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

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Introduction
STUDY PROTOCOL

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

Dominic O'Connor1, Malcolm Brown1, Roy Bowdery2, Martin Eatock3, Claire Hulme4, Anthony Maraveyas5, Rebecca Robinson6, Richard C. Turkington3,7, Rebecca Vince8, Jonathan Wadsley9, Gillian Prue1

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, Faculty of Health Sciences, University of Exeter, Exeter, UK
9Weston Park Cancer Centre, Weston Park Hospital, Sheffield, UK

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 quality of life. Outcomes will be measured at baseline (T1), 16 weeks
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
Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas, representing 90% of all pancreatic neoplasms. PDAC accounted for approximately 458,000 new cases and 432,000 mortalities in 2018, making it the 14th most common and 7th deadliest cancer worldwide. However, epidemiological evidence suggests that age standardized incidence rates have been steadily increasing with figures between 1974–2014 estimating a 1.03% annual rise. 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 2030. 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%. For those suitable for potentially curative resection, followed by adjuvant chemotherapy, patient survival is improved, although 3-year and 5-year survival rates stand at 63.4% and 28.8%, respectively.

Intensive cancer treatments (i.e. surgery and chemotherapy) have debilitating complications including fatigue, pain and impaired physical function. Flowing 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%). When combined with common complications in pancreatic cancer such as a high prevalence of unintentional weight loss (seen in ~90% at diagnosis) and psychological distress, 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 therapy. 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 benefits. Observational data indicates that consistent exercise participation can significantly reduce pancreatic cancer risk by 26% (RR= 0.74, 95% CI 0.61–0.90). 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 life. However, data underlying these guidelines was predominantly obtained from breast cancer trials, due to their high prevalence and survival estimates. 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.

The 2012 study by Ferrucci and colleagues demonstrated 6-months of supervised, 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 life. However, data underlying these guidelines was predominantly obtained from breast cancer trials, due to their high prevalence and survival estimates. 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. 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 group.

Several other clinical studies have shown exercise is safe and feasible in PDAC, both during neo-adjuvant therapy and during adjuvant treatment. However, a limitation of these studies is they are generally home-based and as a result are largely unsupervised. Although this form of exercise can mitigate common barriers to exercise participation (e.g. access, motivation, transportation and cost), supervised exercise typically produces a greater response in self-reported quality of life (Hedges’ g = 0.20, 95% CI (0.14 to 0.26) and physical function (g = 0.27, 95% CI (0.20 to 0.33) may be partly due to under-dosing of the exercise prescription (volume and intensity) during home-based trials. Indeed, a recent study that compared supervised and home-based moderate intensity resistance training (6 months, twice weekly) in those with resectable and non-resectable PDAC (n = 47), found significantly greater improvements in strength and self-reported quality of life within the supervised group. Despite participants self-reporting better adherence to the home-based programme, which is often skewed by self-reporting bias, this suggests that participants may achieve greater and potentially more therapeutic exercise intensities during supervised sessions.

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 disease. 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 PDAC. 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 3.0.

**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 pack. 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 checklist).

**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.

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Figure 1. Study design and patient flow throughout the 16 weeks and follow-up.
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. 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 using the modified rate of perceived exertion (RPE) method, with speed adjusted to elicit the target RPE throughout the session. Aerobic exercise will be performed at an intensity of 4 to 7 RPE. The resistance exercise prescription will use non-linear 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 adherence. 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.

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. and Fairman et al. to record deviations from the protocol.

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:

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 trials.

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 trials. 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 cancer. 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 QoL. 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.

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\textsubscript{peak} \textsuperscript{39}. The assessment 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 cancer\textsuperscript{40}. 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.

**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 interviews\textsuperscript{31}. 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 analysis\textsuperscript{31}. 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. 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 Huberman\textsuperscript{42} 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 research\textsuperscript{43}. 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 cancers. 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.

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 process. 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 the subsequent study, 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/J5IKSN.

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/J5IKSN.

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

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Emer Guinan
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 adatptions may need to be made? The introduction dedicates a paragraph to critising 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 presribed 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.