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Phenotyping individuals with elevated mean pulmonary arterial pressure and elevated pulmonary vascular resistance in the United Kingdom

PHENOTYPING PATIENTS WITH ELEVATED PULMONARY ARTERIAL PRESSURE

PHENOTYPING INDIVIDUALS WITH ELEVATED MEAN PULMONARY ARTERIAL PRESSURE AND ELEVATED PULMONARY VASCULAR RESISTANCE IN THE UNITED KINGDOM

PHENOTYPING PATIENTS WITH ELEVATED PULMONARY ARTERIAL PRESSURE

PROTOCOL VERSION NUMBER AND DATE

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SIGNATURE PAGE

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol, GCP, the Data Protection Act (2018), the Trust's Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research (2017 V3.3), the Sponsor's SOPs, and other regulatory requirements as appropriate.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.
This protocol has been written in accordance to the Sponsor's procedure identified as: SOP029 'Applying for Royal Free Sponsorship' and is intended for use at UK sites **only**.

For and on behalf of the Study Sponsor:

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

.....
Name (please print)

.....
Position

Chief Investigator:

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

.....
Name: (please print)

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I. LIST OF ABBREVIATIONS

6MWD	Six-minute walk distance
BMI	Body mass index
BNP	Brain natriuretic peptide
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CCB	Calcium channel blockers
CI	Cardiac index
COPD	Chronic Obstructive Pulmonary Disease
CTEPH	Chronic thromboembolic pulmonary hypertension
D/TLCO	Pulmonary diffusion/transfer capacity for carbon monoxide
eCRF	Electronic case report form
eDC	Electronic data collection
ERA	Endothelin receptor antagonists
GDS	Global Drug Safety
HES	Hospitals Episode Statistics
HIV	Human immunodeficiency virus
HR	Heart rate
HRQoL	Health-related quality of life
ILD	Interstitial lung disease
ISD	Information service division
LVEDP	Left ventricular-end-diastolic pressure
mPAP	Mean pulmonary arterial pressure
NT-proBNP	N-terminal pro-brain natriuretic peptide
ONS	Office of National Statistics
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PDE-5	Phosphodiesterase-5
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
QoL	Quality of life
RAA	Right atrium area
RAP	Right atrial pressure
RHC	Right heart catheterization
SBP	Systolic blood pressure
SvO2	Mixed venous saturated oxygen
TPG	Transpulmonary gradient
TR velocity	Tricuspid regurgitant jet velocity
WHO FC	World Health Organization functional classification.
WSPH	World Symposium on Pulmonary Hypertension

II. STUDY SUMMARY

Trial Title	Phenotyping individuals with elevated mean pulmonary arterial pressure and elevated pulmonary vascular resistance in the United Kingdom	
Internal ref. no. (or short title)	Phenotyping patients with elevated pulmonary arterial pressure	
Clinical Phase	N/A	
Study design	Retrospective, observational, multicenter study	
Participants	Patients who have undergone at least one right heart catheterization in one of the participating PH specialist or approved centers in the UK.	
Planned Sample Size	2900 patients	
Treatment duration	N/A	
Follow up duration	Maximum 11 years	
Planned Trial Period	Observation period:1 Jan 2009 – 1st March 2020 Data extraction period: 1st November 2020-1st February 2021	
	Objectives	Outcome Measures
Primary	To describe rate of all-cause death and rate of all-cause hospitalization in patients with different levels of mPAP and PVR and diagnosis and in the overall study population.	Hospitalization Mortality Rates
Secondary	To describe and compare patient and clinical characteristics, biomarkers, therapies, quality of life, hospitalization and mortality among patients with different levels of mPAP and PVR and diagnoses and in the overall study population. To describe and compare time to progression to PH in all patients with mPAP <25 mmHg, and in patients with no evidence of pulmonary vasculopathy or with early pulmonary vasculopathy.	Hospitalization Mortality Quality of life Progression to PH
Investigational Medicinal Product(s)	N/A	
Formulation, Dose, Route of Administration	N/A	

III. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
ACTELION PHARMACEUTICALS LTD Gewerbetrasse 16 4123 Allschwil	£600,000

IV. ROLE OF STUDY SPONSOR AND FUNDER

Royal Free Hospital is acting sponsor for this study and will have overall responsibility for the initiation and management of the study. Actelion Pharmaceuticals Ltd.is the funder of the study and has contributed scientifically to the study and been involved in protocol development

V. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Group

The Trial Management Group should meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

Trial Management Group: Membership: Dr Gerry Coghlan, CI
Dr Nina Karia, Trial Manager
Rachel Ochiel, Lead Research Nurse
Ivy Wanjiku, Study Co-ordinator
Karl Salazar, Research Nurse

Scientific Committee: Scientific committee for this study will consist of the following:

- Gerry Coghlan, Royal Free Hospital, London (Chief investigator)
- Nina Karia, Royal Free Hospital, London

- Rachel Ochiel, Royal Free Hospital, London, UK
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- Jim Lordan, Freeman Hospital, Newcastle upon Tyne, United Kingdom
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VI. PROTOOCL CONTRIBUTORS

Dr Gerry Coghlan, Rheumatology Clinical Trials Department, conceived the study; study was initiated and designed with support from Michael Preiss and Rose Ong from Actelion Pharmaceuticals, who also helped with study implementation. Dr Gerry Coghlan is the grant holder. Rose Ong, Federico Ricciardi, and Lilla Di Scala provided epidemiological and statistical expertise in study design and statistical analysis planning. All statistical analyses will be conducted by Federico Ricciardi. The sponsor is responsible for report and publication writing. All authors contributed to refinement of the study protocol and will contribute to interpretation of data and approve the final publications.

VII. DATA COLLECTION SCHEDULE

Table 1 Data Collection Schedule

Data Collection	**At index RHC[a]** (Baseline)	**After index RHC[b]** (Follow-up)
Patient characteristics		
Demographics	X	
Height, weight, BMI	X	X
Clinical characteristics		
Vital signs (e.g. HR, SBP)	X	X
Functional capacity (e.g. WHO FC, 6MWD)	X	X
RHC (e.g. mPAP, PVR, RAP, CI)	X[c]	X
Echocardiography (e.g. RAA, pericardial effusion)	X	X

Data Collection	At index RHC[a] (Baseline)	After index RHC[b] (Follow-up)
Pulmonary function tests (e.g.D/TLCO)	X	X
Electrocardiography (e.g. including RVS, RAD)	X	
CT scans (e.g. extent of lung pathology)	X	X
CTPA scans (e.g. presence of PE or CTED)	X	X
Lung VQ scans	X	X
Laboratory data		
Serum biomarkers (e.g. BNP, NT-pro-BNP)	X	X
Therapies		
PAH therapy class (e.g. ERA, PDE-5 inhibitor)	X[d]	X
Non-PAH therapy class (e.g. CCB, oxygen therapy)	X[d]	X
Comorbidities and medical history		
Diagnosis	X	X
Medical history	X[d]	
Lung/Heart transplant	X[d]	X
Outcomes		
Hospitalization		X (from HES or ISD)
Death		X (from ONS or ISD)
Quality of life	X	X

HES: Hospital Episode Statistics; ISD: Information Services Division; ONS: Office of National Statistics.

a. Includes data available within 12 months before and 3 month after index RHC; if multiple records for the same measurement are available, the record closest to the date of index RHC will be used for analysis. If records are available prior to 12 months, providing there is no interval change between this and the first follow up visit in investigation this can be included.
b. Data from follow-up visits will be collected from all patients every 12 months (within ±6 months window) since the date of index RHC; if multiple records for the same measurement are available, the record closest to each 12-month time point after index RHC will be used for analysis. In addition, all data available within 3 months prior to and including date of change of PAH therapy class (including initiation, , non-routine escalation, de-escalation and discontinuation) will be collected.
c. Data from the last RHC any time before the index RHC (if available) and at date of index RHC will be recorded.
d. Information about all PAH therapies and non-PAH therapies, significant medical conditions, and lung/heart transplant, history and status of pregnancy, family history of PH and history and status of exposure to PH-inducing agents any time before and including date of index RHC will be recorded.

1. ABSTRACT

Accumulating evidence indicates that patients with mildly elevated mPAP below the threshold of 25 mm Hg are at risk of disease progression [1-3] . The 6th WSPH Task Force on Diagnosis and Assessment therefore proposed to define all pre-capillary PH (Groups 1, 3, 4, and 5) by the concomitant presence of mPAP >20 mmHg, pulmonary artery wedge pressure (PAWP) ⩽15 mmHg, and pulmonary vascular resistance (PVR) ⩾3 WU[1-3] . Other analyses suggest that PVR >2 WU could be also considered abnormal [4, 5] .

This retrospective, observational, multicenter study aims to describe patient and clinical characteristics, biomarkers, therapies, quality of life (QoL), and prognosis (in terms of all-cause hospitalization and all-cause mortality) of patients categorized in cohorts based on different levels of mPAP (<21, ≥21-<25, or ≥25 mmHg) and PVR (<2, ≥2-<3, or ≥3 WU). In addition, QoL, hospitalization, and mortality will be compared across patient cohorts. Patients who had undergone an RHC in one of the PH specialist or approved centers in a routine clinical practice setting during the eligibility period January 1, 2009 - December 31, 2017 and fulfilled all the inclusion criteria and none of the exclusion criteria will be considered to be included in this study.

Patient and clinical characteristics, biomarkers, therapies, comorbidities and medical history, and QoL of patients in each cohort at baseline and at follow-up visits will be summarized using descriptive statistics. Change in patient and clinical characteristics, biomarkers, therapies, and QoL from baseline, measured longitudinally after baseline, will be described and compared among cohorts using multivariable regression methods, adjusting for all potential confounders and treatment. Kaplan-Meier estimates of time-to-event endpoints will be tabulated for each cohort and overall. Cox-proportional hazards models will be used to model time from index RHC to first all-cause hospitalization and time to all-cause mortality, adjusting for all potential confounders. All-cause hospitalization rate and all-cause death rate will be calculated for all repeated hospitalizations and the death event, respectively, in each cohort and compared among cohorts using Poisson regression, adjusting for all potential confounders and treatment. One-year mortality risk of each cohort will be estimated using data at baseline and at 1-year follow-up, based on published risk assessment strategies [6-10]. Estimated mortality risk will be tabulated against observed mortality. Score of each domain in CAMPHOR and summary score of emPHasis-10 at baseline and longitudinally after baseline will be compared among cohorts using linear regression, adjusting for all potential confounders and treatment. Due to the observational and retrospective nature of the study, some variables are expected to be missing or incomplete. In addition, this study is not specifically powered to test statistical hypotheses. Cautions will be applied in the interpretation of the statistical and clinical results.

This study provides important information about characteristics and outcomes of patients with different haemodynamic profiles, which will inform decisions on patient management and development of clinical guidelines.

2. RATIONALE

Since the 1st World Symposium on Pulmonary Hypertension (WSPH) held in 1973, pulmonary hypertension (PH) has been defined by the presence of mean pulmonary arterial pressure (mPAP) ≥25 mm Hg as measured by resting right

heart catheterization (RHC). This definition was primarily based on expert opinion due to the lack of high-quality, large-scale studies[11] . Accumulating evidence indicates that patients with mildly elevated mPAP below the threshold of 25 mm Hg are at risk of disease progression [1-3] . The 6th WSPH Task Force on Diagnosis and Assessment therefore proposed to define all pre-capillary PH (Groups 1, 3, 4, and 5) by the concomitant presence of mPAP >20 mmHg, pulmonary artery wedge pressure (PAWP) ⩽15 mmHg, and pulmonary vascular resistance (PVR) ⩾3 WU [12]. Other analyses suggest that PVR >2 WU could be also considered abnormal [4, 5]. This retrospective, observational, multicenter study aims to describe and compare patient and clinical characteristics, biomarkers, therapies, QoL, and prognosis (in terms of all-cause hospitalization and all-cause mortality) among patients categorized in cohorts based on different levels of mPAP (<21, ≥21-<25, or ≥25 mmHg) and PVR (<2, ≥2-<3, or ≥3 WU).

2.1. ASSESSMENT AND MANAGEMENT OF RISK

There is no expected medical risk for the patient related to the current study. This study is an information-collecting (observational) retrospective study and does not require any specific clinical intervention or procedures (e.g., physical or psychological examinations or tests); no drug is given to the patient.

The most important non-medical risk associated with this chart review research is a confidentiality breach and unintended disclosure of patient data. The electronic data collection (eDC) system and server used for data entry and hosting will limit this risk.

The patients included in this study will not receive any direct medical benefit from the proposed research. Patients, doctors, researchers, research institutions, and public and private health care organizations could benefit from the knowledge gained in this study.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. PRIMARY OBJECTIVE

The primary objectives of this study are:

To estimate rate of all-cause death and rate of all-cause hospitalization overall and in each patient cohort, categorized based on the level of mPAP and PVR, and diagnosis (see Cohort definition in Table 3), and in the overall study population.

3.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:

A. To describe patient and clinical characteristics, biomarkers, therapies, and QoL[1] of patients in each patient cohort and in the overall study population, at baseline and longitudinally after baseline.

B. To describe and compare change in patient and clinical characteristic, biomarkers, therapies, and QoL from baseline, measured longitudinally after baseline, across patient cohorts and in the overall study population
C. To describe and compare time to progression to PH in all patients with mPAP <25 mmHg, and in patients with no evidence of pulmonary vasculopathy or with early pulmonary vasculopathy.
D. To estimate the time to first all-cause hospitalization in each cohort and in the overall study population
E. To estimate the time to all-cause mortality in each cohort and in the overall study population
F. To estimate 1-year mortality risk of each cohort and in the overall study population using data at baseline and at 1-year follow-up
G. To compare time to first and rate of all-cause hospitalization across patient cohorts and in the overall study population
H. To compare time to and rate of all-cause mortality across patient cohorts and in the overall study population
I. To compare QoL across patient cohorts and in the overall study population at baseline and longitudinally after baseline

3.3. OUTCOME MEASURES (PRIMARY AND SECONDARY)

Progression to PH :

Progression to PH is defined as the date of RHC after index RHC when the measured mPAP is ≥25 mmHg for the first time.

Hospitalization:

Hospitalization is defined as an inpatient hospitalization event due to any cause recorded in the Hospital Episode Statistics (HES) database in England or the Information Services Division (ISD) hospitalization database in Scotland from the index RHC date, defined as the first RHC within the eligibility period satisfying all inclusion criteria (see Section 6.1), up to the end of the observation period or the data cutoff date of HES or ISD hospitalization data, whichever occurred first. All-cause hospitalization is the main outcome of interest. Separate analyses may be conducted for different reasons for hospitalization (e.g. PH-related).

Mortality:

All-cause mortality is defined as death due to any cause recorded in the Office of National Statistics (ONS) database in England or the ISD death database in Scotland from index RHC date up to the end of observation period or the cutoff date of ONS or ISD death data, whichever occurred first. Additionally, 1-year mortality is defined as the Kaplan-Meier estimated mortality at one year. All-cause mortality is the main outcome of interest. Separate analyses may be conducted for different reasons for death (e.g. PH-related).

QoL:

CAMPHOR

The CAMPHOR is a disease-specific instrument to assess QoL of PAH patients[13]. It comprises three domains that assess overall symptoms (25 items), activity limitations (15 items) and quality of life (25 items). Responses are captured in dichotomous and 3-option response scale[14]. The higher the score represents the worse the quality of life.

Score for each domain in CAMPHOR will be described and compared among cohorts at baseline and at every 12 months after baseline. In addition, change in each domain score from baseline, as measured longitudinally after baseline, will be described and compared among cohorts.

emPHasis-10

emPHasis-10 is a short questionnaire for assessing HRQoL in PAH. The emPHasis-10 questionnaire consists of 10 questions scored in a 6-point scale (from 0 to 5), with a maximum score of 50. The higher the score represents the worse the quality of life [15].

Summary scores of emphasis-10 will be described and compared among cohorts at baseline and at every 12 months after baseline. In addition, change summary score from baseline, as measured longitudinally after baseline, will be described and compared among cohorts.

3.4. TABLE OF OUTCOMES

Table 2. Table of outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To describe rate of all-cause death and rate of all-cause hospitalization in patients with different levels of	Hospitalization Mortality rates	Anytime during the observation period

mPAP and PVR and diagnosis and in the overall study population.		
Secondary Objectives To describe and compare patient and clinical characteristics, biomarkers, therapies, quality of life, hospitalization and mortality among patients with different levels of mPAP and PVR and diagnoses and in the overall study population. To describe and compare time to progression to PH in all patients with mPAP <25 mmHg, and in patients with no evidence of pulmonary vasculopathy or early pulmonary vasculopathy.	Hospitalization Mortality Quality of life Progression to PH	Anytime during the observation period

4. STUDY DESIGN

This is a retrospective, observational, multicenter study to describe and compare patients with different levels of mPAP and PVR in a routine clinical practice setting. Patients observed in this study will be patients who have undergone at least one RHC in one of the participating PH specialist centers in the UK. Only data available per routine clinical practice will be collected within this study.

Patients who had undergone an RHC during the eligibility period 1 January 2009 - 31 December 2017 and fulfilled all the inclusion criteria and none of the exclusion criteria will be considered to be included in this study (

Figure **1**). The observation period will document data available from 1 January 2009 to1st March 2020 . Data extraction will be considered complete for a participating patient if all of the relevant data, as defined in this protocol, available within the observation period (up to1st March 2020) has been recorded in the eCRF. The end of the study will be the date when the last data point from the last patient has been entered on the eCRF.

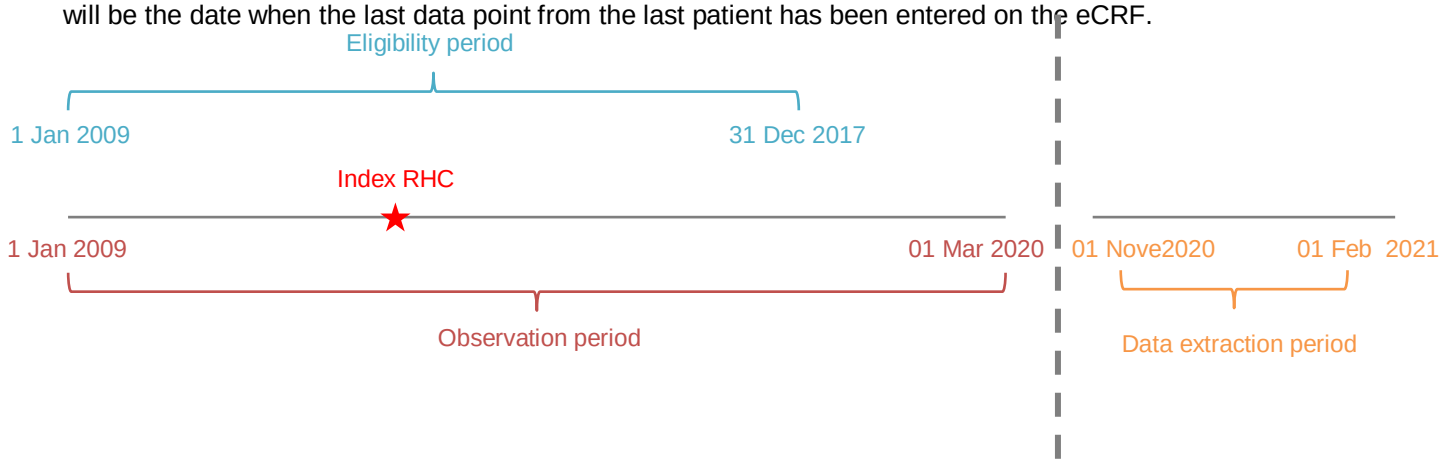

Figure 1 Schematic diagram of study design

5. STUDY SETTING

This is a multi-center study and all study data will be obtained from the data sources described below.

The primary data source for this study will be the medical records generated from routine practice in seven specialist PH centers: the Royal Free Hospital in London; the Royal Brompton Hospital in London; the Hammersmith Hospital in London; the Royal Hallamshire Hospital in Sheffield; the Royal Papworth in Cambridge; the Freeman Hospital in Newcastle upon Tyne, and the Golden Jubilee National Hospital in Glasgow.

Date of death in England will be obtained through linkage to the ONS death database. Date of death in Scotland will be obtained from the ISD death database.

Date(s) of hospitalization in England will be obtained through linkage to the HES database. The HES database contains the records of inpatient admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in England. This includes records of independently funded patients who are treated by an NHS provider and the records of non-English residents. The database also contains the records of admissions to independent (non-NHS) providers where that treatment is funded by the NHS. Cross-border treatments of residents from other countries within the UK and foreign nationals are also recorded in the HES database[1] Date(s) of hospitalization in Scotland will be obtained through linkage to the ISD hospitalization database.

6. PARTICIPANT ELIGIBILITY CRITERIA

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.
The eligibility criteria have been carefully considered to ensure the study results can address the study objectives. It is therefore vital exceptions are not made to the following detailed selection criteria.

Enrolled participants will be entered onto the sponsors subject identification log RFLRDLOG0002 and assigned a study-specific identification number in a pre-agreed format in accordance with next sequential number, site number and last four digits of their NHS number e.g. 001RFH1234. This will enable the trial manager to cross check data between sites.

Patients participating in this non-interventional study will be managed in accordance with routine clinical practice in one of the PH specialist centers participating in this study.

6.1. INCLUSION CRITERIA

- Had at least one RHC in one of the PH specialist or approved centers within eligibility period.
- Aged 18 or above at time of RHC.

6.2. EXCLUSION CRITERIA

- Patients who have missing value for mPAP or PVR at the RHC.

- Received any PAH medications (See Section 7.2) before the RHC.
- Had lung and/or heart transplant any time before the RHC.

Enrolled in any interventional clinical trial with an investigational product 3 months prior to or at the time of RHC
The first RHC within the eligibility period satisfying all inclusion and none of the exclusion criteria is defined as the index RHC.

7. STUDY DETAIL

7.1. COHORT DEFINITION

Patients will be assigned into different cohorts based on their mPAP and PVR levels at the index RHC, as well as the diagnosis recorded (see Table 3). Patients with no evidence of pulmonary vasculopathy is defined as patients who have PVR <2 WU and mPAP <25 mmHg, as measured at the index RHC. Patients with early pulmonary vasculopathy is defined as patients who has PVR ≥2-<3 WU and mPAP <25 mmHg, as measured at the index RHC. All descriptive analyses will be performed on all main cohorts and sub-cohorts and overall. For comparative analyses, comparisons across cohorts will be done as shown in Table 5. Patients will only be assigned to one cohort and will remain in the same cohort regardless of changes in mPAP and PVR after their respective index RHC.

Table 3 Cohort definition at index RHC

Main cohort	Sub-cohort	mPAP (mmHg)	PVR (WU)	Diagnosis*
1	1a	<21	<2	*not applicable*
	1b		≥2-<3	*not applicable*
	1c		≥3	*not applicable*
2	2a	≥21-<25	<2	*not applicable*
	2b		≥2-<3	*not applicable*
	2c		≥3	*not applicable*
3	3a	≥25	<2	*not applicable*
	3b		≥2-<3	*not applicable*
	3c		≥3	PH Gp1
	3d			PH Gp2
	3e			PH Gp3
	3f			PH Gp4
	3g			PH Gp5

PH Group as defined by the treating physician: PH Gp1: Pulmonary arterial hypertension; PH Gp2: Pulmonary hypertension due to left heart disease; PH Gp3: Pulmonary hypertension due to lung diseases and/or hypoxia; PH Gp4: Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions; PH Gp5: Pulmonary hypertension with unclear and/or multifactorial mechanisms

* Patients may be further stratified based on diagnoses at index RHC, including the presence of heart and lung diseases.

7.2. VARIABLES

The following parameters will be used for analysis.

Patient characteristics

- Date of birth, gender, ethnicity
- Height, weight, BMI[1]

Clinical characteristics

- Vital signs[2]: HR, SBP, DBP
- Functional capacity[3], including 6MWD, BDI, WHO FC, shuttle test
- Results of heart catheterization[4], including mPAP, PVR, PAWP, RAP, CI, SvO_2, LVEDP, TPG, DPG, coronaries
- Results of echocardiography[5], including LA size (e.g. area, volume, diameter, or visual impression), LV/RV size and function, LVEF, MR, RA size, RVA, RVDI, TR velocity, estimated PASP (with method for RA pressure measurement), pericardial effusion
- Results of electrocardiography[6], including RVS, RAD
- Results of pulmonary function tests[7], including D/TLCO, FVC, FEV1, FEV1/FVC, TLC
- Results of cardiopulmonary exercise tests[8], including VO_2 max VE/VCO2/ PetCO2, RER
- Results of CT scans[9], including presence and extent of lung pathology (e.g. emphysema, interstitial lung disease), aorta diameter, main pulmonary artery diameter, and PVOD features
- Results of CTPA scans[10], including presence of PE or CTED
- Results of lung ventilation–perfusion (VQ) scans
- Lung and heart transplant

Laboratory data

- Level of serum biomarkers[11], including BNP, NT-proBNP, ACA

Therapy

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[1] BMI: Body mass index

[2] DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure.

[3] 6MWD: 6-min walk distance; BDI: Borg dyspnea index; WHO FC: World Health Organization functional classification.

[4] mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; CI: cardiac index; SvO2: mixed venous saturated oxygen; LVEDP: left ventricular-end-diastolic pressure; TPG: transpulmonary gradient; DPG: diastolic pulmonary vascular pressure gradient.

[5] LA: left atrium; LVEF: left ventricular ejection fraction; MR: mitral regurgitation, RA: right atrium, RVA: right ventricle area/diameter, RVDI: right ventricular dimension index, TR velocity: tricuspid regurgitant jet velocity, PASP: pulmonary artery systolic pressure.

[6] RVS: right ventricular strain; RAD: right axis deviation.

[7] D/TLCO: pulmonary diffusion/transfer capacity for carbon monoxide; FVC: forced vital capacity; FEV1: forced expiratory volume; TLC: total lung capacity.

[8] VO_2max: maximal oxygen uptake; VE: pulmonary ventilation; VCO_2: carbon dioxide production; $PetCO_2$: End-tidal CO2 partial pressure; RER: respiratory exchange ratio.

[9] CT: computed tomography; PVOD: pulmonary venoocclusive disease.

[10] CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; CTED: chronic thromboembolic pulmonary disease.

[11] BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; ACA: anti-centromere antibody.

- Current use of PAH medication class[1], including ERA, PDE-5 inhibitor, oral/inhaled prostacyclin, i.v./s.c. prostacyclin, soluble Guanylate Cyclase-Stimulator. Names of PAH medications will not be collected in this study.
- Current and previous use of non-PAH therapy class[2], including anticoagulant agent, oxygen therapy, diuretic, CCB, HIV treatment. Names of non-PAH medications will not be collected in this study.

Comorbidities and medical history

- PH diagnosis
- PAH subgroups and other relevant information, e.g. agents associated with drug and toxin-induced PAH, etc.
- Pulmonary diseases[3], e.g. ILD, COPD, etc.
- Cardiac diseases, e.g. ischemic heart disease, valvular heart disease, atrial or ventricular arrhythmias, etc.
- Connective tissue diseases, e.g. scleroderma, etc.
- Liver diseases, e.g. cirrhosis, hepatitis, hepatomegaly, etc.
- Renal diseases, e.g. kidney failure, etc.
- Metabolic diseases, e.g. diabetes mellitus, etc.
- Autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus lupus, etc.
- HIV
- Other, e.g. obesity, thromboembolic disorders, etc.
- Family history of PH
- History of pregnancy
- History and status of exposure to PH-inducing drugs and toxins
- Smoking

Outcomes

- Date(s) of hospitalization
- Reason for hospitalization (PH-related or non-PH-related)
- Date of death
- Cause of death (PH-related or non-PH-related)
- CAMPHOR scores for each domain
- emPHasis-10 summary scores

The timing of data collection in this study are summarized in the data collection schedule (Table 1)

RECRUITMENT

Study will only commence once evidence of the following approval/essential documents are in place:

1. The main REC and CAG approval

[1] ERA: Endothelin receptor antagonists; PDE-5: Phosphodiesterase-5

[2] CCB: Calcium channel blockers; HIV: Human immunodeficiency virus

[3] ILD: Interstitial lung disease; COPD: Chronic Obstructive Pulmonary Disease

2. Signed Delegation of Duties and Sponsorship Agreement (RFLRDDOC0022) returned to the RF R&D Office,
3. HRA approval,
4. Final sponsorship and host site confirmation of capacity and capability,
5. The trial initiation procedure completed and the issue of the 'Green-Light' by the RF R&D Office

7.3. INFORMED CONSENT

Per UK local guidelines, a waiver for informed consent for retrospective observational studies will be requested from a named Ethics Committee as well as the Confidentiality Advisory Group (CAG). As such, no individual participation agreement or informed consent form needs to be signed by the patients.

We will identify patients who have opted out of sharing their data for research purposes from the national data opt out service and exclude them from the study. We will also inform potential patients of study through an Ethics approved patient leaflet to be displayed at participating sites.

7.4. END OF TRIAL

End of study will be defined as last data item for the last patient entered on the eCRF.

8. SAFETY REPORTING

8.1. DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant whether it is considered to be related to the intervention or not, that includes a clinical sign, symptom, or condition and /or an observation of a near incident. (This does not include pre-existing conditions recorded as such at baseline)
Serious Adverse Event (SAE)	Any Adverse Event or untoward medical occurrence in a trial participant that can be wholly or partly to the intervention which resulted in any of the following: • Results in death; or • Is life-threatening (places the participant, in the view of the Investigator, at immediate risk of death) • Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition) • Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions) • Consists of a congenital anomaly or birth defect (in offspring of participants regardless of time of diagnosis). • Or is another important medical condition Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition of serious will

	also be considered serious.
Adverse Drug Reaction (ADR)	An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non- investigational) product that is noxious and unintended. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a possibility. An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs

8.2. RECORDING AND REPORTING OF SAFETY EVENTS

This is a retrospective observational study based on secondary use of data from medical chart reviews. In this study, no product names will be collected, therefore adverse events are not collected. During the course of data extraction in this study, if any variables collected for the study falls within the definition of an adverse drug reaction (ADR) i.e. explicitly documented to be related to any of the medications of interest in the study during the observation period, the site personnel will document as per standard practice i.e. for established medicines all serious suspected ADRs will be reported through the yellow card scheme. For new medicines all suspected ADRs will be reported through the black triangle scheme. Similarly, during the course of data extraction in this study, if a patient is recorded in the medical chart as pregnant while taking a medicinal product during the observation period, the site personnel will document as per standard practice. This will all be collected outside of the study database and reported onto a separate study specific ADR and pregnancy log.

All ADR's and pregnancies will be reported to the applicable marketing authorization holder within 2 business days of becoming aware of the event.

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8.3. SAMPLE SIZE CALCULATION

Based on a feasibility survey conducted at the participating sites, it is estimated that data from at least 800 patients with mPAP <21 mmHg, at least 500 patients with mPAP ≥21-<25 mmHg, and at least 5600 patients with mPAP ≥25mmHg will be available (Table 4). This study aims to collect data from all eligible patients with mPAP <21 mmHg and mPAP ≥21-<25 mmHg. For patients with mPAP ≥25mmHg, data from all eligible patients with PVR <2 and PVR ≥2-<3 will be collected, collectively resulting in at least 600 patients.

For patients with mPAP ≥25mmHg and PVR ≥3, all eligible patients will be classified by the PH group as defined by the treating physician. For patients classified in each PH group, patients will be systematically sampled such that for the total number of eligible patients in the PH group ***x***, every ***x/200***th patient will be sampled after ordering the patients by their NHS ID. Non-integers will be rounded down to ensure adequate number of patients enrolled. This sample size will allow for descriptive analyses in each PH group.

Table 4 Sample size

Main cohort	Sub-cohort	mPAP (mmHg)	PVR (WU)	Diagnosis*	Patients available (estimate)	Patients included (estimate)
1	1a	<21	<2	*not applicable*	≥800	≥800
	1b		≥2-<3	*not applicable*		
	1c		≥3	*not applicable*		
2	2a	≥21-<25	<2	*not applicable*	≥500	≥500
	2b		≥2-<3	*not applicable*		
	2c		≥3	*not applicable*		
3	3a	≥25	<2	*not applicable*	≥600	≥600
	3b		≥2-<3	*not applicable*		
	3c		≥3	PH Gp1	≥5000	≥1000 (incl. ≥200 patients in each PH group)
	3d			PH Gp2		
	3e			PH Gp3		
	3f			PH Gp4		
	3g			PH Gp5		

PH Group as defined by the treating physician: PH Gp1: Pulmonary arterial hypertension; PH Gp2: Pulmonary hypertension due to left heart disease; PH Gp3: Pulmonary hypertension due to lung diseases and/or hypoxia; PH Gp4: Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions; PH Gp5: Pulmonary hypertension with unclear and/or multifactorial mechanisms

* Patients may be further stratified based on diagnoses at index RHC, including the presence of heart and lung diseases.

8.4. DATA ANALYSIS

A statistical analysis plan (SAP) will be prepared and finalized before the end of data extraction. The SAP will provide full details of the analyses.

Patient and clinical characteristics, biomarkers, therapies, comorbidities and medical history, and QoL of patients in each cohort and overall at baseline and at follow-up visits will be summarized using descriptive statistics. Absolute and percentage change from index RHC in patient and clinical characteristics, biomarkers, therapies, and QoL from baseline, measured longitudinally after baseline, in each cohort will be summarized using descriptive statistics. Continuous variables and duration of follow up of each cohort will be summarized with mean, standard deviation, median, interquartile range, range, minimum, and maximum. Two-sided 95% confidence intervals of the mean/median will be provided for relevant variables. Categorical variables will be summarized with number of patients, number of missing values, frequency counts, and percentages. Two-sided 95% confidence intervals will be provided for relevant estimates.

Associations between mPAP as well as PVR with patient and clinical characteristics, biomarkers, therapies, comorbidities and medical history, and outcomes will be assessed at baseline and longitudinally after baseline using multivariable regression methods, adjusting for potential confounders and treatment. Association between shuttle walk test and 6MWD will be evaluated at baseline and longitudinally after baseline, if available.

One-year mortality risk of each cohort will be estimated using data at baseline and at 1-year follow-up, based on published risk assessment strategies[6-10]. Estimated mortality risk will be tabulated against observed mortality.

Kaplan-Meier estimates of time-to-event endpoints will be tabulated for each cohort and overall. Cox-proportional hazards models will be used to model time from index RHC to first all-cause hospitalization and time to all-cause mortality, adjusting for all potential confounders and prognostic factors. All-cause hospitalization rate and all-cause death rate will be calculated for all repeated hospitalizations and the death event, respectively, in each cohort and compared among cohorts using Poisson regression, adjusting for all potential confounders and prognostic factors, as well as treatment.

Model-finding techniques may be employed to achieved more parsimonious models.

Comparative analyses will be done among cohorts as specified in Table 5. Inclusion of cohorts in comparative analysis will depend on sample size. Change in patient and clinical characteristics, biomarkers, therapies, and QoL from baseline, measured longitudinally after baseline, will be compared among cohorts using multivariable regression methods, adjusting for all potential confounders and treatment. For all-cause hospitalization analyses, patients will be censored at the end of observation period, date of last contact or the last cutoff date of HES or ISD data, whichever occurred first. For all-cause mortality analyses, patients will be censored at the end of observation period, date of last contact or the cutoff date of death data from ONS or ISD, whichever occurred first. For time to progression to PH analysis, patients will be censored at the end of observation period, date of last contact or death, whichever occurs first. Score of each domain in CAMPHOR and summary score of emPHasis-10 at baseline and longitudinally after baseline will be compared among cohorts using linear regression, adjusting for all potential confounders and treatment.

Kaplan-Meier curves within subgroups will notbe derived unless there are at least 10 events in that specific sub-group. All Kaplan-Meier curves will be drawn up to the time-point when at least 10% of baseline patients are at risk (this is valid overall as in any of the sub-groups). This is also valid for Poisson models, i.e. these will be run if at least 10 events in individual patients are available (overall as in any of the sub-groups).

If sample size allows, patients with mPAP≥25 mmHg or PVR≥3 will be divided into further subgroups. If sample size is limited for certain subgroups, patient groups may be merged for analysis. Depending on feasibility and number of patients that changed therapy during follow up, analyses may be adjusted for any change in treatment; time-dependent models may be used for this purpose. If more than 5% patients received lung and/or heart transplant during follow up, a sensitivity analysis in which patients are censored at time of transplant may be considered. Since data from multiple hospitals are included in the study, hospital may be investigated in the statistical models as confounder and the use of frailty terms for survival models will be evaluated [17]. A sensitivity analysis may be conducted among patients who fell into the mPAP and PVR category for the first time at time of index RHC.

Competing risk analysis will be conducted including the following events: hospitalization, disease progression and death. Adjusted cumulative incidence functions will be derived overall and by sub-group (if the sample size allows).

Due to the observational and retrospective nature of the study, some study variables are expected to be missing or incomplete. Multiple imputations for missing demographic characteristics and disease characteristics at index date will be investigated. Sensitivity analysis using multiple imputation techniques may be implemented. Rules for handling of missing or incomplete data will be described in the SAP [18].

Table 5 Models for comparisons

Model								
1	mPAP <21 mmHg *Cohort 1*	mPAP ≥21 - <25 mmHg *Cohort 2* (reference group)	mPAP ≥25 mmHg *Cohort 3*					
2	mPAP <21 mmHg & PVR <2 WU *Cohort 1a*	mPAP ≥21 - <25 mmHg & PVR <2 WU *Cohort 2a* (reference group)	mPAP ≥25mmHg & PVR <2 WU *Cohort 3a*					
3	mPAP <21 mmHg & PVR ≥2 - <3 WU *Cohort 1b*	mPAP ≥21 - <25 mmHg & PVR ≥2 - <3 WU *Cohort 2b* (reference group)	mPAP ≥25 mmHg & PVR ≥2 - <3 WU *Cohort 3b*					
4	mPAP <21 mmHg & PVR ≥3 WU *Cohort 1c*	mPAP ≥21 - <25 mmHg & PVR ≥3 WU *Cohort 2c* (reference group)	mPAP ≥25 mmHg & PVR ≥3 WU *Cohort 3c-3g*	PH Gp1 *Cohort 3c*	PH Gp2 *Cohort 3d*	PH Gp3 *Cohort 3e*	PH Gp4 *Cohort 3f*	PH Gp5 *Cohort 3g*
5	PVR <2 WU *Pooled cohort 1a, 2a, 3a*	PVR ≥2 - <3 WU *Pooled cohort 1b, 2b, 3b* (reference group)	PVR ≥3 WU *Pooled cohort 1c, 2c, 3c-3g*	PH Gp1 *Cohort 3c*	PH Gp2 *Cohort 3d*	PH Gp3 *Cohort 3e*	PH Gp4 *Cohort 3f*	PH Gp5 *Cohort 3g*
6	mPAP <21 mmHg & PVR <2 WU *Cohort 1a*	mPAP <21 mmHg & PVR ≥2 - <3 WU *Cohort 1b* (reference group)	mPAP <21 mmHg & PVR ≥3 WU *Cohort 1c*					
7	mPAP ≥21 - <25 mmHg &	mPAP ≥21 - <25 mmHg &	mPAP ≥21 - <25 mmHg &					

	PVR <2 WU *Cohort 2a*	PVR ≥2 - <3 WU *Cohort 2b* (reference group)	PVR ≥3 WU *Cohort 2c*					
8	mPAP ≥25mmHg & PVR <2 WU *Cohort 3a*	mPAP ≥25 mmHg & PVR ≥2 - <3 WU *Cohort 3b* (reference group)	mPAP ≥25 mmHg & PVR ≥3 WU *Cohort 3c-3g*	PH Gp1 *Cohort 3c*	PH Gp2 *Cohort 3d*	PH Gp3 *Cohort 3e*	PH Gp4 *Cohort 3f*	PH Gp5 *Cohort 3g*

8.5. DISCUSSION OF THE RESEARCH METHODS

This is a retrospective observational cohort study based on patient medical chart review. The retrospective medical chart review design is a widely applicable research methodology [19].

Different limitations and weaknesses inherent to any retrospective observational studies (e.g., missing data, incomplete record keeping leading to recall bias or misclassification bias, selection bias) should be considered. Exclusion of patients with missing mPAP or PVR values may exclude RHC performed early in the eligibility period, or patients with extremely severe PH. Patients medical records in the PH specialist centers may not have full information about patients' participation in investigational clinical trial with investigational product throughout the observational period, especially among patients with mPAP <21 or ≥21-<25 mmHg; this may result in such patients not excluded in the study. Caution will be taken when interpreting results of main and sensitivity analyses. Furthermore, potential differences in clinical assessments across hospitals and across operators within each hospital may exist. A waiver for informed consent will be requested from Ethics Committees of participating hospitals, and is fundamental to enable deceased patients to be included in this study.

Actions implemented in this study to address the potential risk for misclassification bias include systematic data extraction from the chart review using a standardized electronic Case Report Form (eCRF), online data quality checks upon data entry into the electronic data collection (eDC) system, and training of investigator, study coordinator, or designee to perform data extraction. Precise definition and explicit criteria for variables collected are provided in the eCRF completion guidelines to reduce variability in data extraction and interpretation between investigator, study coordinator, or designee at sites.

9. DATA MANAGEMENT

9.1. DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

Case Report Forms (CRF) will be designed by the CI in collaboration with members of the scientific committee. Electronic case report forms (eCRF) are provided for each patient in electronic format. All data will be entered or imported through an eDC system called the PAHTool by personnel or a designee at each participating site based on information from the source documents, and transmitted in a secure manner to the study server. Data must be entered into the eDC in English.

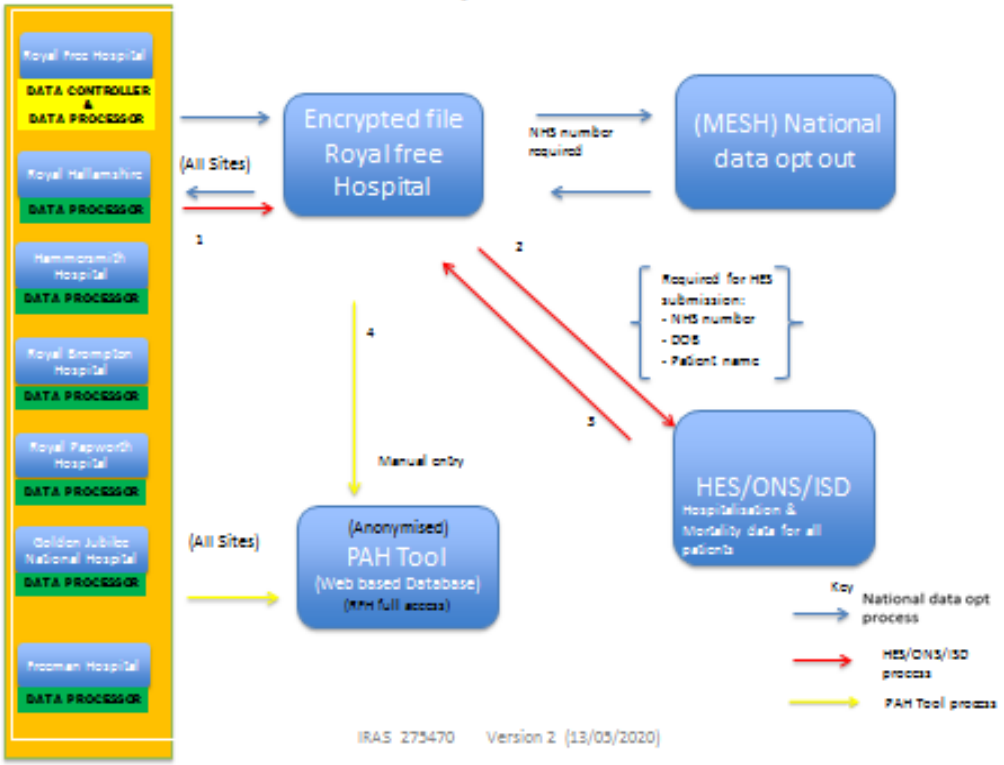
The standardized eDC will be provided for investigators, study coordinators, or designees before start of data extraction. The eDC system (PAHTool) used in this study will allow for data quality checks. Automatic edit checks for data inconsistencies will be pre-programmed, and may result in queries to the site. Data entered may be reviewed for implausible data, missing data, assessments not conducted, and/or incomplete information. This review may result in queries to the participating sites.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the forms. The Staff Delegation of Responsibilities Log RFLRDLOG0004 will identify all study personnel responsible for data extraction, entry, handling and managing the database. The data custodian for this study is Chief Investigator, Dr Gerry Coghlan.

9.2. DATA PROTECTION AND CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act 2018.
Specific patient identifiable information (NHS ID) will be transmitted in a secure manner to NHS Digital and ISD for the purpose of linkage to the hospitalization and death databases. Only the participant's study identification number will be used for communications across sites and for data analysis. The sponsor Participant ID log RFLRDLOG0002 can be used to cross reference participant's identifiable information.

Study Data Flow



9.3. DATA HANDLING AND RECORD KEEPING

The PAHTool eDC system will be created and maintained by INOVULTUS, Lda. and accessed via web browser by authorized users for entry into the study eCRF. Automatic data quality check will be pre-programmed by developer of the PAHTool. Further details on data handling and record keeping will be described in a separate data management plan.

9.4. ACCESS TO DATA

The Investigator(s)/institution(s) will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents.

9.5. TRANSFERRING AND TRANSPORTING DATA

All study data will be stored in a secure server at the Royal Free Hospital. Any necessary transfer of study data with patient identifiable information, for example, for linkage to hospital and death databases, will be done electronically using appropriate encryption process, in accordance with the UK Data Protection Act 2018.

9.6. ARCHIVING

During the course of research, all records are the responsibility of the Investigator and must be kept in secure conditions. The study essential documents along with the study database will be archived in accordance with the sponsor SOP0044. The agreed archiving period for this study will be 10 years. This will include any study databases.

Each PI at any participating site will archive the study essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement.

10. MONITORING, AUDIT & INSPECTION

The study will be monitored according to the self-monitoring report agreed by the Sponsor. It is the responsibility of the CI to ensure that the Sponsor's self-monitoring template is completed and submitted as instructed The RF R&D Office governance team will determine the initial project risk assessment and justify change as the study progresses.

The PI at each collaborating site in addition to site monitoring visits may also be required to complete self-monitoring form(s) and must return the form to the sponsor for review and action. Failure for any PI to comply with requests for on behalf of the sponsor may be escalated in accordance with SOP032 Handling of non-compliance; the site may also be selected for a GCP audit.

It is the Sponsor's responsibility to ensure that any findings identified in the self-monitoring report are actioned appropriately and in a timely manner and that any violations of GCP or the protocol will be reported to the CI & sponsor representative. Any serious breach will be handled according to SOP033 Serious Breach Reporting

Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

The CI will be provided with a copy of the self-monitoring report during the Trial Initiation monitoring visit.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. RESEARCH ETHICS COMMITTEE (REC) REVIEW & REPORTS

Before any site can enter patient data into the study, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D). If conducting the study at Royal Free London NHS Foundation Trust, contact the R&D team for any assistance.

The site must conduct the study in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority/ies as appropriate which was given favourable opinion by the Research Ethics Committee (REC) and the Health Research Authority (HRA) where applicable.

The Chief Investigator will be provided (via the Sponsor) with file indexes TMF Index RLFRDDOC0013 and ISF index RFLRDOC0003 for use with SOP019 'Preparation and Maintenance of the Site File – and SOP054 'Preparation and Maintenance of the Trial Master File'. The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. Refer to R&D OFFICE SOP0016 'Protocol amendments of RFL Sponsored Studies' and R&D OFFICE SOP003 'Reporting amendments'.
Within 90 days after the end of the study, the CI and Sponsor will ensure that the REC is notified that the study has finished.

If the study is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to R&D OFFICE SOP0030 'Study Close Down'

The CI will supply an End of Study report of the study to the REC within one year after the end of the study. The sponsor can provide an End of study Report template RFLRDDOC0005.

11.2. ANNUAL PROGRESS REPORTS (APRS)

The Chief Investigator will prepare the APR in accordance with SOP056. It will be reviewed by the RF R&D Office and sent to the main REC within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, and annually until the study is declared ended.

11.3. NOTIFICATION OF SERIOUS BREACHES OF GCP AND/OR THE PROTOCOL

Any Protocol Deviations or Violations will be documented using RFLRDDOC0006, and entered onto the sponsor's log RFLRDLOG0005. Potential Serious Breaches and Urgent Safety Measures will be recorded both on the Sponsor's Log RFLRDLOG0005 and processed according to SOP0033 (Serious Breach of GCP).
A "serious breach" is a breach which is likely to effect to a significant degree:
(a) The safety or physical or mental integrity of the participants of the study; or
(b) The scientific value of the study.
The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a serious breach

11.4. AMENDMENTS

If the CI wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the trial. Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

11.5. PROTOCOL COMPLIANCE

The study will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 3, November 2017).

11.6. FINANCIAL AND OTHER COMPETING INTERESTS FOR THE CHIEF INVESTIGATOR, PIS AT EACH SITE AND COMMITTEE MEMBERS FOR THE OVERALL TRIAL MANAGEMENT

This study is funded by Actelion Pharmaceuticals Ltd, which manufactures and markets medications for PAH treatment. Actelion is collaborating with the Sponsor for the conduct of the study. Rose Ong and Michael Preiss, Actelion employees, are Steering Committee Members.

11.7. INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

11.8. PEER REVIEW

This protocol has been peer reviewed before it is authorised for use in accordance with the Sponsor's SOP on Peer Review (SOP 055).

11.9. PUBLIC AND PATIENT INVOLVEMENT

Since the current study is retrospective in nature, only personnel involved in the conduct of study will be involved. No patients, service users, and/or their carers will be involved in the study.

12. DISSEMINIATION POLICY

Publication: "Any activity that discloses, outside of the circle of study investigators, any final or interim data or results of the Study, or any details of the Study methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Study have a responsibility to ensure that results of scientific interest arising from Study are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Study in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Study, data shall be consolidated over the duration of the Study, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Study shall lie with the Sponsor in the first instance.

Publication of the study results will be in collaboration with Actelion, and in accordance with the International Committee of Medical Journal Editors standards and the Strengthening the Reporting of Observational Studies in Epidemiology statement [20].

12.1. AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

Authorship eligibility will be determined in accordance to the International Committee of Medical Journal Editors standards. All publications are subject to permission by the Sponsor and Funder. The Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- Members of the Research and Development Office shall be acknowledged as co-authors if they contributed in the design and, or scientific evaluation of the protocol.

If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

All publications related to the Study shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

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1. APPENDICIES

1.1.1. DATA MANAGEMENT

Accopharm clinical trials services will be responsible for data management, which will include eCRF checking, generating data queries and data management reporting.

1.1.2. TRIAL DOCUMENTATION AND ARCHIVING

During the course of research, all records are the responsibility of the Investigator and must be kept in secure conditions. The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP0044. The agreed archiving period for this trial will be 10 years. This will include any study databases.

Each PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement

1.2. APPENDIX 1 – AUTHORISATION OF PARTICIPATING SITES

1. Royal Free Hospital, Pond St, Hampstead, London NW3 2QG
2. Hammersmith Hospital, 72 Du Cane Rd, White City, London W12
3. The Royal Brompton Hospital, Sydney St, Chelsea, London SW3 6NP
4. Royal Hallamshire, Glossop Rd, Sheffield S10 2JF
5. Freeman Hospital, Freeman Rd, High Heaton, Newcastle upon Tyne NE7 7DN
6. Royal Papworth Hospital, Papworth Rd, Cambridge CB2 0AY
7. The Golden Jubilee Hospital, Agamemnon St, Clydebank G81 4DY

1.2.1. REQUIRED DOCUMENTATION

- Current CV's and GCP certificate for research team
- Completed training and delegation logs

1.2.2. PROCEDURE FOR INITIATING/OPENING A NEW SITE

The study manager Dr Nina Karia and co-ordinator Ivy Wanjiku will perform site initiation visits via teleconference for all participating sites prior to commencing the study.

1.2.3. PRINCIPAL INVESTIGATOR RESPONSIBILITIES

1. Attendance at the initiation meeting/teleconference,
2. Training of new members of the trial team in the protocol and its procedures,
3. Ensuring that the ISF is accurately maintained,
4. Dissemination of important safety or trial related information to all stakeholders within their site, safety reporting within the timelines

1.3. APPENDIX 2 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA1	2	28/04/2020	Dr Gerry Coghlan	• Update to data extraction timelines due to delays starting the project to 30th June 2020-30th September 2020 • Update to data flow diagram to include the national opt out process • Addition of a patient leaflet to be displayed at participating sites • Primary objective updated to a single objective. Other objectives are now secondary objectives. Outcome measures updated accordingly • Addition of Actelion (funder) Statistician as an additional

				member if the TSC • Addition of a minimum sample size for each PH group as well as clarification on systemic sampling for each group. • Addition of smoking as a comorbidity. Clarification of the following under clinical characterisation in order to standardise results across all sites: Right Heart Catherterisation updated to heart catheterisation;RA area or diameter updated to RA size and LA characteristics updated to LA size Update to the definition of the index if Right Heart Catheter in the inclusion/exclusion criteria
NSA1	2.5	26/08/2020	Dr Gerry Coghlan	PI change at participating site (Royal Brompton) Dr Stephen John Wort to be replaced by Dr Colm McCabe
NSA 2	3.0	27/10/2020	Dr Gerry Coghlan	Addition of Rachel Ochiel, Ivy Wanjiku, Federico Ricciardi and Patrick Moneuse to SSC members list • Update to study observation period from 1 Jan 2009 - 31 Dec 2019 to 1 Jan 2009 – 1st March 2020 • Update to eligibility period from 1 Jan 2009 -31 Dec 2016 to 1 Jan 2009-31 Dec 2017 • Update to data extraction timelines from 29th May 2020- 30 August 2020 to 1st

				November 2020-1st February 2021 • Exclusion criteria clarified to state Enrolled in any interventional clinical trial with an investigational product 3 months prior to or at the time of RHC • Addition of ECG assessment to the data collection schedule, already mentioned in section 7.2 of the Protocol. • Clarification on self-monitoring requirements

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or HRA.