Title: Structured Cardiac Assessment and Treatment Following Exacerbations of COPD: a pilot randomised controlled trial

Short running title (acronym):

Structured cardiac assessment and treatment following exacerbations of COPD (SCATECOPD)

Key Trial Information

Chief Investigator:	Dr John Steer
Sponsor:	Northumbria Healthcare NHS Foundation Trust
Sponsor Reference Number:	
IRAS Number:	277817
REC Reference:	TBC
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Protocol developers

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.
I 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 clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

On behalf of the Trial Sponsor:
Signature: Date: ...../...../.....

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Name (please print):

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Position: .....

Chief Investigator:
Signature: Date: ...../...../.....

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Name: (please print):

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Statistician:
Signature: Date: ...../...../.....

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Name: (please print):

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Position: .....

Roles and responsibilities

Chief Investigator	The Chief Investigator, John Steer, assumes primary responsibility for the design, conduct and reporting of the study.
Sponsor	The Sponsor, Northumbria Healthcare Foundation Trust, assumes overall responsibility for the initiation and management of the trial.
Protocol developers	The protocol developers, listed above, share responsibility for the trial protocol.
Statistician	The Statistician, Keith Gray, developed the statistical analysis plan. He will oversee final data analysis.
Funder	Chiesi Ltd have had no role in study design or protocol development and will have no role in the analysis or presentation of results.
Trial Steering Group	A Trial Steering Group will be formed with an independent Chair, and will meet at least every 12 months, and send timely reports to the Sponsor and Funder.
Trial Management Group	The Trial Management Group will meet regularly to ensure effective day-to-day running of the trial.

Trial Steering Group

Independent Chair
Patient Representative
Chief Investigator
Co-supervisor
Co-supervisor
Research Fellow
Statistician

Contents

Abbreviations

Protocol version history

Version	Date	Authors	Changes
1.0	05/10/2020	John Steer, Stephen Bourke, David Ripley, Joe Kibbler, Jo Gray, Keith Gray	N/A

Study synopsis

Title	**Structured Cardiac Assessment and Treatment Following Exacerbations of COPD: a pilot randomised controlled trial (SCATECOPD)**
Sponsor	Northumbria Healthcare NHS Foundation Trust
Design	Pilot randomised controlled trial
Population	Patients admitted to hospital with an exacerbation of COPD
Sample size	120
Study duration	12 months
Planned Trial period	Nov 2020 to Feb 2023
Primary Objective	To assess the effect of comprehensive cardiovascular assessment and treatment on the primary endpoint to enable powering of a definitive multicentre RCT
Secondary Objectives	1. Report the rates of CVD; specifically, the rates of undiagnosed or undertreated CVD. 2. Examine the relationship between CVD and the severity of COPD and ECOPD 3. Examine the utility of the primary outcome compared to readmissions, mortality and quality of life. 4. Compare the observed treatment effect between primary and secondary outcomes 5. Examine the relationship between changes in cardiac function (in the intervention group) from baseline to 90 days and E(COPD) severity, comorbid CVD, and outcome. 6. Assess the feasibility of collecting service-use data for an economic evaluation of the intervention in a future RCT 7. Report differences in health costs and estimated quality adjusted life years (QALY) between the 2 study arms.

Lay summary

Chronic obstructive pulmonary disease (COPD) is a common lung disease which can flare up and need admission to hospital. Patients with COPD often have heart disease, which worsens their symptoms and increase the chances of death and hospital admission. In the short period after a flare up of COPD, patients are also at a higher risk of heart attacks and irregular heart rhythms, which cause many of deaths and hospital readmissions experienced. Unfortunately, heart disease is often not recognised or not treated adequately in patients with COPD.

We will test whether carefully finding and treating heart disease in patients admitted to hospital with COPD exacerbation is beneficial. 120 patients will take part in this study. 60 patients will be randomly allocated to 'intervention group' and have detailed tests to identify and then treat heart disease. We will compare their outcomes to 60 patients who do not have this assessment.

In all 120 patients, we will record routine clinical information, simple questionnaires and breathing tests. These tests will be repeated 3 and 12 months later. The 60 patients in the intervention group will have detailed heart tests (blood tests, heart scans, and heart monitors). If we find a heart problem we will start treatment. We will compare the two groups to see if patients in the intervention group spend more time living at home during the year after they start the study.

Scientific Rationale

This project addresses a healthcare priority. Exacerbations of COPD (ECOPD) are a frequent cause of non-elective hospital admission and are associated with high rates of hospital readmission; 43% of patients were readmitted within 90 days following ECOPD according to the most recent national COPD audit report. Mortality following hospital admission for ECOPD is common, with rates of up to 50% in the most unwell patients during the 12 months following admission. Cardiovascular disease (CVD) is common in COPD and is associated with worse quality of life, and higher mortality and readmission rates.(1) The risks of myocardial infarction and hospital admission for atrial fibrillation (AF) are substantially higher than baseline risk during the short period after hospital admission for ECOPD.(2,3)

Despite these known risks, CVD is often undertreated and / or not recognised. Three months after ECOPD requiring hospital admission, a quarter of patients with no past history of cardiac disease have left ventricular (LV) dysfunction and 44% have right heart impairment.(4) In patients with COPD attending pulmonary rehabilitation, 16.5% of patients had impaired LV function (previously undiagnosed in 36%) and 20% had pulmonary hypertension (undiagnosed in two thirds).(5) There are fewer studies investigating rates of CVD and cardiac dysfunction in patients at the time of ECOPD. Many studies rely on ICD coding diagnoses to define CVD and few clarify the presence of undiagnosed CVD. Marcun et al (6,7) performed echocardiography on 127 patients admitted with ECOPD. An abnormality of left ventricular function was identified in 55% of patients and prevalence of heart failure with reduced (HFrEF) and preserved (HFpEF) ejection fraction was 9% and 19% respectively. A subsequent study of 154 patients from the same group (8) reported 10% of patients had HFrEF and diastolic dysfunction was present in over 50%. These studies did not report on treatment or whether abnormalities had been previously recognised. AF has been reported to be present in between 17% and 35%,(9,10) with rates higher in more severe ECOPD, but the proportion of patients with new AF is unknown.

Even if CVD is diagnosed, it is frequently undertreated. Beta blocker and ACE-inhibitor prescriptions are lower in patients with COPD than those without COPD, even when there is evidence of a clear prognostic benefit from their use.(11–13) Following myocardial infarction, patients with COPD are less likely to receive treatment with aspirin and statins than patients without COPD.(14)

In addition to the cardiovascular benefits of treating CVD appropriately, cardiovascular-specific therapies can improve respiratory-specific outcomes in COPD. The CHAMPION (15) study showed that, in the subgroup of patients with COPD, adjusting heart failure drugs using data from an implantable pulmonary artery pressure monitoring device reduced hospitalisations to both heart failure and respiratory disease. In severely unwell patients with ECOPD requiring critical care, unrecognised HFrEF was present in 41%, and these patients had better clinical outcomes suggesting, but not proving, that identifying and treating CVD could improve outcome.(16) Observational studies have shown that patients with COPD receiving treatment with beta-blockers have lower mortality rates.(17) A recent RCT (18) giving beta-blockers to patients with COPD without an indication for beta-blocker therapy did not show a benefit compared to placebo; suggesting that the previously identified improved

outcomes from betablocker therapy are due to the better treatment of previously unrecognised or undertreated CVD.

Pulmonary hypertension is a marker of severe COPD and independently associated with future ECOPD.(19) Pulmonary artery pressures are often elevated at the time of ECOPD and improve following ECOPD recovery.(20) It is unclear how changes in pulmonary artery pressures relate to COPD severity, exacerbation severity and CVD, and whether acute changes in pulmonary artery pressure have an impact on patients' longer term outcome. This project will help us understand more about these relationships.

We propose a randomised pilot study to investigate the impact of a comprehensive cardiac assessment (and standardised treatment of CVD) on days spent alive outside of hospital during 12 months follow up. This patient centred primary outcome measure captures the number and duration of hospital admissions as well as mortality and, whilst it has been used in cardiovascular studies,(21) it is a novel outcome measure in COPD. Data from this pilot study will hopefully lead to a larger, multicentre randomised controlled trial (not part of this proposal). This would be the first study to our knowledge to investigate the impact of treating CVD on outcome in ECOPD and the first study to use this novel patient outcome.

The aims of this project are congruent with many national priorities and recommendations. *Multimorbidity: a priority for global health research*, a report from The Academy of Medical Sciences (April 2018), listed six research priorities. Our proposal addresses Research Priority 6 which highlights the need for research in to integrated healthcare strategies which "improve clinical outcomes, patient-centred outcomes, and the cost-effectiveness of care". The NHS Outcomes Framework identifies: reducing readmissions within 30 days of hospital discharge (Indicator 3b); and reducing mortality from respiratory disease in under 75s (Indicator 1.2) as key markers of healthcare performance. The NICE Multimorbidity Guideline (NG56) recommends that research in to the holistic assessment of multimorbidity should have clear identification of the target population, careful piloting, well planned interventions, and be directed at outcomes relevant to patients (such as quality of life, hospital admission and mortality); the present proposal meets all of these criteria.

Importance to patients and the NHS

The 2017 National Asthma and COPD Audit Programme (NACAP) COPD Advisory Group highlighted, as a key message, the need for a holistic approach to care focusing on multimorbidity.(22) The COPD Advisory Group has patient representation at its heart and can be relied upon to reflect the priorities of both clinicians and patients. This research proposal can yield the following results:

1. Show that a structured cardiovascular assessment and treatment improves outcome. The reduction in readmissions, bed days and mortality could be substantial.
2. Enable a definitive RCT to be designed. Our results will help refine the methodology and enable a power calculation. The proposed RCT could help embed our structured cardiac assessment in the care of patients across the NHS.

3. Provide data to inform a full health economic analysis in the planned subsequent RCT. The costs of hospital admissions are substantial compared to the intervention under investigation.
4. Highlight the burden of CVD, particularly when undiagnosed or under-treated.

These results can then benefit patients by:

1. Highlighting to clinicians the significance of cardiovascular disease for patients hospitalised with ECOPD. An increased awareness will benefit patients with (E)COPD by reducing the diagnostic and treatment gap.
2. Showing, to commissioners and healthcare organisations, the benefit that can be yielded from ensuring sufficient access to cardiovascular diagnostics.
3. Establishing the utility of a novel outcome measure for ECOPD.
4. Improvements in in-hospital mortality rates in ECOPD have been seen over recent years due to improved service delivery; no new treatments have become available. Better diagnosis and management of cardiovascular disease could substantially improve patient outcomes and reduce health resource use.

Hypothesis

A comprehensive, structured cardiovascular assessment, with treatment of problems identified, increases the time patients spend alive outside of hospital following hospital admission for a COPD exacerbation.

Objectives

Primary Objective

To assess the effect of comprehensive cardiovascular assessment and treatment on the primary endpoint to enable powering of a definitive multicentre RCT.

Secondary Objectives

1. Report the rates of CVD; specifically, the rates of undiagnosed or undertreated CVD.
2. Examine the utility of the primary outcome compared to readmissions, mortality and quality of life.
3. Examine the relationship between changes in cardiac function (in the intervention group) from baseline to 90 days, and (E)COPD severity and comorbid CVD.
4. Assess the feasibility of collecting service-use data for an economic evaluation of the intervention in a future RCT
5. Report differences in health costs and estimated quality adjusted life years (QALY) between the 2 study arms.

Study Population

Patients hospitalised to Northumbria Specialist Emergency Care Hospital with an exacerbation of spirometry confirmed COPD.

Inclusion criteria

- Age >35 years
- Current / former smoker & smoking burden >10 pack years
- Clinical diagnosis of COPD, supported by previous obstructive spirometry
- Admission to hospital with the primary cause being an exacerbation of COPD

Exclusion criteria

- Reason for admission not ECOPD in view of attending clinical team.
- Unable to provide informed consent
- Any non-COPD condition likely to limit survival to less than 12 months
- Contra-indication to cardiac CT
- Pregnancy or breastfeeding

Target enrolment/sample size:

120

Anticipated rate of enrolment:

7-8 per month

Estimated study start date:

First patient first visit: 1st November 2020

Estimated study completion date:

Last patient last visit: 28th February 2023

Study Design and Methods

Methods

A randomised (1:1) pilot study of 120 consecutive consenting patients. The intervention group will undergo a comprehensive cardiac assessment and standardised treatment protocols will be followed to treat identified CVD. Patients will be followed for 12 months to gather outcome data. CVD is defined as hypertension, ischaemic heart disease (IHD), HFPEF, HFREF, atrial or ventricular arrhythmia, moderate-severe valvular heart disease or cor pulmonale.

Schedule of Activities

All patients will have the following assessments (conducted face to face unless specified):

	Baseline	90 (+/- 10) days	6 months (+/- 10 days) - telephone	9 months (+/- 10 days) - telephone	12 months (+/- 10 days)
Demographics, comorbidity	X	X			X
Medications	X	X	X	X	X
eMRCD	X	X			X
Spirometry & inspiratory capacity	X	X			
NYHA class	X	X			
Rockwood clinical frailty scale	X				
COPD assessment*	X				
Bedside observations$^{\alpha}$	X				
ABG	X				
ECG	X				
Laboratory tests$^{\beta}$	X				
4m gait speed	X	X			X
SGRQ-C	X	X			X
EQ-5D-5L	X	X			X
Exacerbation frequency	X	X	X	X	X
Hospital admissions / ED attendances		X			X
Primary & community NHS care visits$^{\pi}$		X	X	X	X
Mortality					X
Adverse Cardiovascular Events ‡		X			X

* - includes; BMI, previous spirometry, previous exacerbation / hospital admission / NIV episodes, α- components of NEWS2 scale; π – patient reported resource utilisation proforma; β – full blood count, urea & electrolytes, liver function tests, glucose, albumin, lactate, CRP; ‡ nonfatal stroke or myocardial infarction, and cardiovascular death

In addition to face to face assessments, all patients will be contacted by telephone at 6 and 9 months to complete a primary care resource assessment form. In hospital and at 3, 6 and 9 months following hospital discharge, patients will be provided with a patient resource utilisation proforma to record all contact with community NHS services. This data will be reviewed with the patient at the face to face (3 and 12 months) and telephone (6 and 9 months) assessments. Data regarding frequency of COPD exacerbations will be collected at

these time points; severe exacerbations (requiring admission) will be captured from health records, moderate exacerbations (requiring treatment with antibiotics and/or steroids) will be self-reported.

Those randomised to the structured cardiovascular assessment will also undergo:

	Baseline	90 days
ECG	X	X
Echocardiogram	X	X
Laboratory investigations$^{\beta}$	X	X
24 hour cardiac monitor	X	
CT coronary artery calcification score and CT chest	X$^{\gamma}$	
24 hour BP monitor$^{\delta}$	X	

β – troponin T, NT pro-BNP, fibrinogen, cholesterol profile (admission only), HbA1c (admission only), vitamin D (admission only);. γ - performed at any point during index hospital admission (or within 7 days of admission); δ - performed in patients hypertensive during initial hospital stay, without a prior hypertension diagnosis

Echocardiography will be performed by a trained clinician or British Society of Echocardiography (BSE) trained physiologist with oversight by an independent consultant imaging cardiologist. If image quality is insufficient for accurate assessment of ventricular function, contrast echocardiography using sonicated albumin contrast medium will be performed during inpatient admission. CT Coronary artery calcification score will be performed according to standard local protocol by a trained consultant Cardiologist. Reporting will be performed blinded to the presence of known CVD and knowledge of severity of COPD and ECOPD. Assessment of whether CVD is treated adequately will be made with reference to (inter)national guidance. CT chest will be performed without intravenous contrast according to standard local protocol; emphysema severity and airway wall thickening quantified using commercially available software.

Economic Evaluation

A prospective economic evaluation will be rehearsed to develop and refine methods for a subsequent definitive trial. The main focus will be on how to accurately identify, quantify and value the additional costs of delivering the intervention and the potential resource implications versus usual care. The costing approach will incorporate an NHS perspective (Secondary, Primary & Community care costs), which will help to detect cost-shifting between NHS care sectors. Resources utilised in the intervention group will be identified in terms of CVD investigations, medications and staff time. Subsequent resource utilisation during follow-up will be captured using a number of NHS databases and a patient resource utilisation pro-forma. In-hospital data including A&E attendances and hospital admissions will be collected through case note review and use of hospital coding services. Primary care attendances including GP visits and Nurse visits will be obtained using a patient resource utilisation pro-forma. This will be assessed retrospectively at the four follow up periods (3, 6, 9 and 12 months). This will facilitate the development of a reliable and valid tool to capture resource use. Data on use of services will be combined with appropriate unit cost to produce a cost per trial participant. These will be sourced from a combination of local costings and national databases.(23,24)

Cardiovascular treatments

For any cardiovascular disease identified, treatment will be initiated by the usual care team in keeping with current local (Northumbria Healthcare NHS Foundation Trust) or (inter)national guidelines. No novel treatment regimens are being examined in this study. Communication with the patient's primary care team will be clear and optimisation of treatment will be performed by the GP, in keeping with (inter)national guidance. In order to facilitate optimum communication between secondary care, primary care and the patient, treatment summaries (summarising the relevant current guidance reflecting best practice) will be written by the supervisory team with the input of local General Practitioners and an expert patient representative. Treatment protocols will be accessible online in primary care and published on the trust website. Treatment of patients in usual care arm will be at the discretion of the treating clinicians.

Covid19 precautions

All research activity will adhere to the strict Northumbria Healthcare NHS Foundation Trust infection control procedures active at the time. Additionally, patients will be contacted prior to attending hospital to ensure they are not showing symptoms of Covid19 infection. We will reschedule this appointment if patients are symptomatic. Additional procedures to minimise the risk of transmitting Covid19 include: social distancing will be adopted during all face-to face assessments; members of the research team will wear the necessary PPE as advised by Public Health England and the Trust infection control polices during the assessments and investigations; we will aim to minimise patients' exposure to healthcare professionals during their assessments and aim to limit the waiting times within hospital; and study participants will use a separate entrance to the research and development centre, minimising exposure to healthcare professionals, patients and hospital visitors.

Study Endpoints

Key outcome measures of interest include readmission and mortality. Our primary outcome measure captures both readmission and death, reflects the number and duration of admissions, and places a higher weighting on mortality (particularly if soon after randomisation). To our knowledge this has not been used in a previous trial involving patients with COPD. Secondary outcomes are included to examine the utility of our novel primary outcome, and to gather important descriptive data to enable powering of the subsequent definitive RCT. Readmission, mortality and length of hospital stay will be collected from hospital health records, using Patient Administration System (PAS).

Primary

1. The number of days spent alive outside of a hospital environment during 12 months post hospital discharge

Secondary

1. Time to readmission or death following hospital admission for ECOPD
2. All-cause readmission rates at 90 days and 12 months post discharge
3. All-cause mortality rates at 90 days and 12 months post discharge
4. COPD exacerbation rates, from health records and self-reported, at 90 days and 12 months.
5. Rates of adverse cardiovascular events* at 90 days and 12 months post discharge

6. Rate of new diagnosis of cardiovascular disease at 90 days and 12 months
7. Rate of undertreated cardiovascular disease at baseline, 90 days and 12 months
8. Change in 4 metre gait speed at 90 days and 12 months, compared to baseline
9. Mean change in quality of life measured by St. Georges' Respiratory Questionnaire over 12 months.
10. Health costs and estimated Quality Adjusted Life Years (QALY), measured by health records and patient-completed resource utilisation proforma, at 12 months

In the intervention arm we will also report as secondary outcomes:

11. Changes in right heart function† between baseline and 90 days
12. Relationship between changes in right heart function† and ECOPD severity measured using DECAF score
13. Relationship between changes in right heart function† and comorbid CVD
14. Relationship between right heart function† and COPD severity at baseline.
15. The associations between the primary outcome and right heart function at baseline†.

* nonfatal stroke or myocardial infarction, and cardiovascular death; † Estimated pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) measured by echocardiography.

Statistical plan for data analysis

Adaptive design

Within the present study, an interim statistical analysis will be undertaken after the first 80 subjects have completed follow up. If a realistic extension to this study could achieve clinically and statistically meaningful conclusions regarding the primary outcome we will extend recruitment.

Randomisation

Patients will be randomly assigned 1:1 to the intervention or usual care. Independent stratified randomisation (via sealedenvelopes.com) using the PEARL score (25) (low, medium and high risk) and the presence of known CVD pre-hospital admission will be performed.

Outcome measurements

Changes in the primary outcome between the intervention and usual care groups will be assessed using Student's t-test or Mann-Whitney U test. Time to first event (readmission or death) will be assessed using a Cox proportional hazards regression model. Changes in echocardiographic measurements between two time points will be assessed using paired Student's t-test or Wilcoxon signed-rank test. The relationship between undiagnosed / undertreated cardiac disease and outcome will be examined using logistic regression. In those surviving to the first follow up assessment, correlations between changes in right heart function and measures of COPD severity and exacerbation severity will be examined using bivariate comparisons appropriate to variable distribution. Mean change in QoL will be calculated by area under the curve per unit time; Student's t-test or Mann Whitney U will be used to compare this value between study arms.

Economic evaluation

The methods to estimate an incremental cost-effectiveness ratio for the intervention versus usual care in terms of Quality Adjusted Life Years will be rehearsed (using EQ-5D-5L

administered at baseline, 90 weeks and 12 months post discharge). In particular, issues relevant for sensitivity analysis will be explored to help understand how best to deal with statistical imprecision and other uncertainties in the full trial. For example, data will be bootstrapped to account for the expected skewness evident in economic cost data. The data collected as part of this feasibility study could be used to inform any subsequent pre-trial modelling.

Power calculation

This is a pilot study. The lack of published data regarding both the prevalence of undiagnosed cardiovascular disease in patients hospitalised with ECOPD, and the impact of cardiovascular assessment (and treatment) on our primary outcome means a power calculation is not possible. We have previously successfully recruited 118 patients hospitalised with mild ECOPD over 18 months to a RCT of hospital at home in ECOPD. This recruited from a smaller population than the present proposal (~50% of total population) and involved a complex intervention.

Readmission and mortality rates are high following ECOPD; based on our pilot data, we are optimistic that our chosen sample size will be deliverable and show a treatment effect that will enable a definitive trial to be powered.

Limitations

This study examines the effect of a novel intervention on a novel COPD outcome. The aim is to use the results to power a definitive RCT, but a lack of a treatment effect may mean a definitive trial is superfluous. Adequate echocardiographic images to make reliable measurements can be challenging in patients with COPD, particularly during an exacerbation when they are more breathless. Whilst a reduction in the amount of echocardiographic data available may reduce the ability to diagnose patients with HFpEF, HFrEF or valvular heart disease, this information will be vital in order to adequately power a definitive trial.

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