁵. Currently, there is a paucity of research in cancer populations with lower prevalence, poorer prognosis and higher symptom burden. As such, scientific evidence in PDAC is lacking. To date only three randomized controlled trials (RCTs) involving exercise training have been carried out in pancreatic cancer, with only one including participant's post-resection solely^{16–18}. Yeo *et al.* (2012) demonstrated in 102 participants with resectable pancreatic and periampullary cancer that exercising (90–150mins/week, home-based progressive walking) during adjuvant therapy may be beneficial, with improvements in self-reported levels of pain, fatigue and physical functioning reported after 12 weeks. A noteworthy but non-significant trend towards improved survival was also observed in the intervention group with a hazard ratio of 1.3 (CI 0.7 to 2.5), $p=.56$ for the usual care group¹⁶.

Several other clinical studies have shown exercise to be safe and feasible in PDAC, and reported improvements in physical function and quality of life outcomes both during neo-adjuvant therapy^{19–23} and during adjuvant treatment^{24–26}. A common theme of these studies is their home-based nature. Home-based, unsupervised exercise can overcome common barriers to exercise participation (e.g. access, motivation, transportation and cost)²⁷, especially in response to the recent SARS-CoV-2 (coronavirus) pandemic and associated societal restrictions²⁸. Supervised face-to-face exercise, in the age of SARS-CoV-2, poses considerable risk to vulnerable cancer patients (e.g. aerosol and surface viral transmission) thus the utility of home-based exercise is becoming increasingly widespread in the cancer setting, with digital technology harnessing delivery and remote monitoring / supervision²⁸. However, supervised exercise typically provides the greater benefits to patients on physical function and quality of life outcomes²⁹. As such, where restrictions permit, patients with cancer at high risk for undertaking an exercise intervention (i.e. deconditioned, poor performance status) should still ideally receive face to face supervised exercise²⁸.

Evidence reporting the effects of supervised concurrent exercise in PDAC is largely derived from case studies. An account by Cormie *et al.* (2014) demonstrated 6-months of supervised, progressive, moderate to vigorous intensity concurrent exercise (aerobic: 65–80% maximum heart rate; resistance: 12–6 repetition maximum) in a patient with stage IIB disease undergoing adjuvant chemotherapy, was safe and improved physical capacity, functional ability and quality of life. Recently, McLaughlin *et al.* (2019) reported similar improvements in functional capacity and quality of life in a stage III pancreatic cancer

patient with unresectable disease, following 12 weeks of concurrent exercise (aerobic: 70% HR_{max}, resistance: 60% 1RM 2x/week), delivered during chemotherapy. High intensity exercise has also been shown to be safe in those with PDAC, with aerobic and resistance exercise intensities of 70–80% watt maximum and 70–80% 1RM achievable in a patient with advanced disease²⁴. Of note, all three studies reported a maintenance of body mass and an increase in lean body mass. Since body composition has been cited as a predictor of treatment toxicity, these findings are clinically relevant in PDAC³⁰. Therefore, exercise-induced physiological improvements may aid treatment tolerance, mitigate toxicities and facilitate maximal treatment doses. However, there is a lack of evidence on the feasibility of delivering supervised exercise interventions to individuals with resectable PDAC undergoing adjuvant therapy. This study aims to explore the initial feasibility of delivering a supervised, individualized, and progressive concurrent exercise intervention to individuals with resectable PDAC who are undergoing adjuvant therapy, and provide data required to design a future RCT.

Specific objectives for this study include:

- To investigate the safety and acceptability to the participants of the supervised, individualized and progressive exercise intervention delivered during adjuvant therapy;
- To generate information required to design a full-scale RCT including; 1) recruitment, attrition and exercise adherence rates, 2) determine optimal study design and data collection procedures, 3) participant and clinician perceptions of the intervention, 4) assess the preliminary efficacy of the intervention to improve health related outcomes.

Methods

This is protocol version 4.0.

Study design

This feasibility study is a single-arm trial, with repeated outcome measures prior to commencing adjuvant chemotherapy (T1), at 16 weeks (T2) and 3 months (T3). The total duration of the trial, from patient enrollment to completion will be 7-months. [Figure 1](#) depicts the flow of participants through the study. The study will be coordinated by Queens University Belfast and conducted at a single site, the Northern Ireland Cancer Centre, Belfast (Belfast Health and Social Care Trust). All participants will be assigned to the exercise intervention to establish feasibility and provide justification for future RCT. This trial was registered in March 2020 with ClinicalTrials.gov (Trial ID: [NCT04305067](#)).

Study setting and participants

Participants will be identified and recruited from chemotherapy outpatient clinics in the Northern Ireland Cancer Centre (Belfast, Northern Ireland). The clinical care team will be provided with the eligibility criteria for study participation before each outpatient clinic. Clinicians will be the trial gatekeepers and review each clinic list to identify suitable participants for inclusion in the study. Following this, the lead investigator

will liaise with members of the clinical care team and approach identified participants who were deemed eligible and expressed an interest. Written informed consent will be obtained from each participant, after they have been given sufficient time to review the study information pack³¹. The inclusion and exclusion criteria are detailed below. This protocol has been developed using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see *Reporting guidelines* for completed checklist³¹).

Eligibility criteria. *Inclusion criteria:* 1) histologically proven PDAC; 2) aged ≥ 18 years; 3) at least 3 months post-surgery, recovering from a Whipple's procedure or distal pancreatectomy (R0 or R1 resection); 4) receiving adjuvant chemotherapy (5-fluorouracil or Gemcitabine and/or Capecitabine or 5-FU/leucovorin, irinotecan and oxaliplatin) and have tolerated at least 2 cycles; 5) Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1.

Exclusion criteria: 1) macroscopically remaining tumour (R2 resection or TNM stage IV disease); 2) chronic medical conditions which preclude exercise, including but not limited to congestive heart failure, unstable angina, recent myocardial infarction, breathing difficulties which require oxygen use, and osteoarthritis which causes significant mobility issues; 3) inadequate English language skills which precludes them from comprehending the trial information pack and completion of the studies outcomes measures.

Exercise intervention

Participants will receive a 16-week, individualized, progressive and auto-regulated exercise intervention (i.e. exercise volume and intensity will be altered according to daily variations in the participant's health, physical function, fatigue, and recovery capacity, with adjustments made each session according to the participant's capacity for exercise on the training day), consisting of structured moderate-intensity aerobic and resistance exercise ([Table 1](#)). The exercise intervention will be tailored for each participant according to their baseline physical function assessment, physical activity level, previous exercise experience, and presence of co-morbidities and medical history. All exercise sessions will consist of warm-up, aerobic exercise, resistance exercise (the order of exercise will alternate to avoid cross-interference between training modalities, e.g. week 1 – 4, aerobic completed before resistance; week 5 – 8, resistance completed before aerobic etc) and cool-down. Participants will be encouraged, if possible, to supplement supervised exercise with one self-managed aerobic exercise session weekly to enhance cardiovascular fitness.

The initial 4 weeks of the intervention will be used as a familiarization period, designed to introduce each patient to aerobic and resistance exercise, whilst developing exercise capacity. During the aerobic exercise component, intensity will be prescribed and monitored using the heart rate reserve (HRR) method and modified rating of perceived exertion (RPE), with speed / grade / resistance adjusted to elicit the target intensity. Aerobic exercise sessions will be delivered on a treadmill or cycle ergometer. The resistance exercise prescription will use non-linear

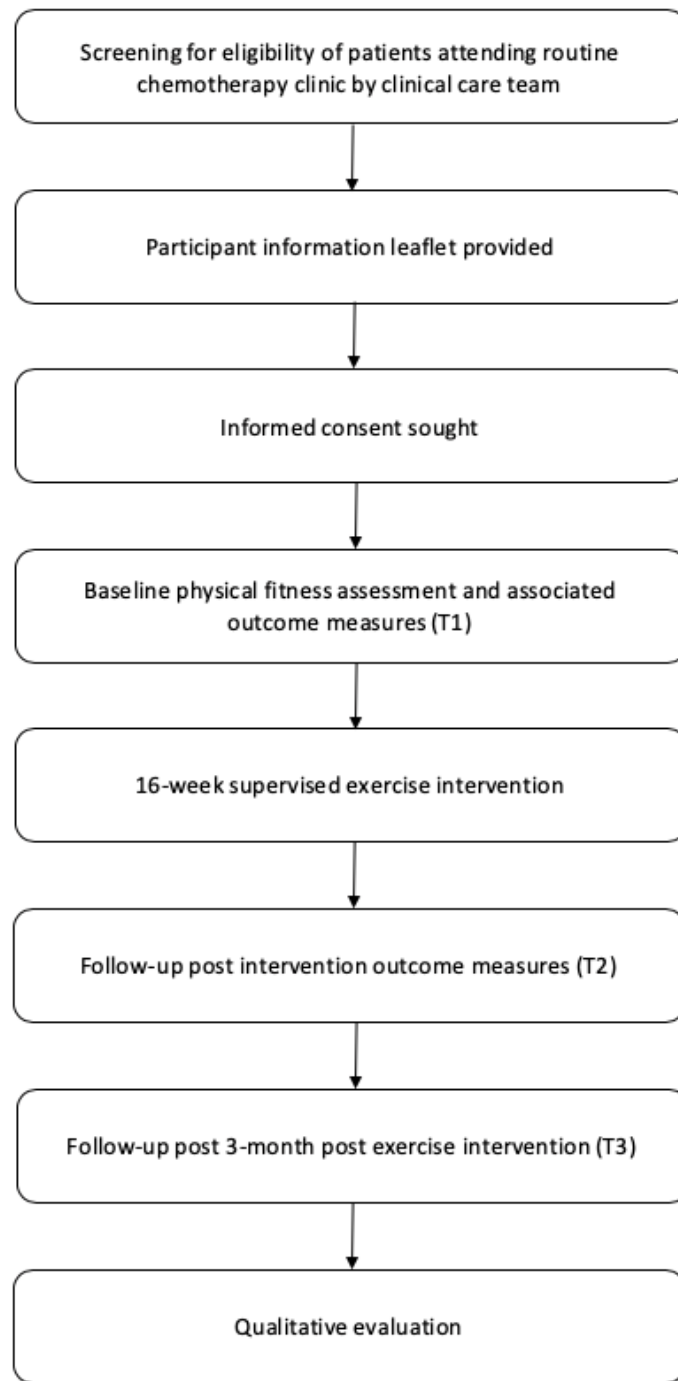


Figure 1. Study design and patient flow throughout the 16 weeks and follow-up.

periodization to maximize the training stimulus and physiological adaptations, whilst minimizing injury risk and training monotony. An auto-regulated, non-linear periodization model may enhance participant adherence³². Resistance intensity will be prescribed using individualized repetition maximum (RM). Resistance exercise will be performed at an intensity of 12 – 6

RM. Progression to higher training loads will be dependent upon the familiarization period and readiness to progress, through a review of the data and in consultation with each patient. Intensity will be monitored and adjusted throughout the intervention, with weights increased or decreased depending on the participant's capabilities.

Table 1. Exercise intervention prescription.

	Aerobic exercise				Resistance exercise		
	Frequency (x/wk)	Intensity		Time (mins)	Frequency	Intensity	Sets x reps
		HRR	RPE				
Week 1	2	40 – 45%	4-6	10	2	12 RM	1 x 12
Week 2	2	40 – 45%	4-6	10	2	12 RM	2 x 12
Week 3	2	40 – 45%	4-6	10	2	12 RM	3 x 12
Week 4	2	40 – 45%	4-6	10	2	12 RM	2 x 12
Week 5	2	40 – 45%	4-6	20	2	12 RM	3x 10
Week 6	2	45 – 50%	4-6	20	2	12 RM	3 x 10
Week 7	2	45 – 50%	4-6	20	2	10 RM	4 x 10
Week 8	2	45 – 50%	4-6	25	2	12 RM	2 x 12
Week 9	2	50 - 55%	4-6	25	2	10 RM	3 x 8
Week 10	2	50 – 55%	4-6	30	2	8 RM	3 x 6
Week 11	2	50 – 55%	4-6	30	2	8 RM	4 x 6
Week 12	2	50 – 55%	4-6	30	2	10 RM	2 x 8
Week 13	2	55 – 60%	4-6	30	2	8 RM	3 x 6
Week 14	2	55 – 60%	4-6	30	2	7 RM	4 x 6
Week 15	2	55 – 60%	4-6	30	2	6 RM	4 x 6
Week 16	2	55 – 60%	4-6	30	2	10 RM	2 x 8

SARS-CoV-2 (Coronavirus) protocol amendment: Home-based, remote supervised exercise

Due to restrictions imposed by the SARS-CoV-2 (Coronavirus) pandemic, amendments have been made to our intervention protocol to allow for home-based, remotely supervised exercise while supervised exercise sessions are not permitted. Exercise prescription and progression has been set in accordance with the ACSM guidelines¹³ and will follow the guide set out for supervised sessions (Table 1). Participants will be encouraged to maintain moderate intensity, corresponding to 4 – 6 RPE during all sessions. The preferred method of aerobic exercise is self-directed walking, although participants can choose other modes (e.g. cycling, interval). Aerobic exercise will not be remotely supervised, but adherence will be monitored using heart rate monitors and exercise diaries. Participants will be instructed to exercise with a family member / spouse. Digital technology (i.e. skype, zoom, facetime, WhatsApp) will be used to provide exercise instruction and guidance during resistance exercise sessions. Resistance exercise sessions were designed to target upper and lower body muscles and will be tailored to each participants capability. Exercise will be completed using body weight to begin. When exercises (sets / reps) can be completed without difficulty, participants will be instructed to increase resistance using the resistance bands provided. Participants will be

encouraged to supplement their home-based programme with one, self-managed aerobic exercise session per week.

Feasibility outcomes

The primary outcome is the feasibility of delivering an individualized and progressive supervised exercise intervention to patients with resectable PDAC, who have undergone surgery and have embarked on adjuvant therapy. Feasibility outcomes will be assessed at intervention completion (T2). As part of this primary objective we will collect data:

- To determine participant eligibility and recruitment rates. Recruitment will be measured as the number of fully enrolled participants as a proportion of approached eligible individuals. Recruitment strategies used will be assessed for future trials in this area.
- To assess adherence to the exercise intervention; intervention fidelity for both aerobic and resistance exercise will be measured by novel methods as described by Nilsen *et al.*³³ and Fairman *et al.*³⁴ to record deviations from the protocol. Specifically, we will record what was prescribed vs what was completed for each participant. This will be done by reporting the frequency of the

following events: permanent discontinuation (treatment discontinuation prior to week 16), treatment interruption (missing ≥ 3 consecutive sessions), dose modification [$\geq 10\%$ of sessions requiring modification (reduction / escalation) of intensity or duration], pre-treatment dose modification (reduction of pre-treatment session intensity), early session termination (termination of session prior to planned duration), and adherence (compliance with the planned dose/session).

- To determine attrition, which will be measured by attendance at baseline and post intervention.
- To determine the rate of adverse events in response to exercise. All exercise related adverse events will be recorded and reported.
- To explore the perceptions and experience of individuals with PDAC of taking part in the intervention.
- To explore the perceptions of individuals with PDAC who decline to take part in the intervention.
- To explore the perceptions and experience of exercise physiologists/clinicians in recruiting to and/or delivering the intervention. (All qualitative data will be collected through semi-structured interviews).

Efficacy outcomes

Secondary efficacy outcomes will be assessed at T1, T2 and T3. Although the study sample size is small and not designed to report on causation, changes from baseline will be measured to provide an indication of efficacy and detect differences. Below we detail the method of measurement for efficacy outcomes:

Physical fitness. Functional exercise capacity will be assessed using the six-minute walk test (6MWT) which is a valid and reliable assessment in individuals with cancer and the distance covered has been shown to be significantly correlated with VO_{2peak} ³⁵. This outcome will be assessed for feasibility as a primary outcome measure in a future RCT by looking at its appropriateness to the population (i.e. shows positive change), clinical relevance and ease of administration. The 6MWT consists of measuring the distance that a participant can walk on a flat, hard surface in a period of 6 minutes. Lower limb muscular endurance will be assessed using the 30 second sit-to-stand test (30STS). The 30STS is a simple assessment which can be easily administered clinically and is a reliable measurement instrument in individuals with cancer³⁶. During this test the participant is required to stand up from and sit down on a chair as many times as possible in 30 seconds.

Pain. Pain will be assessed using the Brief Pain Inventory Short Form (BPI-SF), a widely utilized tool to measure pain and recommended as a core outcome measure in clinical trials³⁷.

Fatigue. Fatigue will be determined using the fatigue subscale of the Functional Assessment for Cancer Therapy-Fatigue

Scale (FACT-F). This questionnaire is a reliable and validated measure of fatigue for clinical trials³⁸. This instrument includes 13-items related to physical fatigue and its effects on functional status.

Health related quality of life. Health-related quality of life (HR-QoL) will be assessed using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, which has been shown to be valid and reliable instrument for assessing HR-QoL in pancreatic cancer³⁹. This tool includes a general QoL measure with an additional hepatobiliary cancer subscale. The EuroQoL five-dimensional questionnaire (EQ-5D-5 L) will be measured at the same time to assess QoL⁴⁰. The EQ-5D-5L is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). It will be used as a general index of health status and an indication of health resource usage, to inform future trial cost-effectiveness.

Physical activity. The physical activity levels of each participant will be assessed subjectively using the International Physical Activity Questionnaire Short Form (IPAQ-SF). The IPAQ-SF is an easily administered 7-day recall tool to measure self-perceived exercise levels, exercise intensities and sedentary/sitting time of each patient.

Repetition maximum testing. Resistance exercise intensity will be prescribed using one-repetition maximum (1-RM). Prior to commencing the exercise programme, each patient will undergo repetition maximum testing on a pin-loaded chest press, seated row, leg press and leg extension. Ideally, a determination of 1-RM for each will be achieved within 5 lifts and recorded in kilograms. Correct lifting and breathing technique will be demonstrated beforehand (reinforced throughout) and patients will complete an incremental warm-up. During the programme, progression (i.e. weight lifted) will be closely monitored and adjusted to facilitate adaptations and in adherence with the principles of training. The purpose of RM testing is to ensure the programme is adequately tailored to the capabilities of each patient.

Health economics. Patients will complete a health economics questionnaire at T2. This questionnaire will detail the use of health and social care services, medications and personal expenses incurred during the trial. The questionnaire alongside the other evidence collected will be used to determine cost-effectiveness of this and a potential further RCT in PDAC.

Qualitative evaluation

Upon study completion (following T3), the impact and experiences of key stakeholders including active participants, eligible participants that declined participation and the research staff, including exercise physiologists and recruiting clinicians, will be collected via face-to-face semi-structured interviews³¹. Interviews will focus on the feasibility, acceptability and potential utility of the supervised exercise intervention. Participants who declined to participate will be given the opportunity to

discuss why they chose not to participate and provide information on what type of intervention, if any, they would participate in. Data from interviews will be tape-recorded and transcribed verbatim. Transcriptions of audio recorded interviews will be analysed using thematic analysis⁴¹. NVivo 12 (QSR International Pty Ltd., Doncaster, VIC, Australia) will be used to aid qualitative data management.

Sample size calculation

As this is a feasibility study, we have not performed a formal sample size calculation. We aim to recruit a convenience sample of 10 participants with PDAC.

Ethical approval

Ethical approval to conduct this study was obtained from the Office for Research Ethics Committees Northern Ireland (ORECNI) in October 2019 (IRAS Project ID: 265923). The study will be performed according to the Declaration of Helsinki. Any modifications to the study protocol will be determined as substantial or non-substantial. Substantial amendments will be agreed upon by Queens University, Belfast and Pancreatic Cancer UK and approved by the Office for Research Ethics Committees Northern Ireland (ORECNI) prior to implementation. Non-substantial amendments will be classified as minor. These will be agreed upon between Queens University, Belfast and Pancreatic Cancer UK. The ethics committee may be notified of non-substantial changes at the discretion of Queens University, Belfast.

Data management and monitoring

All data collected will be anonymized and stored securely in accordance with the EU General Data Protection Regulations (GDPR) 2018. Digital files will be stored on password protected computers and in password protected folders, at the study site in an accessed controlled building. Only members of the study management team will have access to this data for analysis and quality control purposes. Files containing personal identifiers will be stored separately in a locked cabinet, in a locked office, only accessible by the coordinator of the study. Study results will be submitted for publication and communicated in a relevant medical or scientific journal. Anonymity will be maintained, and unique identifiers will be removed in any subsequent outputs.

Data analysis

Data analysis will account for the number of participants screened, numbers participating in the intervention and the numbers unwilling to participate, after eligibility is confirmed with reasons for non-participation. This data will be examined using descriptive analysis to identify differences between participants and non-participants. Patient compliance, utilization and satisfaction with the intervention will be assessed, as will completion rates for the intervention and the outcome measures. The acceptability of the physical outcome measures and questionnaires used in determining health resource use will also be reported. All measures will be scored according to standard practice and analysed for mean changes between baseline, week 16 and 3 month follow up using a one-way repeated measures

analysis of variance (ANOVA). Data analysis will be performed in SPSS (Version 26 software, SPSS Inc, Chicago IL, USA). Preliminary feasibility results will inform the future RCT sample size calculation and the parameters for investigation to determine potential clinical meaningfulness. Transcriptions of audio recorded interviews will be analysed using thematic analysis. Miles and Huberman⁴² described the process of analysing qualitative data; this process consists of three steps that occur simultaneously: data reduction, data display and conclusion drawing/verification process. At each stage, findings will be verified and discussed by the research team in order to assess accuracy of the interpretation, promote inter-rater reliability and ensure rigour in the qualitative phase of the research⁴³. NVivo will be used to aid qualitative data management. Data generated during the intervention and from interviewing will assist in determining the safety and acceptability of the intervention.

Trial status

The PRECISE feasibility study is scheduled to open for recruitment in 2020, with a projected completion date scheduled for January 2022.

Discussion

For the 20% of patients diagnosed with resectable PDAC, both treatment and disease complications can impact physical function and impair quality of life. Exercise is a safe and well accepted adjunct therapy with a wide range of physiological and psychosocial benefits, which have been shown to help mitigate treatment and disease complications in highly prevalent cancers¹³. However, data in PDAC is relatively scarce. To our knowledge, no RCT to date has evaluated the effects of a supervised concurrent exercise intervention in participants with resected PDAC on adjuvant therapy. Data from three case studies has provided promising evidence of the safety and acceptability of moderate to vigorous intensity supervised concurrent exercise in participants with stage IIB to IV PDAC^{24,44,45}.

Due to problems that can undermine large scale evaluation studies such as intervention acceptability, intervention delivery and patient recruitment and retention, the Medical Research Council's (MRC) framework for developing and evaluating complex interventions provides an iterative phased approach to guide the research process⁴⁶. As such, feasibility studies are recommended following intervention development to help identify and mitigate problems prior to larger scale evaluations. This manuscript presents the protocol for PRECISE, a feasibility study determining the potential acceptability of a supervised, and progressive concurrent exercise intervention for individuals with resectable PDAC, currently receiving adjuvant chemotherapy. This feasibility study aims to provide preliminary data that will be used to inform the design of a future definitive RCT.

A limitation of the feasibility study is that this is a single site study and participants must be willing to travel regularly to the Northern Ireland Cancer Centre on days in which they are not scheduled for a clinic visit. To help reduce barriers to recruitment

for those living locally, parking costs at the site will be reimbursed. Should the PRECISE feasibility study be successful there is provision to include two further UK sites, which will increase overall sample size for a subsequent RCT, thus making the results more generalizable to the UK population.

Data availability

Underlying data

No data is associated with this article.

Extended data

Harvard Dataverse: PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma, <https://doi.org/10.7910/DVN/J5IKSN³¹>.

This project includes the following extended data:

- Consent Form – Interview Only Patient

- Consent Form – Interview Only Exercise Physiologist
- Consent Form – Full study
- Semi Structured Interview Schedule (Exercise Physiologist)
- Semi Structured Interview Schedule (Participants)
- Semi Structured Interview Schedule (Non-participants)

Reporting guidelines

Harvard Dataverse: SPIRIT checklist for ‘PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma’, <https://doi.org/10.7910/DVN/J5IKSN³¹>.

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

References

- Adamska A, Domenichini A, Falasca M: **Pancreatic ductal adenocarcinoma: Current and evolving therapies.** *Int J Mol Sci.* 2017; **18**(7): 1338. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- The Global Cancer Observatory: **Source: Globocan 2018.** World Health Organization, 2019; 1–2. [Reference Source](#)
- Saad AM, Turk T, Al-Husseini MJ, et al.: **Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; A SEER-based study.** *BMC Cancer.* 2018; **18**(1): 688. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rahib L, Smith BD, Aizenberg R, et al.: **Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the united states.** *Cancer Res.* 2014; **74**(11): 2913–2921. [PubMed Abstract](#) | [Publisher Full Text](#)
- Lepage C, Capocaccia R, Hackl M, et al.: **Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EUROCARE-5.** *Eur J Cancer.* 2015; **51**(15): 2169–2178. [PubMed Abstract](#) | [Publisher Full Text](#)
- Valle JW, Palmer D, Jackson R, et al.: **Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: Ongoing lessons from the ESPAC-3 study.** *J Clin Oncol.* 2014; **32**(6): 504–12. [PubMed Abstract](#) | [Publisher Full Text](#)
- Neoptolemos JP, Palmer DH, Ghaneh P, et al.: **Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial.** *Lancet.* 2017; **389**(10073): 1011–1024. [PubMed Abstract](#) | [Publisher Full Text](#)
- Conroy T, Hammel P, Hebbar M, et al.: **FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer.** *N Engl J Med.* 2018; **379**(25): 2395–2406. [PubMed Abstract](#) | [Publisher Full Text](#)
- Ferrioli M, Zauli G, Martelli AM, et al.: **Impact of physical exercise in cancer survivors during and after antineoplastic treatments.** *Oncotarget.* 2018; **9**(17): 14005–14034. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Clauss D, Tjaden C, Hackert T, et al.: **Cardiorespiratory fitness and muscle strength in pancreatic cancer patients.** *Support Care Cancer.* 2017; **25**(9): 2797–2807. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hendifar AE, Petzel MQB, Zimmers TA, et al.: **Pancreas Cancer-Associated Weight Loss.** *Oncologist.* 2019; **24**(5): 691–701. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Zabernigg A, Giesinger JM, Pall G, et al.: **Quality of life across chemotherapy lines in patients with cancers of the pancreas and biliary tract.** *BMC Cancer.* 2012; **12**: 390. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Campbell KL, Winters-Stone KM, Wiskemann J, et al.: **Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable.** *Med Sci Sports Exerc.* 2019; **51**(11): 2375–2390. [PubMed Abstract](#) | [Publisher Full Text](#)
- Behrens G, Jochem C, Schmid D, et al.: **Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis.** *Eur J Epidemiol.* 2015; **30**(4): 279–298. [PubMed Abstract](#) | [Publisher Full Text](#)
- Siegel RL, Miller KD, Jemal A: **Cancer statistics, 2019.** *CA Cancer J Clin.* 2019; **69**(1): 7–34. [PubMed Abstract](#) | [Publisher Full Text](#)
- Yeo TP, Burrell SA, Sauter PK, et al.: **A progressive postresection walking program significantly improves fatigue and health-related quality of life in pancreas and periampullary cancer patients.** *J Am Coll Surg.* 2012; **214**(4): 463–75. [PubMed Abstract](#) | [Publisher Full Text](#)
- Wiskemann J, Clauss D, Tjaden C, et al.: **Progressive Resistance Training to Impact Physical Fitness and Body Weight in Pancreatic Cancer Patients: A Randomized Controlled Trial.** *Pancreas.* 2019; **48**(2): 257–266. [PubMed Abstract](#) | [Publisher Full Text](#)
- Steindorf K, Clauss D, Tjaden C, et al.: **Quality of Life, Fatigue, and Sleep Problems in Pancreatic Cancer Patients—A Randomized Trial on the Effects of Exercise.** *Dtsch Arztebl Int.* 2019; **116**(27–28): 471–478. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Nakajima H, Yokoyama Y, Inoue T, et al.: **Clinical Benefit of Preoperative Exercise and Nutritional Therapy for Patients Undergoing Hepato-Pancreato-Biliary Surgeries for Malignancy.** *Ann Surg Oncol.* 2019; **26**(1): 264–272. [PubMed Abstract](#) | [Publisher Full Text](#)
- Ngo-Huang A, Parker NH, Bruera E, et al.: **Home-Based Exercise Prehabilitation During Preoperative Treatment for Pancreatic Cancer Is Associated With Improvement in Physical Function and Quality of Life.** *Integr Cancer Ther.* 2019; **18**: 1534735419894061. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Parker NH, Ngo-Huang A, Lee RE, et al.: **Physical activity and exercise during preoperative pancreatic cancer treatment.** *Support Care Cancer.* 2019; **27**(6): 2275–2284. [PubMed Abstract](#) | [Publisher Full Text](#)
- Valkenet K, Trappenburg JCA, Schippers CC, et al.: **Feasibility of Exercise Training in Cancer Patients Scheduled for Elective Gastrointestinal Surgery.** *Dig Surg.* 2016; **33**(5): 439–47. [PubMed Abstract](#) | [Publisher Full Text](#)
- Marker RJ, Peters JC, Purcell WT, et al.: **Effects of preoperative exercise on**

- physical fitness and body composition in pancreatic cancer survivors receiving neoadjuvant therapy: A case series. *Rehabil Oncol*. 2018; **36**(6): E1–E9.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Niels T, Schneider L: **Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie, Stuttgart, 29. September-3. Oktober 2017: Abstracts.** *Oncol Res Treat*. 2017; **40** Suppl 3: 1–308.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Naito T, Mitsunaga S, Miura S, et al.: **Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer.** *J Cachexia Sarcopenia Muscle*. 2019; **10**(1): 73–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Hart NH, Taaffe DR, Newton RU, et al.: **Delivering Exercise Medicine To Pancreatic Cancer Patients: Is It Feasible, Safe And Efficacious?** *Med Sci Sport Exerc*. 2019; **51**(Supplement): 986.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Hardcastle SJ, Cohen PA: **Effective physical activity promotion to survivors of cancer is likely to be Home based and to require oncologist participation.** *J Clin Oncol*. 2017; **35**(32): 3635–3637.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Newton RU, Hart NH, Clay T: **Keeping Patients With Cancer Exercising in the Age of COVID-19.** *JCO Oncol Pract*. 2020; OP2000210.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Sweegers MG, Altenburg TM, Chinapaw MJ, et al.: **Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials.** *Br J Sports Med*. 2018; **52**(8): 505–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Basile D, Parnofiello A, Vitale MG, et al.: **The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients.** *J Cachexia Sarcopenia Muscle*. 2019; **10**(2): 368–377.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Dominic O: **"PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma"**. Harvard Dataverse, V1. 2020.
<http://www.doi.org/10.7910/DVN/JSIKSN>
32. Fairman CM, Zourdos MC, Helms ER, et al.: **A Scientific Rationale to Improve Resistance Training Prescription in Exercise Oncology.** *Sport Med*. 2017; **47**(8): 1457–1465.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Nilsen TS, Scott JM, Michalski M, et al.: **Novel Methods for Reporting of Exercise Dose and Adherence: An Exploratory Analysis.** *Med Sci Sports Exerc*. 2018; **50**(6): 1134–1141.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Fairman CM, Nilsen TS, Newton RU, et al.: **Reporting of Resistance Training Dose, Adherence, and Tolerance in Exercise Oncology.** *Med Sci Sports Exerc*. 2020; **52**(2): 315–322.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Schmidt K, Vogt L, Thiel C, et al.: **Validity of the six-minute walk test in cancer patients.** *Int J Sports Med*. 2013; **34**(7): 631–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Eden MM, Tompkins J, Verheijde JL: **Reliability and a correlational analysis of the 6MWT, ten-meter walk test, thirty second sit to stand, and the linear analog scale of function in patients with head and neck cancer.** *Physiother Theory Pract*. 2018; **34**(3): 202–211.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Cleeland CS, Ryan KM: **Pain assessment: global use of the Brief Pain Inventory.** *Ann Acad Med Singapore*. 1994; **23**(2): 129–38.
[PubMed Abstract](#)
38. Yellen SB, Cella DF, Webster K, et al.: **Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system.** *J Pain Symptom Manage*. 1997; **13**(2): 63–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Cella D, Butt Z, Kindler HL, et al.: **Validity of the FACT Hepatobiliary (FACT-Hep) questionnaire for assessing disease-related symptoms and health-related quality of life in patients with metastatic pancreatic cancer.** *Qual Life Res*. 2013; **22**(5): 1105–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Devlin NJ, Brooks R: **EQ-5D and the EuroQol Group: Past, Present and Future.** *Appl Health Econ Health Policy*. 2017; **15**(2): 127–137.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Braun V, Clarke V: **Using thematic analysis in psychology.** *Qual Res Psychol*. 2006; **3**(2): 77–101.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Miles MB, Huberman A: **An expanded sourcebook: Qualitative data analysis (2nd Edition).** 1994.
[Reference Source](#)
43. Mays N, Pope C: **Qualitative Research: Rigour and qualitative research.** *BMJ*. 1995; **311**(6997): 109 LP–112.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Cormie P, Spry N, Jantas K, et al.: **Exercise as medicine in the management of pancreatic cancer: A case study.** *Med Sci Sports Exerc*. 2014; **46**(4): 664–670.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. McLaughlin M, Christie A, Campbell A: **Case Report of Exercise to Attenuate Side Effects of Treatment for Pancreatic Cancer.** *Case Rep Oncol*. 2019; **12**(3): 845–854.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. Craig P, Dieppe P, Macintyre S, et al.: **Developing and evaluating complex interventions: The new Medical Research Council guidance.** *Int J Nurs Stud*. 2013; **50**(5): 587–92.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 11 February 2021

<https://doi.org/10.21956/amrcopenres.13995.r26611>

© 2021 Parker N. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Nathan H Parker 

Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

This is a well written manuscript describing a study protocol to examine the feasibility of a supervised, progressive aerobic + resistance exercise program for patients following pancreatic cancer resection. The authors have done an excellent job outlining the rationale for their exercise program, and the benefits of this program are clear. Additionally, they have described some protocol modifications to account for changing circumstances in the COVID-19 pandemic. As outlined in my comments below, I think the manuscript will benefit from some increased details regarding exercise prescription and feasibility evaluation.

Introduction

Paragraph 4, 2nd sentence - I believe "there" should be "their" in this sentence.

Eligibility criteria

The authors should more precisely define "have tolerated at least 2 cycles" - will plans for dose reduction or switching regiments exclude patients?

How recent must CT scan confirming no persistent or recurrent disease have been performed? For example, can a patient be enrolled if CT scan was 1 month ago? 2 weeks?

Exercise Intervention

It would be helpful to see a list of resistance training exercises that participants will perform. Additionally, it would be helpful to include more detail about how the RM recommendations will be updated to accommodate the now home-based nature of the exercise program. For example, how will RM be determined for body weight exercises like a squat or chair stand? Does the shift to body weight exercises change the set/repetition targets?

Guidelines for progression could be more clearly outlined; i.e., how will interventionists decide that sets and reps can be completed without difficulty? And, once participants have progressed to resistance bands, how will further progression be guided?

How will heart rate monitoring be employed, and how will patients be instructed to perform moderate-intensity aerobic exercise?

Feasibility outcomes

How will "exercise related adverse events" be defined? Are there minimum criteria for injury or severity of issues that patients will report in order to count them?

It would be helpful to see structured or semi-structured interview guides that will be used to gauge perceptions and experiences of individuals who participated, individuals who did not participate, and providers.

Efficacy outcomes

The "Repetition maximum testing" paragraph seems to apply to in-person exercise programming, whereas it should be made clear how in-person RM testing will be translated to home-based exercise prescriptions. For example, how will a chest press 1RM be translated to body weight push ups and/or resistance tube chest press?

It would be helpful to reference or include in appendices the health economics questionnaire that will be used.

Same comment as above for qualitative evaluation - the authors should include some guiding questions for these interviews.

Regarding sample size calculation - do the authors plan to compare their feasibility outcomes to published standards? It would help to reference these.

Discussion

Does the final paragraph of the discussion still apply to the home-based intervention?

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?

Partly

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

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exercise oncology

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, however I have significant reservations, as outlined above.

Reviewer Report 22 September 2020

<https://doi.org/10.21956/amrcopenres.13995.r26546>

© 2020 Guinan E. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Emer Guinan

School of Medicine, Trinity College Dublin, University of Dublin, Dublin, Ireland

The authors have adequately addressed my comments.

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?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: exercise oncology in upper GI cancers

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.

Version 1

Reviewer Report 25 June 2020

<https://doi.org/10.21956/amrcopenres.13977.r26505>

© 2020 Guinan E. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Emer Guinan

¹ School of Medicine, Trinity College Dublin, University of Dublin, Dublin, Ireland

² School of Medicine, Trinity College Dublin, University of Dublin, Dublin, Ireland

This paper is a protocol for an intervention study planning to examining the feasibility of a supervised, individualised and progressive concurrent exercise intervention to individual with respectable PDAC who are undergoing adjuvant therapy. Exercise has significant potential to act as a supportive intervention for patients with PDAC who are receiving adjuvant therapy however this population have been grossly understudied, making this an important piece of work.

Introduction

The introduction provides quite a detailed overview of the literature. What isn't clear to me is what the future holds for this trial – i.e. if feasibility is demonstrated what would an RCT in this cohort look like and importantly what would the primary outcome be? Survival benefits are discussed for example – I assume that wouldn't be the primary endpoint? I think that it would be beneficial to have some focus on a key target for exercise and the importance of that for this cohort.

I can understand that the priority for this trial is to deliver a supervised intervention however given that we are living through COVID-19 what adaptations may need to be made? The introduction dedicates a paragraph to criticising home exercise interventions however we are all having to adapt to telehealth in recent times. What adaptations may be required to this protocol and does the introduction allow room for those adaptations to be made?

Methods

Exercise Intervention

How many sessions of supervised exercise will take place weekly?

The protocol states that 'The exercise intervention will be tailored for each participant according to their baseline physical function assessment, physical activity level, previous exercise experience, and presence of co-morbidities and medical history' – how will that level of tailoring be applied?

The protocol states 'During the aerobic exercise component, intensity will be prescribed using the modified rate of perceived exertion (RPE) method, with speed adjusted to elicit the target RPE throughout the session' – speed of what? Will treadmills be the only exercise modality? Why only speed adjusted and not incline for example? Will other exercise modalities be available? Do the authors see this as individually supervised or group-based exercise?

It would be useful to include a table or diagram to represent the exercise intervention. There is a lot in the description about autoregulation and tailoring to individual needs and the per protocol prescription is unclear. For example, what will be different about the first four weeks

'familiarisation period' to the remainder of the programme in terms of aerobic exercise prescription?

Feasibility Outcomes

Adherence will be assessed using the methods reported by Nilsen et al and Fairman et al which is a very comprehensive approach. Given that aerobic intensity will be prescribed using a modified Borg how do the authors plan to report dose modifications?

Efficacy Outcomes

I would encourage the authors to consider a potential primary outcome for an RCT at this point. Make sure that it is included in the battery of efficacy outcomes and that the feasibility of the assessment methods are recorded as part of the feasibility analysis.

Given that nutritional symptoms are going to be a primary concern for these patients, their families and the wider MDT, why are measures of body weight, body composition or nutritional symptoms not included as efficacy outcomes?

Data Analysis

The protocol states - All measures will be scored according to standard practice and analysed for mean changes between baseline, week 16 and 3 month follow up - using what analysis?

Discussion

The closing line of the discussion is - Should the PRECISE feasibility study be successful there is provision to include two further UK sites, which will increase overall sample size for the subsequent study, thus making the results more generalizable to the UK population. - this is unclear to me - what is the subsequent study - a larger feasibility study? An RCT? If an RCT there should be a clear indication throughout as to what the primary outcome would be and why it is important.

Overall Comments

Overall this is a very important and much needed piece of work. The exercise protocol needs to be described more clearly. While adaptations and tailoring will naturally be needed in this cohort the standard protocol needs to be clear to allow fidelity to be evaluated. I would like to see some consideration of how this intervention will consider the nutritional consequences of pancreatic resection. How will side effects impact recruitment, adherence etc and what measures will be put in place to support patients to exercise despite nutritional symptoms? This will be a challenging cohort to recruit and the authors should carefully consider recruitment strategies. There is a PPI representative in the author list which is great to see.

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?

Partly

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

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: exercise oncology in upper GI cancers

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, however I have significant reservations, as outlined above.

Author Response 29 Jul 2020

Dominic O'Connor

Dear Dr Guinan,

Thank you for your review. We have addressed each comment individually in the order in which you presented them.

Introduction

Our primary outcome for this study is feasibility. Our introduction provides a brief overview of the current literature in the area. We have included a section in the discussion regarding future RCT's.

We have approval for a study amendment to include home-based, remote supervised exercise. This has been added to the manuscript within the methodology, and our introduction has been edited to better reflect the utility of home-based exercise in the current climate.

Methods

Our protocol description has been amended to give greater detail and understanding of the protocol. Exercise sessions will be completed 2x/week. The tailoring of the exercise intervention will include aerobic exercise mode (treadmill / cycle ergometer), and the intensity (treadmill – speed / grade, cycle ergometer – speed / resistance) and duration of aerobic and resistance exercise. These modifications will reflect the individuals' physical condition before entry into the study and before each exercise session and will be based on clinical judgement of the study investigator.

Participants will be consulted prior to study entry on previous exercise history and have the options of completing aerobic exercise on a treadmill or cycle ergometer. Speed / grade of the treadmill, and resistance on the cycle ergometer will be used to manipulate aerobic exercise intensity. Details have been added to the intervention section Exercise sessions will be individual in light of the current Covid-19 social distancing restrictions.

A table representing the exercise intervention has been included and gives an indication as to the difference between week 1-4 and the remainder of the intervention.

Aerobic exercise will also be monitored via RPE and heart rate reserve and this has been added to the manuscript to make this clearer. Items from the Nilsen et al paper which will be included in the reporting will include permanent discontinuation (treatment discontinuation prior to week 16), treatment interruption (missing ≥ 3 consecutive sessions), dose modification [$\geq 10\%$ of sessions requiring modification (reduction / escalation) of intensity or duration], pre-treatment dose modification (reduction of pre-treatment session intensity), early session termination (termination of session prior to planned duration), and adherence (compliance with the planned dose/session).

We have considered a primary outcome for a future RCT and will assess its feasibility in this population.

The statistical analysis will be carried out using a one-way ANOVA.

Wording at the end of the discussion has been amended to make clearer the subsequent study is an RCT.

We do highlight body composition as a key outcome in the introduction, and body weight will be recorded at each visit alongside standard anthropometric outcomes. Nutritional support is not a component of this feasibility trial but all patients will have continuing access to the oncology and community dietetics service throughout their treatment.

We thank you for your comments. We have recently carried out PPI (focus groups / survey) to discuss recruitment strategies with this challenging population.

Competing Interests: No competing interests were disclosed.