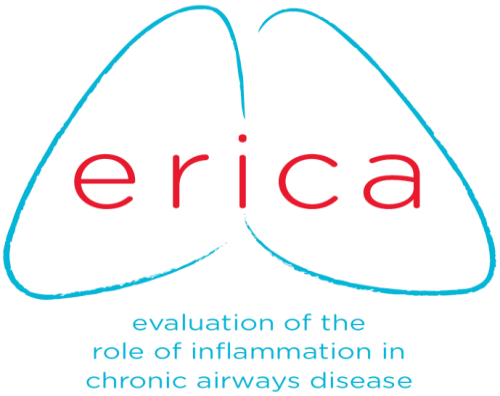


Study Title:	Evaluation of the Role of Inflammation in non pulmonary disease manifestations in Chronic Airways disease (COPD)
Protocol Number:	ERICA
REC Number:	11/EE/0357
Protocol Version and date:	1.1, dated 15 May 2012

Chief Investigator:	Dr Ian Wilkinson
CI Address:	Clinical Pharmacology Unit, Box 110 Addenbrooke's Hospital Hills Road Cambridge CB2 0QQ
Telephone:	01223 336086

Study Sponsor:	Cambridge University Hospitals NHS Foundation Trust & the University of Cambridge

1. TRIAL MANAGEMENT COMMITTEE AND PROTOCOL CONTRIBUTORS

Chief/Principal Investigator

Dr Ian Wilkinson

Honorary Consultant in Clinical Pharmacology

Clinical Co-Lead Investigator

Professor Michael Polkey

Principal Investigators

Dr Charlotte Bolton

Dr Jonathan Fuld

Professor William MacNee

Professor John Cockcroft

Professor Michael Polkey

Dr Ian Wilkinson

Collaborators

Dr Joseph Cheriyan

Dr Carmel McEniery

Professor David Menon

Professor Dennis Shale

Dr Ruth Tal-Singer

Professor David Lomas

Curtis Rambaran

Protocol Signatures

I give my approval for the attached protocol.

Chief Investigator

Name: Dr Ian Wilkinson

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

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

Principal Investigator

Name:

Signature: _____

Date: _____

TABLE OF CONTENTS

2. ABBREVIATIONS

COPD:	Chronic Obstructive Pulmonary Disease
SNIP:	Sniff Nasal Inspiratory Pressure
CV:	Cardiovascular
SOP:	Standard Operating Procedure
ICF:	Informed Consent Form
GP:	General Practitioner
HES:	Hospital Episode Statistics
MRIS:	Medical Research Information Services
PIS:	Patient Information Sheet
REC:	Research Ethic Committee
RBH:	Royal Brompton Hospital
TSB:	Technology Strategy Board
ERICA:	**E**valuation of the **R**ole of **I**nflammation In non-pulmonary disease manifestations in **C**hronic **A**irway disease
ATS	American Thoracic Society
CRF	Case Report Form
ECG	Echocardiogram
IMT	Intima-media Thickness

3. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

4. SYNOPSIS:

Study Title	Evaluation of the Role of Inflammation in non pulmonary disease manifestations in Chronic Airways disease (COPD)
Sponsor Reference	A092362
Study Design	Observational, non-interventional, Epidemiological Cohort study
Study Participants	Adult COPD patients
Planned Sample Size	Approximately 800
Follow-up duration	6 monthly up to two years. Registered with HES and MRIS for long-term follow-up.
Planned Study Period	October 2011 – October 2013
Aims	The overall aim of this study is to identify new biomarkers in patients with COPD in order to stratify risk or entry into future trials of novel interventions. We will conduct an epidemiological, cohort study to specifically address the following aims: a) To determine how effectively plasma fibrinogen predicts the CV and/or skeletal muscle manifestations of COPD b) To determine how other biomarkers predict the longer term outcomes including death, disability and hospital admission c) To investigate the extent to which subsets of COPD patients with cardiovascular or muscle manifestations overlap d) To investigate the extent of inter-relationships between clinical biomarkers for COPD
Outcome measures	This is an observational study assessing a range of different biomarkers. The ones of primary interest in powering the study are: • Plasma fibrinogen • Pulse Wave Velocity (PWV) • Quadriceps Maximum Voluntary Contraction (QMVC) The additional parameters that will also be assessed are Carotid IMT, spirometry, a range of plasma and urine biomarkers, questionnaire data concerning health symptoms, longer term health outcomes, hospital admissions, and physical functioning.

5. BACKGROUND

COPD is the fourth leading cause of death globally and the only major cause that is predicted to increase in the coming decades [1, 2]. Although COPD is initially a pulmonary disease (traditionally caused by cigarette smoke, but increasingly by biomass fuel exposure), it is a complex condition in which outcome is in large part driven by cardiovascular and systemic components. Indeed, COPD is increasingly being recognized as a heterogeneous condition, involving extra pulmonary manifestations including reduced fat-free mass, muscle dysfunction, exercise limitation and increased cardiovascular morbidity [3-7].

The role of inflammation in COPD is well-recognised. A range of inflammatory markers and cytokines are raised in COPD subjects, and relate to the severity of lung function and important clinical outcomes such as admission, cardiovascular events and death [8-10]. Elevated fibrinogen (indicating a systemic 'inflammatory' phenotype) is a robust, stable biomarker that occurs in at least 25% of patients with COPD, and is associated with increased morbidity and mortality[8]. Inflammation modulates large artery stiffness [11], an independent determinant of cardiovascular mortality [12], and anti-inflammatory therapies reduce arterial stiffness [11], providing a novel mechanism by which inflammation may drive cardiovascular risk. Inflammation is also thought to be related to muscle weakness [13, 14], which is found in a substantial minority of patients with COPD [3], and is associated with increased mortality [15]. Indeed, reduced performance on a 6-minute walk test is associated with an increased risk of both death and admission with acute exacerbation of COPD [4].

Despite the associations between inflammation *per se* and cardiovascular and muscle outcomes, there are sparse data on how fibrinogen maps to other clinically measurable, bed-side biomarkers that have a more intuitive, or proven relation to cardiovascular and muscular outcomes, such arterial stiffness (pulse wave velocity), muscle strength (quadriceps maximum voluntary contraction) and exercise capacity (6 minute walk). Moreover, given the heterogeneity of COPD, it is unlikely that all patients will present with both cardiovascular and muscle manifestations of the disease. Although there is evidence of 'cross talk' between cardiovascular and muscle aspects [16, 17], the extent to which these manifestations overlap in COPD patients is unknown. However, a better understanding of the interplay between inflammation, muscle and cardiovascular structure and function will clarify the degree to which distinct COPD 'sub-types' can be identified. This is likely to result in more appropriate tailoring of therapies to individual patients; personalised medicine in practice.

6. AIMS

The overall aim of this study is to identify new biomarkers in patients with COPD in order to stratify risk or entry into future trials of novel interventions.

We will conduct an epidemiological, cohort study to specifically address the following aims:

a) To determine how effectively plasma fibrinogen predicts the CV and/or skeletal muscle manifestations of COPD
b) To determine how other biomarkers predict the longer term outcomes including death, disability and hospital admission
c) To investigate the extent to which subsets of COPD patients with cardiovascular or muscle manifestations overlap
d) To investigate the extent of inter-relationships between clinical biomarkers for COPD

7. OUTCOME MEASURES:

This is an observational study assessing a range of different biomarkers. The ones of primary interest in powering the study are:

- Plasma fibrinogen
- Pulse Wave Velocity (PWV)
- Quadriceps Maximum Voluntary Contraction (QMVC)

The additional parameters that will be assessed are Carotid IMT, spirometry, a range of plasma and urine biomarkers, questionnaire data concerning health symptoms, longer term health outcomes, hospital admissions, and physical functioning.

8. STUDY DESIGN

Summary of study design

This will be a multi-centre, observational, cohort study of patients with COPD. Five UK centres with an interest in COPD are undertaking this observational study. Patients will be assessed at baseline and followed-up by questionnaire every 6 months for up to two years or longer if TSB extension funding can be secured. Patients will be registered for long-term health outcomes through HES and MRIS.

Patients will be recruited from the following sources:

- COPD Clinics and COPD research databases to which the study investigators are clinically linked
- Advertisement including media-based methods
- Local GP networks – PICS

A number of COPD patients may be involved in related observational cohort studies run by the local PI's. If a patient is participating in one of the following studies; ARCADE, ECLIPSE, PROACTIVE, MRC ABPI consortium WP4 and Longitudinal determination of skeletal muscle dysfunction in COPD, which does not exclude their participation in other studies, they may also take part in ERICA with their consent. The patients who consent into the ERICA study will be asked to allow access to the previously collected data that is specifically required for ERICA in order to save the repetition of measurements and the patient's overall participation.

Data from the assessments performed for the existing studies may only be used as part of the ERICA study if enrolment into ERICA has been within 3 months of the assessments being performed.

For new patients where no existing data are available or the data provided are outside of the 3 month window, all study assessments will be performed over at least two visits as appropriate.

9. STUDY POPULATION

Patients diagnosed with COPD and fulfilling the inclusion/exclusion criteria will be recruited to the study. A sufficient number of subjects will be recruited to ensure complete and evaluable data in approximately 800 patients.

Patients will be eligible for inclusion in the study only if all of the following criteria are met:

Inclusion criteria

- Aged ≥40years
- Able to provide consent
- Clinical diagnosis of COPD
- Post-bronchodilator spirometry FEV_1/FVC ratio <0.7 and $FEV_1 \leq 80\%$ of predicted normal.
- Current or ex-smoker with a smoking history of at least 10 pack years.
- Clinical stability > 4 weeks from any exacerbation requiring treatment with oral steroids or anti-biotics or hospitalization

Patients will not be eligible for inclusion in the study if any of the following criteria apply:

Exclusion criteria:

- Lack of informed consent
- Pregnancy
- Current participation in an ongoing CTIMP
- Known diagnosis of alpha1 anti-trypsin deficiency
- Known neurological co-morbidities with skeletal muscle involvement

10. STUDY PROCEDURES

Following identification by the local PI and Clinical Care Team of potentially eligible patients, all patients will be given a minimum of 24 hours to read the Patient Information Sheet and decide whether they wish to participate in the study.

All study assessments will be performed at the patients local study site. Patients will attend for their study visits as directed by their study doctor; however it is anticipated that the study assessments will be performed over 2 visits. (Dependent on the patient's time/physical restrictions)

All assessments must be carried out within a 3 month period, including any assessments previously carried out as part of their participation in an existing study. The following measurements will be carried out as part of this study:

- Informed, written consent obtained.
- Lifestyle and medical history questionnaire St George's Respiratory Questionnaire; (Health Questionnaire) MRC Dyspnoea Questionnaire and the COPD Assessment test (CAT score)
- Height
- Weight
- Post-bronchodilator spirometry (with salbutamol)
- Fat-free mass (bioimpedance)
- Short physical performance battery
- 6 minute walk test
- Quadriceps maximum voluntary contraction
- SNIP
- Seated and supine blood pressure
- Arterial stiffness
- Carotid intima-media thickness
- 12 lead ECG
- 50 ml venous blood sample including genetics
- 10 ml spot urine

A detailed description of each assessment is outlined below:

Life style and history questionnaire

The participant questionnaire has been designed for the ERICA study and includes questions concerning COPD disease severity, CV history, physical function and current drug therapy. It will take approximately 20 minutes to complete.

COPD Assessment test – CAT score

The COPD Assessment Test (CAT) is a new questionnaire for COPD patients; designed to measure the impact of COPD on the patient's life, and how this changes with duration. The CAT is a simple test consisting of 8 questions and will take approximately 5 minutes to complete.

St George's Respiratory Questionnaire (Health Questionnaire)
The St Georges Respiratory Questionnaire for COPD (SGRQ-C) health status instrument, a recent adaption of the St Georges Respiratory Questionnaire, will be administered to patients during the study and will take approximately 15 minutes to complete.

MRC Dyspnoea Questionnaire
The modified MRC dyspnoea assessment (response range set by a numeric scale) will be performed as a self-administered questionnaire and take approximately 5 minutes to complete.

Post bronchodilator spirometry
Standard clinical spirometry assessments will be made with patients seated. This will involve the assessment of forced vital capacity and forced expiratory volume in 1 second as per Investigator Manual guidelines. The patient will be given up to 400micrograms of salbutamol inhaler. Approximately 15 minutes later, the patient will be asked to forcefully exhale after a maximum inhalation for approximately 6 seconds.

Fat free mass – Bioelectical impedance
Fat-free mass will be assessed using the standard bioelectrical impedance tests. This is a painless, quick and non-invasive method which involves sending a very small current through the body. The flow of current encounters resistance due to different tissue components, which can be used to derive the fat free mass, using standardised equations. The current is not felt by the patient and will take approximately 5 minutes to complete.

Short physical performance battery
This is a simple field test of lower limb function, to provide a marker of disease severity and patient frailty. The test is comprised of assessment of standing balance, usual gait speed and ability to stand from a chair. Patients will be instructed on how to perform each manoeuvre as per Investigator Manual guidelines and will be carefully supervised throughout. The entire test takes less than 5 minutes to complete.

Six minute walk test
A 6 minute walk test will be conducted in all patients to assess exercise tolerance, according to ATS guidelines. This is a simple, self-paced exercise test, where patients are asked to walk at their own pace for 6 minutes, including breaks if necessary. The distance covered on a flat, hard surface (ie. walking track) with minimal blind turns or obstaclesis will be recorded as the 6 minute walking distance.

Quadriceps maximal voluntary contraction
Maximal voluntary contraction of the quadriceps muscle will be assessed following a standard procedure, with patients seated in a custom-designed quads chair, with hip and knee flexion of 90^{o} and a strain gauge connected to a strap attached to the patient's ankle. After an appropriate warm-up, patients will be instructed to perform a maximum contraction by extending the knee fully for 2-3 seconds. At least 5 contractions should be performed at 20-30 second intervals, with the best effort recorded.

SNIP

Inspiratory muscle strength will be assessed by measuring the maximal SNIP. A bung size-specific to the patient is placed in the nostril deemed by the investigator to be most patent. The patient is asked to make a maximum voluntary sniff effort via a peak flow meter and the greatest effort will be recorded in the CRF. The sniff meter display is visible to the patients to provide feedback. More than 5 efforts are permitted if necessary to achieve a maximal response.

Brachial Blood Pressure - as per routine care

Blood pressure will be recorded in the non-dominant arm using a validated oscillometric sphygmomanometer. Measurements will be made following at least 5 minutes of seated rest and again, following at least 10 minutes of supine rest. All measurements will be made in triplicate; the last two measurements will be averaged and entered in the CRF.

Arterial stiffness

Radial artery waveforms will be recorded with a high fidelity micromanometer from the wrist of the non-dominant arm, immediately following assessment of brachial blood pressure. Briefly, the micromanometer will be used to applanate (or flatten) the artery, which equalises the circumferential pressures and allows an accurate and highly reproducible pressure signal to be recorded within approximately 15 seconds. The sphygmoCor system will be used to generate a corresponding central (aortic) waveform by applying a validated generalised transfer function, from which central blood pressure will be calculated, together with the augmentation index.

Aortic pulse wave velocity will be measured immediately, using the same device. A three lead ECG will be attached to the patient (for R-wave gating) and then the micromanometer will be placed sequentially over the carotid and femoral arteries, each for approximately 15 seconds. The system software calculates the pulse wave velocity value at the completion of each measurement. All measurements will be made in duplicate, and the mean values (central blood pressure, augmentation index and pulse wave velocity) recorded in the CRF.

Carotid IMT

Subjects will be asked to rest supine for at least 5 minutes prior to any measurements being undertaken. Using a high resolution ultrasound scanner with a 10MHz linear-array transducer, the common carotid artery will be identified and scanned, 2 cm below its bifurcation. Carotid IMT will be obtained automatically using validated system software. Measurements will be repeated three times, and the average of the median values will be recorded in the CRF. This procedure will take approximately 5 minutes to complete.

12 lead ECG

A standard 12 lead ECG will be recorded with the patient resting supine to allow optimal recording. Electrodes will be attached to the prepared skin with the ECG leads. The patient will be asked to relax and lay still. Procedure will be repeated if quality of tracing is of poor.

Blood Biomarkers

Venous blood will be taken by a member of the study team, using the appropriate tubes and sent for analysis. The total blood draw (including blood for storage and DNA analysis) taken will be up to 50ml.

The following parameters will be determined:-

Local NHS biochemical and haematological laboratory

- Urea, electrolytes, creatinine, glucose
- Full lipid profile including LDL, HDL and triglycerides
- Glycosylated haemoglobin (HbA1c)
- Fibrinogen, high-sensitivity CRP
- Full blood count - plasma and serum will be removed to examine other circulating factors known or likely to be important in COPD and its non-pulmonary manifestations. Plasma and serum will be collected in separate tubes, centrifuged, aliquotted and stored in a -80^{o}C freezer, for analysis at a later date.

Urine analysis will be undertaken for estimation of protein excretion and stored for proteomic analysis at local suitably certified laboratory at a later date.

A biomarker assay of a proportion of Cambridge samples will be conducted at GSK based at Addenbrooke's hospital.

DNA Analysis

Whole blood will be stored for DNA analysis, to examine various genetic polymorphisms known or likely to be important in COPD and its non-pulmonary manifestations. This will be stored at suitably certified laboratories at the local sites and sent for central analysis at the end of the study.

Follow-up

All patients will have an active follow-up every 6 months for up to two years, by a postal or telephone questionnaire, depending on preference. Patients who fail to return or return incomplete questionnaires by post will then be telephoned. This information will be requested from the patients and is designed to capture events and changes related to respiratory, skeletal muscle and CV function including changes in therapy, which have occurred since the assessments were performed. Patients will be consented to permit future contact, and separate REC approval would be sort for any future research contact beyond 2 years.

Patients will be asked to consent to the use of information held by the NHS and records maintained by the NHS Medical Research Information Service. This will allow the research team to be notified of long-term outcomes including hospital admissions and the timing and cause of death.

The rationale for using these data will be clearly explained in the patient information sheet. Patients will also be asked for permission to be contacted regarding participation in future studies. ERICA would require patient's consent to access their medical records and to be registered with HES/MRIS for the purpose of defining/validating any events that they may have had.

Table1: Existing studies that may participate in ERICA

Study Acronym	Study site	REC Approval Ref No& Approval Date
ARCADE	Cardiff	11/WSE02/7/ February 2011
ECLIPSE (Extension)	Cambridge, Edinburgh, RBH	05/Q1606/173/March 2006
PROACTIVE	RBH, Edinburgh	10/S1102/37/September 2009
MRC ABPI consortium WP4 - Extension to ECLIPSE	Cambridge, Edinburgh	11/LO/0711 29 June 2011
Longitudinal determination of skeletal muscle dysfunction in COPD	Cambridge	11/H0304/4 21February 2011

Definition of the end of study

The end of study will be defined as the last follow-up questionnaire completed by the final patient. We will obtain consent for patients to be re-contacted through registration with HES and NHS Medical Research Information Centre for long-term follow up.

Subject Withdrawal

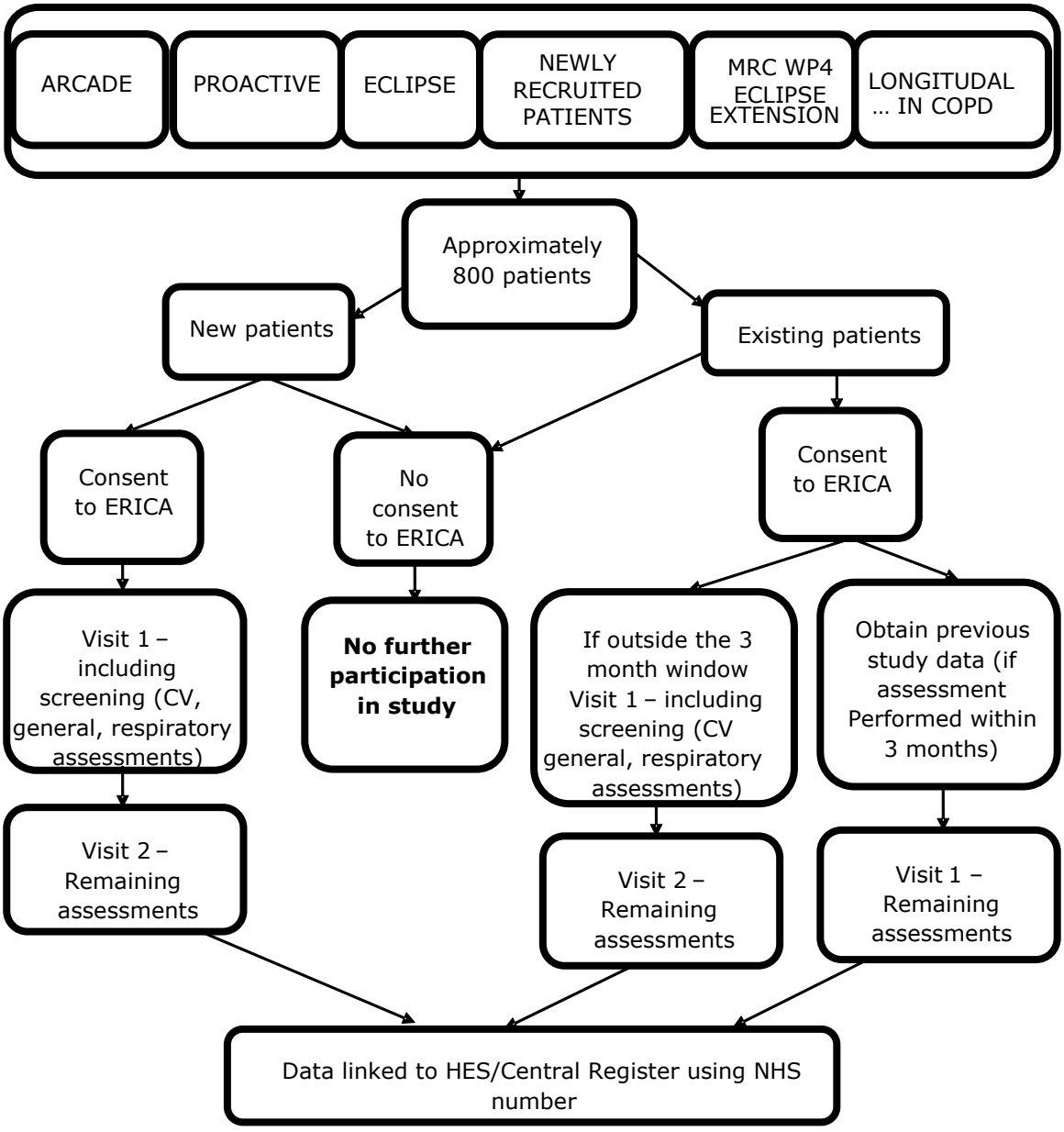
If a patient who has consented to participate in the study withdraws for any reason other than lost to follow-up, the subject will be given the following options concerning the Genetic samples already collected:

- Genetics research continues per the patient's original consent
- Any remaining sample is destroyed

Standardisation – Staff and Equipment

Delegated study staff will be appropriately trained to undertake each assessment will be provided with an investigator's manual prior to the start of the study. Study staff will undergo training and certification at each site to ensure standardization and precision. Telephone questionnaires will be pre-arranged for a mutually convenient time undertaken by trained staff who understand the nature of sensitive questions. Equipment will be calibrated at baseline and throughout the study at specific intervals.

11. STUDY FLOW CHART



12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Power calculations

The study is powered based on tertile analysis for pulse wave velocity (PWV) and quadriceps strength (maximum voluntary contraction, MVC), as the most robust cardiovascular and muscle biomarkers. Assuming an average PWV of 10 (SD 1.0) m/s, and that 0.4 m/s is the minimum relevant clinical difference, 230 patients per tertile will provide 90% power at $P<0.01$ (to allow for multiple testing) to detect this difference between the top and bottom tertiles. Similarly, assuming an average MVC pf 32 (SD 8) kg, and that a gain in MVC of 3 kg is worthwhile clinically, 220 patients per tertile will provide 90% power at a significance of $P<0.01$. Thus, to allow for dropouts and incomplete datasets, an adequate recruitment ensure complete data in approximately 800 patients (yielding 266 patients per tertile)

Data Analysis

The relationship between biomarkers and fibrinogen will be tested by stratifying subjects into tertiles of fibrinogen and then comparing the levels of other biomarkers between the bottom and top tertiles. Regression analysis will also be used to determine relationship between fibrinogen and other biomarkers treated as continuous variable, and multiple regression models constructed to determine independent relationship and to control for known confounders such as blood pressure and ages.

An interim analysis will be conducted after approximately 50% of recruitment. This will be lead by the CCTU in collaboration with appropriate GSK experts.

Survival analysis and cox proportional hazard ratios will be used to assess relationship between biomarkers and clinical outcomes, with appropriate covariates included in the models. The primary outcomes will be all cause mortality, cardiovascular mortality, and MACE. We will also assess the relationship between biomarkers and severity and frequency of COPD exacerbations.

Phenotypic Analyses

The cross-sectional data available at visit 1 will assist in determination of subject phenotypes. Phenotypes associated with progression of disease will be based on longitudinal data.

13. DATA MANAGEMENT

Outcome data will be collected from the patients themselves, from medical record review and information routinely collated by the NHS (Hospital Episode Statistics, NHS Information Centre and NHS Central Registry).

Data Handling and Record Keeping

All data will be transferred into a Case Report Form (CRF) All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the Principal Investigator for the timing, completeness, legibility and accuracy of the CRF pages.

All study data will be entered onto a validated Electronic CRF database.

Source Data

To enable peer review, monitoring, audit and/or inspection, each Principal Investigator will agree to keep records of all participating patients (sufficient information to link records e.g. CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

Medical Records Review

GP and/or hospital records may be reviewed, as necessary. Researchers with appropriate honorary contracts, research passports or members of the direct clinical care team will conduct the hospital medical records review. In order to facilitate data collection in GP surgeries, Primary Care Research Network (PCRN) support may be applied for.

NHS Central Register and/or Hospital Episode Statistics

Applications will be made to the relevant bodies to access outcome data routinely collected by the NHS. This may include Hospital Episode Statistics and mortality information in the Central Register held by the NHS information Centre. The applications and resulting data will be managed by the Coordinating Centre at Addenbrooke's Hospital.

The use of Trusted data Linkage Service' as part of the HES/MRIS application will require consent and approval from the Ethics and Confidentiality Committee (ECC) of the NIGB before datasets that include identifiable data can be linked.

Identifiable Data Transfer from Local Site to Coordinating Centre

All identifiable data will be securely sent to the Coordinating Centre by recorded delivery or via nhs.net and stored in a separate, password-encrypted database in compliance with the Data Protection Act and approved by the co-sponsors, with permission for access given to delegated study-staff. Consent will be sought for the transfer of identifiable information.

Patient Identifiable Data to be transferred will include:

- Name
- Date of birth
- Gender
- NHS number

- Home Address and post code
- Telephone number

14. INFORMED CONSENT

The investigator or designee will obtain informed, written consent from each patient before participation in this study. A contact number for the study team will be provided on the Patient Information Sheet to enable patients to ask any questions they may have. The voluntary nature of participation and the ability to withdraw an individual's consent at anytime will be emphasized.

The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. Should a patient require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators. Patients who do not fully understand the information provided will not be enrolled on to the study.

Entry into the ERICA study will require a specific consent to i) access data from existing studies which is to be sent and kept centrally and ii) have the additional/new assessments undertaken.

To satisfy ERICA's secondary outcome measures, the following will all require patient's consent; long-term follow-up via MRIS and HES; the storage of their samples in a central tissue bank; genetic sample analysis and future use of these samples.

15. SAFETY

Safety Reporting

SAE's relating to study procedures will be reported.

Reporting Procedures for Serious Adverse Events

The study team at the participating sites should report the SAE's to the Sponsor at Addenbrooke's Hospital using either of the following methods:

i) Fax - 01223 348494
ii) E-mail address – r&denquiries@addenbrookes.nhs.uk

Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal results that are found in any clinical/study assessment will be reviewed by the local team and fed back to the patients and GP where the abnormality is deemed clinically relevant. Any further investigation or treatment required will be provided by the usual NHS clinical route.

16. REGULATORY ISSUES

Non-CTIMP Status

This research project does not constitute a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC as there is no study medication. All medication taken when patients enter the study (baseline) and during the study will be recorded in the study CRF.

Ethical Approval

The ERICA study will be applying for formal Research Ethics Committee approval. Patients participating in any of the pre-specified observational studies may be included in ERICA and will be asked to separately consent, as part of the ERICA study, to assess any relevant data previously collected.

MRIS/HES Approval

An application will be made to the MRIS. As part of this process, approval will be sought from the National Information Governance Board for Health and Social Care (NIGB). This can only proceed with Research Ethical Committee approval.

NHS Permissions

NHS Research and Development Approval will be obtained for each Hospital Trust involved in the study prior to study commencing.

17. ETHICS

Participant Confidentiality

All documents will be stored securely and only accessible by study staff and authorised personnel. All investigators and study site staff involved in this study must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Identifiable data will be held separately to the CRF database in a secure, password-controlled database to facilitate the follow-up correspondence.

Other Ethical Considerations

Participants will not be anonymised to ensure the long-term follow up is maintained.

18. FUNDING

The ERICA study is funded by MRC Technology Strategy Board.

19. INDEMNITY AND INSURANCE

The ERICA study is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation made in respect should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for non-negligent harm arising through participation in the clinical trial.

20. PEER REVIEW

The ERICA protocol has been peer-reviewed by the MRC/TSB board

21. AUDITS

The ERICA study may be subject to inspection and audit by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

22. PUBLICATION POLICY

In accordance with the Research Governance Framework for Health and Social Care and GCP, results will be appropriately published and disseminated. A publication plan will be agreed by the ERICA collaborators.

23. STUDY STEERING COMMITEE

The ERICA study will have a steering committee with an independent chair person as described in the ERICA Consortium Agreement. (TSB Project ID (File Ref: 101024, TP number: 9157-6118)

24. DECLARATION OF HELSINKI AND ICH GOOD CLINICAL PRACTICE

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the ICH Good Clinical Practice Guidelines, the protocol and applicable local regulatory requirements and laws.

25. GCP TRAINING

All study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with your Trust's policy.

26. PROTOCOL COMPLIANCE AND BREACHES OF GCP

The investigator must not implement any deviation from the protocol without formal written agreement from the Sponsor and Chief Investigator. If this necessitates a subsequent protocol amendment, or halt to the study, this should be submitted to the REC & R&D Department for review and approval if appropriate. Potential/suspected serious breach of GCP must be reported immediately to the Sponsor.

27. REFERENCES

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28. APPENDICES

Measurements	ARCADE	ECLIPSE Extension	PROACTIVE	Longitudinal determination of skeletal muscle dysfunction in COPD	MRC WP4 consortium	ERICA
ERICA Participant Questionnaire						
Height	■	■	■	■	■	
Weight	■	■	■	■	■	
Bronchodilator spirometry	■	■	■	■	■	
SNIP						
Fat-free mass (bioimpedance)	■	■	■	■	■	
Short physical performance battery					■	
6 minute walk test	■	■	■		■	
Quadriceps maximum voluntary contraction			■	■	■	
Seated and supine blood pressure	■	■		■	■	
Arterial stiffness (PWV)	■			■		
12 lead ECG			■		■	
50 ml venous blood sample	■		■		■	
Full blood count	■	■	■	■		
St. George's respiratory questionnaire				■	■	
MRC dyspnoea score		■	■	■	■	
Carotid intimal-medial thickness	■					

Key

■ Performed

| | Not performed