




BRIEF REPORT

Findings of a feasibility study of pre-operative pulmonary rehabilitation to reduce post-operative pulmonary complications in people with chronic obstructive pulmonary disease scheduled for major abdominal surgery [version 1; peer review: 2 approved]

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Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of complications and death following surgery. Pulmonary complications are particularly prominent. Pulmonary rehabilitation is a course of physical exercise and education that helps people with COPD manage their condition. Although proven to improve health outcomes in patients with stable COPD, it has never been formally tested as a pre-surgical intervention in patients scheduled for non-cardiothoracic surgery. If a beneficial effect were to be demonstrated, pulmonary rehabilitation for pre-surgical patients with COPD might be rapidly implemented across the National Health Service, as pulmonary rehabilitation courses are already well established across much of the United Kingdom (UK).
Methods: We performed a feasibility study to test study procedures and barriers to identification and recruitment to a randomised controlled trial testing whether pulmonary rehabilitation, delivered before major abdominal surgery in a population of people with COPD, would reduce the incidence of post-operative pulmonary

Open Peer Review

Reviewer Status  

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1

2

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report



report

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Any reports and responses or comments on the

complications. This study was run in two UK centres (Oxford and Newcastle upon Tyne).

Results: We determined that a full randomised controlled trial would not be feasible, due to failure to identify and recruit participants. We identified an unmet need to identify more effectively patients with COPD earlier in the surgical pathway. Service evaluations suggested that barriers to identification and recruitment would likely be the same across other UK hospitals.

Conclusions: Although pulmonary rehabilitation is a potentially beneficial intervention to prevent post-operative pulmonary complications, a randomised controlled trial is unlikely to recruit sufficient participants to answer our study question conclusively at the present time, when spirometry is not automatically conducted in all patients planned for surgery. As pulmonary rehabilitation is a recommended treatment for all people with COPD, alternative study methods combined with earlier identification of candidate patients in the surgical pathway should be considered.

Trial registration: [ISRCTN29696295](https://www.isrctn.com/ISRCTN29696295), 31/08/2017

Keywords

pulmonary rehabilitation, respiratory

article can be found at the end of the article.

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Introduction

In the United Kingdom, chronic obstructive pulmonary disease (COPD) affects approximately 3.7 million people¹, is responsible for approximately 30,000 deaths per year, and is the fifth most common cause of death². COPD is an independent risk factor for postoperative complications (odds ratio OR 1.35 (CI 1.30–1.40)) and death (OR 1.29 (CI 1.19–1.39))^{3–6}. Complications include pulmonary and cardiac events, sepsis, renal insufficiency and an increased reoperation rate³. Surgical patients with COPD thus represent a high-risk group in whom there is an unmet need to improve post-operative outcomes.

Pulmonary rehabilitation

Pulmonary rehabilitation is “A physical exercise and education programme, tailored for each person. It includes information on looking after the body and lungs, advice on managing symptoms, including feeling short of breath, nutrition and psychological support. People who smoke are given advice on how to stop.”⁷

Pulmonary rehabilitation is usually delivered in an outpatient setting, consisting of one hour of exercise and one hour of education, twice weekly for six weeks. It has profound benefits on breathlessness, exercise capacity and quality of life (number needed to treat (NNT)=2)⁸, no side effects are reported⁹. Pulmonary rehabilitation is associated with decreased hospital admissions (NNT=3–4), and mortality (NNT =~6) following COPD exacerbations^{10–13}. Crucially, pulmonary rehabilitation is inexpensive⁹. Its effect is so powerful that it has a negative cost per quality adjusted life year (QALY), meaning it saves money for the NHS¹⁴. The main challenges facing pulmonary rehabilitation are the barriers to its uptake, as attendance and completion of the programme is often poor^{15,16}.

Improving post-operative outcomes

Despite adoption in the National Institute for Health and Care Excellence (NICE) guidelines¹⁷ for stable COPD, pulmonary rehabilitation is not regularly offered to pre-surgical patients with COPD¹⁸. We believe that pulmonary rehabilitation merits investigation as a potential means to improve postoperative outcome in people with COPD undergoing surgery for the following reasons:

- A handful of small surgical studies suggest beneficial effects of pulmonary rehabilitation on the incidence of postoperative pulmonary complications^{19–23}. Differing endpoints, small sample sizes and restriction to specific surgical groups limits conclusive interpretation.
- In the National Emphysema Treatment Trial (NETT)^{24,25}, lung volume reduction surgery was compared with medical management of COPD. All patients underwent pre-operative pulmonary rehabilitation. In the thoracic surgical population of NETT similar outcomes (in terms of functional exercise capacity and health related quality of life, assessed prior to surgery) were observed to what would be expected in the treatment of non-surgical patients with COPD. In fact, approximately 10% of participants in NETT decided against lung volume

reduction surgery because they felt so much better after pulmonary rehabilitation.

- Shortened durations of pulmonary rehabilitation are efficacious^{8,26}. This is important, because an adapted course may be necessary to fit within surgical time frames.
- Pulmonary rehabilitation is widely available and standardised across the NHS in over 200 UK centres. This has important implications for scalability.

Pre-operative pulmonary rehabilitation needs sufficient time between the decision to operate and the operation, requires cross specialty working, and involves patients with two conditions (COPD and a surgical condition). A randomised controlled trial is therefore justified, as the current evidence base is either not specific to a surgical population or is case series based and therefore subject to selection bias. Furthermore, it is unclear whether a randomised controlled trial of pulmonary rehabilitation before surgery would be practical. This study investigated the feasibility of running such a large randomised controlled trial. The feasibility study design matched the expected full study design except in scale.

Methods

This feasibility study was run as an open, parallel group, randomised trial with an allocation ratio of 1:1. The study was conducted across two research sites (Oxford and Newcastle upon Tyne), chosen as two areas with different demographics and incidence rates of COPD. Ethical approval was granted by the South Yorkshire Research Ethics Committee (approval number 17/YH/0220). Written informed consent was obtained from all participants prior to the start of the study. The primary aim of the study was to determine feasibility for a randomised controlled trial and focused on recruitment rate, barriers to recruitment and uptake of pulmonary rehabilitation. The trial was registered on ISRCTN on 19 August 2017 ([ISRCTN29696295](https://www.isrctn.com/ISRCTN29696295)).

Study procedures

Inclusion criteria:

- Adult patients aged 18 years or older with COPD
- Has capacity to take part in this study
- Scheduled for elective major (body cavity) surgery OR laparoscopic surgery that is anticipated to last longer than 2 hours
- People with more than 20 pack years smoking history were approached to take part in the study if spirometry subsequently confirmed COPD.

Exclusion criteria

- Inability to give informed consent
- Insufficient command of English to understand the study documentation
- Unable to participate in pulmonary rehabilitation treatment according to British Thoracic Society guidelines²⁷.

- Patients scheduled cardiac, thoracic and orthopaedic surgery and orthopaedic surgery

Patient involvement in study design: As we anticipated that recruitment to this study may be challenging, we discussed the study design with patient groups consisting of people with COPD who had either undergone surgery, or those who had experienced pulmonary rehabilitation. The key messages from these patient representatives were to ensure that transport to and from pulmonary rehabilitation would be provided, and that a flexible approach to scheduling would be necessary so pulmonary rehabilitation could fit with other appointments.

Participant identification and recruitment: To determine the best point in the surgical pathway to recruit participants, research nurses screened for study participants from the following sources.

- From the surgical multidisciplinary team (MDT) meetings
- In oncology clinics
- From the electronic patient record for patients scheduled for surgery
- From hospital anaesthetic preoperative assessment clinics
- From cardiopulmonary exercise testing clinics

Participants were initially approached by their clinical team, and in those who agreed to take part in the study informed consent was taken at the first research visit.

The study aimed to collect 48 full data sets (24 in each centre, 12 pulmonary rehabilitation, 12 control arm). To achieve this 48 dataset target, based on known drop-out rates from pulmonary rehabilitation¹⁸ and potential further data loss due to surgical scheduling, we anticipated that we would need to recruit 72 patients. This sample size was chosen pragmatically, with the aim to test efficacy of recruitment, randomisation, how best deliver a control arm the best way to conduct the study across multiple sites and importantly to enable us to evaluate the performance of the primary outcome measures (e.g. for ceiling and floor effects).

Pulmonary rehabilitation: A pragmatic, exploratory approach was used to explore what is practically deliverable and tolerated by patients, working closely with local pulmonary rehabilitation teams in Oxford and Newcastle upon Tyne. The aim was for patients to be enrolled in 3 pulmonary rehabilitation sessions per week, for 3 or 4 weeks, depending on timing of surgery. Pulmonary rehabilitation of this shortened duration has been shown to be effective²⁶. Patients were to attend standard NHS pulmonary rehabilitation groups run for patients with COPD.

Control arm: Patients randomised to the control arm would receive standard care including advice on smoking cessation, exercise and appropriate referral and education for those with newly diagnosed COPD.

Research assessments

Recruited participants were randomised 1:1 to either pulmonary rehabilitation or treatment as normal, minimised for study site and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, using an online randomisation service (Sealed Envelope Limited, London, UK). Participants were assessed prior to pulmonary rehabilitation or control treatment (preoperative assessment) and following surgery during hospital inpatient stay on postoperative days 3, 5, and 8 and again at a 6-week and 6-month follow-up (Figure 1 and below). Other than a 6-minute walk test, the research data consisted of self-report questionnaires on mood, symptoms, and quality of life. Data obtained from the NHS clinical record included various perioperative risk scores, co-morbidity scores, and measures relating to the operation and outcomes.

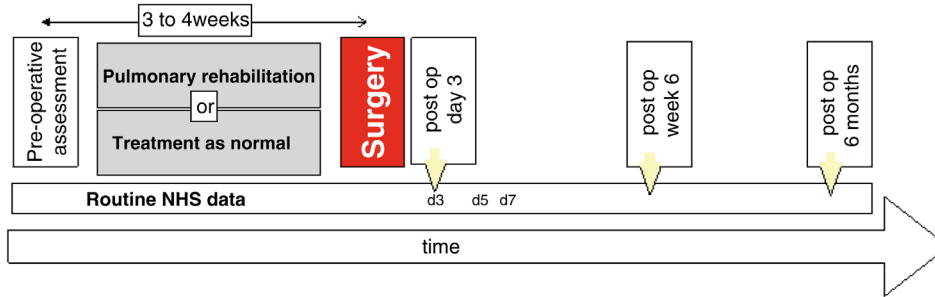
Preoperative (prior to pulmonary rehabilitation or control treatment)

- Medical, surgical, anaesthetic assessment including comorbidities including full detailed smoking histories.
- Physiology
 - Spirometry
 - 6 minute walk test
 - Cardiopulmonary exercise testing (CPET)
 - Physical activity monitoring (accelerometry-based wristwatch) – monitored for one week.
 - Preoperative risk assessment scoring using POSSUM-R, Charlston Co-morbidity Index, ASA grade.
- Psychology and health-related quality of life
 - Dyspnoea questionnaires (Dyspnea-12 questionnaire)
 - Anxiety (State and Trait Anxiety Inventory), Depression (Center for Epidemiological Studies Depression Scale), Fatigue (Fatigue Severity Scale), COPD Assessment Test (CAT)
 - Health status assessment with EQ-5D-5L and WHO disability assessment schedule.

Post-operative measures

- These measures will be collected on postoperative days 3, 5, and 8 during hospital inpatient stay.
 - Surgical factors (duration of operation, blood loss), measured once only
 - Time to mobilisation
 - Assessment of activities of daily living (Barthel).
 - Intensive care admission, discharge, mortality
 - Patient-related outcome measures, including time to return to normal activities.

Overview of study



	Pre-operative assessment	post operative day 3	post operative day 5	post operative day 7	post operative week 6	post operative 6 months
D12	√				√	√
CAT	√				√	√
QOR-15	√	√				
WHODAS	√				√	√
EQ-5D-5L	√				√	√
STAI	√				√	√
CESD	√				√	√
6 min walk test	√					
P-POSSUM	√					
Charlston	√					
ASA	√					
Barthel	√	√	√	√		
POMS		√	√	√		
Clavien-Dindo		√	√	√		
Time to mobilise (one reading)		√	√	√		
Surgery duration		√				
Surgery blood loss		√				
ICU admission		√	√	√		
CPET data anaerobic threshold VO2 max	√					
Spirometry	√					
Clinical assessment inc smoking history and comorbidities	√					

Figure 1. Overview of study methods. Data in yellow boxes is research data collected from the patient, whereas the data in pink relates to that collected from the patients’ clinical record. Abbreviations: NHS; National Health Service, D12; Dyspnoea-12 questionnaire, CAT; COPD assessment test, QOR-15; quality of recovery score, WHODAS; World Health Organisation (WHO) disability score, STAI; Spielberger state and trait anxiety inventory, CESD; Center for epidemiologic studies depression scale, P-POSSUM; Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality, Charlston; Charlston Morbidity Index, ASA; American Society of Anesthesiologists Physical Status Classification System, Barthel; Barthel scale, Clavien-Dindo; The Clavien-Dindo Classification of surgical complications, ICU; intensive care unit, CPET; cardiopulmonary exercise test.

- Morbidity tracking using the postoperative morbidity survey instrument and Clavien-Dindo surgical complication score.
- Postoperative measures collected on day 5 post-surgery only
 - Health status questionnaires: Dyspnea, Anxiety, Depression, CAT EQ-5D-5L and WHO disability assessment schedule
 - Smoking history
- Data collected at discharge from hospital
 - Date of discharge (i.e. length of hospital stay)
 - Destination of discharge
- Postoperative measures collected during 6-week follow-up visit.
 - Health status questionnaires: Dyspnea, Anxiety, Depression, CAT EQ-5D-5L and WHO disability assessment schedule
 - Readmissions to hospital, morbidity tracking as above (from medical record).
 - Smoking history
- Postoperative measures collected 6 months following surgery

Following confirmation that patient remains alive (NHS Spine and communication with general practitioner) we will invite the patient to attend a follow up assessment and collect the following measures.

 - Health status questionnaires: Dyspnea, Anxiety, Depression, CAT EQ-5D-5L and WHO disability assessment schedule
 - Readmissions to hospital, morbidity tracking as above (from medical record).
 - Smoking history

Feasibility measures collected throughout the study

Key feasibility measures

- Can we recruit at a sufficient rate to run an RCT?
- What is severity (GOLD/MRC) of the recruited patients and how does this compare with the screened patients
- Whether it is feasible to deliver the pulmonary rehabilitation intervention in the time available. This will include assess the impact of changing surgical dates, e.g. earlier (so insufficient rehabilitation delivered), later (so effect of rehabilitation wearing off).
- Number of complete data sets collected

- Percentage of missing data
- Barriers to uptake of pulmonary rehabilitation

To detail recruitment, retention and dropouts (including a screening log) at all the potential drop out points

- Number of patients identified in clinic with spirometry defined COPD, and their MRC and GOLD scores
- Number of patients invited to participate in the study, and their MRC and GOLD scores
- Number who accept invitation
- Number who decline invitation but agree to participate in qualitative study
- Number who decline invitation/don't reply
- Number of patients who attend research assessment
- Number of patients who sign consent form
- Number of patients who complete pulmonary rehab or control treatment (i.e. compliance with study intervention)
- Number of patients who have surgery in allocated timeframe (3 months following the second research visit)
- Number of patients who continue the study during postoperative period
- Number of patients in whom we can collect 6-month follow up data.

Logistics. To collect measures relating to

- Scheduling of research appointments within suitable timeframes
- Scheduling of pulmonary rehabilitation sessions within the surgical waiting time
- Effectiveness of transport to/from pulmonary rehabilitation. Although we plan to contribute transport costs for the study there needs to be consideration for when pulmonary rehabilitation is offered as a treatment.
- Factors relating to scheduling, including effect of changes in operation date.
- Feasibility of tracking patients postoperatively-either in person and/or via electronic and paper based patient records

Performance of measures including ceiling and floor effects

Outcome measures being collected to get an estimate of

- Central tendency
- Spread
- Data loss

- Loss to follow up
- Event rate of postoperative complications, to help with sample size calculation for main study

Effectiveness of randomisation

- Check for post randomisation dropouts because of allocation to unfavoured treatment group
- Do the "treatment as normal" patients seek exercise sessions elsewhere?
- Is the drop-out rate from the study similar in both groups?
- Does the randomisation system work?

Health economics. We know there is health economic benefit for pulmonary rehabilitation in the treatment of COPD - does this translate to a surgical population?

- EQ-5D-5L measured at baseline, at day 5, 6 weeks and 6 months post operatively
- Resource use will be measured, including primary care, pulmonary rehabilitation, hospital services(e.g. before during and after surgery)

Plans to mitigate against bias / outcome integrity

- Assessors will be blinded to treatment group.
- We will trial ways to ensure that the outcomes chosen are as fair as possible and are collected in a way that avoids bias. This will include objective criteria scoring by blinded individuals.

Outcome measures: We anticipated that the primary research outcome measures for a future randomised controlled trial would be morbidity, mortality, length of hospital stay and hospital readmissions so we collected data on this to help with future study design.

Progression criteria to substantive study

The progression criteria to a substantive study were as follows:

- Recruitment rate greater than 66% of predicted for the present study - this would account for a minimum rate that would result in a practical number of centres for a randomised controlled trial.
- Screened and recruited patients similar in severity - assessed by clinical judgment
- Compliance with treatment approximately in line with national COPD audit figures
- To be confident that there were no insurmountable barriers to the uptake and running of pulmonary rehabilitation for these patients.

Results

Recruitment commenced in Oxford in January 2018 and in Newcastle upon Tyne in May 2018. A total of 266 patients were screened of which 65 met the inclusion criteria. As of January 2019, one participant had been recruited in Oxford and two in Newcastle upon Tyne. At this point it was determined that running a randomised controlled trial of pulmonary rehabilitation would not be feasible and the study was terminated in March 2019. Further details are presented in [Figure 2](#). We have not presented the research data here due to interpretability and confidentiality issues arising from only acquiring two datasets.

We found that the main barrier to study recruitment in both centres was associated with the way the surgical pathway is organised, especially with regards to two specific aspects; surgical timelines and identification COPD.

Barriers to identification of study participants

In Oxford, challenges were faced in identifying patients with COPD soon enough before surgery.

It was challenging to identify patients with COPD at surgical clinics and multidisciplinary meetings as patients had just received a diagnosis of cancer, but a definitive treatment plan had yet to be instituted. At this point the focus is on the surgical condition rather than medical conditions such as COPD. Medical records focused mostly upon surgical condition and respiratory records were often in separate (unavailable) notes and smoking histories were rarely present. This made screening laborious and time inefficient.

The definitive decision on whether to operate would only be made following neoadjuvant treatment. Oncology clinics were assessed as an identification point, but we found that potential participants attended too many different clinics to find a suitable point for screening.

Screening the electronic patient record for patients scheduled for surgery did not successfully identify additional people with COPD. Therefore, COPD was often not formally diagnosed until the following the anaesthetic preoperative assessment clinic which usually occurred 2–3 weeks before surgery, with cardiopulmonary exercise testing (CPET) testing taking place at a similar time before surgery.

The difficulty in identifying potential participants with COPD was somewhat unexpected. As audit data from the pre-operative cardiopulmonary exercise testing clinics in both Oxford and Newcastle-upon-Tyne suggested that COPD was present in 10 to 15% of the 2,000 to 3,000 patients each year passing through those clinics. This meant that our pool of potential participants was around 300 in each centre each year.

Vascular surgery clinics were also assessed; these non-cancer patients have a more clearly defined pre-surgical pathway. However, we found that due to changes in surgical practices,

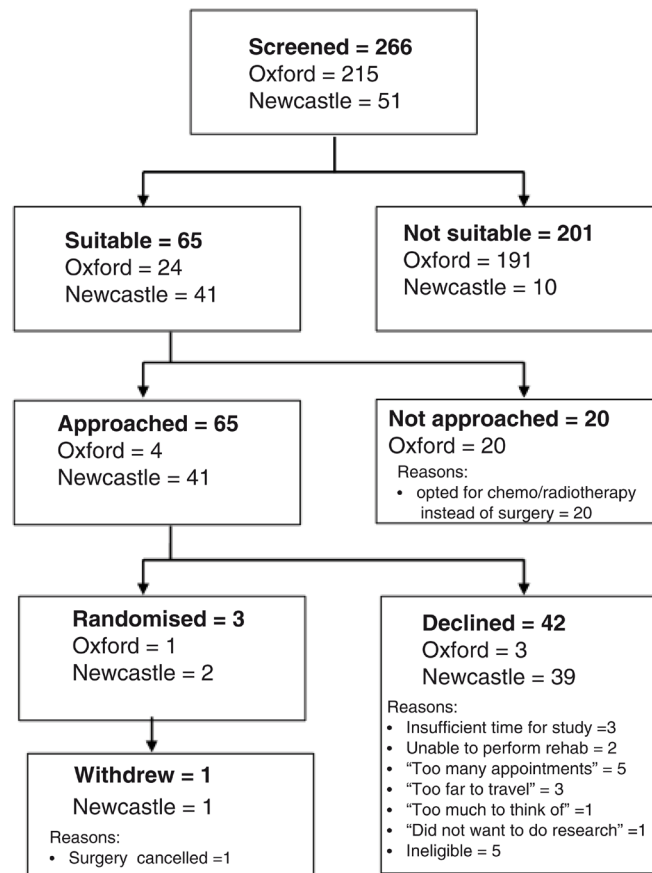


Figure 2. Flow diagram of participant identification and recruitment.

most patients with respiratory disease were treated endovascularly and thus recruiting from this clinic was also deemed low yield.

At anaesthetic pre-assessment clinics, the main challenge was that potential participants with undiagnosed COPD may not have been formally diagnosed after the pre-assessment clinic (when patients were sent for lung function tests); this made confirmation of eligibility difficult, and further lessened time for study inclusion.

Barriers to recruitment of study participants

In Newcastle upon Tyne, surgical patients attend the anaesthetic pre-assessment clinic about one month before surgery, this is in contrast to Oxford where the time between anaesthetic assessment and surgery is often much shorter. In Newcastle-upon-Tyne we were more successful at identifying patients with COPD, but despite this only two patients were recruited into the study (one of whom subsequently withdrew).

National survey of preassessment clinics

We discussed increasing the number of sites for the study with three other potential UK sites (two teaching hospitals and one

large district general hospital) who performed evaluations of their services, taking into account the preliminary findings of this work. This would help us evaluate whether the identification and recruitment issues were generalisable to other centres. However, we found that in all three centres the main point of identifying COPD was found to be at anaesthetic pre-assessment clinics, which occur two to three weeks prior to operation date (similar to Oxford).

CPS, in his role as Royal College of Anaesthetists National Clinical Lead for Perioperative Medicine, surveyed perioperative medicine and preoperative assessment clinics in 110 hospitals in England over the course of 2017²⁸. This piece of work found that the usual time interval between anaesthetic preassessment and surgery was often only 2–3 weeks, but with wide variability (unpublished observations). This is equivalent to current practice in Oxford.

Discussion

Pulmonary rehabilitation is a potentially valuable treatment for improving the health status of people with COPD prior to surgery. We established that a full randomised controlled trial is not feasible. As a result of this study we have identified an

unmet need in the early identification of COPD in patients presenting for surgery.

Although the study was only run in two UK centres, further scoping work in three additional centres and a related England-wide survey of anaesthetic services means that we are reasonably confident that similar challenges in identification and recruitment would be found if a randomised controlled trial were to run across the UK, and thus we believe that our findings are generalisable.

Pulmonary rehabilitation is an integral part of the NICE guidelines for the treatment of COPD, and therefore every person with COPD should be offered this treatment (alongside the other components of therapy recommended by NICE). This raises the question about whether a randomised controlled trial is actually the most appropriate methodology for future work. Barriers to pulmonary rehabilitation are well recognised, even when implemented as a clinical treatment^{15,16}. These barriers can be even more pronounced when tested as an optional research intervention²⁹. We provided free transport and offered flexible scheduling for potential participants. These were recommended by our patient liaison group during the study design phase to help overcome barriers to taking part in pulmonary rehabilitation, but clearly were insufficient to enable us to recruit at a sufficient rate.

We therefore speculate that if it we could identify COPD at the beginning of the patient's surgical journey, patients would be much better placed to have appropriate management and optimisation of their COPD. Spirometry is cheap, widely available and reliable; and thus perfect for a simple primary care test which should be offered much more widely, and would allow for early optimisation of drug therapy. Pulmonary rehabilitation could occur in a more timely fashion as this intervention could be integrated and planned alongside chemo- and radio-therapy, rather than in the weeks immediately preceding surgery. Patients with COPD would benefit even if they do not eventually proceed to surgery, with potential cost savings for the NHS^{14,30}. Potential solutions to this are illustrated in Figure 3.

This study has demonstrated the considerable challenge in performing additional interventions in the immediate period before surgery. However, the duration of the patient's journey from referral to surgery can take several months and remains an ideal period to optimise COPD if appropriate patients are identified earlier in the process. Some UK hospitals have recently implemented initiatives to 're-design' this surgical pathway, which may help overcome this barrier³¹. The importance of identifying and engaging with patients early after the "moment of contemplation" of surgery is clearly a critical success factor for interventions such as pulmonary rehabilitation; which are known (from other contexts) to require a defined period of time to implement and provide benefit. However, we should take caution from evidence from studies in lung

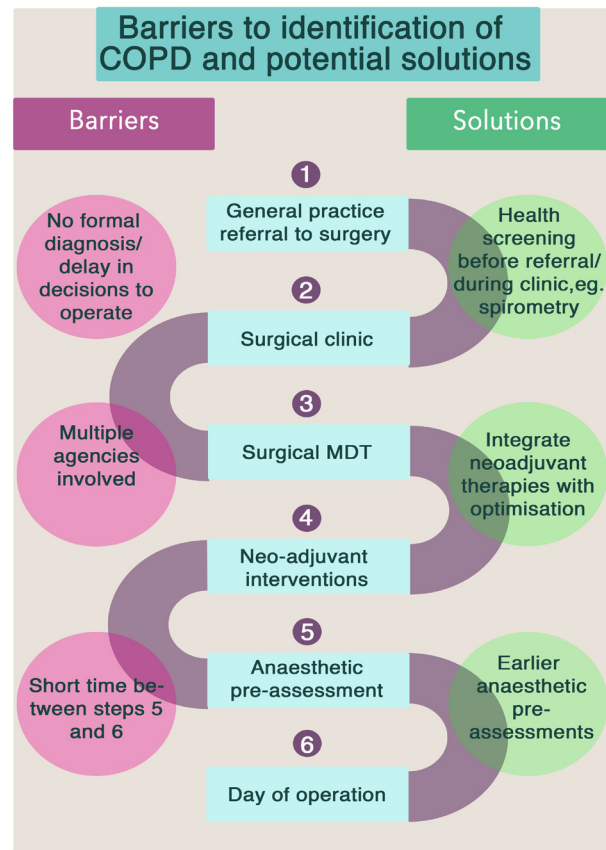


Figure 3. A summary of the challenges to identification (and thus treatment) of COPD for surgical patients and potential solution.

cancer which show that the time of diagnosis is a difficult time to consider pulmonary rehabilitation³². Although there may be an opportunity to provide pulmonary rehabilitation whilst neo-adjuvant therapy is being provided patients often do not want to engage with pulmonary rehabilitation at a time when they are dealing with a new, life changing diagnosis and having burdensome, potentially toxic cancer treatment¹⁴. Thus, it might turn out that pulmonary rehabilitation can only really feasibly delivered once cancer treatment has finished. There is emerging evidence that exercise therapies enhance cancer survival^{33,34} and that a recommendation from the oncologist may be influential in the view patients might take.

Pulmonary rehabilitation represents an important part of the NICE guidelines for the treatment of COPD and is readily available in the NHS. We know that patients will benefit from pulmonary rehabilitation, even if it is consequently shown not to have a specific effect upon postoperative pulmonary complications. Patients who consequently do not require surgery will still benefit. We have shown that a randomised controlled trial is not feasible, so we need to approach this in a different way using alternate methodologies.

Ethics approval and consent to participate

Ethical approval was granted by the South Yorkshire Research Ethics Committee (approval number 17/YH/0220). Written informed consent was obtained from all participants prior to the start of the study.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Open Science Framework: CONSORT checklist and flow diagram for 'Findings of a feasibility study of pre-operative pulmonary rehabilitation to reduce post-operative pulmonary complications in people with chronic obstructive pulmonary disease scheduled for major abdominal surgery'. <https://doi.org/10.17605/OSF.IO/4ZQNK35>

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Feasibility of an RCT of pulmonary rehab for 3 weeks vs standard of care in COPD patients before major surgery.

Really well written - clear statements of the scale of the problem and clear statements of the need for evidence. Clear rationale for plausibility of intervention. Clear focus on the purpose of THIS study - is pre-operative pulmonary rehabilitation feasible? (rather than does it work).

Decision-making points about whether to proceed to a "full" study were defined and the feasibility endpoints were well designed.

Even the methodology BEFORE feasibility acknowledges a likely problem - authors were assuming a drop out of 1/3 of pts who had been recruited! - "this 48 dataset target, based on known drop-out rates from pulmonary rehabilitation and potential further data loss due to surgical scheduling, we anticipated that we would need to recruit 72 patients".

Points of the pathway to identify potentially eligible participants comprehensively explored - Only 3 randomised! Thorough evaluation of why - i.e. issues identified related to the confirmation of diagnosis of COPD within a pathway towards major body cavity surgery. Not only in the 2 participating centres but also in 3 further centres (in detail) plus findings from a UK national survey of preop units.

IMPLICATIONS for future research:

Agree wholeheartedly with the authors' conclusion that under current UK surgical pathway conditions, an RCT of pulmonary rehab as prehabilitation for COPD before major surgery is not feasible. There is a commendable readiness on the part of the investigators to change their outlook in the face of this feasibility study evidence.

Why is it that such a large proportion of the patients who WERE identified as having COPD and were eligible (n = 45 , figure 2), declined to participate - often on the basis that they had "too many

appointments/too much to think about/too far to travel? As the authors put it: "patients often do not want to engage with pulmonary rehabilitation at a time when they are dealing with a new, life changing diagnosis and having burdensome, potentially toxic cancer treatment".

The authors make a key point that when pulmonary rehab is framed as an "optional" research extra, then it seems acceptable to opt out. I concur with their suggestion that pulmonary rehab could instead be framed (in those hospitals which have the resource) as an important part of the surgical pathway; and that future research into effectiveness might be better conducted by comparing clinical outcomes after surgery in hospitals with or without "Surgery School" (in a manner akin to research into the effectiveness of Enhanced Recovery Pathways).

IMPLICATIONS for practice:

It is striking that pulmonary rehabilitation is a proven and effective therapy (with a great benefit in terms of QALYs) which is meant to be offered to ALL patients with a diagnosis of COPD, yet so few patients with COPD (300 participants per year being assessed for major surgery in each of the 2 sites are estimate to have the condition) arrived at the preop clinic having already had experience of pulmonary rehab.

So wider questions - implied by the authors in the discussion, but perhaps worth stating explicitly are things like:

- Why are so many people with COPD undiagnosed?
- Why do many of those *with* a diagnosis still have no personal experience of pulmonary rehabilitation?
- Why are we having to use attendance at hospital for assessment for surgery as an opportunistic moment to introduce pulmonary rehabilitation?

These might be addressed by better education of the general population and health care professionals.

A philosophical question: Is it ethical to proceed to perform major surgery when patients have opted out of engaging with prehabilitation?

In the current scenario there is (very) limited clear cut evidence that pulmonary rehabilitation has utility and might improve clinical outcomes after surgery? It appears that an RCT of this therapy isn't possible in the UK without a radical overhaul of surgical pathways. How should we now proceed to find this evidence (whichever way the evidence pans out)?

Minor issues:

Please make sure the pulmonary rehab program is clearly defined. In the introduction - pulmonary rehab is explained as 1 hour of exercise and 1 hour of education twice a week for 6 weeks. - What is the format of education delivered for 2 hours a week for 6 weeks?

Attendance - the logistics of getting to classes appears to be a problem or possibly a factor in refusals. Could classes be virtual?

Figure 2 - typo in box 3 left hand side - should read 45 were approached (not 65).

Page 4 top line - is this a typo? exclusions: "Patients scheduled cardiac, thoracic and orthopaedic surgery and orthopaedic surgery"

Page 8 typo? "COPD may not have been formally diagnosed (UNTIL) after the pre-assessment clinic".

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

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

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: perioperative medicine

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

Reviewer Report 30 September 2020

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Ianthe Boden 

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This is a well-conceived and beautifully reported feasibility study that provides vital information required by clinical trialists and grant funding bodies to consider the design of future research in the field of pre-operative optimisation in this high-risk surgical cohort.

A preexisting diagnosis of COPD significantly increases a person's risk of suffering a complication after major surgery. There is preliminary evidence that for patients with COPD awaiting thoracic surgery that pulmonary rehabilitation (a supervised twice-weekly program of tailored education and physical exercise) in the weeks immediately prior to surgery may reduce the risk of postoperative complications and improve recovery after surgery. Pulmonary rehabilitation is an

established clinical program within developed countries. There is definitive evidence of the benefit and cost-effectiveness of pulmonary rehabilitation as a primary therapy to improve symptoms and quality of life for people with stable COPD. However, it is yet to be established as an effective program to preoptimise patients with COPD awaiting major abdominal surgery. This is an intriguing possibility.

This paper reports the results of a multicentre randomised controlled trial that assessed the feasibility of conducting a trial of preoperative pulmonary rehabilitation for patients with COPD and awaiting major abdominal surgery. This trial was pre-registered with feasibility outcomes specified a priori.

Despite a strong research group with significant experience and track record, two well-resourced centers of excellence as investigating sites, and a well conceived protocol to provide evidence based preoperative pulmonary rehabilitation, this trial was found to be unfeasible due to exceptionally low recruitment uptake.

Despite all their best efforts (free transport to pulmonary rehabilitation and flexible appointment times) the reasons were reported as being predominately outside the control of researchers; namely established presurgical pathways and finite time scale from time of listing for surgery to date of surgery often being shorter (2 - 3 weeks) than the time period allowable of being able to provide an effective dose of preoperative pulmonary rehabilitation (4 - 6 weeks).

However, I was unable to determine the exact proportions of the various reasons for eligible patients to not be recruited into the trial as the numbers in the flow chart in the box of 'Declined' patients do not add up to the total stated of n=42. I would also suggest that the 'not approached' group are actually ineligible/not suitable as they are not listed for surgery so no longer are eligible criteria. The flow chart's numbers are all a bit off with boxes following the arrows of flow not adding up to the box prior to it in flow order. This requires clarification.

A few other comments that could be considered within reporting of this paper:

1. It was unclear how a diagnosis of COPD was determined in the eligibility criteria. GOLD standard? Spirometry? Medical record report/coding?
2. The discussion considers that to overcome the barriers identified that the pre-surgical pathway would need to be altered to ensure that a COPD morbidity is recognised earlier and these patients are fed into a pulmonary rehab program at a much earlier time frame than the preoperative anaesthetic assessment clinic.
I would be interested to hear from the authors what interventions have been recently tested within the CURRENT surgical pathways that prevent postoperative complications e.g preoperative physiotherapy to teach patients breathing exercises inserted into preanaesthetic clinics (Boden *et al.*) or inspiratory muscle training (Kendall *et al.*), and how these could be considered within this specific surgical cohort of patients with COPD. Should more be done to implement these findings within existing pathways? Or should energy be spent in changing the pathway to get more patients into prehab/pulmonary rehabilitation?
3. Also, what reflections do the authors have of their findings in contrast to the emerging body of evidence for 'pre-habilitation' in a general surgical cohort (not refined to COPD)? Recent

Spanish (Barabaran Garcia *et al.*) and Canadian (Carli *et al.*) studies did not appear to have limitations to recruiting to a high-intensity preoperative exercise program within 4-6 weeks of surgery. Is this a factor related to the cohort of patients with COPD or related to the different countries? Or something else? A UK trial of prehab for vascular surgery patients also did not have issues with recruitment. I think it would be wise for the authors to discuss these differences in trial conduct.

The authors should be congratulated on ensuring that this data is available and published in the interests of transparent reporting. It is often disheartening to report null results or trial conduct 'failures'. However, in the interests of future efficient research activities, the paper published here presents excellent information and thought-provoking concepts that challenge our thinking about how, when, and what to do with patients prior to surgery to improve their postoperative outcome. Thankfully the authors did not bury their data along with their disappointment when their hypothesis was unable to be tested to its fullest. This paper is an excellent point of learning for all of us working in the perioperative medicine sector. Thank you.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

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

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Physiotherapy, critical care, perioperative medicine, health economics, clinical trials, postsurgical recovery

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.

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