TITLE:

A randomised trial of surgery versus no treatment to RESTORE cardiopulmonary function in severe pectus excavatum

ACRONYM:

RESTORE

PROTOCOL VERSION NUMBER AND DATE:

2.0 4th July 2024

SPONSOR:

South Tees Hospitals NHS Foundation Trust

FUNDER:

National Institute for Health and Care Research, Health Technology Assessment Programme

TRIAL IDENTIFIERS

IRAS Number: 331910

ISRCTN: 11359779

Sponsor Reference: R&D reference: 23/082

Protocol reference number: ACU017

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The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigators agree to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the relevant Standard Operating Procedures (SOPs), and other governance requirements.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

The undersigned also confirm that they will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:	Date of signature
Chief Investigator: **Prof Enoch Akowuah**	Date of Signature
Co- Chief Investigator: **Mr Joel Dunning**	Date of Signature
Study Statistician: **Dr Thomas Chadwick**	Date of Signature

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3 List of abbreviations/glossary

ACU	Academic Cardiovascular Unit (at South Tees Hospitals)
(S)AEs	(Serious) adverse event(s)
AESI	Adverse events of special interest
BIDQ	Body Image Disturbance Questionnaire
CBA	Cost-benefit analysis
CEVR	Centre for the Evaluation of Value and Risk in Health
CEA	Cost Effectiveness Analysis
CI	Chief Investigator
CPET	Cardiopulmonary exercise test
CRF(s)	Case report form(s)
CT scan	Computed tomography scan
CUA	Cost-utility analysis
CV	Curriculum vitae
DCE	Discrete choice experiment
ECG	Electrocardiogram
EDC	Electronic data capture (system)
ESTS	European Society of Thoracic Surgery
GDPR	General Data Protection Regulation
GP	General Practitioner
GPAQ	Global Physical Activity Questionnaire
HADS	Hospital Anxiety and Depression Scale
HEAP	Health economics analysis plan
HRA	Health Research Authority
HRQoL	Health-related Quality-of-Life
HRUQ	Health resource usage questionnaire
HTA	Health Technology Assessment (programme)
IDMEC	Independent data monitoring and ethics committee
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number (a public research registry)
ITT	Intention-to-treat
Lung function tests: FEV1 FVC TL_{CO} K_{CO}	 Forced Expiratory Volume Forces Vital Capacity Transfer capacity (for carbon monoxide) Carbon monoxide transfer coefficient
MAR	Missing at random
MCID	Minimal clinically important differences

MDT	Multi-disciplinary team
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR (HTA programme)	National Institute for Health and Care Research (Health Technology Assessment programme)
NIHR RDN	NIHR Research Delivery Network
Non-CTIMP	Non-Clinical Trial of Investigational Medicinal Product
PAG	Patient advisory group
PCAPES	Phoenix Comprehensive Assessment of Pectus Excavatum Symptoms
PE	Pectus excavatum
PF	Physical function
PoTS	Postural tachycardia syndrome
PPI	Patient and public involvement
PSS	Personal social services
QALY	Quality-adjusted life years
RCT	Randomised-controlled trial
R&D	Research and development
REC	Research ethics committee
SAP	Statistical analysis plan
SCTS	Society for Cardiothoracic Surgery
SD	Standard deviation
SF-36 MCS SF-36 PCS SF-36-PF	Mental component summary (MCS), physical component summary (PCS) and physical functioning (PF) domains/scores of the SF-36 health survey
SOC	Standard of care
SOPs	Standard operating procedures
TMF	Trial master file
TMG	Trial management group
TSC	Trial steering committee
TTQ	Time and travel questionnaire
USM	Urgent safety measure
WHO	World Health Organisation
WTP	Willingness to pay

4 Key Study Contacts

Chief Investigator	Professor Enoch Akowuah Consultant Cardiothoracic Surgeon and Professor of Cardiac Surgery The James Cook University Hospital Marton Road Middlesbrough TS4 3BW enoch.akowuah@nhs.net
Co-Chief Investigator	Mr Joel Dunning Consultant Thoracic Surgeon The James Cook University Hospital Marton Road Middlesbrough TS4 3BW joel.dunning@nhs.net
Academic Cardiovascular Unit (ACU) Key Contacts	Principal Research Manager: Dr Lisa Chang Senior Research Manager: Dr Leanne Ayrton-Marsay Academic Cardiovascular Unit The James Cook University Hospital Marton Road Middlesbrough TS4 3BW stees.pectusrestoretrial@nhs.net
Sponsor	South Tees Hospitals NHS Foundation Trust The James Cook University Hospital Marton Road Middlesbrough TS4 3BW tvra.projects@nhs.net
Funder	National Institute for Health and Care Research: Health Technology Assessment Programme NIHR Coordinating Centre Alpha House Enterprise Road Southampton SO16 7NS
Wider Research Team	Prof James Wason, Prof of Biostatistics at Newcastle University Dr Thomas Chadwick, Senior Statistician at Newcastle University.

	Prof Luke Vale Professor of Health Economics at The London School of Hygiene and Tropical Medicine. Dr Cristina Fernandez-Garcia, Research Associate, Health Economics Group at Newcastle University. Rebecca Maier, Head of the Academic Cardiovascular and Thoracic Unit at South Tees Hospitals NHS Foundation Trust. Mr James Andrews, Consultant Paediatric Surgeon at Glasgow Children's Hospital. Prof Jonathan Wyllie, Consultant Paediatrician at South Tees Hospitals NHS Foundation Trust. Dr Gillian Wallace, Consultant in Respiratory Medicine at North Tees University Hospital. Prof Gerard Danjoux Consultant Anaesthetist at South Tees Hospitals NHS Foundation Trust. Prof Babu Naidu, Consultant Thoracic surgeon and Professor at University of Birmingham. Dr Rebecca Thursfield, Paediatric Respiratory Consultant, Alder Hey Children's Hospital. Prof Peter McCulloch, Chair of IDEAL Collaboration, Oxford University. Alistair Renton-Levett, Principal Clinical Scientist (Lead Physiologist for CPET), South Tees Hospitals NHS Foundation Trust. Mr Philip Longhurst, Patient representative for the RESTORE Trial. Dr Claire Pryor, Patient representative for the RESTORE Trial.
Independent Data Monitoring and Ethics Committee Membership	Prof Karen Redmond (Chair) Mr Adrian Marchbank (member, clinician) Dr Catherine Best (member, statistician)
Trial Steering Committee Membership	Dr Ben Gibbison (Independent Chair) Prof Dawn Jaroszewski (Independent member, expert clinician) Ms Lynne Evans (Independent member, patient representative) Dr Rodolfo Hernandez (Independent member, expert health economist)Prof Enoch Akowuah (member, CI)

5 Study Summary

Study Title	A randomised trial of surgery versus no treatment to RESTORE cardiopulmonary function in severe pectus excavatum – The RESTORE Trial
Short Title	RESTORE Trial
Study Design	Prospective, Pragmatic, Superiority, Randomised Control Trial, and an observational cohort. RESTORE will recruit 200 participants with severe pectus excavatum (PE) to the randomised controlled trial from around 12 centres. The observational cohort will recruit up to 100 participants from the group that is accepted for surgery by the national Multi-Disciplinary Team (MDT).
Research Question/Aim(s)	**Main Aims:** To establish the impact of corrective surgery for PE on physical function, cardiopulmonary function, and its cost effectiveness. **Primary Objective:** To determine whether corrective pectus surgery is superior to no surgery as measured by change in patient-reported quality of life and functional health scores (SF-36v2) physical function score at 1 year. **Primary Economic Objective:** To estimate the incremental cost per quality-adjusted life year (QALY) of corrective pectus surgery compared with conservative treatment over 1 year. **Secondary Objectives, to compare:** • Cardiopulmonary function (Percentage predicted peak VO_2 on Cardiopulmonary Exercise Test (CPET)) • Health related quality of life (HRQoL) (SF-36v2 (MCS and PCS scores) and EQ-5D-5L)) • Disease specific quality of life indicators (Nuss and Phoenix Comprehensive Assessment of Pectus Excavatum Symptoms (PCAPES) Questionnaires) and symptoms including syncope.

	• Depression and anxiety (on the Hospital Anxiety and Depression scale (HADS score)) • Body Image Disturbance Questionnaire (BIDQ) • Major complications including reoperations, infections and readmissions after surgery • Operative technical success (CT scan) • Costs to the NHS and patients at 1 year and over the patients' lifetime • Incremental cost per quality adjusted life year (QALY) of corrective pectus surgery compared with conservative treatment over the patients' lifetime • Patient preference estimated by a discrete choice experiment (DCE) • Net benefit of the intervention • Effectiveness and cost effectiveness of surgery by subgroups including sex, age, operation type and severity of PE. We will also assess the impact of change in each measure by combining the randomised and embedded observational cohort.
Study Participants	**Setting:** Secondary/tertiary care; approximately 12 NHS cardiothoracic surgical centres will take part. **Target Population for the Randomised Trial:** Patients ≥12 years old with severe PE (Haller Index of >3.25 on cross-sectional CT scan imaging) and exhibiting any physical symptoms attributable to the pectus abnormality. **Inclusion Criteria:** • ≥ 12 years old. • PE deformity with a Haller Index of >3.25 on CT scan. • At least one of the following criteria: ○ Significant level of shortness of breath or exercise ability perceived to be below that of their peers (e.g., limited by vigorous

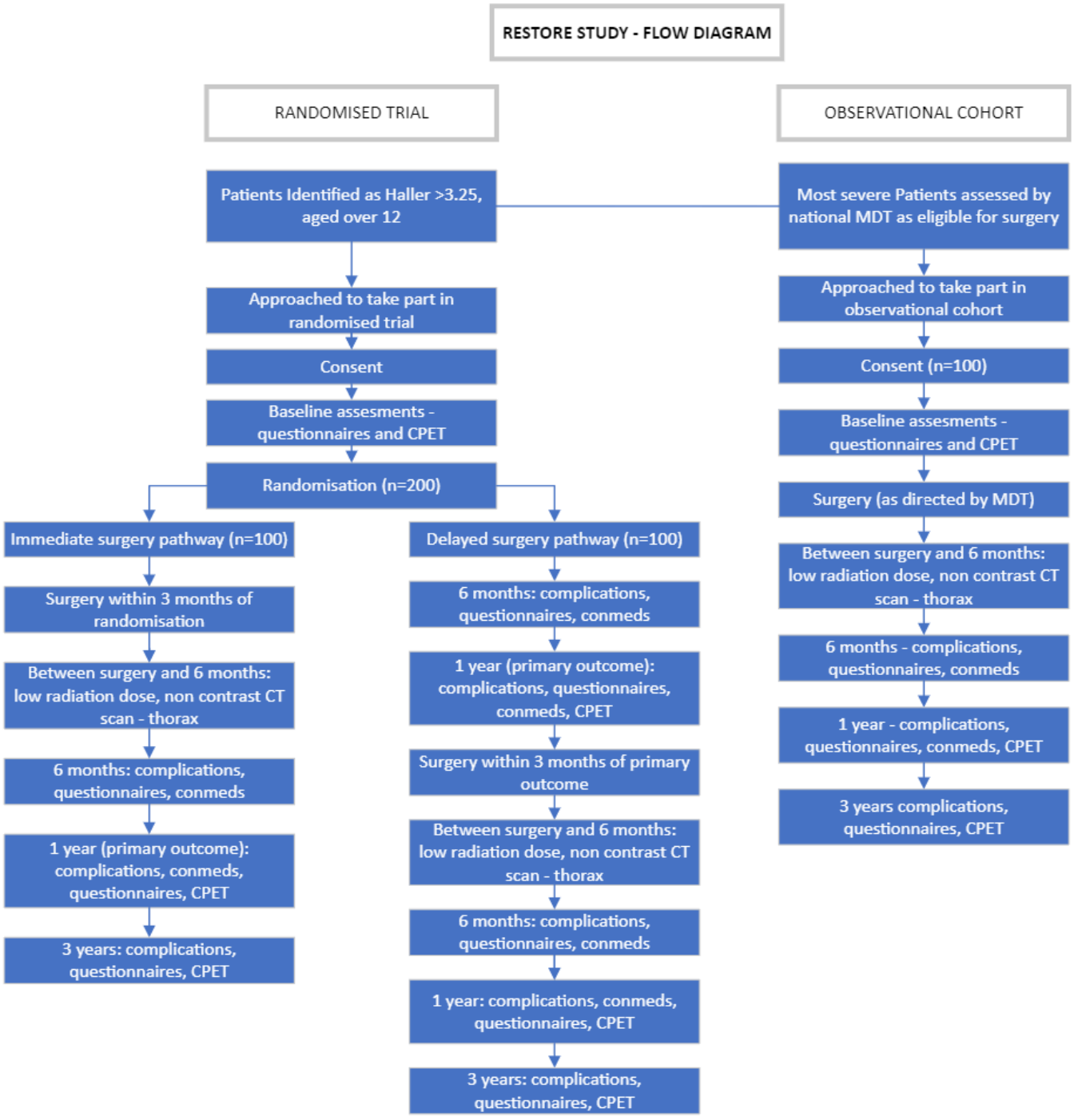
	activities such as running or lifting heavy objects); o Presyncope or syncope on exercise; o Arrhythmias that may be due to the pectus abnormality; o Dysphagia or swallowing abnormalities in the absence of any other cause. • Provide informed consent/assent. • Fit to undergo surgery. **Exclusion Criteria:** • Not fulfilling the inclusion criteria.Symptoms relating to causes other than PE. • Received previous surgery for PE. • Unwilling to have surgery for PE. **Target Population for the Embedded Observational cohort:** Patients ≥12 years old accepted by the NHS England approved national MDT surgical pathway for the most severe PE with severe symptoms. I**nclusion Criteria:** • ≥ 12 years old. • Confirmed as eligible and fit for surgery via the national MDT surgical pathway. • Providing informed consent to take part in the embedded observational cohort and agreeing to 5 years follow up. **Exclusion Criteria:** • Not fulfilling the inclusion criteria • Willing to join the full randomised trial group of the RESTORE Trial. Patients due to receive repeat surgery for their PE are able to join the cohort study as long as they fulfil all eligibility criteria.

Randomisation	Randomisation with allocation concealment will utilise a centralised, web-based system to minimise bias. Eligible participants will be assigned in a 1:1 ratio to early surgery (intervention) or late surgery (control), stratified by planned surgery type (Nuss/Ravitch), age (under, or, 16 and over years old), CPET findings (under and equal to 85% predicted VO_{2peak} (or an invalid test), or, over 85% predicted VO_{2peak}).
Trial interventions	The intervention under study is corrective surgery for PE. There are two operations that are commonly performed for PE. The **Nuss procedure** (also known as minimally invasive repair of PE) in which two small incisions are made either side of the chest and large metal bars are placed across the chest that can push the sternum forward immediately without the need to cut the costal cartilages. These bars are left in place for up to 3 years and then removed. The **Ravitch procedure** which is an open operation whereby the costal cartilages either side of the sternum are cut, a horizontal osteotomy may be made across the sternum and then the sternum is brought forward and fixed in place by metal plates or a bridge. Both Nuss and Ravitch operations will be used in this trial, dependent on clinical presentation, surgeon and unit judgement, experience, practice and in discussion with the patient. **RESTORE will compare:** **Intervention group (early surgery):** corrective surgery for PE (Nuss or Modified Ravitch procedure) within 3 months after randomisation. **Control group (no surgery prior to primary outcome):** surgery delayed for at least 1 year after randomisation and following primary outcome measures 1 year after randomisation; surgery will be performed within 3 months of these measures.

	An embedded observational cohort of non-randomised patients meeting MDT criteria for most severe PE will be evaluated using the same measures.
Outcomes	**Primary Outcome:** Change in SF-36v2 Physical Function score. This is measured at baseline and one year after randomisation (control group) one year after surgery (intervention group). **Secondary Outcomes:** **Secondary clinical effectiveness outcomes:** Change in VO_{2peak} in CPET testing; HRQoL and component domains (EQ-5D-5L, SF-36v2); impact of surgery on symptoms (including syncope) and acceptability (Nuss and PCAPES Questionnaires, BIDQ, and HADS); major complications (including redo surgery, infections, and mortality). **Health-economic outcomes:** The primary economic outcome will be the incremental per QALY based upon responses to the EQ-5D-5L at 12 months. Other health economic outcomes will be costs to the NHS and personal social services and QALYs at 12 months and modelled costs, QALYs and incremental cost per QALY gained over the estimated patient lifetime. In addition to these outcomes, we will also estimate monetary benefits (using data from an embedded Discrete Choice Experiment) and net benefits. **Long term outcomes:** Consent will be sought to follow all patients up for 5 years post-surgery, this would be subject to further funding being awarded after review of our primary outcome results.
Planned Size of Sample	**Randomised trial:** 200 randomised patients **Cohort:** 100 patients

Follow up duration	**Intervention group (early surgery):** outcomes will be measured at baseline, 6 months, 1 year, and 3 years after surgery. **Control group (late surgery group):** outcomes will be measured at baseline, 6 months, 1 year post-randomisation, and 6 months, 1 year and 3 years after surgery. At least 75% of all randomised participants will have 3 year follow-up within the trial. It is expected that for a proportion (<25%) of participants (in the late surgery group), the trial will end before they have reached their 3-year post surgery follow-up. **Embedded observational cohort:** outcomes will be measured at baseline, 6 months, 1 year, and 3 years after surgery.
Planned Study Period	The trial length will be 76 months from 1st February 2024. Planned timelines are: • Months 1-6: protocol, REC/HRA approval, contracting, database/randomisation system. • Months 7-12: open all UK centres. • Months 7-15: internal pilot. • Months 7-31: recruitment. • Month 46: Initial data lock once last patient has 1 year primary endpoint data with primary analysis and dissemination from month 51. • Month 71: Second data lock • Months 72-75: data analysis. • Months 72-76: report writing, dissemination. **Primary Outcome Reporting:** An early initial data lock will allow analysis of the primary outcome and reporting to allow NHS commissioners in England to make an expedited decision.

6 Trial Flow Diagram



NOTE: Data from some baseline assessments may be collected from assessments performed as standard care prior to consenting to the trial. For post-operative assessments, the day of surgery will be considered as D0, e.g., the timing of the 1 year CPET, is 1 year after surgery. See Section 12.1 for further details.

7 Governance

7.1 Role of the Sponsor

The Sponsor of this research is South Tees Hospitals NHS Foundation Trust; they take overall responsibility for the trial and hold the main contract for RESTORE with the Department of Health.

7.2 Role of the Funder

RESTORE has been funded by a grant from the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme.

The NIHR Research Delivery Network (NIHR RDN) are providing additional resources at participating Trusts.

The NIHR HTA are responsible for funding the study but are not part of the day-to-day trial conduct, data analysis and interpretation, manuscript writing, or dissemination of results.

7.3 Role of Trial Management Group (TMG)

The day-to-day supervision of the trial will be the responsibility of the Trial Management Group (TMG), who will report to the Trial Steering Committee. The TMG will meet regularly throughout the trial.

The TMG will consist of:

- The Chief Investigator
- The Co-Chief Investigator
- Academic Cardiovascular Unit (ACU) members, including the Senior Research Manager
- Study Statistician(s)
- Health Economist(s)
- The Sponsor, and other members of the wider research team, including PPI co-applicants may attend TMG meetings, as required.

Responsibilities of the TMG will include, but not be limited to, obtaining and managing study approvals, site set-up and management, data quality, trial documentation and reporting obligations.

7.4 Role of the Independent Data Monitoring and Ethics Committee (IDMEC)

An Independent Data Monitoring and Ethics Committee (IDMEC) will meet at planned intervals throughout the study to review data to ensure patient safety and the ethical trial conduct. The IDMEC will run in accordance with a trial-specific charter, which will be agreed at its first meeting. The IDMEC will consist of an independent chair, and at least two other independent

members. Independence will be defined as not employed by any organisation directly involved in trial conduct.

The IDMEC will meet at planned intervals throughout the study and report to the Trial Steering Committee.

7.5 Role of the Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will provide overall supervision of the trial, and will monitor progress, conduct and advise on the trial. The TSC will consider the recommendations of the IDMEC, and act where required. The TSC carries the responsibility for deciding if the trial should be stopped early. Terms of reference for the TSC will be agreed at the first meeting.

The TSC will consist of an independent chair and at least two other independent members. Independence will be defined as not employed by any organisation directly involved in trial conduct.

The TSC will meet at planned intervals throughout the study and report to the Sponsor and Funder.

8 Background

Pectus excavatum (PE) is a congenital condition found in between 1 in 400 and 1 in 1000 people (1), it can occur at or soon after birth, although for most it occurs during the pubertal rapid growth phase. In PE, the sternum which lies over the heart can be pushed towards the spine, narrowing the space in the chest. For most, PE does not impact health, and most patients who present to physicians are concerned about the psychological impact resulting from the deformity of the chest wall, but for those with severe PE, narrowing of the chest cavity causes pulmonary and cardiac compression. This can lead to impaired heart function (due to restricted right ventricular filling which results in a fixed stroke volume and cardiac output), especially during exercise (2-6). Affected individuals may not feel any symptoms at rest but develop symptoms, typically tachycardia, dyspnoea, syncope, dizziness and pain when they participate in exercise (7-17). These symptoms limit their exercise ability, impair physical function and reduce health related quality of life (HRQoL). Surgery for PE lifts the sternum away from the heart, to allow cardiac output and respiratory function to increase during exercise, which relieves these symptoms.

In 2018 in England, 110 paediatric cases were performed in 18 centres and 195 adult cases in 28 centres. In 2019 the NHS England Clinical Panel decommissioned pectus surgery in England, although it is still funded in the devolved nations. This decision was based on the lack of high-quality comparative data demonstrating an improvement in physical or cardiopulmonary function. There is an urgent need for high quality evidence to inform guidelines, practice, and future commissioning decisions.

Our literature review identified 9 studies that looked at improvement in cardiopulmonary exercise tolerance in patients with severe PE. Together these studies document 498 patients with severe PE and impaired exercise physiology as measured on cardiopulmonary function testing. Seven studies reported clinically and statistically significant improvements in all parameters of cardiopulmonary function testing. For the other 2 studies, O'Keefe et al reported significant improvements in O2 pulse and in respiratory function as measured by FEV1 and FVC (8). Bawazir et al (14) was the only study that did not demonstrate an early improvement, but of note, this same group from France published the study by Sigalet et al 2 years later (11) which then reported a significant improvement in cardiopulmonary exercise later after surgery. There were a wide range of ages across these studies from a mean age of 30 years (6) to a mean age of 13 years in the paediatric studies (17, 18). The Haller index was above 3.25 in all studies; for those with exercise intolerance the mean Haller was higher, at a mean of 4.5.

The improvements were similar in the studies looking at the Nuss procedure and the Ravitch operation with the maximal improvement tending to be after bar removal in the patients having the Nuss procedure.

In conclusion, data from the 9 cohort studies worldwide (n=495) (6-14) are of limited quality and suggest a benefit of pectus surgery to improve cardiopulmonary function. In the largest study, 130 patients underwent CPET testing pre and post-surgery, with significant improvement in cardiopulmonary outcomes post-repair (6). There have also been several systematic reviews and meta-analyses (19-22). These suffer from the same weaknesses as the primary studies described above including the absence of a control group, lack of randomisation, and failure to measure outcomes that patients tell us are important.

9 Rationale for RESTORE

In 2019 the NHS England Clinical Panel decommissioned pectus surgery in England, although it is still funded in the devolved nations. This decision was based on the lack of high-quality comparative data demonstrating an improvement in physical or cardiopulmonary function. There is an urgent need for high quality evidence to inform guidelines, practice and future commissioning decisions.

RESTORE will be the first randomised-controlled trial (RCT) to assess the impact of corrective surgery for PE on physical function and cardiopulmonary outcomes. Including patients from the age of 12 will ensure findings are widely applicable to the broadest range of patients. This study will directly influence NHS commissioning for pectus surgery, following the commissioning call by NHS England for this trial.

10 Trial Objectives

10.1 Primary Objective

To determine whether corrective pectus surgery is superior to no surgery as measured by change in SF-36v2 physical function score at 1 year.

10.2 Primary Economic Objective

To estimate the cost effectiveness of corrective pectus surgery compared to conservative treatment over 1 year.

10.3 Secondary Objectives

To compare:

- Measure of cardiopulmonary function, including VO_{2peak} on CPET as % predicted.
- HRQoL (SF-36v2 and EQ-5D-5L).
- Symptoms (Nuss and Phoenix Comprehensive Assessment of Pectus Excavatum Symptoms (PCAPES) Questionnaires) including syncope.
- Depression and anxiety (HADS score).
- Body Image Disturbance Questionnaire (BIDQ).
- Major complications including reoperations, infections and readmissions after surgery.
- Operative technical success (CT scan performed after surgery).
- Costs to the NHS and patients at 1 year and over the patients' lifetime.
- Patient preference estimated by a discrete choice experiment (DCE).
- Incremental cost per QALY gained over the patients' lifetime.
- Net benefit of the intervention.
- Effectiveness and cost effectiveness of surgery by subgroups including sex, age, operation type and severity of PE.

10.3.1 Observational Cohort Objectives

- Assessment of the change over time of important outcome measures in the most severe group of patients receiving surgery for PE.
- Assessment of change over time in important outcome measures across the entire population of patients receiving surgery for PE.

11 Trial Design

11.1 Summary of Patients in the Randomised Controlled Trial

Two hundred participants with severe PE will be recruited to a randomised controlled trial. These participants will be randomised on a 1:1 basis to either an early-surgery group or a delayed-surgery group.

11.2 Inclusion Criteria for the Randomised Trial

1. ≥ 12 years old.
2. A PE deformity with a Haller Index of >3.25, as measured by the internal width of the chest measured at the widest point divided by the distance from the back of the sternum to the anterior vertebral body at its minimum point on CT scan.
3. The participant must satisfy at least one of the following criteria:
    a. Significant level of shortness of breath or exercise ability perceived to be below that of their peers (e.g., limited by vigorous activities such as running or lifting heavy objects).
    b. Presyncope or syncope on exercise.
    c. History of arrhythmias that may be due to the pectus abnormality.
    d. Dysphagia or swallowing abnormalities in the absence of any other cause.
4. Provide informed consent/assent.
5. Fit to undergo surgery.

11.3 Exclusion Criteria for the Randomised Trial

1. Patients not fulfilling the inclusion criteria.
2. Symptoms relating to causes other than PE.
3. Received previous surgery for PE.
4. Unwilling to have surgery for PE.

11.4 Summary of Patients in the Embedded Observational Cohort

One hundred patients ≥12 years old accepted by the NHS England approved national MDT surgical pathway for the most severe PE with severe symptoms.

11.5 Inclusion Criteria for the Embedded Observational Cohort

1. ≥ 12 years old.
2. Confirmed as eligible and fit for surgery via the national MDT surgical pathway.
3. Providing informed consent to take part in the embedded observational cohort.

11.6 Exclusion criteria for the Embedded Observational Cohort

1. Patients not fulfilling the inclusion criteria.
2. Patients who are willing to join the full randomised trial group of the RESTORE Trial.

Patients accepted to the national MDT should be given the option to participate in the randomised trial or the cohort. If patients choose to be part of the randomised controlled trial then must fulfil the full eligibility criteria for this prior to randomisation. Patients due to receive repeat surgery for their PE are able to join the cohort study as long as they fulfil all eligibility criteria for the cohort.

11.7 Trial Setting

The trial will be conducted in 12-15 NHS cardiothoracic surgical centres. Further centres may be added following agreement by the TMG and Sponsor.

11.8 Surgical Expertise

All participating surgeons will confirm that they have performed more than 20 Nuss procedures to offer the Nuss operation and/or more than 20 Ravitch procedures in order to offer the Ravitch operation within the trial. Quality outcomes of any deaths, bar displacements or need for re-operation for the most recent 20 cases will also be submitted for review to the TSC in order to endorse surgical expertise. Any surgeon not achieving these parameters may refer patients to another centre, or perform the surgery under in-person supervision by a surgeon who previously met the target, until their target number of cases, and quality outcomes have been obtained.

Surgeon expertise will be endorsed by the Trial Steering Committee prior to participation and after review of case numbers and quality outcomes.

The co-Chief Investigator (CI) will also visit all units during the trial and will observe each unit performing the Nuss procedure and the Ravitch procedure in order to ensure uniformity of the procedure.

Improvement in the Haller index will be documented and any units where the improvement in the Haller index is not consistently less than 3.25 will have an additional site visit and individual case discussions of their cases with the co-CI. We will check this quality metric regularly and at least every 5 cases per unit and report to the oversight committees.

11.9 Primary Outcome Measure

The primary outcome is the SF-36v2 Physical Function score change between testing before randomisation and 1 year later (control group) or 1 year after surgery (experimental group).

Primary Economic Outcome:

- Incremental cost per QALY at 1 year

11.10 Secondary Outcome Measures

Secondary outcomes measures are:

- Measures of cardiopulmonary function (including percentage of predicted VO_{2max} on CPET).
- Quality of life measures including those that of impact on mental well-being (EQ-5D-5L and SF36v2 mental component scores, and HADS).
- Symptoms (Nuss and Phoenix Comprehensive Assessment of Pectus Excavatum Symptoms (PCAPES) Questionnaires).
- Body Image Disturbance Questionnaire (BIDQ)
- Need for revision surgery (complications including the need for unplanned redo surgery and syncope).
- Adverse events of special interest.
- Major surgical complications.
- Costs to the NHS and patients at 1 year and over the patients' lifetime.
- QALYs at 1 year and over the patients' lifetime.
- Incremental cost per QALY gained over the patients' lifetime.
- Patient preferences (discrete choice experiment).
- Net benefit of the intervention.

12 Trial Procedures

12.1 Schedule of Events/Data Collection

	All groups			Early surgery group and embedded observational cohort					Delayed surgery group						
	Consent	Baseline	Randomisation	Index surgery	6 months post-op	12 month post-op	~30-36months	>36 months post op (and >6 months Nuss bar removal)	6 months post-randomisation	12 month post-randomisation and pre-op	Index surgery	6 months post-op	12 month post-op	~30-36months	>36 months post op (and >6 months Nuss bar removal)
Window			*within 6 months of consent*	*within 3 months of randomisation for early-surgery group*	*±4 weeks*	*±4 weeks*		±4 weeks	±4 weeks	±4 weeks	*within 3 months of 12-month post-rand assessment*	*±4 weeks*	*±4 weeks*		±4 weeks
Consent	X														
Eligibility review		X													
Randomisation			X												
Surgery				X							X				
Nuss bar removal							X							X	
Demography		X													
Medical history[1]		X													
Medications		X		X	X	X		X	X	X	X	X	X		X
CT scan		X[2]													
Echo		X[2]													
Lung function testing		X[2]													
Cardiopulmonary exercise test (CPET)		X[3]				X		X		X[4]			X		X
Low-radiation CT					X[5]							X[5]			
Questionnaires:															
SF-36v2		X			X	X		X	X	X		X	X		X
EQ-5D-5L		X			X	X		X	X	X		X	X		X
Nuss		X			X	X		X	X	X		X	X		X

	All groups			Early surgery group and embedded observational cohort					Delayed surgery group						
	Consent	Baseline	Randomisation	Index surgery	6 months post-op	12 month post-op	~30-36months	>36 months post op (and >6 months Nuss bar removal)	6 months post-randomisation	12 month post-randomisation and pre-op	Index surgery	6 months post-op	12 month post-op	~30-36months	>36 months post op (and >6 months Nuss bar removal)
Window			*within 6 months of consent*	*within 3 months of randomisation for early-surgery group*	*±4 weeks*	*±4 weeks*		±4 weeks	±4 weeks	±4 weeks	*within 3 months of 12-month post-rand assessment*	*±4 weeks*	*±4 weeks*		±4 weeks
Phoenix Comprehensive Assessment of Pectus Excavatum Symptoms (PCAPES)		X			X	X		X	X	X		X	X		X
Hospital anxiety and depression scale (HADS)		X			X	X		X	X	X		X	X		X
Body image disturbance (BIDQ)		X			X	X		X	X	X		X	X		X
Health Resource Usage (HRUQ)		X			X	X		X	X	X		X	X		X
Time and travel (TTQ)					X				X						
Global Physical Activity Questionnaire (GPAQ) (completed as part of CPET assessment)		X				X		X		X			X		X
Discrete Choice Experiment[6]						X (@16 mon)							X (@16 mon)		
Adverse events				X	X	X		X			X	X	X		X
Rehospitalisations				X	X	X		X			X	X	X		X
Further (unplanned) pectus interventions				X	X	X		X			X	X	X		X

[1]Including previous mental health service use
[2]data collected from SOC assessments, these may have been performed up to 12 months prior to consent.
[3]data collected from SOC assessment if ≥16 years of age and performed within 12 months of consent or if <less 16 years and within 6 months of consent. Repeated as a study assessment if participant is under 16 years and previous assessment was performed >6 months prior to consent or if ≥16 years and previous assessment was performed >12 months prior to consent.
[4]may be performed from 9 months post-randomisation.
[5]Post-operative SOC low-dose CT scan, may be performed from day 1 up to 6 months post-index surgery.
[6]See section 14.2: to be performed at month 16

Identification and Recruitment of Participants

Potential participants will be identified from outpatient clinics at participating hospitals, from new referrals, and from wide and targeted advertising of the study using social media and our established patient groups (Pectus support UK Facebook group and the pectus charity group) to ensure that patients with severe PE are given the opportunity to take part.

A new page on pectus on the Society for Cardiothoracic Surgery website (https://scts.org/patients/lungs/procedures/13/pectus_treatments/) will also post details about how to join the study and these will also be present on the dedicated patient facing website for the trial.

Additionally, the research team will continue to engage with the national MDT for PE which reviews the most severe cases in England and allows a restricted pool of patients to receive surgery. All of these patients will all be offered the chance to take part in RESTORE, and can choose to take part in either the observational cohort or the randomised trial.

Recruitment at individual centres will commence once national approvals are in place, local capacity and capability is approved and after the 'green light' to open the site has been issued by the Clinical Trials Unit. Recruitment will continue until 200 patients have been randomised and 100 enrolled in the observational group.

12.2 Informed Consent

Patients with PE will be sent, be able to download from a website, or, given a patient information sheet describing the study and will be able to speak to a member of the research team about the trial. Conversations with patients about the trial should be documented in the patient notes.

If a patient with PE is seen in clinic and the clinician identifies that this patient might be eligible for the RESTORE Trial, the trial will be discussed with the patient (and where appropriate the patient's parent or legal guardian). Consultations for this group of patients often occur via remote means (e.g., video call); patients may also be approached about the trial during this remote consultation.

As part of routine care, the clinician will (have) request(ed) lung function testing (FEV1, FVC, TL_{CO}, K_{CO}), echocardiography, CT Thorax (A RESTORE CT scan manual is available for details of the end expiratory and end inspiratory non contrast low dose CT thorax protocol), and also a CPET (A RESTORE CPET manual is available). These assessments are all part of an NHS funded evaluation of a patient with PE.

Once the clinician has access to all these test results they are able to discuss entry into the RESTORE Trial with the patient/parent or guardian and after opportunity for questions, a delegated and trained member of the research team will seek consent. As this may be a remote consultation, or patients seen in person may wish to consent at a later date, consent

may be achieved remotely, if required. This includes via electronic methods of consent. Electronic signatures may include signatures that are scanned, an electronic representation of a handwritten signature, or the use of advanced or qualified electronic signature systems. Remote consent may also be obtained by return of the consent form with a wet-ink signature. Counter-signature will be provided by the trained and delegated member of the research team seeking consent. Where the consent is a wet ink signature on a posted consent form, the counter signature by the research team member will be on a later date to the patient signature and date. A copy of the consent form will be returned to the participant by post or electronically.
Those over the age of 16 years will be able to provide informed consent. Those under the age of 16 who are Gillick-competent will be able to sign a consent form. Those under the age of 16 at the time of consent who are not Gillick-competent will be asked to complete an assent form, and informed consent obtained from (a) parent or guardian. If a participant turns 16 during the course of the study and completed an assent form they will be asked to provide consent for their continuation in the study.
Patients will have sufficient time to consider the information before providing consent.
A selection of different Participant Information Sheets and Consent forms/Assent forms will enable patients across a wide age range to participate, these will include information sheets for the randomised controlled trial and the observational cohort.
Translations of the information sheets and consent forms/assent forms will also be available.

12.3 Confirmation of Eligibility

Following consent, a thoracic surgeon on the delegation log will confirm the patient's eligibility prior to randomisation (randomised trial) or study entry (cohort) by reviewing the full eligibility criteria, completing the eligibility proforma, and documenting confirmation of eligibility in the medical notes. Baseline assessments used for the eligibility confirmation may be carried out prior to consent but the final signoff of eligibility must be after consent (where remote consent is taken this must be after the date of research team member who counter signs the consent form).
If after baseline assessment, the patient meets all criteria for the trial the research team must ensure that they have an operative date available for surgery within the next 3 months prior to requesting randomisation, or that there is a date within 3 months at a participating centre that the patient is willing to travel to. Patients will be asked to choose the sites that they would be willing to travel to and they will also be able to state a preferred site as well as their preferred type of operation, if they have a preference.
If the patient would prefer to be randomised nearer to a date convenient to them then this is acceptable; randomisation should be within 6 months of consent.

12.4 Screening Log and Screen Failures

All potentially eligible patients who are approached about the study should have their details added to the electronic screening log.

Those patients who are not subsequently found to be eligible will be considered a screen fail. Those that decline participation should be asked why, and their reason recorded on the log where this is given.

The NIHR HTA panel requested that we specifically monitor a number of aspects of trial recruitment to ensure the trial targets under-represented groups. The screening log will contain details of the following for every patient approached/who approaches the trial team about the trial:

- Age
- Year of birth
- Sex at birth
- Ethnicity
- Postcode
- Reason the patient did not take part or was ineligible, if applicable
- Randomised Controlled Trial or Observational Cohort participant

Redacted screening logs with personal identifiers other than those listed above (e.g., name, NHS numbers, contact details etc removed), should be sent to the Clinical Trials Unit monthly for monitoring purposes.

12.5 Patient ID

Each participant will be given a unique study ID number at the point of consent. This study ID number will be used to identify the individual participant throughout the study and will not be re-assigned to any other participant.

12.6 Randomisation

For patients consenting to the randomised controlled trial, randomisation should take place within 6 months of the date of consent and following confirmation of eligibility. Randomisation will be undertaken by delegated members of the clinical research team using a validated web-based system (CASTOR). The randomisation system will use permuted random blocks of variable length, block sizes are not disclosed here to ensure allocation is not predictable. Eligible and consenting participants will be randomly assigned in a 1:1 ratio to one of two arms:

GROUP A (intervention): Allocated to receive early surgery within 3 months of randomisation.

OR

GROUP B (control): Allocated to receive late surgery, at least one year after randomisation and up to 15 months after randomisation.

Randomisation will be stratified by:

- Planned surgery type (Nuss or Ravitch).
- Age (under 16 at the time of randomisation, or, 16 or over at the time of randomisation).
- Baseline CPET findings (≤ 85% predicted VO_{2peak} (or an invalid test), or, over 85% predicted VO_{2peak}).

Once randomised the patient must have a date for surgery within 3 months given to them, if randomised to early surgery. If randomised to late surgery this date should be scheduled for any time more than a year after the randomisation date and within 3 months of their one year assessments.

12.7 Observational Cohort

NHS England agreed in 2023 to commission a small number of procedures annually for patients with the most severe PE and severe symptoms. The current national criteria requires a patient to have severe PE with exercise intolerance and one of 5 criteria. These are:

1. Syncope or pre-syncope,
2. Arrhythmias due to the pectus abnormality,
3. Dysphagia without any other obvious cause,
4. Evidence of cardiac compression on Cardiac MRI or equivalent imaging,
5. The potential to have complications which would impede other surgery such as scoliosis surgery.

It is expected that round 30-50 patients per year will be accepted by the National MDT.
These patients should be offered the opportunity to take part in the randomised controlled trial and the observational cohort, unless they are redo patients in which case they will only be able to take part in the cohort.
The MDT-approved patients who decline the randomised controlled trial and consent to take part in the observational cohort will follow the same assessment protocol as in the randomised trial, to allow evaluation of their outcomes.

12.8 Blinding

Study participants, clinicians and the ACU team will be aware of treatment allocation. The Statistical Analysis Plan (SAP) will be developed by statisticians who are unaware of treatment allocation and will be finalised and signed-off prior to unblinded data being reviewed by the IDMEC. The SAP will contain full details of the final analyses, with details of who will perform these analyses. Some statisticians may have access to unblinded data for the purposes of

creating IDMEC reports. Limited members of the research team will have access to the closed IDMEC reports, unless the IDMEC request that unblinded information is released. In the case that a major amendment is proposed to the SAP, this will be approved by an appropriate blinded statistician.

12.9 Informing General Practitioners of Trial Participation

General Practitioners (GPs) will be informed of their patient's decision to participate. A letter providing information about the study and inviting GPs to contact the investigators, if they have questions, will be sent following consent.

12.10 Assessments

12.10.1 Questionnaires

Physical functioning, overall quality of life, and symptom burden are assessed using a range of questionnaires.

Patients can choose to complete the questionnaires:

- On paper, with data entered onto the database by the research team at individual sites.
- Via direct data entry to the on-line database by the patient. Patients must be set up on the CASTOR system and an email link will be sent to them at the required times.
- Via direct data entry to the on-line database by the research team if administration is over the phone with the patient, or in person.

Questionnaires to be completed are:

- Bespoke medical history and concomitant medications
- SF-36v2 and EQ-5D-5L will measure physical function and health related quality of life. Both are well validated questionnaires.
- Nuss and Phoenix Comprehensive Assessment of Pectus Excavatum Symptoms (PCAPES) Questionnaires will be used to determine symptoms. The Nuss questionnaire is validated; the PCAPES Questionnaire has been extensively used and validation is soon to be published.
- The validated HADS questionnaire will measure depression and anxiety.
- The validated Body Image Disturbance Questionnaire (BIDQ).
- A bespoke Health Resource Usage questionnaire (HRUQ) will collect data on health care visits. This will be developed from those used in previous studies and relate to services potentially used by participants.
- A time and travel questionnaire (TTQ) will collect data on time and travel costs borne by participants in accessing and using services.

- The Global Physical Activity Questionnaire (GPAQ) will collect information on physical activity as part of the CPET.

All questionnaires will be completed at the following time-points for each group of patients, with exceptions noted in brackets:

Early surgery group

- Baseline (Medical history only taken at this time)
- 6 months following surgery (not GPAQ, TTQ is only taken at this timepoint)
- 12 months following surgery
- 36 months following surgery (or 6 months after bar removal)

Late surgery group

- Baseline (Medical history only taken at this time)
- 6 months following randomisation (not GPAQ, TTQ is only taken at this timepoint)
- 12 months following randomisation
- 6 months following surgery
- 12 months following surgery
- 36 months following surgery (or 6 months after bar removal)

Observational cohort group

- Baseline (Medical history only taken at this time)
- 6 months following surgery (not GPAQ, TTQ is only taken at this timepoint)
- 12 months following surgery
- 36 months following surgery (or 6 months after bar removal)

12.10.2 Questionnaire Feedback to Clinical Teams

If patients score very highly on the HADS to indicate a high level of depression, the trial team will feed this information back to site research teams. The site research teams will ensure that the general practitioner for the patient is contacted in order for NHS services to make a full assessment of their needs and provide psychological support from the appropriate services as required.

12.10.3 Routine Care Tests (CT, Echocardiogram)

A range of routine care tests will be used as part of the dataset for the trial. These include:

- Baseline echocardiograms
- Baseline CT to measure the Haller index
- Baseline Lung Function Tests.
- CT scan up to approximately six months following surgery to measure Haller index
- Baseline CPET

These tests would expect to be routinely performed as part of the evaluation of patients with a pectus abnormality prior to consideration for entry into the trial and the NHS England protocol confirms that these should be available to all patients being evaluated for pectus surgery and funded by the NHS as part of routine care.

The CPET[1*], lung function testing and the cross sectional imaging (CT) must be within a year of the randomisation date. An echocardiogram can be within the last 3 years.

Post-surgery low-dose CT scans are considered part of the routine care pathway, this may be at any point until approximately 6-months after surgery. A RESTORE CT manual details the process for gaining images for individual imaging departments at participating centres, and confirms the parameters required for the trial database.

The Haller Index, the Correction Index, the Cardiac Compression Index, Vertebral index, Titanic index, torsion angle and the Asymmetry index are included in the dataset.

There are changes in the Haller index that can be seen by comparing measurements taken on end-inspiration and end-expiration. Therefore, we would like the CT Scan to be performed in both end-expiration as well as end-inspiration and we will record the pectus indices for each.

12.10.4 Cardiopulmonary Exercise Test (CPET)

CPET tests will occur 3 times per patient for the cohort and early surgery groups and four times in the late surgery group.

The key agreed requirements for CPET testing in RESTORE are:

1. A patient's CPET assessments will be performed at the same testing centre.
2. The patient must have undergone CPET testing within a year of consent.
3. If a patient performs a suboptimal test that does not yield useful results this should be repeated within 2 months. If they perform a second suboptimal test then it will be recorded as a suboptimal test. This applies to pre-operative and post-operative tests.
4. The test must be performed with cycle ergometry. Treadmill or handcrank is not acceptable.
5. The patient's exercise history will be obtained using the Global Physical Activity Questionnaire** (GPAQ and analysis guide on the WHO Website https://www.who.int/publications/m/item/global-physical-activity-questionnaire).
6. Full details of the test and all parameters being collected for entry into the trial database are detailed in the RESTORE CPET manual.

*due to the physiological changes in children, those under the age of 16 should have a repeat CPET at baseline, if it was conducted more than 6 months prior to consent.

**where GPAQ has already been collected as part of the baseline CPET, the data will be included in the trial database. If not already collected at the time of the baseline CPET, the GPAQ should be administered.

7. Once data is entered into the trial database this will be reviewed by a central observer.

12.10.5 Medical History

A full medical history will be recorded for each patient at baseline and will include details of all clinically significant past cardiovascular medical conditions and all clinically significant on-going cardiovascular or other medical conditions relating to a patients PE. Review of other hospital notes (and GP notes) may be required to complete the medical history. Past history will include a history of depression or self-harm and patients must be asked if they have received support from mental health services in the past (an answer of yes or no will be required in the study database), asthma, diagnosis of postural tachycardia syndrome (PoTS), or cardiac arrhythmias. A medical history questionnaire will allow self-completion of most of this baseline information.

12.10.6 Concomitant Medications

A list of selected medications currently taken by the patient, and their total daily dose, will be recorded at time points during the trial:

Baseline, 6 months, 1 year and 3 years post-randomisation/enrolment for those in the cohort and early-surgery group.

Baseline, 6 months and 1 year post-randomisation and 6 months, 1 year and 3 years post-surgery for the late-surgery group.

A current medication questionnaire will allow self-completion of this information.

12.11 Trial Interventions

The RESTORE trial will compare:

- **Intervention group (early surgery):** corrective surgery for PE (Nuss or Modified Ravitch procedure depending on patient characteristics, patient choice and surgical expertise) after randomisation.
- **Control group (no surgery prior to primary outcome):** surgery delayed for at least 1 year after randomisation and following primary outcome measures 1 year after randomisation; surgery will be performed within 3 months of these measures.

Patients should not receive vacuum bell therapy during their participation in the trial (from the point of consent).

12.12 Decisions Regarding Surgical Type

RESTORE allows both Nuss and Ravitch operations to be performed, with planned surgery type needing to be agreed and documented prior to randomisation following discussion between the patient and surgeon. Randomisation will be stratified based on surgical type.

12.12.1 Nuss

The aim of the Nuss procedure in the RESTORE Trial is slightly different to the aim of surgery for psychological benefit as the most important element of the surgery is to lift the sternum and ribs off the heart to normalise the Haller index. This is often further than the distance required for surgery just for psychological benefit and sometimes the chest must be raised below the xiphisternum to also lift the lower costal margin off the heart.

It is likely that patients in the RESTORE Trial may be more severe than patients having surgery only for psychological benefit and thus they may require more bars and the sternum is more likely to require lifting with a rultract or skyhook system.

At the time of surgery, surgeons will be required to complete a surgical proforma, with data then entered into the database by site research teams. This will require details on:

1. Type of bars used (any manufacturer is acceptable for the trial).
2. Number of bars placed (the expectation is that patients are likely to need multiple bars).
3. Whether sternal lifting was used (whilst this is not mandatory, units will be expected to have this available if required by the operating surgeon at the time of surgery).
4. Number of stabiliser plates (we are not stipulating a minimum number).
5. Any additional manoeuvres undertaken to prevent displacement. (for example pericostal sutures, hammock procedure etc and number of each).
6. Whether the pericardium was breached.
7. Whether any intraoperative complications occurred – intercostal stripping, rib fracture, requirement for costal incisions to allow further sternal lifting.
8. Whether cryoanalgesia was used and what levels.

Bar removal should be performed between 2.5 to 3 years post-surgery. A final set of outcome measures will be conducted more than 6 months after bar removal. Thus, if the patient has the bar removed at 3 years the final outcome measures should be performed at 3.5 years.

Of note, it is important that we obtain as many 3-year outcome measures as possible. For some patients who are randomised in year 2 and then are allocated to deferred surgery a later bar removal (at the 3-year point) will be after the end of the trial, where final outcome measures will not be recorded. For these patients, removal of the bars at around the 2.5 year point may allow the capture of the final outcome measures and should be given consideration, where possible. This will affect only a small number of cases and will be at the investigator's discretion, with clinical benefit the priority.

12.12.2 Ravitch

The Ravitch operation is a very different procedure if performed to improve physical symptoms compared to psychological benefit. If ribs are left in their normal position and only the sternum

is raised then the ribs may continue to compress the heart and an improvement in physical symptoms will be less likely to occur. Therefore, the Ravitch should aim to lift the whole of the chest and the ribs and costal cartilages and not just the sternum. Thus, resection of costal cartilage and lifting of the sternum with a Lorenz bar or a mesh behind it is not acceptable for this study. The ribs must also be lifted, and this most usually requires lateral rib fractures and sternal plating with methods such as the elastic stable repair with rib plates. Of note, rib plates across the sternum can easily fracture so multiple rib plates are required or plates thicker than the usual 1.5 mm plates will be required.

At the time of surgery, surgeons will be required to complete a surgical proforma, with data then entered into the database by site research teams. This will require details on:

1. Which costal cartilages have been resected (left and right)
2. Whether a horizontal osteotomy was performed.
3. The method of sternal lifting.
4. Number of rib plates placed, their location and thickness.
5. Whether cryoanalgesia was used and what levels.

12.13 Follow-up Beyond Index Surgery

Hospital readmissions and any further pectus interventions after the index surgery will be captured as part of the study dataset until 3 years post-surgery.

12.14 Safety Reporting

Adverse events (AEs) are defined as any new medical occurrence, or a worsening of a pre-existing medical condition in a patient that has received a study intervention, or undergone procedures required by the study, which does not necessarily have to have a causal relationship to the study intervention or its procedures.

Serious adverse events (SAEs) are defined as any adverse event which:

- results in death;
- is life-threatening;
- requires hospitalisation, or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

Adverse Events of Special Interest (AESIs) in this study are defined as disease-related complications. All AESIs, mortalities, procedure-related AEs and Expected Adverse Events from consent until 3-years post-index surgery follow-up point, participant withdrawal or study termination will be entered into the electronic data capture (EDC) system. No other events need to be entered into the EDC. See Figure 1.

Figure 1: Schematic to show adverse event expedited reporting and recording requirements

Expected/AESI	Related	Serious	Reporting requirement
✓	✓	✓	Record in EDC **If mortality expedited reporting** (within 24hours of awareness)
✓	✓	X	Record in EDC
✓	X	✓	Record in EDC
✓	X	X	Record in EDC
X	✓	✓	**Expedited reporting** (within 24hours of awareness) and record in EDC
X	✓	X	Record in EDC
X	X	✓	DO **NOT** record in EDC unless a **mortality**
X	X	X	Do **NOT** record in EDC

12.14.1 Expedited Event Reporting

The ACU will perform expedited reporting to the Research Ethics Committee (REC) in accordance with Safety Reporting Requirements for non-Clinical Trials of an Investigational Medicinal Product (non-CTIMPs). This reporting will be Urgent Safety Measures (USM) and SAEs that are related to surgery and unexpected., For all SAEs, Principal Investigators will perform an initial assessment of intensity, causality and expectedness in accordance with foreseeable complications associated with the interventions (as listed in Table 2). Where the SAE is a mortality (due to any cause) or is judged as both unexpected (i.e. the event not appear in table 2) and possibly, probably or definitely related to the study intervention or if there is any concern or doubt, then these will be reported to the ACU within 24 hours of the site becoming aware of the event. The ACU will then perform a further assessment of expectedness and bear the responsibility of reporting to the REC, as required.

For expedited reporting from site to the ACU, the primary mechanism will be the EDC. The appropriate case report forms (CRFs) should be completed with the initial information within 24 hours of awareness of the event. If the EDC is unavailable, the initial report may be provided via a SAE form (a template form is available in the study document pack). This should be sent via email within 24 hours of awareness of the event to: stees.pectusrestoretrial@nhs.net. The email should be followed with data entry into the EDC as soon as it is feasible.

See the following section for further detail regarding the AESIs and expected AEs.

12.14.2 Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest in this study are defined as disease-related complications. These are listed in Table 1.

All AESIs will be recorded in patient medical notes and the EDC system. AESIs will be recorded from the point of participant consent until the 3-year post-index surgery follow-up point, participant withdrawal or study termination.

Table 1: AESIs (disease-related complications)
• Prolonged (>1 month) absence from work/education
• More than 6 months of regular opiate medications for pain.
• New diagnosis of respiratory or cardiovascular illness
• Hospital admission due to pectus symptoms, including shortness of breath, syncope, or pre-syncope, dysphagia, arrhythmias, and pain

12.14.3 Expected Adverse Events/Foreseeable Complications

The interventions for PE are significant surgical procedures and some adverse events may be considered as 'expected' as a result of the surgery; these are listed below in Table 2.

All expected AEs will be recorded in patient medical notes and the EDC, from the point of study intervention until the 3-year post-index surgery follow-up point, participant withdrawal or study termination..

Table 2: Expected Adverse Events
• Death
• Any repeat unplanned pectus/chest surgery occurring after the index procedure for any reason (not Nuss bar removal)
• Hospital readmission related to PE procedure after discharge from index hospital stay
• Post-operative bleeding leading to transfusion or reoperation.
• Unplanned intensive care admission during the index hospital stay
• Surgical site infection requiring antibiotics or dressings
• Bar infection requiring intravenous antibiotics
• Infection requiring bar removal
• Seroma of surgical site

• Haematoma of surgical site
• Pneumothorax requiring post-operative chest drain insertion
• Pleural effusion requiring post-operative chest drain insertion
• Chronic pain requiring early Nuss bar removal or requiring >6months off work/education
• Chronic pain post-surgery following either Nuss or Ravitch procedures
• Significant migration (rotation and displacement) of the Nuss bar (migration needing surgery or requires further imaging) • Hospital admission for pectus symptoms
• Osteomyelitis
• Prolonged air leak over 7 days
• Bar or plate fracture
• Bar or plate displacement
• Recurrence of PE
• Thoracic outlet syndrome
• Brachial plexus injury
• Bar or plate infection
Intra-operative complications
• Cardiac perforation
• Bleeding from mammary artery
• Stripping of intercostal space preventing bar placement in that space.
• Any complications requiring sternotomy or thoracotomy

12.14.4 Pregnancy Reporting

Pregnancy should be reported as soon as it is known (within 24 hrs of the site awareness) using the appropriate pregnancy reporting form. Pregnancies should be followed to determine the outcome.

Participants who become pregnant may remain in study.

12.15 Patient Withdrawal

Participants may withdraw from the study at any time if they wish to, without giving reason and without any adverse consequences to their continued treatment. This decision should be

recorded in the participant's medical notes. Data collected up to the point of withdrawal from the study as a whole will be retained.

If a patient signals their intention to withdraw, they should be asked if they only wish to withdraw from certain elements of the trial such as the CPET test or answering the psychological questionnaires. Patients are permitted to remain in the study if there was a particular part of the outcome measure assessments that they wanted to withdraw from. Analysis will be on an intention to treat basis. The Trials office should be contacted immediately if a patient expresses an intention to withdraw from the study.

All patients will be made aware of their right to withdraw from the study, and this information will be included in the patient information sheet.

13 Statistics

13.1 Sample Size

Thirty-five individuals with severe PE who had not received surgery were asked to complete the SF-36v2 questionnaire to determine baseline physical function (PF). This revealed a standard deviation (SD) of 27.4 (similar to that from the NIHR UK Mini-Mitral trial) (25). The published minimal clinically important differences (MCID) for SF-36v2 PF, including in 12-17 year olds is 10 (23,24).

Using a conservative choice of SD=30.0, a sample size of 170 is needed to have 90% power (in fact 89.99% using the 2-sample t-test and a two-sided 5% type I error rate) to detect a difference of 15 in the SF-36v2 PF score at one year. To account for dropouts and missing data (patients are likely to be young, and more likely to move away from home during the trial), the sample size has been increased by 15% to 200 participants.

13.2 Statistical Analyses

The primary analysis of the primary outcome of change in SF-36v2 PF score at one year (1 year post-baseline in the control arm, 1 year post-surgery in the intervention arm) will be undertaken on an intention-to-treat (ITT) population using a linear mixed-effect model, adjusted for all stratification variables and surgical technique will be included in the model via a binary covariate. To address the concerns about the impact of participants of mixed ages, we will perform a sub-group analysis in children (<16 years). Secondary analyses will include three-year follow-up data to evaluate how physical functioning evolves or stabilises with time after surgery.

Secondary outcome measures will be analysed similarly, using appropriate regression techniques. For all analyses, point estimates, confidence intervals, and p-values, where appropriate, will be presented.

We will assess the impact of missing outcome data by examining its extent, and whether it is missing at random (MAR) or is informative. We will consider the use of multiple imputation

methods and sensitivity analyses if data is missing to a sufficient extent; in the event of differential missing data rates between arms, sensitivity analyses will be undertaken, including a tipping point analysis that determines how different from MAR the missing data would need to be to change the conclusion of the study.

The embedded observational cohort analysis will firstly examine the change over time in each outcome measure within the parallel cohort of severe patients. Summary statistics will be presented for these outcomes in this population. These measures will then be examined in the entire patient population, combining the trial participants with this additional cohort. A Bayesian power prior approach will be used at this stage to down-weight the cohort data if inconsistent with the trial data. Data from the same timepoints will be used as for the clinical trial analysis, while consideration of the three-year follow-up will include examination of the change over time in the overall population in addition to comparisons between trial arms.

A full statistical analysis plan (SAP) will be developed and agreed with the IDMEC and TSC prior to any data being provided to the statistician(s) or analysis being undertaken. Outcome data will be analysed at two timepoints with the primary effectiveness and cost effectiveness analyses occurring once one year data is available for all participants, and further analysis once all three year follow-up data is available.

14 Health Economics

14.1 Economic Analyses

The study will include a within trial and model based economic evaluation. Full details of the health economics analyses will be set out in the Health Economics Analysis Plan (HEAP). This plan will be written to be consistent with the SAP. The within trial analysis will be conducted on an ITT principle. Results will be presented as a cost-utility analysis (CUA) from the NHS and personal social services (PSS) perspective for the one year trial follow-up. For the within trial analysis, a broader perspective incorporating costs to patients and their families will form part of sensitivity analysis. For the longer-term model, costs and outcomes will be extrapolated over a lifetime time horizon. Finally, the assessment of patient preferences via the discrete choice experiment (DCE) will enable a cost-benefit analysis (CBA) where costs and outcomes are valued in commensurate units. For the within trial analysis discounting will not be performed. For the model-based analyses, costs and effects occurring after one year will be discounted at the recommended rates, currently 3.5% per annum (26).

For the within trial cost-utility analysis Intervention costs will be derived from a micro-costing exercise conducted at individual study centres. Centre level data will be supplemented with participant level data e.g. procedure time, collected using case report forms (CRFs). Costs will also include perioperative and post-operative complications which may incur additional costs (and reduce HRQoL). These additional costs will relate to initial management (e.g.

radiological imaging, blood tests, blood transfusions, visits to theatre, etc.), management of long-term sequalae and patient costs (travel, time off usual activities). Incidence of complications will be collected on CRFs (EDC) and management costs will be derived from the micro-costing exercise and routine sources (27). CRFs will also be used to collect secondary care services use. Use of primary care services e.g. general practice visits and use of PSS, will be collected using HRUQ administered at baseline, 6, 12 and 36 months post-surgery for all groups and also 6, 12 months post-randomisation for the late-surgery group. Participants' use of private health care will also be collected with the HRUQ. Time and travel costs borne by participants in accessing and using services will be estimated from responses to a time and travel questionnaire (TTQ) administered at 6 months.

The unit costs of NHS and PSS resource use will be estimated from study specific estimates and routine data sources (27). Unit costs will be combined with information on the use of services to estimate a cost for each participant. For patient costs, the time and travel costs of accessing care will be estimated using the responses to the TTQ and data on the use of services. To this will be added the monetary cost of any private health care. For each randomised arm a mean cost will be calculated.

For the CUA, QALYs will be derived from responses to the EQ-5D-5L administered at baseline, 6, and 12 months. Responses to the EQ-5D-5L will be converted into utility values using recommended scoring algorithms and QALYs estimated using the area under the curve approach and a mean QALY per arm calculated. As part of sensitivity analysis, we will map the responses to the SF-36v2 questionnaire will be converted to SF-6D scores (version 2) and QALYs estimated using the same approach as described above. Not capturing HRQoL decrements over the recovery period is a bias in favour of surgery. To address this, we will explore in a sensitivity analysis how large these decrements would need to be in order to change any conclusions. We will then interpret these in consultation with our patient advisory group and the findings of other clinical studies.

To estimate the incremental cost per QALY gained at 1 year an appropriate regression model (e.g. a general linear model) will be fitted to estimate marginal costs and QALY gains; controlling for baseline covariates (e.g., age, sex, EQ-5D score, pre-randomisation use of health services, socio-economic status). Data will be presented as point estimates and bootstrapping techniques will be used to characterise imprecision (28). The results will be presented as cost and QALY plots and as cost-effectiveness acceptability curves (CEACs)(29).

14.2 Discrete Choice Experiment

A DCE will be conducted to understand how patients might prefer alternative managements that might differ in their attributes and levels. A DCE involves presenting individuals with a

series of hypothetical alternative choice sets, usually pairwise, differing in their attributes and levels, and asking them to indicate their preferred alternative in each set. The key attributes reflecting the aspects of management (might relate to surgery or not, risks of complications, long term outcomes, etc.) will be identified from the literature and from discussions with both the PAG and other stakeholders. The DCE, in the form of web-based survey (although an alternative paper-based approach will be available if needed) will be completed by the study participants at month 16 (to avoid overburdening study participants at 1 year when primary outcomes are assessed, and to allow for tolerance on surgery dates). This will ensure that there is sufficient time to develop and pilot the DCE. Appropriate regression models will be used to analyse the responses collected from the DCE. The inclusion of a cost attribute will enable marginal willingness to pay (WTP) for a unit change in each attribute to be calculated. For each trial participant outcome levels that map onto each attribute level will be estimated. These will be combined with WTP for a unit change in each attribute which will form part of a cost-benefit analysis (CBA) presenting both costs and benefits in commensurate units, which enables a comparison to be made between strategies. The CBA will be presented as incremental net benefits. To estimate incremental net benefits we will fit an appropriate regression model controlling for baseline covariates (e.g., age, sex, pre-randomisation use of health services, socio-economic status). Data will be presented as point estimates and bootstrapping techniques will characterise imprecision with the results presented as incremental net benefit curves, alongside the probability that each treatment would be considered cost effective.

14.3 Longer Term Economic Model

The 1 year follow-up of the trial may not capture all of the costs and health outcomes associated with the interventions, as some events will be incurred over a longer timeframe. Therefore, an economic decision model will extrapolate costs and outcomes over the lifetime of the patient. The economic model will describe outcomes of surgery or no surgery, with persisting impacts of any complications over the patient lifetime. To make the best use of the available data we anticipate the model will be a microsimulation model. We will work with our PAG and co-applicant team to design a model reflecting the patient journey both with and without surgery. The model will be constructed following guidelines for best practice in economics modelling. The use of services both with and without surgery will be modelled using data obtained from the trial, the longer term outcomes (which will be treated as longitudinal observational data of the effects of surgery). Further data will be systematically derived from the literature and from expert clinical input (e.g. the Centre for the Evaluation of Value and Risk in Health (CEVR) Cost Effectiveness Analysis (CEA) Registry, etc.). The model will be used to produce estimates of costs, QALYs (from the EQ-5D and SF-6D utility scores). Cost-

effectiveness will be reported as incremental cost per QALY gained (at both 1 year and over the patient's lifetime). The model will be probabilistic, and distributions; the choice of which will depend upon the data available and recommendations for good practice in modelling. The results will be presented as point estimates of costs, QALYs, incremental costs, QALYS, and measures cost-utility. They will also be presented as plots of costs and QALYs and cost-effectiveness acceptability curves. The model will be developed in a suitable software package (e.g. R).

For the economic evaluation we expect to replicate the sub-group and sensitivity analyses proposed for the Statistical Analysis where these are relevant to the estimation of costs and QALYs. For all analyses deterministic sensitivity analysis will be combined with the combined with the trial based stochastic or model based probabilistic analysis to explore other forms of uncertainty (e.g. different cost assumption, inclusion of participant costs, modelled Net monetary benefits).

15 Trial Timelines

The trial length is anticipated to be 76 months from 1st February 2024.

Planned timelines are:

- Months 1-6: protocol, REC/HRA approval, contracting, database/randomisation system.
- Months 7-12: open all UK centres.
- Months 7-15: internal pilot.
- Months 7-3:1 recruitment.
- Month 46: Initial data lock once last patient has 1 year primary endpoint data with primary analysis and dissemination from month 51.

Primary Outcome Reporting: Early data lock will allow analysis of the primary outcome and reporting to allow NHS commissioners in England to make an expedited decision.

- Month 71: Second data lock.
- Months 72-75: Data analysis.
- Months 72-76: Report writing, dissemination.

16 Internal Pilot

Key assumptions about recruitment and processes will be tested in a 9-month internal pilot running from month 7 (projected start of recruitment) to month 15 with pre-specified progression criteria.

Progression Criteria	Red	Amber	Green
% Threshold	≤74%	75-99%	100%
Total Randomised Trial Recruitment	≤52 patients	53-69 patients	70 patients
Average Recruitment Rate(per centre/month)	≤0.74	.75-.99	1
Total number of centres opened	≤7	8-10	12

This includes a monthly target for recruitment per site. A comprehensive review of the trial and its processes will be undertaken at the end of the pilot to identify any barriers to completion of assessments and trial activities (including deviations from specified timing of completion), and to ensure that we are reaching and recruiting an inclusive and representative population. We will work with our TMG and Patient Advisory Group (PAG) to find solutions and make adjustments accordingly.

Progression to the main trial will be discussed with the TSC at the end of the pilot phase, with a particular focus on any amber criteria to enable solutions; a dialogue between the trial team, TSC and funder will allow any uncertainty regarding progression to be discussed and a plan agreed. Recruitment will continue across all centres whilst these meetings and discussions are ongoing. The internal pilot will also provide an opportunity to refine recruitment strategies where needed.

This includes any additional strategies to ensure the sample is representative.

- Opening centres in the NHS is a challenge for all trials, with additional delays being seen following COVID. Centres will be opened in a phased approach, with a focus on early engagement with R&D departments to ensure that all centres can open to recruitment in a timely manner. If sites are not able to open, and we see less than anticipated recruitment per centre, additional centres will be recruited beyond the 12 already identified.
- The primary outcome will be measured using the randomised trial data and thus all recruitment criteria for the pilot relate to the randomised trial recruitment only. We will measure the recruitment rate/site/month from 6 weeks following opening of a centre to ensure time has been given for all trial processes to bed in, including to accommodate the necessary scheduling of baseline assessments that will be needed prior to randomisation.
- To meet our randomised recruitment target of 200 participants, 70 participants need to be recruited and randomised by the end of the pilot; this will enable recruitment targets

across the rest of the trial to be met, and allow for seasonal fluctuation (this population is often young and important factors such as GCSEs, A-Levels, University exams etc are likely to lead to some dips in recruitment to avoid surgery at times that would disrupt these).

- If 70 participants have been recruited during the pilot, and all centres are open, average recruitment rates could be as low as 0.68/centre/month to still meet recruitment targets and timelines. If 53 participants or more have been recruited, all centres are open, and sites are recruiting one patient a month in the last three months of the pilot, recruitment targets and timelines should still be met.
- If both overall recruitment or site recruitment rates are below expected, further sites would be opened following discussion with the TMG, TSC and Sponsor; 26 centres were performing PE surgery prior to decommissioning in England.

17 Definition of the End of the Trial

The trial will end once post-index surgical follow up at three years for all patients in the early surgery group has been completed and the database is confirmed as locked (second lock); around half the patients in the late surgical group will also have completed three years of follow up at this point.

Consent for longer term follow up beyond the trial will be sought at the point of consent.

18 Patient and Public Involvement (PPI)

This trial has been developed in close collaboration with patients and the public. A variety of PPI events have shaped the development of this trial to ensure that the research team will deliver a project that is widely accessible and acceptable to patients and will provide answers of relevance to patients and their clinical care providers. The research team also includes two patient co-applicants.

A Patient Advisory Group (PAG) will meet regularly to discuss the trial and to review patient-facing information and processes. This group consists of the 6 most active patient members from the Royal College of Surgeons of England event including the author of the book Pectus & Me that collated 41 patient stories of patient experiences for the event and is now published on the SCTS website (https://scts.org/ebook/index.html).

Members of the PAG will also comment on the site initiation slides which will be developed for study site training and/or be given the opportunity to attend a few at the early training sessions with participating sites so that we can ensure that any patient questions or concerns are covered and shared so sites are aware of how to address these when they start approaching patients. PAG meetings will be chaired by our patient co-applicants, allowing trial progress (and any issues) to be discussed.

We will work with our PPI co-applicants and PAG members to closely monitor patient recruitment through regular meetings and discuss ways to sustain or improve involvement of under-served groups, as necessary.

19 Equality, Diversity, and Inclusivity

We have identified that a number of patients groups could be under-served by RESTORE. These include those that are yet to be diagnosed as PE being the cause of their shortness of breath, those who are less educated, those from ethnic minorities and those who are non-English speakers.

A number of measures will address this, both in the recruitment processes for the trial, and in the ongoing monitoring to understand and address any issues with follow up, and completion of assessments or differential withdrawals.

1) Social media platforms will advertise the study, enabling messaging to travel beyond the traditional approach from the hospital setting.
2) Platforms such as BePartofResearch and engaging with GP practices through the national research infrastructure, will be used to ensure that potential participants who may yet to have reached secondary and tertiary care settings are aware of the trial.
3) We will engage with PE support groups to further spread the news of the trial and the centres that are open. In particular the national patient groups, which includes members of the RESTORE PAG who are planning a national GP education programme and the trial will be part of this educational programme.
4) A travel budget will allow participants and a partner or carer to travel for surgery and baseline and follow up assessments as needed.
5) Multiple modes of follow up where possible will ensure participants are not visiting the hospital unnecessarily, and where possible sites should offer the opportunities for follow up (for example CPET testing) at a more local hospital, even where the surgical centre is further away.
6) We will translate the Participant Information Sheet into multiple languages to enable equal access to potentially eligible participants. Interpreters will also be available for completion of questionnaires when necessary, with costs reimbursed to sites as appropriate. We will place the multilingual education material on the SCTS website and our RESTORE website and it will also go on our social media groups.
7) We have established a Patient Advisory Group (PAG) and will continue to ensure that the membership is diverse to ensure that multiple perspectives feature.
8) PPI co-applicants and PAG members have reviewed patient documents to ensure the language used is understandable by the public.

9) Study progress will be shared with participants at their follow-up visits, and study results will be sent as user-friendly newsletter at the end of the study. This will be stated in the Participant Information Sheet and appear on the website.
10) The trial plans to open centres across the UK, including in areas with higher proportions of ethnic minorities, and those with large geographical catchments to ensure we reach across the largest possible population of people with PE.
11) The trial team will actively monitor number of participants from under-represented groups, including those experiencing income deprivation at our study meetings.

20 Remuneration

No direct remuneration will be provided for patients to participate in the trial; however, reimbursement for travel and associated expenses will be available to support participants and carers, which may include travel to other centres for surgery and CPET testing.

21 Monitoring and Quality

Study conduct will be assured with a robust monitoring plan. The study will employ a risk-based monitoring approach, focussing on critical processes to ensure study integrity, participant safety and security, and on data validity.

The Trial Management Group will assess the risk level of the trial and review this at regular intervals throughout the course of the project. This risk assessment will form the basis of the monitoring plan.

Monitoring will be conducted in accordance with the monitoring plan, by ACU representatives trained and competent to do so.

Breaches of study compliance will be reported to the TSC, the Sponsor, and the Research Ethics Committee, as necessary. Protocol deviations and violations and any associated recovery and action plans will be documented in study records, namely in Case Report Forms (CRFs), the Investigator Site Files (ISFs) or the Trial Master File (TMF).

22 Information Governance

Participants' personal data

shall be treated in confidence and in compliance with the UK Policy Framework for Health and Social Care, the Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR). When processing or archiving personal data, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

Study data will be entered into a web-based electronic data capture (EDC) system (called CASTOR). This application is designed to be in full compliance with the applicable regulations.

Each participant will be assigned a unique identification number upon recruitment. The trial database and randomisation system will be password protected and only researchers collecting and analysing data will have access to this database. Access to clinical study information will be based on individuals' roles and responsibilities.

All personal information will be kept confidential at the recruiting sites unless there is specific consent and approval for transfer of this to another site for study-related purposes. RESTORE includes options to transfer between participating hospitals as part of the trial, including for CPET scans and surgery which are made clear to patients in the participant information sheet and require specific consent.

The database for the trial will include:

Date of Birth, Sex at Birth, Medical History, Ethnicity, Postcode.

For the purposes of completing questionnaires online, the database will also contain patients email addresses through which links to the questionnaires will be sent.

Patients may also be sent scanned/completed copies of their consent form via their email address if this is their preference, and their email address may also be used during the remote consent process, if applicable.

Any paper documentation will be stored securely in the relevant research offices at sites. Neither hard copies nor electronic files containing personal information will be removed from the research offices or stored in a non-secure manner electronically.

23 Data Sharing and Data Access

All source data, study documents, participant notes should be made available for monitoring and audits by the Trials Unit, the Sponsor, and local NHS host organisations.

Study documentation must be retained in a secure location during the conduct of the study.

Personal identifiable data, beyond the minimal data set contained in the database, will be retained for up to 5 years following the end of RESTORE, after which it will be destroyed.

Patients will have the option to consent to longer term follow up beyond the end of the trial. Where patients consent to this, personal data beyond the minimal dataset contained in the database, will be kept until the 5 years after the last data collection for the longer term follow up before being destroyed.

All electronic data will be stored on secure network systems, to which only the relevant site and central study research team staff have access.

For the purposes of this study, the South Tees Hospitals NHS Foundation Trust will act as the Data Controller.

At the end of the trial, the trial dataset will be available to other researchers on request and following approval by the Chief Investigator, co-Chief Investigator and Sponsor.

24 Dissemination

The findings of the study will be disseminated to stakeholders for the RESTORE research, including patients, NHS England and the clinical community nationally and internationally.

The PAG and lay co-applicants will work with the trial team to inform the dissemination plans to patients and the public.

Findings will be reported to the funder, Society for Cardiothoracic Surgery (SCTS), the writing committee of the European Society of Thoracic Surgery (ESTS), National Institute for Health and Care Excellence (NICE) and presented at conferences including the European Society of Thoracic Surgeons and the Chest Wall International Group.

The Chief Investigator and co-Chief Investigator will be responsible for ensuring the results of RESTORE are disseminated through peer reviewed journals once the analyses are complete. Authorship on the primary findings manuscript and subsequent manuscripts will be in accordance with the guidelines of medical journals and will be confirmed by the TMG, with final approval by the Chief Investigator and co-Chief Investigator.

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