Full Study Title:

Observational Cohort Study of Hospitalised Patients with Acute Respiratory Conditions: "CHESTY"

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Funder:	NIHR Post-Doctoral Fellowship (Dr Neil Greening) Sanofi Genzyme Research Grant

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and / or Sponsor.

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TABLE OF CONTENTS

1. AMENDMENT HISTORY 9
2. SYNOPSIS 15
3. ABBREVIATIONS 19
4. BACKGROUND AND RATIONALE 21
5. OBJECTIVES 22
5.1 Primary Objectives 22
5.2 Secondary Objectives 22
5.3 Exploratory Objectives 22
6. STUDY DESIGN 23
6.1 Summary of Trial Design 23
6.2 COVID-19 Adaptations 24
6.3 Trial Setting 25
6.4 Primary, Secondary and Exploratory Endpoints 25
7. TRIAL PARTICIPANTS 31
7.1 Overall Description of Study Participants 31
7.2 Core study participants (hospitalised and non-hospitalised participants with chronic lung condition) 32
7.3 Healthy controls 32
8. STUDY PROCEDURES 33
8.1 Informed Consent 33
8.2 Screening and Eligibility Assessment 34
8.3 Study Assessments 35
8.3.1 Mandatory study assessments 35
8.3.2 Optional study assessments 35
8.4 Subsequent Assessments 41

8.6 Discontinuation/Withdrawal of Participants from Study Treatment 42
8.7 Storage and analysis of research sample 43
9. CATALINA Sub-Study 1 45
9.1 Background 47
The Collaboration In COPD ExaceRbatiOns (CICERO) 47
9.2 CATALINA Sub-study rationale 48
9.3 CATALINA Sub-study objectives and outcome measures/timepoints 49
9.3.1 Objectives 49
9.3.2 Outcome measures 49
9.4 CATALINA Sub-study design 51
9.5 CATALINA Sub-study setting 51
9.6 CATALINA Sub-study participant eligibility criteria 52
9.7 CATALINA Sub-study procedures 52
9.7.1 Recruitment 52
9.7.2 Consent 53
9.7.3 Early study discontinuation 53
9.7.4 Withdrawal of consent 55
9.7.5 CATALINA Sub-study procedures and visit schedule 56
9.7.5.1 Visit schedule 57
9.7.5.2 Study assessments 59
9.8 CATALINA Sub-study statistics and data analysis 63
9.9 CATALINA Sub-study data management 64
9.9.1 Data Collection 64
9.9.2 eCRF Development 64
9.9.4 CICERO Data Manager 65
9.9.5 Data Transfer 66

9.9.6 Legal Requirements 66
9.10 CATALINA Sub-study monitoring, audit and inspection 67
9.10.1 Audits 67
9.10.2 Monitoring 67
9.10.3 Archiving 67
9.11 Human biological material 68
9.12 CATALINA Sub-study Ethical and regulatory considerations 68
9.13 CATALINA Sub-study finance and insurance 69
9.14 CATALINA Sub-study participant compensation 69
9.15 CATALINA Sub-study dissemination policy 69
10. SAFETY REPORTING 70
10.1 Definitions 70
10.1.1 Adverse Event (AE) 70
10.1.2 Adverse Reaction (AR) 70
10.1.3 Severe Adverse Events 70
10.1.4 Serious Adverse Event or Serious Adverse Reaction 70
10.1.5 Expected Serious Adverse Events/Reactions 71
10.1.6 Suspected Unexpected Serious Adverse Reactions 71
10.2 Reporting Procedures for All Adverse Events 71
10.3 Reporting Procedures for Serious Adverse Events 72
11. STATISTICS 72
11.1 Description of Statistical Methods 72
11.2 The Number of Participants 73
11.3 Procedure for Accounting for Missing, Unused, and Spurious Data. 73
11.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan 73
12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES 73

13. CODES OF PRACTICE AND REGULATIONS 73
13.1 Ethics 73
13.2 Sponsor Standard Operating Procedures 73
13.3 Declaration of Helsinki 74
13.4 ICH Guidelines for Good Clinical Practice 74
13.5 Approvals 74
13.6 Participant Confidentiality 74
14. DATA HANDLING AND RECORD KEEPING 74
15. STUDY GOVERNANCE 75
15.1 Trial Management Group (TMG) 75
16. FINANCING AND INSURANCE 75
17. PUBLICATION POLICY 76
18. REFERENCES 76

1. AMENDMENT/MODIFICATION HISTORY

Amendment/Modification No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
SA 01	2.0	28-Feb-22	Neil Greening	Inclusion of permission to access research records to enable sharing of existing research data. Updates to the PIS and Consent Forms. Creation of separate Baseline and FU questionnaire booklets.
SA 02	3.0	19-Dec-22	Neil Greening	Addition of capturing exacerbations of the 'matched control' group who have a chronic lung condition. These participants are invited to attend the research unit when they experience an exacerbation. A follow up visit will also be conducted at 2 months post exacerbation visit.
SA 03	4.0	15-Apr-24	Hamish McAuley	1. Minor administration and minor amendments 2. Addition to secondary objectives. 3. Extension to the study end date.

				4. Increase to the number of participants to be recruited. 5. Amendment o participant population. 6. Additional exploratory endpoints and study investigations/ procedures. 7. Removal of exploratory endpoints. 8. Changes to length of participation in the study and timing of study visits.
SA 04	5.0	30-Jun-25	Hamish McAuley	1. Addition of CATALINA sub-study. 2. Change from single to multi-site. Additional sites to undertake CATALINA sub-study only. 3. Addition of RESPECK device to the main CHESTY study. 4. Clarification of muscle strength testing procedures. 5. Addition of invitation letter to be sent prior to outpatient clinic appointments for

				potential new patients. 6. Extended window for CHESTY outpatient visits 7. Clarifications in language in CHESTY PIS
NSA 02	5.1	20-Aug-2025	Zoe Swann	1. Correction from "mandatory" to "non-mandatory" for certain CATALINA sub-study assessments (blood gas, echocardiography, spirometry, chest X-ray, and CT scan of chest) as they are usually collected as part of routine clinical care. 2. Addition of Sarcopenia Quality of Life Questionnaire (SarQoL) to main CHESTY study.
NSA03	5.1 (protocol was not updated)	12-Sept-2025 (date of amendment)	Zoe Swann	1. Addition of new site (UCLH).

NSA04	5.1 (protocol was not updated)	15-Apr-2026 (date of amendment)	Jill Clanchy	1. Addition of new sites (KGH and C&W)
SM05	6.0	12-May-2026	Jill Clanchy Hamish McAuley Lorna Latimer	**1.** Revision of Respeck device protocol: extension in time the device is due to be worn to 30 days post discharge. 2. Clarification of Respeck device processes and questionnaire procedures. 3. Addition of optional 30 day post discharge study visit to facilitate Respeck device return and end point assessment completion. Table 1 updated. 4. Addition of surface EMG during physical and strength assessments and muscle mass and turnover assessment using stable isoptopic tracers (COSIAM). 5. Revision of description for recruitment strategy of healthy controls.

				6. Addition of Muscle Phenotyping Exploratory (MPES) Sub-study 2 (appendix 1). 7. Revision to CATALINA SAE in section 10.1.5 and 10.3. 8. Revision to Protocol deviation reporting process in section 11.4. 9. CATALINA Sub-study timelines, recruitment target and no. of sites amended (section 9) and CATALINA Sub-study now referred to as sub-study 1. 10. Addition of MuscLe, heArt aNd metabolic hEalth in people with Long-term cOndiTions (LANCELOT RTB) Research Tissue Bank (REC: 22/WA/0348 IRAS: 318250). 11. Updated University of Leicester logo. Figure 1 updated to reflect additional post discharge FUp visit. 12. Updated recruitment to include individuals who

				previously consented to being contacted for future research, and clarified to recruit those currently under the care of hospital respiratory outpatient services for chronic respiratory diseases in sections 2.0 Synopsis, 6.1, 7.1, 8.1 and 8.2. 13. Section 7.2 - Inclusion criteria 1 for core study updated to include those currently under care of hospital respiratory outpatient services for chronic respiratory disease.
NSM05	6.1	09-Jul-2026	Dr Hamish McAuley & Jill Clanchy	CHESTY and MPES Sub-study 2 ONLY: Clarifications to the protocols: a) That a total maximum of four DXA scans will be performed across both the CHESTY study and the MPES Sub-study 2 (section 8.3.2 and table 1 updated). b) That the "Early post-discharge visit" in the CHESTY study protocol and the assessments associated

				with this visit are optional (table 1).

2. SYNOPSIS

Study Title	Observational Cohort Study of Hospitalised Patients with Acute Respiratory Conditions
Study acronym	CHESTY
Chief Investigator	Dr Neil Greening
Trial Design	Observational cohort study
Trial Participants	1. Patients admitted to hospital with an acute respiratory condition or patients with chronic respiratory disease under respiratory outpatients follow-up. . 2. Healthy control group consisting of participants without lung disease.
Planned Sample Size	500
Follow-up duration	36 months (+up to 90 days)
Planned Trial Period	End of recruitment 31st October 2029, end of study 30/10/33
Primary Objective	• To characterise and predict short term clinical outcomes of patients admitted to hospital with an acute respiratory condition including exacerbation of underlying chronic lung diseases.
Secondary Objectives	• To measure long term clinical outcomes of hospitalised patients with an acute respiratory condition. • To develop a risk stratification tool at time of hospitalisation that can prospectively identify selected patients for targeted intervention • To characterise the natural recovery from hospitalisation and assess tools measuring hospital associated disability.

	• To develop a risk stratification tool for risk of future hospitalisation that can prospectively identify selected patients for targeted intervention • To develop pilot data for an NIHR programme development grant focused around acute phenotyping and the reduction of length of stay/re admissions
Primary Endpoint	• 30 days hospital readmission rate • Length of index hospital admission • 30 days mortality rate
Secondary Endpoints	Long term clinical outcomes and health care utilization: • Total number of hospital readmission due to same underlying chronic lung disease over 52 weeks • Total number of non-hospitalized exacerbations of underlying chronic lung disease over 52 weeks • Time from consent to death (respiratory causes) • Time from consent to death (all causes)
Exploratory Endpoints	Questionnaires: • Breathlessness: Extended MRC dyspnoea score (eMRC) • Rockwood Clinical Frailty Scale • Health Status: COPD Assessment Tool (CAT) or Asthma Control Questionnaire (ACQ) • Functional: London Chest Activities of Daily Living Questionnaire (LCADL) • Sarcopenia Questionnaire (SARC-F) • St. George's Respiratory Questionnaire (SGRQ-C) • Chronic Respiratory Questionnaire (CRQ) • Patient Health Questionnaire 8 (PHQ-8) • Generalised Anxiety Disorder 7 questionnaire (GAD-7) • EuroQol five domain five level questionnaire (EQ5D-5L) • General Practice Physical Activity Questionnaire (GPPAQ) • Malnutrition Universal Screening Tool (MUST) • Sacrcopenia Quality of Life Questionnaire (SarQoL)

Physiological/ physical function measures:

- Height
- Body mass
- Waist circumference
- Heart rate
- Blood pressure
- Electrocardiogram (ECG)
- Forced Expiratory Volume in 1 second (FEV1)
- Forced Vital Capacity (FVC)
- Lung volume measurements & Transfer Factor
- Fractional exhaled nitric oxide (FeNO)
- Short physical performance battery (SPPB)
- Handgrip strength
- Quadriceps strength
- Surface electromyography (EMG)
- Handheld oscillometry
- Physical activity monitoring
- Fried's Frailty Phenotype
- Rockwood Clinical Frailty Scale
- Accelerometery
- Fracture Risk Assessment Tool (FRAX)
- Breathing patterns (Respeck wearable device)

Biomarkers:

- Throat & Nasal swab (viral PCR)
- Sputum samples
- RNA, Protein multiplex, immunology
- Sputum inflammatory differential
- Sputum eosinophil count (percentage)
- Sputum microbiome/metagenomics
- Blood samples
- Cardiac biomarkers (e.g. Troponin & NT-proBNP)
- FBC including eosinophils count
- Vitamin D level
- HbA1C
- Fungal sensitisation screen

	• Immunoglobulins level • Serum and plasma biomarkers • Leukocyte immunophenotyping and storage for genetics analysis • Urine biomarkers (e.g. lipidoproteinomics, protein multiplex) • Breath Volatile Organic Compounds (VOC) Muscle wasting measurement: • Quadriceps size (measured by ultrasound) • Body composition using BIA or DEXA scan • Skeletal Muscle Biopsy • Thigh MRI • Muscle mass and turnover assessment using stable isoptopic tracers
Sub-studies	1. CATALINA Sub-study 1 (synopsis section 9) 2. MPES Sub-study 2 (separate appendix 1)

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
ACQ	Asthma Control Questionnaire
BIA	Bioelectrical impedance
BRC	Biomedical Research Centre
BTS	British Thoracic Society
CI	Chief Investigator
CAT	COPD Assessment Tool
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRQ	Chronic Respiratory Questionnaire
CT	Computed Tomography
DEXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
eMRC	Extended MRC dyspnoea score
EC	Ethics Committee (see REC)
ECG	Electrocardiogram
EQ5D-5L	EuroQol five domain five level questionnaire
EMG	Electromyography
FeNO	Fractional exhaled Nitric Oxide
FEV	Forced Expiratory Volume
FRAX	Fracture Risk Assessment Tool
FVC	Forced Vital Capacity
GAD-7	Generalised Anxiety Disorder
GCP	Good Clinical Practice

GP	General Practitioner
GPPAQ	General Practice Physical Activity Questionnaire
ICF	Informed Consent Form
LCADL	London Chest Activities of Daily Living Questionnaire
MUST	Malnutrition Universal Screening tool
NHS	National Health Service
PCR	Polymerase chain reaction
PHQ—8	Patient Health Questionnaire 8
PIL/S	Participant/ Patient Information Leaflet/Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARC-F	Sarcopenia Questionnaire
SarQoL	– Sarcopenia Quality of Life Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SPPB	Short physical performance battery
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWRQ-C	Chronic Respiratory Questionnaire
UHL	University Hospitals of Leicester NHS Trust
VOC	Volatile Organic Compound

4. BACKGROUND AND RATIONALE

Emergency hospital admissions due to acute respiratory illness represent a major burden on the modern healthcare system. These include conditions like pneumonia and respiratory infections in patients with no pre-existing lung condition. However, many admissions are in patients with underlying chronic respiratory disease. Severe exacerbations of asthma and chronic obstructive pulmonary disease (COPD) resulting in hospitalisation are recognised as an imperative point for intervention. The Royal College of Physician (RCP) and the British Thoracic Society (BTS) national audit identified the COPD population as particularly high risk with a 45% readmission rate and 12% mortality at 3 months[1]. Population studies in COPD have suggested that by the second hospitalisation patients are on a significant downward trajectory[2].

To date there is limited understanding of the acute event on both medium and long-term outcomes, in particular interventions to reduce risk of readmission or death. We have previously demonstrated novel markers as both predictors of diagnosis[3 4] and prognosis[5] (e.g. quadriceps ultrasound and breath biomarkers). We have also previously performed a randomised trial of early inpatient rehabilitation[6], which did not reduce subsequent hospitalisation and currently are trialling a novel intervention of anti-IL-5 therapy in patients with eosinophilic COPD.

In this observational study we aim to characterise patients admitted to, or at risk of hospital admission with an acute respiratory condition, or acute worsening of their chronic lung condition. This will allow us to identify predictors of future risk, as well as develop potential interventions.

5. OBJECTIVES

5.1 Primary Objectives

To characterise and predict short term clinical outcomes of patients admitted to hospital with an acute respiratory condition including exacerbation of underlying chronic lung diseases

5.2 Secondary Objectives

- To measure long term clinical outcomes of hospitalised patients with acute respiratory condition.
- To develop a risk stratification tool at time of hospitalisation that can prospectively identify selected patients for targeted intervention
- To develop a risk stratification tool for risk of future hospitalisation that can prospectively identify selected patients for targeted intervention
- To characterise the natural recovery from hospitalisation and assess tools measuring hospital associated disability.
- To develop pilot data for an NIHR program development grant focused around acute phenotyping and the reduction of length of stay/ readmissions

5.3 Exploratory Objectives

To establish potential biomarkers for targeted interventional trials (precision medicine approach).

To describe the microbiomic profile patients admitted with acute respiratory condition.

To describe the health care related quality of life, the burden of symptoms and the physiological impact (including the risk of sarcopenia) associated with hospital admission with an acute respiratory illness.

To describe breathing pattern disorders and identify causes of dysregulated breathing using the Respeck device. Data from the Respeck device will be analysed using existing machine learning techniques at the University of Edinburgh.

6. STUDY DESIGN

6.1 Summary of Trial Design

This will be an observational cohort study, recruiting patients who have been admitted to hospital with an acute respiratory condition or who are at risk of admission due to their chronic respiratory condition. Acute respiratory conditions may include exacerbations of existing chronic lung diseases such as asthma, COPD, interstitial lung disease, bronchiectasis and pleural disease, or acute illness' including pulmonary embolism, pneumonia, or any other respiratory infection. Patients will be screened and recruited either during hospitalisation or currently under the care of hospital respiratory outpatient services for a chronic respiratory disease. Follow up will be conducted over 36 months (+ up to 90 days) following recruitment. Baseline study visits (see **Table 1**) will be completed during or within 90 days of a routine clinical follow up appointment or while in hospital. Participants recruited while in hospital will be invited to attend up to three further optional follow up visits during the year following their admission to assess clinical recovery in addition to annual follow up for 36 months plus a brief additional early post-discharge visit at 30 (+14) days after leaving hospital. Participants recruited under the respiratory outpatient clinic will be invited to undergo follow up assessments annually which may be remotely or alongside any routine face to face clinical follow up appointments.

Participants will be offered the choice to undertake the follow up assessments via any of the following routes:

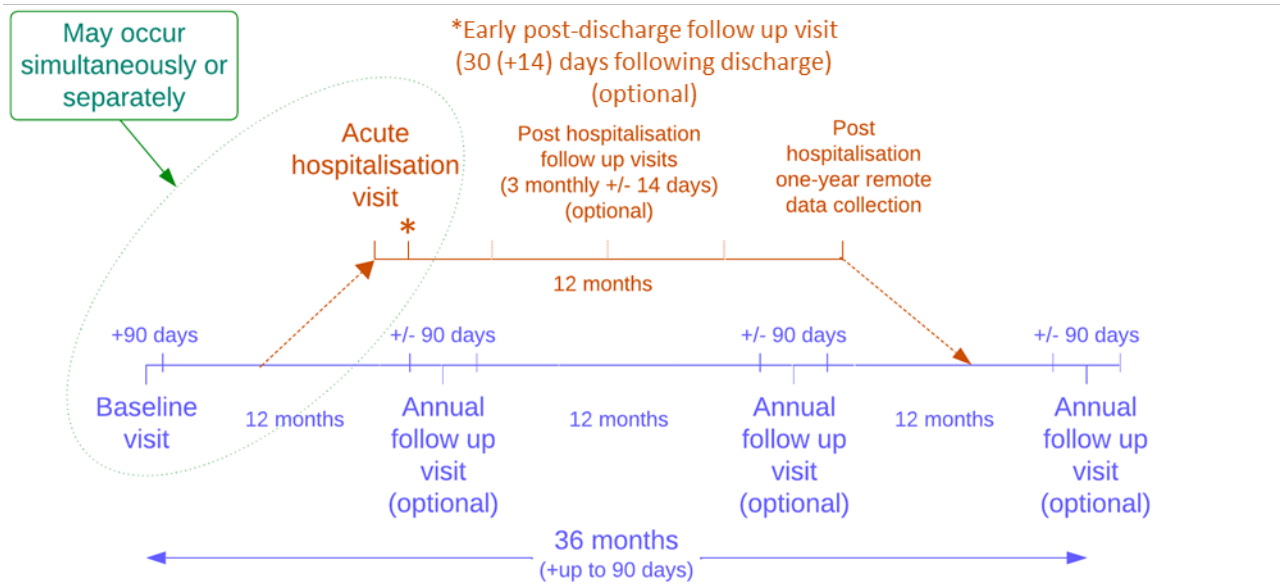
- a telephone consultation or
- a face-to-face visit either in the Biomedical Research Centre (BRC) or
- during a research visit from another ethically approved study or
- during routine clinical follow up organised by the hospital clinical team.

Participants can choose not to attend any further follow up visits after recruitment. Any planned clinical follow-up arranged by the hospital team will occur according to clinical needs. If a participant is admitted to hospital during their participation in the study they will be invited to complete an additional study visit during their acute admission (within 7 days of hospitalisation) as well as up to three further additional visits during the 12 months following discharge. A remote visit will be carried out at 12 months post-discharge (+/- 30 days) for hospitalised patients to collect data about health care utilisation (e.g. hospitalisation rate, length of stay in hospital, death rate, antibiotic/steroid prescriptions) from both primary and secondary healthcare records. The participants are not required to attend this one year post discharge visit as data will be collected remotely.

Healthy controls

A separate component of this study will recruit 'controls' without lung disease. These will be 'healthy' or clinically stable participants who will be invited to undergo a baseline (V1) only.

Figure 1. Study design – core participants (hospitalised and non-hospitalised patients)



6.2 COVID-19 Adaptations

In accordance with national public health policy, participants with known active COVID-19 infection will not be seen in person until they have completed the recommended period of isolation. All participants will be contacted by telephone or text prior to scheduled follow up study visits to determine whether they have any current or recent COVID-19 symptoms. All participants reporting such symptoms will be required to have a negative COVID-19 PCR swab or complete the recommended isolation period, prior to rescheduling their study visits.

The study will operate within host protocols for infection prevention including the use of PPE and social distancing during research visits. The study will adhere to restrictions on research activity instructed by the Trust R&I team in the event of further pandemic waves or restrictions. As a consequence of these adaptations, there is a risk that some study investigations or study visits for participants may be either delayed or missed. If staffing capacity allows then remote follow up visits will continue to be conducted. In all instances, the reasons for missed or delayed investigations or appointments will be recorded on the CRF and Protocol Deviation Log and marked as COVID-19 related.

6.3 Trial Setting

The main CHESTY study is a single centre study. Recruitment will be from patients attending outpatient appointments and inpatients admitted to University Hospitals of Leicester NHS Trust (UHL). The Trust is the second largest acute hospital trust for hospital admissions in the UK with a catchment population circa. 1.2 million.

The CATALINA sub-study 1 (see Chapter 9) will be a multi-centre study across the UK. Recruitment will occur during hospital admission for COPD.

6.4 Primary, Secondary and Exploratory Endpoints

Primary Endpoint

- 30 day hospital readmission rate
- Length of index hospital admission
- 30 day mortality rate

Secondary Endpoints

Long term clinical outcomes and health care utilisation:

- Total number of hospital readmission due to same underlying chronic lung disease over 52 weeks
- Total number of non-hospitalised exacerbations of underlying chronic lung disease over 52 weeks
- Time from index admission to death (respiratory causes)

Time from index admission to death (all causes)

Exploratory Endpoints

Questionnaires:

- Breathlessness: Extended MRC dyspnoea score (eMRC)
- Rockwood Clinical Frailty Scale
- Health Status: COPD Assessment Tool (CAT) or Asthma Control Questionnaire (ACQ)
- Functional: London Chest Activities of Daily Living Questionnaire (LCADL)
- Sarcopenia Questionnaire (SARC-F)
- St. George's Respiratory Questionnaire (SGRQ-C)
- Chronic Respiratory Questionnaire (CRQ)
- Patient Health Questionnaire 8 (PHQ-8)
- Generalised Anxiety Disorder 7 questionnaire (GAD-7)
- EuroQol five domain five level questionnaire (EQ5D-5L)
- General Practice Physical Activity Questionnaire (GPPAQ)
- Malnutrition Universal Screening Tool (MUST)
- Sarcopenia Quality of Life Questionnaire (SarQoL)

Physiological/ physical function measures:

- Height
- Body mass
- Waist circumference
- Heart rate
- Blood pressure
- Electrocardiogram (ECG)
- Forced Expiratory Volume in 1 second (FEV1)
- Forced Vital Capacity (FVC)
- Lung volume measurements & Transfer Factor
- Fractional exhaled nitric oxide (FeNO)
- Short physical performance battery (SPPB)
- Handgrip strength
- Quadriceps strength
- Surface electromyography (EMG)
- Handheld oscillometry
- Physical activity monitoring
- Fried's Frailty Phenotype
- Rockwood Clinical Frailty Scale
- Accelerometery
- Fracture Risk Assessment Tool (FRAX)
- Breathing patterns (Respeck wearable device)

Biomarkers:

- Throat & Nasal swab (viral PCR)
- Sputum samples
    - RNA, Protein multiplex, immunology
    - Sputum inflammatory differential
    - Sputum eosinophil count (percentage)
    - Sputum microbiome/metagenomics

- Blood samples
    - Cardiac biomarkers (e.g. Troponin & NT-proBNP)
    - FBC including eosinophils count
    - Vitamin D level
    - HbA1C
    - Fungal sensitisation screen
    - Immunoglobulins level
    - Serum and plasma biomarkers
    - Leukocyte immunophenotyping and storage for genetics analysis

- Urine biomarkers (e.g. lipoproteinomics, protein multiplex)
- Breath Volatile Organic Compounds (VOC)

Muscle wasting measurement:

- Quadriceps size (measured by ultrasound)
- Body composition using BIA or DEXA scan
- Skeletal Muscle Biopsy
- Thigh MRI
- Muscle mass and turnover assessment using stable isoptopic tracers

Table 1: Schedule of core CHESTY study procedures for hospitalised and non-hospitalised participants

Study Assessment	Baseline	Acute hospital admission visit	Early post-discharge follow up visit (optional)	Post hospitalisation follow up visits	Post hospitalisation one-year remote data collection	Annual follow up visits (optional)
Time window	Under routine clinical follow up or within 7 days of admission for hospitalised patients	Within 7 days of admission	30 days following discharge from hospital (+14 days)	Up to 3 in total 3 monthly from hospitalisation (+/- 14 days)	12 months from hospitalisation (+/- 14 days)	12 monthly from recruitment (+/- 90 days)
Informed Consent‡	x					
Demographics‡	x					
Admission diagnosis (for hospitalised patients only)	x	x				
Treatment received (for hospitalised patients only)	x	x				
Severity illness scores (DECAF, BTS asthma severity, CURB-65, etc.) (for hospitalised patients only)	x	x				
Past Medical History including co-morbidities	x	x		x		x
Medications	x	x		x	x	x
Anthropometric measurements (Height, weight, waist circumference)	x	x		x		x
Clinical assessment & Clinical Observations	x	x		x		x
ECG findings	x	x				
Any performed images* (e.g. Chest X-Ray/CT -scan)	x	x		x		x
ABG findings*	x	x		x		x
Biological Samples: · Throat & Nasal swabs (Viral PCR) · Sputum · Blood · Urine	x	x	x	x		x

· Breath Volatile Organic Compounds (VOC)						
Lung function tests: · Pre and post bronchodilator spirometry (FEV1, FVC) · Lung volumes & transfer factor · FeNO · Handheld Oscillometry	x	x	x	x		x
Healthcare Questionnaires	x	x	x	x		x
Short Physical Performance Battery (SPPB)	x	x	x	x		x
Handgrip strength	x	x	x	x		x
Quadriceps strength	x	x	x	x		x
Quadriceps muscles ultrasound	x	x	x	x		x
Body composition (DEXA[$]/BIA)	x	x	x	x		x
Physical activity monitor	x	x		x		x
RESPECK Device^	x					
Skeletal Muscle Biopsy†	x	x	x	x		x
Thigh MRI	x	x	x	x		x
30 days hospital readmission rate					x	
30 days mortality rate					x	
Total number of hospital readmission due to same underlying chronic lung disease over 52 weeks					x	
Total number of non-hospitalized exacerbations of underlying chronic lung disease over 52 weeks					x	
Time from index admission to death (respiratory causes)					x	
Time from index admission to death (all causes)					x	
Cause of death (if applicable)					x	

‡Mandatory for all participants. All other procedures are optional.
*Only if performed as part of standard clinical care.
†Only performed in a small group of participants
^To be worn for 30 days after hospital discharge and includes regular completion of COPD Assessment Test symptom questionnaire via supplied telephone device.
[$]A total maximum of four DEXA scans will be performed on any single participant within the CHESTY study including those performed as part of the sub-studies.

Table 2: Schedule of healthy control participants in the main CHESTY study.

Study Assessment	Baseline
Informed Consent‡	x
Demographics‡	x
Past Medical History including co-morbidities	x
Medications	x
Anthropometric measurements (Height, weight, waist circumference)	x
Clinical assessment & Clinical Observations*	x
ECG findings	x
Any performed images* (e.g. Chest X-Ray/CT -scan)	x
ABG findings*	x
Biological Samples: · Throat & Nasal swabs (Viral PCR) · Sputum · Blood · Urine · Breath Volatile Organic Compounds (VOC)	x
Lung function tests: · Pre and post bronchodilator spirometry (FEV1, FVC) · Lung volumes & transfer factor · FeNO · Handheld Oscillometry	x
Healthcare Questionnaires	x
Short Physical Performance Battery (SPPB)	x
Handgrip strength	x
Quadriceps strength	x
Quadriceps muscles ultrasound	x
Body composition (DEXA/BIA)	x
Physical activity monitor	x
Skeletal Muscle Biopsy†	x
Thigh MRI	x

‡Mandatory for all participants. All other procedures are optional.

*Only if performed as part of standard clinical care.

†Only performed in a small group of participants

6.5 Co-participation in other studies

As this is an observational cohort study, co-participation in other ethically approved studies including interventional trials is permissible. The participants from other ethically approved studies who meet the eligibility criteria for CHESTY study can be recruited. We will also ask permission to access their previous research records, with permission and approval from the other research study team and only where consent is in place. Only relevant data and information will be used. This may mean that some of the investigations and information in the study visits may have already been completed and therefore where possible, this means that an assessment would not need to be repeated as part of the patient's participation in this study.

To reduce the burden of multiple visits for the participants, data obtained from planned visits from any interventional trials can be used for the follow up visits data collection with the permission of the PI of the co-participating studies and participant consent.

6.6 The CATALINA sub-study

The CATALINA Study is an observational study led by the University Hospitals Leuven (UZ Leuven), Belgium under the guidance of the CICERO ERS CRC (a European Respiratory Society Clinical Research Collaboration) with aims and objectives substantively matching those of the CHESTY study. Given the overlapping aims of these two studies the protocol used in the CATALINA study has been incorporated as a sub-study within the CHESTY study to facilitate wider data collection and contribution to this consortium. For ease of reference, further details regarding the CATALINA sub-study are provided in Section 9 of this protocol. Participants recruited to this sub-study will be issued with participant identifiers indicating that they are following this sub-study protocol and data collected from these participants will be entered directly into the CATALINA electronic database held at Imperial College London (IRAS project ID 301381).

7. TRIAL PARTICIPANTS

7.1 Overall Description of Study Participants

Participants admitted to hospital with an acute respiratory condition including exacerbation of an underlying physician diagnosed chronic lung disease or under the hospital's respiratory outpatients clinic for routine follow up of a chronic respiratory condition. The study will also include healthy controls (healthy volunteers) without lung disease.

Participants who had consented to previous versions of the protocol would not be recalled and reconsented. However, if an individual had consented to an earlier protocol version was subsequently seen clinically - we would invite them to join the trial as a new participant on the new version of the protocol.

7.2 Core study participants (hospitalised and non-hospitalised participants with chronic lung condition)

7.2.1 Inclusion Criteria (Core study participants)

1) Hospital admission with an acute respiratory diagnosis, or currently under the care of hospital respiratory outpatient services for a chronic respiratory disease
2) Participant is willing & able to give informed consent for participation in the study
3) Aged 18 years or above
4) Able (in the Investigators opinion) & willing to comply with all study requirements

7.2.2 Exclusion Criteria (Core study participants)

1) Unstable or life-threatening cardiac disease including myocardial infarction or unstable angina during current admission.
2) Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.
3) Known pregnancy

7.3 Healthy controls

The study will include controls (healthy volunteers who do not have a chronic respiratory disease) to compare the exploratory endpoints.

Controls who were part of the study up to and including Protocol V3.0 will form part of a standalone group in analysis.

7.3.1 Inclusion Criteria (Healthy Controls)

1) Aged 18 years or above
2) No underlying respiratory disease as self-reported
3) Able (in the Investigators opinion) & willing to comply with all study requirements

7.3.2 Exclusion Criteria (Healthy Controls)

1) Hospitalised due to an acute respiratory illness in the last 6 weeks prior to consent
2) Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.
3) Known pregnancy

8. STUDY PROCEDURES

8.1 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed.

Potentially eligible participants will be initially approached by a member of their usual healthcare team to see if they would like to take part in the study either on admission to hospital on the ward,via routine clinic appointments, or by a member of the research team if the individual had previously consented to being contacted about future research. In the case of healthy controls, the recruitment database will be used where participants have provided consent to be contacted for future research and initial approach will be via the research team. Written versions of the Summary Information Sheet, PIS and ICF will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol and any risks involved in taking part. It will clearly state that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The consent will also cover the participants agreement to access their primary care records (historical and during the trial), as well as to the storage of their biological specimens for future ethically approved research.

After the participant has had a full discussion with the researcher and been given the PIS, some participants may agree to enter the study straight away. In this case, informed consent may be taken at this time. Otherwise, the participant will be given enough time to reflect on whether they wish to consider taking part in the study. Due to the nature of the study (acute illness resulting in hospitalisation), consent may be obtained during the hospital stay. Written ICF will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed ICF will be retained at the

study site within the Trial Master File (TMF) or Investigator Site File (ISF). A copy of the signed ICF will be given to the participant and a copy retained in the medical notes.

Participants who are unable to sign the consent form themselves either due to physical or language difficulties but are able to provide informed consent may do this through a witness/translator whose relationship to the participant should be documented on the consent form and who should sign the appropriate declaration on the consent form. A witness/translator can be a family member or trusted friend, member of the research team, a healthcare professional, or a routine hospital translator. For those participants who consented to the study via a witness/translator, the study team will make every effort to ensure that the participant fully understands their involvement in the study and provides continued willingness to participate.

8.2 Screening and Eligibility Assessment

Outpatients with chronic respiratory disease:

Potential participants to the study will be identified by members of the clinic healthcare team using the inclusion criteria of the study. Potential participants will be contacted/approached by a member of the healthcare team and asked if they would like to consider taking part in the study. If the patient is willing to consider participating in the study, they will be approached by a member of the research team for further information and consent. On many occasions the healthcare team will also be members of the research team. Potential participants may also be contacted in advance of attending a routine clinical outpatient appointment via post by the study team who may send a copy of the participant information sheet alongside an explanatory coversheet to allow participants more time to consider participation prior to be formally approached face to face at the time of their routine outpatient appointment. Potential participants who have previously consented to being contacted about future research studies may be contacted directly via telephone by a member of the clinical and/or research team to discuss the study. A participant information sheet will be provided via post in this instance to allow the individual additional time to consider taking part.

Hospitalised Patients:

Potential participants to the study will be identified as soon as practically possible when they are admitted to the University Hospitals of Leicester by members of the healthcare team using the inclusion criteria of the study. Potential participants will be approached by a member of the healthcare team and asked if they would like to consider taking part in the study. If the patient is willing to

consider participating in the study, they will be approached by a member of the research team for further information and consent. On many occasions the healthcare team will also be members of the research team.

Healthy Controls:

Healthy controls will be identified and invited by either clinical or research members of the team via social contacts, word-of-mouth, advertising in local GP Practices, social media and from lists of patients previously agreed to be contacted for future research kept at the NIHR Leicester BRC – Respiratory. They will be provided a specific Healthy Controls Patient Information Sheet (PIS) and Informed Consent Form (ICF) or those relating to relevant sub-studies involving healthy controls and will be given sufficient time to consider their participation in the study.

8.3 Study Assessments

8.3.1 Mandatory study assessments

The mandatory components of the study represents data collection which include but are not restricted to:

Demographics:

The date of birth/age, gender at birth, ethnicity, occupation, smoking history include vaping, will be recorded. The participants home address postcode will be collected to be used (with their permission) to link the outcomes of this study with environmental exposure such as pollution and weather.

8.3.2 Optional study assessments

The following assessments are optional study assessments as detailed in Table 1.

Admission diagnosis & Severity illness score:

If hospitalised, current cause of hospital admission will be recorded. Severity illness score include e.g. CURB-65 score, DECAF score, etc.

Past Medical History including co-morbidities:

Previous past medical history including details of previous exacerbations of any underlying chronic lung disease will be taken. Most recent previous spirometry will be obtained. Baseline and acute breathlessness will be measured using the extended MRC dyspnoea grade.

Medications:

All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded on CRFs. Any recent changes to medication will be recorded, including antibiotic and steroid prescription. Acute medication will also be recorded.

Anthropometric measurements:

Height, weight and waist circumference will be recorded.

Clinical assessment & Clinical Observation:

Oxygen saturations, blood pressure, temperature, respiratory rate and pulse will be measured, or taken from the clinical observations at the time point nearest to study recruitment. Results of physical examination will also be recorded when performed as part of routine clinical care within 12 months of study recruitment.

ECG Test:

A 12-lead ECG may be taken either by the research team or as part of their clinical care. At least the following ECG parameters will be recorded from this ECG: heart rate (HR) and arrhythmias.

ABG findings:

Only, if performed as part of standard clinical care. Results performed as part of routine clinical care within the previous 12 months will be recorded.

Radiology Report and Images:

Radiological imaging will be done as part of the clinical management of the patient. For hospitalised patients, most patients will routinely have a chest X ray on admission, and some will have a CT scan clinically (e.g. of chest). Participation in the study will allow saving a copy of any performed images in a pseudo-anonymised format at the BRC images archive. Current and historical imaging will be included.

Blood results:

Blood results at baseline (within the previous 12 months) taken as part of standard clinical care and will be reviewed and recorded in the CRF.

Additional Blood Tests

Optional blood sampling (up to 100 mls per visit) will be collected into suitable tubes using an aseptic technique. In all cases of blood donation, the subject will be given clear instructions regarding care of the venepuncture site.

Blood samples will be used for biomarkers identification, genetics analysis and other routine clinical tests (if not performed as part of standard clinical care) such as and not limited to full blood count, kidney function, liver function, C-Reactive protein, cardiac enzymes including Troponin and NT-proBNP, Vitamin D, fungal sensitisation, HbA1c and Immunoglobulins level.

Clinical samples will be analysed by the pathology department at the investigator site. Research specific samples will be analysed and stored at the investigative site.

Reviewing and acting on abnormal results will remain the responsibility of the clinical team who will have ordered and requested the investigations. The results of any additional clinical tests arranged by the research team will be reviewed by the study physician for clinical significance. If clinically significant the appropriate medical reporting lines will be followed.

DNA/RNA samples:

As part of the optional blood tests specified above, specific samples can be analysed for genetic testing related to respiratory conditions. The participants will decide when signing the ICF, if they are happy for their samples to undergo genetic analysis. The results will not be communicated back to the participants.

Dual energy x-ray absorptiometry (DEXA)

Participants will be invited to undergo DEXA scanning for more accurate assessment of body composition and to provide appendicular measurements, which will be optional. It is a similar procedure to having a chest x-ray, but requires the patient to lie down. The proportion of muscle, fat and bone density in the body is measured. The radiation dose from each DEXA scan is equivalent to radiation from less than 1/10th of a chest x-ray. Chest x-rays expose the patient to a minimum amount of radiation. A total maximum of four DEXA scans will be performed on any single participant within the CHESTY study including those performed as part of the sub-studies.

Bioelectric impedance analysis (BIA)

Participants will be invited to undergo BIA testing for assessment of body composition. This procedure varies depending on the precise equipment used but may involve sitting, standing or lying down with electrodes similar to those used for ECG recording sited on the patient's skin or with the patient

standing upon and simultaneously holding metal electrode surfaces. BIA is obtained following the transmission of a low current of electricity through the body at several oscillating frequencies allowing the derivation of outcome measures including fat-free mass, lean mass and total body water. This procedure is painless and carries no risk from the electrical currents used.

Sputum collection

Spontaneous or induced sputum samples can be collected. In the case of induced sputum sample collection all subjects will have a baseline FEV_1 measured. Sputum collection will be collected using the principles as defined by the European Respiratory Society Guidelines and the local Trust infection control guidance. All equipment used for sputum induction will be de-contaminated according to local working instructions.

The procedure may be stopped prematurely if: (1) the subject's FEV_1 drops by greater than 20% of the post-salbutamol FEV_1 baseline value, (2) the subject feels any discomfort and does not want to continue with saline inhalation procedure or (3) the investigator feels that it is unsafe to continue with the saline inhalation.

Urine Collection

Urine will be collected from participants. It will be collected into a suitable container, processed through centrifugation and stored at the investigative site.

Throat & Nasal swab (viral PCR)

Throat and Nasal swab will be obtained according to local SOP and the samples will be stored in the BRC lab facility and processed at external laboratory facility following standard procedures.

Breath Volatile Organic Compounds (VOC)

This will involve tidal breathing into a breath collection device for a few minutes to measure volatile organic compounds. The samples will be processed and analysed in University of Leicester laboratory facilities according local agreed SOP.

Lung function

Lung function testing may include spirometry (pre and post bronchodilator), lung volumes and transfer Factor measurements, FeNO and oscillometry:IOS (Impulse Oscillometry) and forced oscillation technique (FOT). All of these are non-invasive clinical tests.

Healthcare Questionnaires

Questionnaires regarding the subjects' health and disease status will be completed. These will include measures of health status, psychological status, and cognition. All questionnaires are validated in this population. Participants may be asked to complete the questionnaires or they may be facilitated by a researcher (paper or electronic). The following questionnaires may be used, however a participant would be asked to complete no more than 8 questionnaires at a single timepoint.

- Breathlessness: Extended MRC dyspnoea score (eMRC)
- Rockwood Clinical Frailty Scale
- Health Status: COPD Assessment Tool (CAT) or Asthma Control Questionnaire (ACQ)
- Functional: London Chest Activities of Daily Living Questionnaire (LCADL)
- Sarcopenia Questionnaire (SARC-F)
- St. George's Respiratory Questionnaire (SGRQ-C)
- Chronic Respiratory Questionnaire (CRQ)
- Patient Health Questionnaire 8 (PHQ-8)
- Generalised Anxiety Disorder 7 questionnaire (GAD-7)
- EuroQol five domain five level questionnaire (EQ5D-5L)
- General Practice Physical Activity Questionnaire (GPPAQ)
- Malnutrition Universal Screening Tool (MUST)
- Sarcopenia Quality of Life Questionnaire (SarQoL)

Physical performance

Short Physical Performance Battery (SPPB) test, handgrip strength measurements and quadriceps size measured using ultrasound (see below) and strength will be performed to assess physical performance according to local SOPs. These are routine measures of frailty, non-invasive, and validated assessments.

Quadriceps Muscle Ultrasound

Quadriceps ultrasound will be performed as per Standard Operating Procedure (SOP). Measures will be taken at mid-point of the thigh and three measures (within 10%) of rectus femoris cross sectional area will be taken and the mean recorded. Three measures of quadriceps thickness will be taken and the mean recorded. Images of the quadriceps will be taken (linked anonymised) for later analysis of grayscale (muscle quality).

Physical Activity Monitors

Participants will be fitted with a blinded accelerometer. The devices are well tolerated, and weigh less than 100g. Accelerometers will be worn for two weeks at each visit. Monitors will be initialised to record triaxial acceleration (g) at 50 Hz. Participants will post the monitors back to the Leicester

Respiratory BRC where the data will be downloaded. The data will be transferred to the Diabetes Research Centre, University of Leicester for analysis following completion of procedural agreements.

Skeletal Muscle Biopsy

Skeletal Muscle Biopsy will only be performed in a small number of participants. Muscle biopsy of vastus lateralis (quadriceps) or another appropriate muscle for sampling will be taken under local anaesthetic. An incision (approx. 5mm) will be made in the skin and a biopsy of muscle taken, using either a core needle biopsy device or forceps. A steristrip and bandage are then applied. Alternatively, a single stitch may be required. Muscle biopsies using this technique are well tolerated with minimal complications. There is a small risk of haematoma (bruising) and the site of biopsy will ache for about 24 hours. Participants are able to perform all normal tasks following biopsy. Patients on anticoagulants (e.g. Direct Oral Anticoagulants (DOACs), warfarin, clopidogrel, treatment dose heparin injection) will be precluded from biopsy. Aspirin and prophylactic dose of heparin are not contraindications for the procedure.

Regional MRI scan of the thighs

Measurement of muscle cross-sectional area will be taken. Quadriceps will be identified anatomically, based on distance from tendon/muscle interface and used as the outcome. Total thigh muscle cross-sectional area (in cm2), fat cross-sectional area (in cm2) and muscle quality will also be collected.

Breathing Patterns using the RESPECK Wearable Device:

This optional sub-study will be assessing artificial intelligence/machine learning algorithm technology using the Respeck device which will enable us to describe breathing pattern in people perceiving breathlessness, identify causes of dysregulated breathing and develop an algorithm to be used in clinical care to better support self-management at home to increase physical activity using a personalised approach to avoid post-exertional symptom exacerbation (PESE). COPD patients who have been admitted to the Glenfield hospital who have suffered an exacerbation will be recruited in order to study breathing patterns during the recovery period.

Participants will attend the research unit or undergo bedside assessments within their inpatient ward and will be provided with the Respeck wearable sensor device and asked to wear it until 30 days following hospital discharge (one occasion). The Respeck device is a non-CE marked device, and is a simple wearable device that is worn as a plaster on the chest (lower left costal margin) for recording respiratory rate and respiratory flow/effort, intensity and type of physical activities and cough/speech episodes. Participants will also be provided with a mobile device to enable data from the device to be

communicated wirelessly over Bluetooth to the mobile application. The tri-axial accelerometer and gyroscope data from the Respeck device are communicated wirelessly over Bluetooth to a mobile application for processing and onward transmission to a server in GoogleCloud. Each sensor reading is tagged with a time-stamp which is encrypted when stored on the phone and communicated to the server. All data on the server is anonymised with a unique study ID, ensuring no personal information is stored. Participants will be provided with instructions on the device. At the end of the monitoring period, participants will be asked to return in person to the research unit to return the device and undergo pulmonary function testing (PFT). These measurements will provide objective assessments of lung function that can be linked with the wearable-derived respiratory data collected during the preceding monitoring period.

When the participant attends the research unit to provide consent, they will also be asked to complete the following questionnaires:

1. eMRC dyspnoea score
2. General Anxiety Disorder 7 (GAD-7) Questionnaire
3. Patient Health Questionnaire-8 (PHQ-8)

In addition, participants will be asked to complete the COPD Assessment Test (CAT) regularly during the monitoring period using the mobile phone provided. Participants will be encouraged to complete the CAT questionnaire at least 3–4 times per week throughout the 30-day post discharge monitoring period. This will allow temporal comparison between self-reported respiratory symptom burden and wearable-derived respiratory measurements.

Participants who are pregnant will not be eligible for the Respeck device, since pregnancy can affect breathing patterns. Participants will be asked if they are pregnant prior to consent.

Data handling and record keeping will be in accordance to the CHESTY study procedures. All study data will be inputted onto paper CRFs and transcribed onto REDCap alongside the Main CHESTY study data. Clinical paperwork will be filled in the medical notes as is standard practice.

The special category data from the from the Respeck device will be transferred to the Centre for Speckled Computing at the University of Edinburgh.

8.4 Subsequent Assessments

All participants:

Subsequent assessments are described in section 6.1. These will take place annually for 3 years. Study assessments including sampling similar to those performed at the acute phase visit can be repeated. Participants are allowed to opt out of any or all assessments in these follow up visits.

Hospitalised participants:

Participants recruited following an acute admission to hospital will be invited to attend up to three optional follow up visits within 1 year from hospital discharge. In addition, participants recruited as outpatients who are subsequently hospitalised during their 36 months follow up will be invited to undergo both an optional acute admission visit and invited to attend up to three optional follow up visits within 1 year from hospital discharge. Study assessments including sampling similar to those performed at the acute phase visit can be repeated. The participants are allowed to opt out of any or all assessments in these follow up visits. Remote data collection will be completed for all hospitalised patients 12 months after discharge using primary and secondary healthcare records, participants are not required to attend a face to face or telephone visit. In case of hospital readmission, participants may be asked to undergo an optional similar set of assessments performed at the acute phase visit.

Final visit:

The final visit will occur at either 36 months post recruitment or 12 months following discharge if admitted to hospital between 24- and 36-months following recruitment. The longest duration of follow up will therefore be 48 months.

8.5 Definition of End of Study

The end of study is 18 months following the final data capture.

8.6 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time and does not need to provide a reason. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation

- An adverse event which requires discontinuation of the study or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study or results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

Participants can still be included in the study if no follow up visits occur, as this will not affect primary outcome of the study. If a subject withdraws informed consent then the information and research samples collected up until that point may still be used in the study and may still be shared with academic and industry partners.

The reason for withdrawal will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.7 Storage and analysis of research sample

Research samples will be collected as detailed in section 6.3. Full requirements for research sample collection and storage are detailed in the study laboratory manual provided with the Investigator Site File. A full chain of custody will be maintained for all samples throughout their lifecycle. The Chief Investigator will keep full traceability of collected biological samples from the subjects whilst in storage.

Routine blood samples will be processed by the University Hospitals of Leicester NHS Trust central pathology labs and will be collected at room temperature from the study site. These samples will likely be taken as part of routine care at the acute phase visit during the index admission but will be considered research samples at any follow up visits. These samples are not stored for the purposes of the study and are either used or destroyed during the testing process. The results of these blood tests will be printed and stored within the Case Report Form (CRF), as well as uploaded into the database.

All research samples will be stored within the NIHR Leicester BRC – Respiratory, the clinical sciences wing laboratories at University of Leicester, or within the College of Life Sciences at the University of Leicester for the duration of the study and will be transferred to a registered research tissue bank after the completion of the study. Either the NIHR Leicester BRC Respiratory Tissue Bank (17/EM/0231) or the MuscLe, heArt aNd metaboliC hEalth in people with Long-term cOndiTions (LANCELOT RTB) Research Tissue Bank (REC: 22/WA/0348 IRAS: 318250) both at the Glenfield

Hospital, Leicester. All samples are stored in accordance with the Human Tissue Act 2014. The informed consent form relating to that sample will be retained for the lifetime of that sample to provide evidence of participant consent for the use and storage of that sample. If samples are destroyed, any sample disposal will be according to local laboratory procedures.

During the lifetime of the study or after samples are transferred to the Respiratory Research Tissue Bank, pseudonymised research samples and data may be transferred to external academic and or industry collaborators including outside the UK for further analysis. Any export of research data or samples will be performed after completion of appropriate materials transfer agreement.

The following samples will be processed and analysed by the research team at the NIHR Leicester BRC - Respiratory and the clinical sciences wing laboratories at University of Leicester to answer secondary and exploratory outcomes and for future ethically approved research and retained until they are used up;

- Throat & Nasal swab (including Viral PCR)
- Urine sample
- Sputum sample
- Blood samples including:
    - FBC [i.e. viable leukocytes]
    - Serum and plasma samples
    - Samples for genetic analysis (DNA and RNA)
- Breath Volatile Organic Compounds (VOC) sampling
- Skeletal Muscle Biopsy

Any samples that would be classed as potentially hazardous should be packaged, stored and transported in accordance with UoL Health and Safety, Hazardous substance policy https://uniofleicester.sharepoint.com/sites/staff/health-safety/SitePages/Policy-and-Procedure.aspx.

9. CATALINA SUB-STUDY 1

Title of the study: The CATALINA sub-study 1 **Delivery of an international multi-centre prospective cohort study in patients hospitalized for an acute exacerbation of COPD within the CHESTY study**	
Funding and support: **Funding Partners:**	**Clinical Research Collaboration (CRC) under the umbrella of the European Respiratory Society (ERS) with Funding Partners providing financial support** **AstraZeneca UK Limited (Cambridge, UK)** **F. Hoffmann-La Roche Limited (Basel, Zwitserland)** **GlaxoSmithKline Biologicals SA (Rixensart, Belgium)**
Study design:	**An academic international multi-centre prospective cohort study**
Study duration:	**Longitudinal follow-up of 1 year**
Indication:	**Chronic Obstructive Pulmonary Disease (COPD)**
Study population: **Main criteria for inclusion:** **Main criteria for exclusion:**	**Adult males and females with COPD** • Age 18 years and older • New or prior diagnosis of COPD by medical doctor (based on clinical history and pulmonary function test with an FEV1/FVC < 0.7) • Current hospitalization with suspicion of an acute exacerbation of COPD (AECOPD) • Inclusion within 48 hours post hospital admission • Patients unwilling or unable to comply with study procedures • Patients not requiring treatment with systemic corticosteroids and/or antibiotics as a minimum therapy for the index AECOPD • Patients with a confirmed positive test result for COVID19 within 2 week period before hospital admission
Study objective:	**Collection of high-quality longitudinal clinical data and bio-samples:** • Data from standard care • Centre-specific data • Bio-samples (blood, sputum, nasal swab, urine)
Study visits (V): **Unscheduled visits (UV):**	**Day 0 – hospital admission for the index AECOPD** **V1 – Day 1 – obtain informed consent within 48 hours of admission** **V2 – Day 4 – at 72 hours after consent or earlier if discharged** **V3 – Day X – discharge (only if ≥6 days in hospital)** **V4 – Day 90 – at 3 months from study inclusion** **V5 – Day 180 – at 6 months from study inclusion** **V6 – Day 365 – at 12 months from study inclusion** **First readmission for respiratory reasons after the index event:** **UV1 – Repeat V1 assessments** **UV2 – Repeat V2 assessments** **UV3 – Repeat V3 assessments**
General objectives:	• To generate high-quality longitudinal clinical data (incl. biological samples) • covering an international real-life population of patients with COPD, hospitalized for an exacerbation, in all age groups and stages of disease severity

	• To establish standard operating procedures for sample collection, processing and local bio-banking • To determine phenotypes of exacerbations, identify biomarkers and treatable traits; and explore how these relate to known exacerbation phenotypes • To better understand the natural history and prognosis of COPD in patients experiencing severe exacerbations with the aim of creating and validating prognostic tools to support medical decision making • To cultivate the development of a phenotyped COPD patient database in relation to the type of exacerbation for future trial cohorts • To serve as an exploratory dataset to design future interventions studies for specific patient subgroups	
Study endpoints: ***(among others)***	**Primary endpoint:** • All-cause mortality **Key secondary endpoints:** • Hospital care intensification from baseline • Readmission for a severe AECOPD within 30 and 90 days **Additional secondary endpoints:** • Mortality from COPD exacerbation • (Severe) treatment failure within 30 and 90 days • Change or implementation of a do-not-resuscitate order • Cumulative use of systemic corticosteroids • Change in lung function • Change in PROM and PREM scores • New or worsening comorbidities following the index exacerbation • Trajectories of inflammatory and other biomarkers **Endpoints will be evaluated at different study visits, as considered applicable, and may be evaluated over time in terms of 'total days' and 'time-to'.**	
Planned cohort:	**A total of 1000 patients within a 4 years enrolment period, with completed 1-year follow-up in the subsequent year**	
Cohort justification:	**Based on previous clinical research experience, it is anticipated that each centre will be recruiting 25-40 patients per year, resulting in a cohort between 250-400 patients at the end of the first phase with 11 participating centres; and ≥ 570 patients by the end of the first lifecycle of CICERO with up to a maximum of 25 participating centres in phase 2**	
Timelines:	**CICERO's first lifecycle** **CATALINA study recruitment (UK)** **CATALINA study 1-year follow-up** **CATALINA study data cleaning and analysis** **CATALINA end of study**	**2022 – 2032** **Aug/2025 – Apr/2027** **Apr/2027 – Apr/2028** Apr/2028 – Apr/2032 **Apr/2032**

9.1 Background

Marcus Tullius Cicero was a famous Roman (b. 106 BC) with enterprise in politics, philosophy and oration. Cicero was recognised as a forefather of modernising Latin and Latin prose, and for providing the building blocks of many European languages. His most famous of work De Officis was the second book to be printed in Europe after the Gutenberg Bible (c1455), establishing his relevance to both the European and global community. One of Cicero's most famous quotes is "Quousque tandem abutere, patientia nostra" said to Lucius Sergius Catilina (b. 108 BC) upon exposure of the plot to overthrow Rome (c. 63 BC). "When do you mean to stop abusing our patience", the translation of Cicero's most famous quote, is highly relevant when pointing to the necessity and urgency of this new Clinical Research Collaboration (CRC):

The Collaboration In COPD ExaceRbatiOns (CICERO)

Despite almost 23 million patients living with chronic obstructive pulmonary disease (COPD) in Europe today, morbidity and mortality associated with the disease remains unacceptably high. Outcomes following an exacerbation of COPD have not changed for many decades and, in Europe, COPD accounts for more than 1.1 million hospital admissions annually, with an estimated mortality of more than 10% within 3 months post admission. The majority of current and guideline approved interventions have focused on the prevention of exacerbations, but the acute crisis itself has been left understudied. In the case of a severe event, often leading to hospital admission, there is real deficiency of data. Healthcare practitioners and patients struggle to define the event, there are no recommendations on what to do with regard to characterising or monitoring when it occurs, and we are left with recommendations of acute treatments that have not changed for approximately four decades. Our patients tell us that there is a "need to improve the management of exacerbations, which even beyond the physical experience are disturbing and very painful…" (ELF COPD patient). This indicates an urgent need for a better understanding of exacerbations and standardised hospital-based procedures to improve the outcomes of COPD patients with severe exacerbations, at the time of the event and in the follow-up period. The need is thus high to redefine priorities and to overcome the main barriers to fighting against COPD.

The CICERO CRC has the overarching aim to understand and improve outcomes in severe COPD exacerbations across Europe, asking, as Cicero did, "When will our patience for drastic improvements be stopped?". Central to the improved management of COPD exacerbations, is the standardisation of diagnosis, available diagnostics and treatment allocation, with stringent aims to the reduction in post-exacerbation readmission. However, access to large patient cohorts is required to do so and cannot

be addressed solely at an individual country level. CICERO will develop and internationally expand a network of expert centres, which can operate with standardised protocols and collect clinical, functional and imaging data alongside repeated bio-sampling during and after hospital admission for an exacerbation of COPD.

The CATALINA study, a prospective cohort study initiated by the CICERO CRC, has been designed to collect standardised, longitudinal clinical data and biological samples in 20 centres; and aims to recruit up to 1000 patients hospitalised for an acute COPD exacerbation by the end of CICERO's first lifecycle, with a 1 year follow-up data in the following year. Ultimately, the study intends to serve as an exploratory dataset to design future intervention studies for specific patient subgroups.

9.2 CATALINA Sub-study 1 rationale

What is the problem?

Different COPD audits across Europe have highlighted a huge heterogeneity in the management of acute exacerbations of COPD requiring hospitalization and its outcomes. Differences in resources and an insufficient understanding of the complexity of the sentinel COPD exacerbation event are at the origin of the problem.

What are the unmet needs?

Many studies have focused on the prevention of exacerbations, but little attention has gone to the management, follow-up and readmission of these most critical events. According to the recent European COPD audit, severe exacerbations have a 5% in-hospital mortality increasing to more than 11% within 3 months post admission and more than 20% at one year.

To alleviate the enormous burden of COPD exacerbations, the scientific field has to focus on exacerbations, particularly hospitalised and severe events, trying to understand both risk factors and the underlying mechanisms that lead to the acute manifestation of a COPD exacerbation. This could pave the way to identify novel and potential targets of intervention; develop approaches to predict outcomes and methods to improve associated morbidity.

Why do we need a CRC for (hospitalised) COPD exacerbations?

COPD exacerbations are complex events that are poorly defined and loosely managed. We need detailed phenotypic characterisation, assessment of potential comorbid conditions that mimic exacerbations, biomarkers to guide standardised interventions, prognostication tools, and dedicated follow-up.

Notwithstanding the importance of non-hospitalised events, the focus of the CRC will be on hospital admission as index event in this primary phase. Hospitalised exacerbations are not only key from a clinical and health economic perspective but can provide the optimal setting for accurate data collection and the study of new interventions and delivery of unified multi-centre clinical trials.

By initiating the CATALINA study, the CICERO CRC is focussing on a standardised set of high-quality data in centres with expertise and infrastructure, in addition to internationally increasing the development of such additional centres. This will enable a group of experienced international researchers to answer fundamental questions about epidemiology, genetics, pathophysiology, clinical management and prognosis of COPD. CICERO has no ambition to provide population-based data on current practice (audit) but seeks to better understand, innovatively treat and standardise exacerbations of COPD across Europe and beyond.

9.3 CATALINA Sub-study 1 objectives and outcome measures/timepoints

9.3.1 Objectives

The CATALINA study objectives are:

- To generate high-quality longitudinal clinical data (incl. biological samples) covering an international real-life population of patients with COPD, hospitalized for an exacerbation, in all age groups and stages of disease severity
- To establish standard operating procedures for sample collection, processing and local bio-banking
- To determine phenotypes of exacerbations, identify biomarkers and treatable traits; and explore how these relate to known exacerbation phenotypes
- To better understand the natural history and prognosis of COPD in patients experiencing severe exacerbations, with the aim of creating and validating prognostic tools to support medical decision making
- To cultivate the development of a phenotyped COPD patient database in relation to the type of exacerbation for future trial cohorts
- To serve as an exploratory dataset to design future interventions studies for specific patient subgroups

9.3.2 Outcome measures

Main outcome parameters (among others) will include:

Primary endpoint:	All-cause mortality
Key secondary endpoints:	Hospital care intensification Readmission for a severe AECOPD within 30 and 90 days
Other secondary endpoints:	Mortality for AECOPD (Severe) treatment failure within 30 and 90 days Change or implementation of a do-not-resuscitate order Cumulative use of systemic corticosteroids Change in lung function Change in PROM and PREM New or worsening comorbidities following the index event Trajectories of inflammatory and or other biomarkers

Endpoints may additionally be evaluated over time, in term of 'total days' (e.g., in hospital/healthcare utilization/…) and 'time-to' (e.g., death/readmission/(severe) treatment failure/…).

Hospital care intensification includes requirement of (non-)invasive respiratory therapy and physiological support with inotropes.

As multiple clinical interventions may indicate that an initiated therapy is failing, treatment failure is defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics for respiratory reasons, step-up in hospital care or readmission, and all-cause mortality; and is further specified for the hospitalization period of the index event and the follow-up period after discharge in the table below. As drug regimens and treatment intensifications are region-specific and are not always related to failure of disease control, severe treatment failure will be defined as the composite of step-up in hospital care and mortality.

Table 3: CATALINA Treatment Failure
Treatment failure

During hospitalization of the index event day 1 to day X	After hospital discharge day X to day 365
Treatment intensification for respiratory reasons (TI)	
Prolongation of systemic corticosteroids >5 days Upgrade of antibiotics*	New course of systemic corticosteroids New course of antibiotics
Step-up in hospital care or readmission for respiratory reasons (SH)	
Hospital care intensification**	Hospital care intensification Readmission
All-cause mortality	

Table legend:
*Change or narrowing of the initial antibiotics given as part of the standardized acute treatment during the index event – *consisting of 5 days of fixed dose systemic corticosteroids and 5 of antibiotics* (as per local guidelines) – based on proven bacterial cultures is not to be considered as treatment failure, but as good clinical practice.
**Hospital care intensification includes requirement of (non-)invasive respiratory therapy and physiological support with inotropes
Note: day 1: study inclusion; day X: day of discharge, at the investigator's discretion; day 365: end of follow-up.

9.4 CATALINA Sub-study 1 design

The CATALINA study is designed to be embedded in a real-life hospitalisation setting following a severe acute exacerbation of COPD. As such, the study visits have been scheduled to coincide with clinical routine practice following the hospital admission and data will be mainly collected from clinical routine assessments, with the exception of the study-specific bio-sample collection and centre-specific tests.

9.5 CATALINA Sub-study 1 setting

The CATALINA sub-study will be delivered in NHS hospitals with experience of treating patient with COPD and of conducting clinical research. Specific study assessments will be completed alongside clinical care wherever possible to reduce the burden and inconvenience on participants.

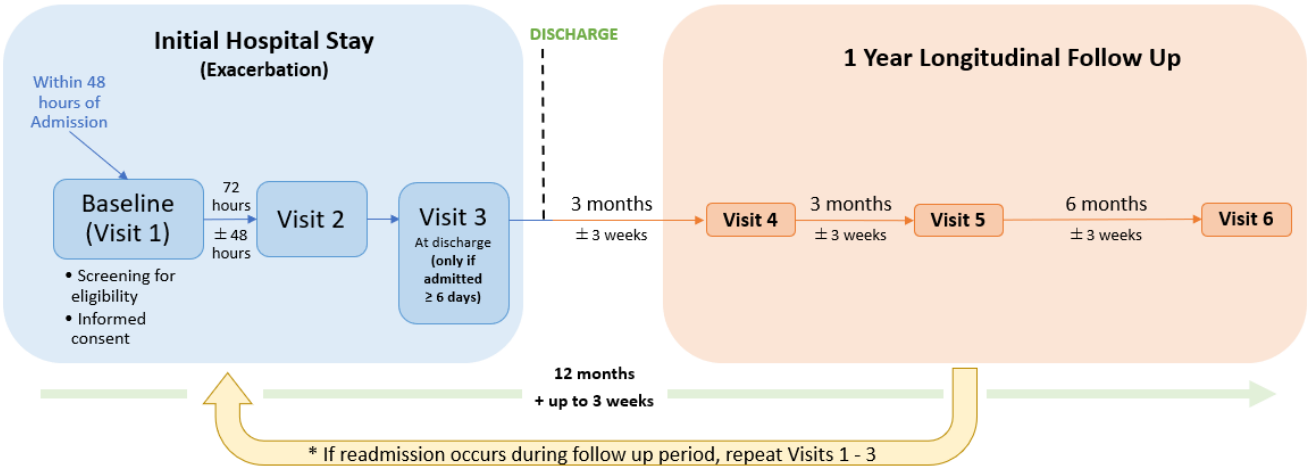


Figure 2: Flowchart of Catalina sub-study design

9.6 CATALINA Sub-study 1 participant eligibility criteria

Inclusion criteria:

1. Age 18 years and older
2. New or prior diagnosis of COPD by medical doctor (based on clinical history and pulmonary function test with an FEV1/FVC < 0.7)
3. Current hospitalization with suspicion of an acute exacerbation of COPD (AECOPD)
4. Inclusion within 48 hours post hospital admission
5. Voluntary written informed consent of the participant or his/her legally authorized representative obtained prior to any study procedure

Exclusion criteria:

1. Patients unwilling or unable to comply with study procedures
2. Patients not requiring treatment with systemic corticosteroids, antibiotics or both as a minimum therapy for the index AECOPD
3. Patients with a confirmed positive test result for COVID19 within a 2-week period before hospital admission.

9.7 CATALINA Sub-study 1 procedures

9.7.1 Recruitment

One of the inclusion criteria is to obtain written informed consent within 48 hours from hospital admission. Information obtained during routine assessment on emergencies and available in the patient's medical records enable eligibility screening for participation in the study. Eligible participants may be approached in the emergency department, the hospital ward and on the intensive care unit – with respect for and prioritising the patient's clinical and personal needs at all times.

Potential participants may only be approached, consented and enrolled in the study by members of the local study team comprised of staff members of the participating centre. Depending on the patient's clinical status and wishes, information about study participation can be provided verbally in person and/or by handing a Summary Participant Information Sheet, providing a one-page study summary in layman's terms. To those who are interested in taking part in the study, a copy of the Long Participant Information Sheet will also be provided, as well as sufficient time to consider participation, ask questions and discuss with family/friends. Following the decision to participate, written informed consent will then be obtained by means of the participant's dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be a member of the local study team, suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original consent form will be filed in the Investigator Site File and a note on study participation filed in the patient's medical records.

Personal data of the CATALINA sub-study participant will be pseudonymised (i.e., encoded by a unique 7-digit identification number) and processed securely, accurately and in accordance with data protection principles. Personal data in electronic format, will need to be stored on computers/laptops only accessible by staff members of that participating centre with the appropriate delegation. Personal data in manual files, will need to be stored in locked filing cabinets, cupboards and/or rooms only accessible by staff members of that participating centre with the appropriate delegation.

9.7.2 Consent

Specific CATALINA sub-study consent will be obtained from participants participating in this sub-study. This may be in addition to or in place of consent to the CHESTY study. Consent to the CHESTY study on its own will not be considered consent to participate in the CATALINA sub-study.

CATALINA sub-study consent will be obtained following the process described in section 8.1.

9.7.3 Early study discontinuation

Participants may at any time without reason and without any penalty choose to either (1) stop their CATALINA sub-study participation, or to (2) withdraw their consent for the processing of their personal data, and consequently stop their CATALINA sub-study participation. The participant's request must always be respected without prejudice or consequence to further treatment. As a

result, all CATALINA sub-study-related visits and assessments will be stopped, and no new clinical data or biological samples will be sent to the Sponsor. In such case the investigator must make a reasonable effort to contact the participant (e.g., via telephone, e-mail, letter) in order to document the primary reason for this decision. The investigator must also take into account the consequences of the participant's specific request with regards to the: (1) further use of personal data/study data, (2) use of human biological materials already collected, (3) safe transition to alternative treatment options, etc. as applicable below.

The investigator may also decide at any time during the course of the CATALINA sub-study, to temporarily interrupt or permanently discontinue the study if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Similarly, the Sponsor, Ethics Committee or authorized regulatory authority can decide to halt or prematurely terminate the study when new information becomes available whereby the rights, safety and well-being of study participants can no longer be assured, when de integrity of the study has been compromised, or when the scientific value of the study becomes obsolete and/or unjustifiable.

Circumstances requiring early discontinuation of the CATALINA sub-study, include but are not limited to:

- Study participation while in violation of the inclusion and/or exclusion criteria
- Study participation while in violation of the scheduled study visits and assessments

Note: A COVID19 positive test result after patient enrolment is not a reason for study discontinuation.

Where a participant terminates and/or interrupts/discontinues study participation early, this will not affect the participants clinical care and the investigator will ensure adequate medical care and follow-up.

In case of early CATALINA sub-study discontinuation, the Sponsor may continue to retain and use the pseudonymised clinical data and biological samples already collected before the date of early CATALINA sub-study discontinuation, as well as any results from analysis.

If the participant's biological samples were already used or tested before the decision to stop their CATALINA sub-study participation, the Sponsor still has the right to use the results of those tests. Similarly, biological samples that were collected (but not yet tested) before the decision to stop participant's CATALINA sub-study participation, and the data obtained from them, may still be used by the Sponsor. The participant can ask for these samples to be destroyed. To avoid misinterpretation of study results, this may be delayed until the end of the study.

9.7.4 Withdrawal of consent

Participants may voluntarily choose to withdraw their consent for the processing of their personal data, and consequently stop their study participation, for any reason at any time. As a result, all study-related visits and assessments will be stopped, including the analyses of the collected pseudonymised clinical data and biological samples. No new clinical data or biological samples will be sent to the Sponsor, and those already collected before withdrawal will no longer be used. The participant's personal data already collected before withdrawal of consent will be retained to avoid misinterpretation of study results.

The participant's consent, early CATALINA sub-study discontinuation, and withdrawal of consent for the processing of their data are to be documented in the participant's medical records as well as the dedicated Consent Forms by means of the participant's dated signature and dated signature of a member of the local study team. This team member must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Consent Form will be given to the participant, and the original Forms are to be filed in the Investigator Site File.

For CATALINA sub-study participants whose status is unclear because they fail to appear for CATALINA sub-study visits without stating an intention to discontinue or withdraw, the investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the CATALINA sub-study participant to clarify their willingness and ability to continue their participation in the CATALINA sub-study (e.g. dates of telephone calls, registered letters, etc.). A CATALINA sub-study participant should not be considered lost to follow-up until due diligence has been completed.

9.7.5 CATALINA Sub-study 1 procedures and visit schedule

	Admission index AECOPD / First readmission			Follow-up		
CLINICAL ROUTINE	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time	Inclusion within 48 hours of admission	At 72 hours after consent or earlier if discharged	Discharge (only if ≥ 6d in hospital)	3 months from inclusion	6 months from inclusion	12 months from inclusion
Permitted window	N.A.	+ 48 hours	N.A.	± 3 weeks	± 3 weeks	± 3 weeks
Eligibility check and informed consent	✓					
Study endpoints		✓	✓	✓	✓	✓
Medical history	✓					
Demographics	✓		✓	✓	✓	✓
Clinical examination	✓	✓	✓	✓	✓	✓
Medication (current and past)	✓	✓	✓	✓	✓	✓
Scores (Charlson, CURB65, DECAF)	✓					
PROM and PREM questionnaires	✓	✓	✓	✓	✓	✓
Routine blood	✓	✓	✓	✓		✓
Nasopharyngeal swab (per local guidelines/on clinical indication only)	✓	✓	✓	✓	✓	✓
Blood gas**	✓					
Spontaneous sputum	✓		✓	✓		✓
Electrocardiogram*	✓					
Echocardiography**	✓ (if feasible)			✓		
Pre-bronchodilator spirometry**	✓			✓	✓	✓
Plethysmography and DLCO				✓		✓
6 minutes walking distance				✓		✓
Chest X ray**	✓					
CT scan of chest**	✓					

9.7.5.1 Visit schedule

		Admission index AECOPD / First readmission			Follow-up		
STUDY ASSESSMENTS		Visit 1	Visit 2	(Visit 3)	Visit 4	Visit 5	Visit 6
Time		Inclusion within 48 hours of admission	At 72 hours after consent or earlier if discharged	Discharge (only if ≥ 6d in hospital)	3 months from inclusion	6 months from inclusion	12 months from inclusion
Permitted window		N.A.	+ 48 hours	N.A.	± 3 weeks	± 3 weeks	± 3 weeks
SAMPLE COLLECTION FOR BIOBANK							
Serum-plasma		✓	✓	✓	✓	✓	✓
Spontaneous sputum		✓	✓				
Spontaneous or induced sputum					✓		✓
Nasopharyngeal swab for microbiome – virome		✓			✓		
Nasosorption (Hunt swab) for cytokine		✓	✓		✓		✓
Urine		✓	✓		✓		✓
CENTRE-SPECIFIC TESTS (optional)							
Physical activity					✓		✓
Quadriceps force			✓		✓		✓
Handgrip force			✓		✓		✓
FeNO			✓		✓	✓	✓
Forced Oscillometry Test			✓		✓	✓	✓
Breath analysis	ReCIVA breath sampler	✓	✓	✓	✓		
	Imec breath sampler	✓		✓	✓		

Abbreviations: CAT, COPD assessment test; CFS, clinical frailty scale; DLCO, diffusing capacity for CO; FeNO, fractional exhaled nitric oxide; GAD7, generalised anxiety disorder assessment-7; HCAHPS, hospital consumer assessment of healthcare providers and systems; mMRC, modified medical research council; N.A.: not applicable; NRS Scale, Numerical Rating Scale for Breathlessness; PHQ9, patient health questionnaire-9; PREM, patient reported experience measure; PROM, patient reported outcome measure.

Table legend

Visit 3 or discharge visit will only be performed if patient is hospitalised for at least 6 days, to gather all information from hospital admission. PROM includes the CAT, CFS, mMRC, NRS Scale, PHQ9, PROactive Survey, and GAD7 questionnaire; PREM includes the HCAHPS questionnaire.

Merged cells: assessment to be performed only once during any of the study visits.

**mandatory test at admission – only to be repeated on clinical indication*

***clinically recommended test – if not available, preferentially in the first 6 months of study. These tests will only be undertaken as part of routine clinical care. Data will be obtained from medical records.*

9.7.5.2 Study assessments

Routine clinical assessments

The routine clinical assessments, as indicated in the flowchart, will be performed (when applicable) with the institution's facilities, according to the manufacturer's instructions and the department's standard operating procedure(s).

The data generated from the following assessments will be recorded in, or print-outs will be added to the study worksheets as source documentation and entered in the eCRF:

Eligibility

Eligibility for study participation will be checked against the inclusion and exclusion criteria *(cfr. Section 9.6)*.

Study endpoints

Study endpoints *(cfr. Section 9.3.2)* will be verified against medical records.

Demographics

Patient demographics and medical history of COPD and comorbidities and medical history will be recorded.

Clinical examination

A comprehensive physical examination, including vital signs and a cardio-respiratory evaluation, performed by a medical doctor will be recorded.

Concomitant medication

Medication and treatment for COPD and comorbidities received during study participation *(i.e., from time of screening until last study visit)*, as well as prior to study enrolment for the severe acute exacerbation of COPD *(i.e., the index event)* will be recorded.

Predictors of mortality

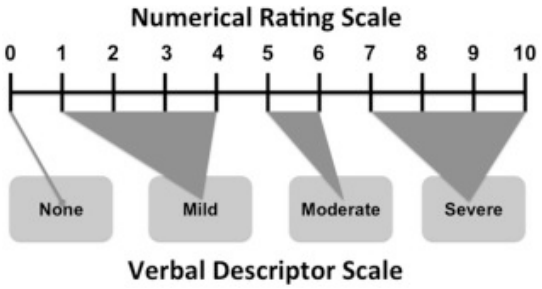
The Charlson Comorbidity Index, the CURB-65 Score and DECAF Score will be recorded.

Self-administered

The COPD Assessment Test (CAT), Clinical Frailty Scale (CFS), modified Medical Research Council questionnaires (mMRC), General Anxiety Disorder-7 (GAD7) and Patient Health Questionnaire-9 (PHQ-9) completed by the participant will be recorded as patient reported outcome measures (PROMs), in addition to the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) as a patient reported experience measure (PREM). Patients will also complete a 0-10 Numerical Rating Scale for Breathlessness

(NRS), anchored at 0 = not breathless at all and 10 = breathlessness as bad as you can imagine. Study personnel will check each questionnaire for completeness.

Figure 3 – Numerical Rating Scale



Routine blood sample

Analysis results obtained from blood sampling will be recorded.

Sputum sample, spontaneous or induced

Analysis results obtained from sputum sampling, either provided spontaneously or following induction when expectoration cannot be achieved without assistance, will be recorded.

Electrocardiogram (ECG)

Findings from a standard 12-lead resting ECG will be recorded.

Chest X-ray

Findings from a chest X-ray will be recorded.

Arterial blood gas

Arterial blood gas findings will be recorded, and should be performed (if tolerable) with the participant breathing room air. Whether or not the participant is receiving supplemental oxygen at the moment of collection, as well as the oxygen flow (in L/min) should be clearly documented.

Spirometry

The actual and percent predicted values obtained from a spirometry, performed pre and post-bronchodilator administration in accordance with ATS/ERS guidelines and patient's clinical need, will be recorded.

Plethysmography and DLCO

The actual and percent predicted values obtained from a body
plethysmography and diffusion capacity test, performed in accordance with ATS/ERS guidelines, will be recorded.

6-Minute Walk Test

The 6-Minute Walk Test performed in accordance with ATS/ERS guidelines will be recorded. The participant should complete all tests, if applicable, using the same amount of supplemental oxygen throughout study participation unless this poses a risk to the participant. Participants without prior experience should perform a practice walk prior to the actual test to eliminate variability due to any learning effects. To avoid bias due to exhaustion sufficient time to rest prior to the actual test must be provided to the participant.

Echocardiography

Echocardiography results will be recorded. The implementation of the CATALINA SOP is advised, if compatible with local regulation, to maximally standardize data collection within the Consortium.

Chest CT-scan

Findings of a full chest low-dose high resolution computed tomography (HRCT) will be recorded. The implementation of the CATALINA SOP is advised, if compatible with local regulation, to maximally standardize data collection within the Consortium.

If the CT-scan cannot be performed within the first 3 months of study participation (+ 3-month window allowed), a historical CT-scan taken up to 12 months before study enrolment can be used. The raw pseudonymised imaging data will be centrally collected for future research purposes.

Study-specific assessments

Sample collection for biobank

The study-specific assessments for the generation of the CATALINA biobank through sample collection, as indicated in the flowchart, will be performed using locally available and suitable equipment, according to the CATALINA study-specific operating procedure(s). Instructions on sample collection, processing and storage in the local biobank are available in the Biobanking Manual. The pseudonymised samples will be centrally collected at the end of the study for batch analysis. The centralized biobank, and as such shipping details, are yet to be determined.

Sample details (such as availability, date of collection and volume) will be recorded in the study worksheets as source documentation and entered in the eCRF:

Blood sample

Blood samples will be obtained via venipuncture for serum and plasma analysis.

Sputum sample

Sputum samples will be obtained following spontaneous expectoration or sputum induction.

Nasopharyngeal swab

Specimens will be obtained by swabbing the nasopharyngeal mucosa.

Urine sample

Mid-stream urine samples will be requested from the study participant.

Study-specific assessments - Centre-specific tests

Integrated in the CATALINA study are a number of tests to further enrich the database, optional for all centres in the Consortium willing to participate to ensure local feasibility. These centre-specific tests will be performed using locally available and suitable equipment, or alternatively as advised, according to the CATALINA study-specific operating procedure(s).

The data generated from the following assessments will be recorded in, or print-outs will be added to the study worksheets as source documentation and entered in the eCRF:

Physical activity

The study participant's physical activity level will be tracked using a portable validated activity monitor. Physical activity is strongly reduced during exacerbations and failure to increase physical activity is associated with relapse. The physical activity monitor will also be accompanied by a survey on their physical activity, the PROactive questionnaire.

Peripheral muscle strength

Peripheral muscle strength will be tracked by measuring isometric maximum voluntary contractions of the hand and quadriceps, consisting of maximal muscle contractions conducted against a resistance at a fixed joint angle. Peripheral muscle weakness presents negative and important clinical implications (such as reduction in exercise tolerance, quality of life and survival), and is an important target of comprehensive COPD management.

Handgrip strength

Hand grip strength will be measured using a handheld dynometer.

Quadriceps strength

Quadriceps strength will be measured using a seated strain gauge.

FeNO measurement

Measurement of fractional nitric oxide (NO) concentration in exhaled breath is a non-invasive method to measure airway inflammation. The NO fraction is measured during a slow, controlled exhalation through the mouthpiece of a breath analysis device.

Forced oscillometry test (FOT)

FOT is a non-invasive method to measure respiratory mechanics, by superimposing small-amplitude pressure oscillations on the normal breathing through the mouthpiece of a FOT device. By measuring the magnitude of change in the pressure and flow, mechanical properties of the lung can be determined. Waves of lower frequencies travel deep into lungs until the alveoli, while those of higher frequencies are reflected from the larger airways. Consequently, variables calculated at different frequencies facilitates the characterization of different regions in the lungs.

Breathomics (breath sampling)

Breathomics is a non-invasive method to analyse in breath samples exhaled (1) volatiles (volatile organic compounds, VOC analysis) and (2) non-volatiles, which are either analysed in exhaled breath condensate (EBC analysis) or directly as exhaled particles (PEx analysis). Breath samples will be collected for:

VOC analysis using the ReCIVA breath sampler (Owlstone, Cambridge, UK) following the manufacturer's standard operating procedures.

9.8 CATALINA Sub-study 1 statistics and data analysis

The following data handling and Statistical Analysis Plans (SAP) will be performed on the completed data collection of the Full Analysis Set *(i.e., ideally 1000 patients across the CATALINA study, or the actual number determined by enrolment success and available funding)*:

While the study is ongoing:

- To ensure the access to high-quality raw data at the end of the study, data quality checks will be conducted every 6 months
- To allow for advances in knowledge and statistical methods during the study resulting from 2 interim (I) SAPs:
    - I-SAP 1: covering the index hospitalization period, focusing on baseline data (including study visits 1, 2 and 3 - at 48h of hospital admission, day 3 and day of discharge)
    - I-SAP 2: covering the 3-month data, focusing on readmission risk and secondary endpoints (including visit 4 and unscheduled visits 1, 2 and 3 - at 3 months after study inclusion)

The generated findings will be used to (1) ensure access to a comprehensive and scientifically up-to-date dataset at the end of the study enabling its primary objective to be achieved *(i.e., phenotyping severe COPD exacerbations)*, (2) keep the respiratory field up-to-date through (inter)national Congress presentations of

the I-SAP findings, which will also (3) motivate current and future CRC members to participate and to expand the European Consortium of clinical research centres and investigators, industry partners and patient organizations.

At the end of the study:

The planned analyses (which will be *a priori* outlined in a Final Statistical Analysis Plan (F-SAP), finalized based on the findings generated by I-SAP1 and I-SAP2, and posted on ClinicalTrials.gov) will be performed:

- **F-SAP:** covering 6 and 12-month data, focusing on primary and secondary endpoints *(including visits 5, 6 and unscheduled visits 1, 2 and 3 - at 6 and 12 months)*

As such, each SAP would only be performed once, on the completed data collection of the Full Analysis Set.

9.9 CATALINA Sub-study 1 data management

9.9.1 Data Collection

Source Data will be collected and recorded in the study participant's files/medical records.

CATALINA study worksheets will be provided and may be used for capturing some specific data in order to facilitate completion of the electronic case report form (eCRF). Any such worksheets will become part of the study participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the study).

It remains the responsibility of the investigator to check that all data relating to the study, as specified in the study protocol, are entered into the eCRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

An eCRF will be made available by the Sponsor for each study participant. The study data will be transcribed from the source records (i.e. participant's medical file or study-specific source data worksheets) into the eCRF by study staff. Transcription to the eCRF will be done as soon as possible after a study visit and in a pseudonymized manner using a unique identifier.

The eCRFs will be available for review at the next scheduled monitoring visit (as applicable).

9.9.2 eCRF Development

An eCRF for data capture has been developed by Imperial College London (UK) using REDCap (IRAS project ID 301381), a browser-based software and workflow methodology for clinical and translational research database development. The collected data will be safely stored within an ISO27001 secure environment at Imperial College London. Imperial College London is cognisant of and compliant with all current data

protection and information security legislation, are internationally recognized, and have formal ISO27001 and UK Statistics Authority accreditation.

Imperial College London will host, develop the front-end interface and various back-end follow-up tools, database architecture and back-up services. Throughout the entire study, Imperial College London will actively participate in the process of data management and export, and will also handle the maintenance, updating and expansion of the web application and server. The eCRF will be accessible at all sites with password protection. It will encompass pseudonymized data of the enrolled patients' process, outcome and bio-sample parameters.

9.9.3 Data Validation

All data relating to the study must be prepared and validated by the investigator. Any eCRF entries, corrections and alterations must be made by the investigator or other authorized study staff.

It is the local investigator and designated staff's responsibility to ensure adequate source documentation for all collected data and bio-samples, and for their correct and complete input into the eCRF; which will be monitored remotely by the CICERO data manager. Particular attention will go to the monitoring of the outcome parameters. The database will also be checked for outliers after recruitment has completed. These outliers will be linked to the original on-site source documents for revision via queries to the local study teams. On-site monitoring is not feasible within the current funding budget, but may be reconsidered in the future. The investigator must certify the accuracy of the collected data and sign off on the final eCRF. After review for completeness, plausibility and correctness by the CICERO data manager, the data will be locked allowing statistical analyses to be performed according to the statistical analysis plan.

Proper audit trails must be available to demonstrate the validity of the study data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

9.9.4 CICERO Data Manager

The CICERO Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed.

9.9.5 Data Transfer

Any study participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the study-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the study must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (cfr 9..9.6 Legal Requirements).

9.9.6 Legal Requirements

All source data will be locally kept in a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Study staff whose responsibilities require access to personal data agree to keep the data confidential.

The investigator and the Participating Site(s) shall treat all information and data relating to the study disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the study as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The investigator will maintain all source documents and completed eCRFs that support the data collected from each study participant, and will maintain the Investigator Site File (ISF) containing all study documents as specified in ICH-GCP Chapter 8 entitled “Essential Documents for the Conduct of a Clinical Trial”, and as specified by applicable regulatory requirement(s).

The investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the study. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

Secondary use (i.e., sharing and further processing of the collected and pseudonymized personal data and bio-samples) for future, unspecified, scientific research purposes will be based on an explicit broad consent obtained from the study participant (or if applicable from their legal representatives) and in line with CICERO's Data and/or Materials Access Policy.

9.10 CATALINA Sub-study 1 monitoring, audit and inspection

9.10.1 Audits

The participating investigator will permit direct access to study data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such eCRFs, source records and other study related documentation (e.g. ISF, etc.) must be kept current, complete and accurate at all times.

9.10.2 Monitoring

In accordance with ICH-GCP E6(R2) the Sponsor is responsible for monitoring the study to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the study procedures have been followed as shown in the approved protocol, and that relevant study data have been collected and reported in a manner that assures data integrity. To this end source data will be compared with the data recorded in the eCRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the study will be performed by qualified individuals (independent from the site study staff), as applicable. The Sponsor and investigator/participating site will permit direct access to the study data and corresponding source data, and to any other study related documents or materials to verify the accuracy and completeness of the data collected. More details about the monitoring strategy will be described in a study specific Monitoring Plan (MP).

9.10.3 Archiving

As specified in ICH-GCP E6(R2) section 8.1 Addendum the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final eCRF and ISF). The Sponsor should ensure that the Investigator has control of and continuous access to the eCRF data reported to the Sponsor during the study.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the study.

The Sponsor is responsible for archiving study specific documentation (such as but not limited to the study protocol, any amendments thereto, the final Clinical Study Report (CSR) and the study database) according

to ICH-GCP E6(R2). Source data and site-specific study documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the study. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents will require written authorisation from the Sponsor.

9.11 Human biological material

Bio-samples collected during delivery of the CATALINA sub-study protocol include sputum, blood, urine and nasal swabs collected at fixed time-points and locally stored for future central analysis in line with UK and EU regulations and future material transfer agreements. These bio-samples will be used to measure biomarkers over time and for exploratory research to investigate variants associated with disease phenotypes that may reveal underlying endotypes. Standardized laboratory protocols have been developed for collection, handling, and storage of bio-samples, and all site staff will be trained in sample collection and handling (see Biobanking manual). Bio-samples will be stored locally and held for batched analysis, requiring shipment to a central repository (to be determined).

The bio-samples will only be used (1) for the purpose of this protocol or future approved protocols, (2) in line with applicable laws and regulations relating to the use of human biological samples for scientific research, and (3) in line with the informed consent of the study participant.

At all stages, the traceability will be guaranteed. Transfer of bio-samples will therefore be subject to a material transfer agreement.

9.12 CATALINA Sub-study 1 Ethical and regulatory considerations

Participation in the CATALINA sub-study involves additional visits, procedures, and data collection beyond the main CHESTY study, increasing the time commitment and potential burden on participants. To ensure informed and voluntary participation, patients will be given clear, separate information sheets and consent forms for each study, with dedicated time to discuss the differences. Patients may choose to participate in CATALINA without enrolling in CHESTY, and this will be made explicit during the consent process. The additional procedures in CATALINA, such as more frequent respiratory assessments and blood sampling, will be clearly explained. Unfortunately, due to the absence of translated materials and interpreter services, non-English speaking individuals will be excluded from participation, which may limit the diversity of the study population but is necessary to maintain ethical standards of informed consent.

9.13 CATALINA Sub-study 1 finance and insurance

To cover costs and efforts inherent to delivery of the CATALINA sub-study, local investigators will receive a one-time set-up fee and a fixed budget on a per-patient basis (specified in the Site Agreement) to relieve the administrative burden and to enhance patient enrolment. The CATALINA sub-study is funded as a Clinical Research Collaboration (CRC) under the umbrella of the European Respiratory Society (ERS, www.ersnet.org/ers-funding/clinical-research-collaboration.html), with industry partners providing financial support.

Insurance will be provided by University of Leicester and fall under the main CHESTY study policy.

9.14 CATALINA Sub-study 1 participant compensation

Participants enrolled in the CATALINA sub-study will be compensated with £77 following the completion of Study Visit 5 and £77 following the completion of Study Visit 6.

9.15 CATALINA Sub-study 1 dissemination policy

Dissemination and publication of results and analysis of data and samples collected as part of the CATALINA Sub-study will be governed by the CICERO Publication Policy. This document is available on request from the CATALINA trial managers.

10. SAFETY REPORTING

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE or adverse experience is: any untoward medical occurrence in a patient or clinical investigation participant, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses related to the study.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or

- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.1.5 Expected Serious Adverse Events/Reactions

The patients being studied are frail and have a high hospital readmission rate and mortality rate. Given this is an observational study and the rates that are expected we would reasonably expect that hospitalisation or death are not routinely reported as SAEs. Only SAEs related to study procedures will be reported. Deaths are to be reported ONLY for the CATALINA Sub-study 1 following UoL SOPs.

10.1.6 Suspected Unexpected Serious Adverse Reactions

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information

10.2 Reporting Procedures for All Adverse Events

Only AE's directly related to study procedures will be reported. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to a study procedure as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from the study (see section 8.6). A participant may also voluntarily withdraw from a procedure or the study due to what he or she perceives as an intolerable AE. If either of these occurs, the participant will be asked to undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

10.3 Reporting Procedures for Serious Adverse Events

All SAEs, except those expected ones defined in section 10.1.5 that do not require immediate reporting, must be reported to the Sponsor within 24 hours of discovery or notification of the event. If an SAE for the CATALINA sub-study 1, in addition notify CICERO. All SAEs must be reported using the appropriate reporting form and in accordance with the Sponsor SOP for processing and reporting SAEs. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form. The Principal Investigator or a delegate physician are responsible for the review and sign off of the SAE and the assessment of causality and expectedness. The Sponsor will perform an initial check of the information and ensure monthly line listings of all reported SAEs are reviewed by the Director of Research and Development.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

11. STATISTICS

11.1 Description of Statistical Methods

For the primary outcome for the Main CHESTY study, (readmission and mortality rate) regression analysis will be used. Time to event will be analysed using Cox regression or competing risk regression, depending on outcome and competing risks. Logistic regression analysis will be used when looking at risk at particular time points. Number of events will be measured based on likely Poisson distribution using a negative binomial analysis. Cut off for statistical significance will be taken at 95% confidence (i.e. p<= 0.05). Changes in outcome measures will be measured appropriate for each variable (e.g. paired t test, Mann-Whitney, repeated measures analysis). Other outcomes are exploratory and statistical analyses for these outcomes will be performed as appropriate for hypotheses derived in this exploration.

The primary analysis will be performed as an intention to treat analysis, stratified on diagnosis. Secondary analyses and exploratory analyses will be performed per-protocol.

11.2 The Number of Participants

This study plans to recruit up to 500 patients. There is no power calculation as it is an observational cohort study, but 500 patients should allow for factors influencing hospital readmission to be identified. There will be a small number of healthy controls for comparative measures.

11.3 Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data is not anticipated for the primary outcome, as hospitalisation data is collected routinely through hospital databases. Multiple imputation will be used for data where there is limited missing data and variability allows imputation. Other data will be excluded if missing and treated as per-protocol. For exploratory analyses only participants who have samples obtained will be used.

11.4 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan should be described and justified in any publication and/or in the final report, as appropriate. UoL SOPs will be followed to report protocol deviations, this includes the CATALINA sub-study.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures (SOPs). The University of Leicester operate a risk-based audit programme to which this study will be subject.

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

The study team will be responsible in ensuring the site files are maintained and conducting QC checks on the study data to ensure all data is complete and accurate.

13. CODES OF PRACTICE AND REGULATIONS

13.1 Ethics

The study will obtain ethical approval from an approved NHS Research Ethics Committee (REC) and will be registered on a the publicly accessible clincialtrials.gov database.

13.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines. Where applicable for study procedures and assessments local trust and Respiratory BRC SOPs will be adhered to.

13.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki.

13.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

13.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material or supporting documents will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and host institution(s) for written approval. The study will not start until Sponsor Green Light has been issued.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Copies of all approvals will be retained in the TMF.

13.6 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All the research samples will be labelled with the study name, initials, participants ID, visit number and the date of collection. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the General Data Protection Regulation (GDPR) and the Data Protection Act (2018) which requires data to be anonymised as soon as it is practical to do so.

14. DATA HANDLING AND RECORD KEEPING

All study documentation containing identifiable patient data will be managed in accordance with ICH GCP, the UK Policy Framework for Health and Social Care (2017), the Data Protection Act (2018) and the EU General Data Protection Regulation (GDPR).

Source Data is defined as the first place data is recorded, this will include:

- Medical Records
- Paper CRFs
- Laboratory Reports
- Printouts from equipment (i.e. spirometry)
- Participant reported outcome questionnaires
- Respeck wearable device data

Data collection tools will comprise of:

- Study Database (transcribed from CRFs) and direct source data entry
- Participant reported outcome questionnaires

Study data will be collected on a paper CRF labelled with the participant' initials and their study number only. Paper CRFs will be kept in locked offices at the Respiratory BRC, Glenfield Hospital, accessed only by the research team. Access to the offices within the research unit is restricted. All study data will be entered on a bespoke, secure electronic database (held in University of Leicester server). Access to this database is password protected and limited to the research members of the study.

The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file. A copy of the patient consent form and information sheet will be placed in the hospital notes of all participants and a copy of the signed informed consent form will be retained in the Investigator Site File.

All study visits summaries and AEs will be recorded in the hospital notes. Research data will be stored for six years after the study has ended. Long-term storage will comply with the University of Leicester archiving Standard Operating Procedure.

15. STUDY GOVERNANCE

15.1 Trial Management Group (TMG)

The Trial Management Group will comprise of both academic and clinical staff. The group will meet at least every twelve months and report back to the NIHR Leicester Respiratory BRC Scientific Committee. The TMG also be responsible for conducting the study, maintaining the study documents, co-ordinating study publications and analysis plans and schedule.

16. FINANCING AND INSURANCE

Research Costs

Funding of the study will be provided by the NIHR Post-Doctoral Fellowship Grant to the Chief Investigator (ref. PDF-2017-10-052), Sanofi Genzyme Research Grant to Dr Adam Wright.

NHS Treatment Costs

Participants will receive normal NHS care during their inpatient hospital stay and clinical follow up will be part of their normal clinical care.

NHS Support Costs

No addition costs to the NHS, beyond normal, usual clinical care are anticipated.

Indemnity will be provided through the University of Leicester for design and management of the study. Indemnity for conduct of the research will be provided by the NHS.

17. PUBLICATION POLICY

Industry and academic partners adopt the principal criteria for authorship eligibility which are detailed in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations Dec. 2019). Publication strategy will be agreed by the study TMG. The funders of the study will be acknowledged as appropriate.

18. REFERENCES

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