Statistical Analysis Plan

(Version 1.0)

Structured Cardiac Assessment and Treatment Following Exacerbations of COPD: A Pilot Randomised Controlled Trial

(SCATECOPD)

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Abbreviations

ABG: Arterial Blood Gas

ACE: Angiotension Converting Enzyme

AF: Atrial Fibrillation

BP: Blood Pressure

BSE: British Society of Echocardiography

COPD: Chronic Obstructive Pulmonary Disease

CVD: Cardiovascular Disease

DMEC: Data Monitoring and Ethics Committee

ECG: Electrocardiograph

HFpEF: Heart Failure with Preserved Ejection Fraction

HFrEF: Heart Failure with Reduced Ejection Fraction

LV: Left Ventricle or Left Ventricular

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NYHA: New York Heart Association

PEARL: Previous Admissions, Extended MRC Dyspnoea Score, Age, Right and Left Ventricular Failure Score

QALY: Quality Adjusted Life Years

QoL: Quality of Life

SCA: Structured Cardiac Assessment

SCATECOPD: Structured Cardiac Assessment and Treatment Following Exacerbations of COPD

SGRQ: St. George's Respiratory Questionnaire

UC: Usual Care

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1. Introduction

This document details the proposed presentation and analysis for the main paper reporting the results from a pilot randomised controlled trial, Structured Cardiac Assessment and Treatment Following Exacerbations of COPD (SCATECOPD). SCATECOPD aims to assess the effect of comprehensive cardiovascular assessment and treatment on the primary endpoint to enable powering of a definitive multicentre RCT.

The results reported in this paper will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan. Any subsequent analyses of a more exploratory nature will not be bound by this strategy and will be detailed in a separate analysis plan.

Suggestions for subsequent analyses by oversight committees, journal editors or referees will be considered carefully in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and justified in the final report to the funder. The analysis will be carried out by an identified, appropriately qualified, and experienced statisticians, who will ensure the integrity of the data during their processing.

This statistical analysis plan is based on the latest version of the protocol (version 1.5; 10th November 2021).

2. Background Information

2.1 Rationale

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.

2.2 Objectives of the trial

2.2.1 Primary objectives

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

2.2.2 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 estimate quality adjusted life years (QALYs) between the 2 study arms.

2.3 Trial Design

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.

2.3.1 Study population

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

2.3.2 Eligibility

Inclusion criteria	*Exclusion 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	• 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

2.3 Randomisation

Patients will be randomly assigned 1:1 to the intervention or usual care. Independent stratified randomisation (via sealedenvelope.com) using the PEARL score (Echevarria et al., 2017) (low, medium and high risk) and the presence of known CVD pre-hospital admission will be performed.

2.4 Definitions of primary and secondary outcomes

Outcomes will be assessed at three time points: baseline, 90 days, and 12 months after hospital discharge.

2.4.1 Primary Outcomes

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

2.4.2 Secondary Outcomes

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 measures of right heart function at baseline†.

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

2.5 Trial reporting

The trial will be reported according to the principles of the CONSORT statements (Moher et al., 2001).

3. Analysis population

Population definitions

The Intention to Treat (ITT) population will be all participants randomised, irrespective of treatment received.

4. Descriptive Analysis

4.1 Participants throughput

The flow of patients through the trial will be summarised for both arms using a CONSORT diagram. The flow diagram will describe the numbers of participants randomly allocated, who received allocation, withdrew consent, and included in the ITT population.

4.2 Baseline comparability of randomised groups

We compare the differences (or the scores) between two treatment groups (SCA vs. UC) using appropriate statistical method. If the variable of interest is continuous and normally distributed, we will then use t-test to evaluate the group differences, otherwise we use Mann-Whitney U test. In case of categorical data, we will use Chi Squared analysis or Fisher's Exact Test (where appropriate) to analyse the independencies of those groups. In the case of comparing the proportion of both treatment groups we use two proportion Z test.

The following characteristics will be described separately:

1) By-arm description at admission (SCA and UC are our treatment groups)

	SCA (n=57)	UC (n=58)	p (H_0 = no between-group difference)
Sociodemographics			
Age (y)			T test
Sex (% female)			Two proportion z test
Residence			
Home (%)			Chi squared (using n)
Sheltered Accommodation (%)			
Residential Home (%)			
Nursing Home (%)			
Formal carers (%)			Two proportion z test
Current smoking (%)			Two proportion z test
PYH (median, IQR)			MWU
Disease severity			
BMI (weight/height in metres^2)			T test
Preadmission FEV1 (% predicted)			T test
eMRCD (median, IQR)			MWU
PEARL score (median, IQR)			MWU
Patient reported ECOPD in past year (median, IQR)			MWU
ECOPD admissions in past year (median, IQR)			MWU
Previous NIV for ECOPD (%)			Two proportion z test

LTOT (%)			Two proportion z test
Home NIV (%)			Two proportion z test
Rockwood CFS (median, IQR)			MWU
Secondary care for COPD (%)			Two proportion z test
Cardiovascular comorbidity			
Mild LVSD (%)			Two proportion z test
Moderate-severe LVSD (%)			Two proportion z test
Heart failure without LVSD (%)			Two proportion z test
Right-sided heart failure (%)			Two proportion z test
Myocardial infarction (%)			Two proportion z test
Atrial fibrillation (%)			Two proportion z test
Angina (%)			Two proportion z test
Hypertension (%)			Two proportion z test
High cholesterol (%)			Two proportion z test
Stroke/Transient ischaemic attack (%)			Two proportion z test
Peripheral vascular disease (%)			Two proportion z test
Diabetes (%)			Two proportion z test
Chronic kidney disease (%)			Two proportion z test
Other comorbidity			
Asthma (%)			Two proportion z test
Bronchiectasis (%)			Two proportion z test
OSA (%)			Two proportion z test
Diabetes (%)			Two proportion z test
Chronic kidney disease (%)			Two proportion z test
Charlson comorbidity index (median, IQR)			MWU
Charlson comorbidity index (age-adjusted; median,			MWU

PYH – cigarette pack year history; BMI – body mass index; FEV1 = forced expiratory volume in 1 second; CFS – clinical frailty score; OSA - obstructive sleep apnoea.

2) Characteristics of admission

	SCA (n=57)	UC (n=58)	p (H_0 = no between-group difference)
ECOPD markers			
Consolidation (%)			Two proportion z test
Acidosis (pH <7.3)			Two proportion z test
Eosinophil count (x10^9/L)			T test or MWU
DECAF score* (median, IQR)			MWU
Symptoms			
Increased dyspnoea (%)			Chi squared (using n)
Increased sputum volume (%)			
Increased sputum purulence (%)			
2+/3 cardinal symptoms (%)			Two proportion z test
CRP (median, IQR)			T test or MWU
Acute NIV (%)			Two proportion z test
Length of stay (days; median, IQR)			MWU
Inpatient events			
Sputum culture positive (%)			Two proportion z test
Viral PCR positive (%)			Two proportion z test
Acute kidney injury (%)			Two proportion z test
Any antibiotics (%)			Two proportion z test
IV antibiotics (%)			Two proportion z test
DNACPR status			

New DNACPR(%)			Chi squared (using n)
Existing DNACPR (%)			
No DNACPR at discharge (%)			
Died during admission (n)			

*eMRCD 5a =1, eMRCD 5b = 2; eosinophils < 0.05 = 1; Consolidation yes = 1; pH <7.3 = 1, AF o/a *or* ECG rhythm AF = 1

3) Diagnoses made during admission

	SCA (n=57)	UC (n=58)	
Heart failure (SCATECOPD classification)			
Moderate-severe LVSD	5	2	
HF without moderate-severe LVSD	13	4	
Heart failure (ESC classification)			
HFrEF	4	2	
HFmrEF	3	1	Need definition in
HFpEF	7	1	
Right sided heart failure†	15	4	
Myocardial infarction	2	2	
Atrial fibrillation	1	2	
Mild coronary artery disease (CACS 1-100)*	10	0	
Moderate-severe coronary artery disease (CACS	30	0	
Uncontrolled hypertension†	14	0	
Uncontrolled diabetes	7	1	

*Without pre-admission diagnosis of MI or angina; †BP above target range at discharge BP assessment, or antihypertensives increased during admission.

†Right sided heart failure may or may not coexist with left-sided heart failure as defined by SCATECOPD/ESC classifications

4) Treatment

Treatment changes during admission:

	SCA (n=57)	UC (n=58)	
Treatment started:			
Antiplatelet/anticoagulation*			
Beta blocker			
ACE-inhibitor/Angiotensin receptor blocker			
Statin			
Other antihypertensive			
Antidiabetic medication			
Sacubitril/valsartan			
Mineralocorticoid antagonist			
SGLT2-inhibitor			
Treatment intensity altered:			
Antiplatelet/anticoagulation†			
Beta blocker			
ACE-inhibitor/Angiotensin receptor blocker			
Statin			
Other antihypertensive			
Antidiabetic medication			
Sacubitril/valsartan			
Mineralocorticoid antagonist			
SGLT2-inhibitor			

4.3 Completeness of follow-up

All reasonable efforts will be taken to minimise loss to follow-up. The number of percentage of participants with follow-up information at day 90, month 6th or 9th after discharge will be reported, please see the table below.

	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			X
NYHA and eMRCD class	X	X			X
Rockwood clinical frailty scale	X				
COPD assessment	X				
Bedside observations	X				
ABG	X				
ECG	X				
Laboratory tests	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		X			X
Primary & community NHS care visits		X	X	X	X
Mortality		X			X
Adverse Cardiovascular Events		X			X

4.4 Adherence to SCATECOPD protocol

In addition to face-to-face assessments, all patients will be contacted by telephone at 6 and 9 months to complete an assessment of healthcare resource use. In hospital and at 3-, 6- and 9-months following hospital discharge, patients will be provided with a health service utilisation form and asked to use this 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.

Clinical stability is required at the 90-day review for accurate assessment of spirometry and, for those randomised to structured cardiovascular assessment, for echocardiography. The 90-day review appointment will therefore be delayed, if necessary, until participants are in a period of clinical stability, which is defined as more than 6 weeks after completion of a course of steroids and/or antibiotics for a diagnosed COPD exacerbation.

Those randomised to the structured cardiovascular assessment will also undergo:

	Baseline	90 days	β – troponin T, NT pro-BNP, fibrinogen, cholesterol profile (admission only),
ECG	X	X	

Echocardiogram	X	X	HbA1c (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
Laboratory investigations[β]	X	X	
24 hour cardiac monitor	X		
CT coronary artery calcification score and CT chest	X[γ]		
24 hour BP monitor[δ]	X		

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 SonoVue contrast agent will be performed during inpatient admission.

CT Coronary artery calcification score will be performed by radiographers according to standard protocol. Reporting will be performed blinded to the presence of known CVD and knowledge of severity of COPD and ECOPD by a trained consultant cardiologist. Assessment of whether CVD is treated adequately will be made with reference to prespecified local or (inter)national guidance. CT chest will be performed without intravenous contrast according to standard local protocol; emphysema severity and airway wall thickening quantified using validated software. Slots for CT scanning for of the study are available at the start of the morning list so it is anticipated that all patients will be able to have a CT scan before being discharged. If this is not possible patients can have their CT scan on an urgent outpatient basis, within 7 days of discharge. This will avoid discharge being delayed for study investigations.

Patients who require 24-hour blood pressure monitoring will either have this test during their inpatient stay or it will be done soon after discharge (a member of the research team will fit the monitor at the patient's place of residence and collect it the following day).

The number of participants breaching the assigned protocol will be reported.

5. Comparative Analysis

For all outcomes, primary analysis will be performed on the ITT population at 90 days post randomisation.

5.1 Primary

Two statistical methods will be used here, *first*, we will use Poisson Regression (or Negative Binomial Regression, when overdispersion occurs) in examining the association between the number of days spent alive outside of a hospital and the treatment (SCA vs. UC). The analysis will adjust for various demographic variables (such as age and sex); *second*, to examine the association between time to event (death) and its risk factors we will use the Cox proportional hazards regression model. The log-rank test will be fitted to compare both treatment (SCA vs. UC) while adjusting for covariates (such as demographic, disease severity, and exacerbation frequency) (Collett, 2015). The proportional hazard assumption will be checked by test or graphs (e.g., plots of log (-log (survival function)) versus time or plots of Schoenfeld residuals versus time) (Schoenfled, 1982). Results will be presented in tables or figures.

5.2 Secondary

For all outcomes (both primary and secondary) the characteristics (profiles), will be presented. Descriptions of all baseline characteristics, follow-up measurements using suitable measures of tendencies means and median with the associated standard deviation, 95% confidence interval and interquartile ranges for continuous variables and frequency and proportions for categorical variables (including binary variables) will be given. To test for significance between the arms, a generalised linear model (GLM) will be used to account for baseline characteristics. Analyses will be performed by intention to treat, with secondary analyses of primary and secondary outcome based on protocol adherence.

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 generalized linear model (Logistic or Poisson regression). For 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 (AUC) per unit time; Student's *t*-test or Mann Whitney U will be used to compare these scores between study arms.

5.3 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 (Cook & DeMets, 2007; Friedman et al., 2015). 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.

5.4 Pre-specified subgroup analyses

Any subgroup analyses will be post-hoc. Based on specified hypothesis the participants will be sub grouped with respect to its baseline characteristics.

5.5 Significance levels

The critical alpha 5% (thus p-value < 0.05 will be considered statistically significant) will be used and the 95% confidence interval will also be presented.

5.6 Statistical software employed

Analysis will be done in R (Version 4.2.1) and Stata (Version 17) where appropriate.

6. References

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