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NAtional cohort study of Idiopathic AnD heritable pulmonary arterial hypertension

Submission date 03/07/2013	**Recruitment status** Suspended	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 14/08/2013	**Overall study status** Completed	
Last Edited 09/07/2020	**Condition category** Circulatory System	

Plain English summary of protocol

Current plain English summary as of 04/10/2018:
Background and study aims
High blood pressure in the lungs is a rare condition that can shorten life. Although the cause of this disease is usually unknown, in about 70% of heritable and 15-20% of cases with unknown cause there is a change in a gene (a mutation) that controls how blood vessels grow and function. The gene is called BMPR2. Although mutations in BMPR2 are a risk factor for high blood pressure in the lungs, not everyone with a mutation gets the disease. Additional genetic and environmental factors are likely to contribute. We suspect that mutations in other genes are responsible for some cases. In this study we aim to recruit patients and follow them up for several years. We hope to discover new mutations for this disease and to find out what factors lead to poor outcome, and to understand what triggers disease in patients with mutations.

Who can participate?
Adults with high blood pressure in the lungs, their relatives and controls

What does the study involve?
Subjects are enrolled into a national study. Patients will be seen at their routine follow-up and have additional blood samples taken. Relatives will be seen every year and have tests and blood samples taken.

What are the possible benefits and risks of participating?
It is not known whether you will gain any personal benefit from this research. However, information from this study could improve our understanding of the disease and help doctors to treat patients better in the future.

Where is the study run from?
All pulmonary hypertension centres in the UK

When is the study starting and how long is it expected to run for?
The study is expected to start in September 2013 and will run for at least 5 years.

Who is funding the study?
The British Heart Foundation (UK) and Medical Research Council (MRC), UK.

Who is the main contact?
Professor Nicholas Morrell
Tel: 01223 331666
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Previous plain English summary:
Background and study aims
High blood pressure in the lungs is a rare condition that can shorten life. Although the cause of this disease is usually unknown, in about 70% of heritable and 15-20% of cases with unknown cause there is a change in a gene (a mutation) that controls how blood vessels grow and function. The gene is called BMPR2. Although mutations in BMPR2 are a risk factor for high blood pressure in the lungs, not everyone with a mutation gets the disease. Additional genetic and environmental factors are likely to contribute. We suspect that mutations in other genes are responsible for some cases. In this study we aim to recruit patients and follow them up for several years. We hope to discover new mutations for this disease and to find out what factors lead to poor outcome, and to understand what triggers disease in patients with mutations.

Who can participate?
Adults with high blood pressure in the lungs and their relatives can participate in this study.

What does the study involve?
Subjects are enrolled into a national study. Patients will be seen at their routine follow-up and have additional blood and urine samples. Relatives will be seen every 6 months and have tests, blood and urine samples.

What are the possible benefits and risks of participating?
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Where is the study run from?
The study will be run from all pulmonary hypertension centres in the UK and Dublin, Ireland.

When is the study starting and how long is it expected to run for?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT01907295

Protocol serial number
A092860

Study information

Scientific Title
NAtional cohort study of Idiopathic AnD heritable pulmonary arterial hypertension

Acronym
NAIAD

Study objectives
Current study hypothesis as of 18/10/2019:
Idiopathic and heritable forms of pulmonary arterial hypertension (PAH) are devastating conditions associated with high morbidity and mortality. The disease is usually diagnosed late by finding a markedly increase mean pulmonary arterial pressure, the result of progressive narrowing and remodeling of the pulmonary vasculature, and leading to the failure of the right ventricle. This disease tends to present in the middle decades of life, with a female predominance (f:m 2.3:1). Untreated, it carries a 3 year mortality of 60%. A major breakthrough in our understanding of the pathobiology of PAH was the identification of heterozygous disease causing mutations in the gene coding the bone morphogenetic protein type 2 receptor (BMPR2) in families with PAH. Although research over the last 10 years has provided important clues, the precise cellular and molecular mechanisms leading to the disease manifestation remain incompletely understood. In addition, the penetrance of this mutation in families is low, on average approximately 20%. The existence of discordant monozygotic twins points to the presence of important environmental factors. A further 15-26% of apparently sporadic cases of idiopathic PAH harbour mutations in BMPR2. Data is now emerging that patients with mutations present earlier and die of their disease at an earlier age than patients without BMPR2 mutations. The exact aetiology remains unknown and patients appear to progress at different rates, and respond differently to existing treatments. This study will provide a more complete understanding of the aetiology and natural history of idiopathic and heritable PAH from a

detailed analysis of their genetic influences and the contribution of potential environmental factors, linked to deep phenotyping of a national cohort. Identification of the critical environmental and additional genetic factors leading to the disease manifestation in PAH will lead to strategies for disease prevention and may identify pathways for the development of novel therapies, and provide a basis for mechanistic studies in vitro and in vivo.

Funding has been awarded from the British Heart Foundation and the Medical Research Council to establish and maintain a UK & Ireland cohort study of heritable and idiopathic pulmonary arterial hypertension (March 2013-2018). The purpose of this study is to set up a national cohort study of patients with idiopathic PAH, and PAH due to mutations in BMPR2. Family members with and without BMPR2 mutations will also be studied. The identification and follow up of patients with and without BMPR2 mutations, and possibly other mutations, will provide important information on the clinical course of genetic causes of PAH. It will also provide a platform for the identification of novel genetic variation in the BMPR2 negative patients. The longitudinal follow up and sampling of unaffected BMPR2 mutation carriers, and mutation negative family members, will provide information on penetrance, and whether different mutations confer specific risks. In addition, the cohort will provide samples for hypothesis driven studies to ascertain genetic or environmental triggers for this disease. The cohort will further provide a basis for future research and prevention studies or experimental medicine interventions targeting the BMPR2 pathway. Patients and relatives will be followed up longitudinally for sampling and clinical assessment and data will be collected and semi-anonymised.

Previous study hypothesis:
Idiopathic and heritable forms of pulmonary arterial hypertension (PAH) are devastating conditions associated with high morbidity and mortality. The disease is usually diagnosed late by finding a markedly increase mean pulmonary arterial pressure, the result of progressive narrowing and remodeling of the pulmonary vasculature, and leading to the failure of the right ventricle. This disease tends to present in the middle decades of life, with a female predominance (f:m 2.3:1). Untreated, it carries a 3 year mortality of 60%. A major breakthrough in our understanding of the pathobiology of PAH was the identification of heterozygous disease causing mutations in the gene coding the bone morphogenetic protein type 2 receptor (BMPR2) in families with PAH. Although research over the last 10 years has provided important clues, the precise cellular and molecular mechanisms leading to the disease manifestation remain incompletely understood. In addition, the penetrance of this mutation in families is low, on average approximately 20%. The existence of discordant monozygotic twins points to the presence of important environmental factors. A further 15-26% of apparently sporadic cases of idiopathic PAH harbour mutations in BMPR2. Data is now emerging that patients with mutations present earlier and die of their disease at an earlier age than patients without BMPR2 mutations. The exact aetiology remains unknown and patients appear to progress at different rates, and respond differently to existing treatments. This study will provide a more complete understanding of the aetiology and natural history of idiopathic and heritable PAH from a detailed analysis of their genetic influences and the contribution of potential environmental factors, linked to deep phenotyping of a national cohort. Identification of the critical environmental and additional genetic factors leading to the disease manifestation in PAH will lead to strategies for disease prevention and may identify pathways for the development of novel therapies, and provide a basis for mechanistic studies in vitro and in vivo.

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with and without BMPR2 mutations will also be studied. The identification and follow up of patients with and without BMPR2 mutations, and possibly other mutations, will provide important information on the clinical course of genetic causes of PAH. It will also provide a platform for the identification of novel genetic variation in the BMPR2 negative patients. The longitudinal follow up and sampling of unaffected BMPR2 mutation carriers, and mutation negative family members, will provide information on penetrance, and whether different mutations confer specific risks. In addition, the cohort will provide samples for hypothesis driven studies to ascertain genetic or environmental triggers for this disease. The cohort will further provide a basis for future research and prevention studies or experimental medicine interventions targeting the BMPR2 pathway. Patients and relatives will be screened for the BMPR2 mutation before recruitment into to the study. They will be followed up every 6 months with for sampling and clinical assessment and data will be collected and semi-anonymised.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East of England-Hatfield, 01/08/2018, REC reference: 13/EE/0203

Study design
Multicentre observational cohort study

Primary study design
Observational

Study type(s)
Screening

Health condition(s) or problem(s) studied
Idiopathic, heritable and anorexigenic pulmonary arterial hypertension

Interventions
Current interventions as of 04/10/2018:
PAH patients will be seen at their local centre by their service team but they will have additional blood samples taken. Relatives of PAH patients will be seen every year at their nearest PAH centre. Subjects will be followed up long term for the length of the study. Tests will include:
1. Epidemiology Questionnaire to assess factors affecting health
2. An echocardiogram (ECHO) to assess the size, shape, pumping action and the extent of any damage to the heart
3. Lung function tests, which include blowing measurements to assess gas volumes within the lungs, as well as assessment of how the lungs exchange gases
4. Optional right heart catheterisation (RHC) to determine how much blood the heart is pumping during rest and exercise
5. Optional cardiac magnetic tesonance tests to measure heart function (to be done only once)
6. Six minute walk test to measure exercise capacity
7. Cardiopulmonary exercise test (bicycle exercise test), which will indicate how much blood the heart pumps during rest and different levels of exercise
8. Electrocardiogram (ECG) to measure the electrical activity of the heart
9. Blood tests

Previous interventions:
PAH patients will be seen at their local centre by their service team but they will have additional bloods and urine samples taken. Relatives of PAH patients will be seen every 6 months at their nearest PAH centre. Subjects will be seen for up to 5 years depending on when they are recruited in to the study. Tests will include:

1. CAMPHOR questionnaire to assess your quality of life
2. Epidemiology Questionnaire to assess factors affecting health
3. An echocardiogram (ECHO) to assess the size, shape, pumping action and the extent of any damage to the heart.
4. Lung function tests which include blowing measurements to assess gas volumes within the lungs as well as assessment of how the lungs exchange gases.
5. Optional right heart catheterisation (RHC) to determine how much blood your heart is pumping while you are resting and on exercise. Optional Cardiac Magnetic Resonance tests. To measure heart function. (to be done only once)
6. Six minute walk test. To measure exercise capacity
7. Cardiopulmonary exercise test. A bicycle exercise test, which will indicate how much blood your heart pumps while resting and with different levels of exercise.
8. Electrocardiogram (ECG), a test that measures the electrical activity of the heart
9. Blood tests
10. Urine

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
Recruitment of significant numbers of cases of heritable and idiopathic PAH to the cohort.

Measured at 5 years

Key secondary outcome(s))
1. Recruitment of significant numbers of relatives of patients with HPAH for follow up.
2. Identification of novel causal genetic variation underlying heritable and idiopathic PAH.
3. Identification of novel biomarkers of disease progression or response to therapy from patient samples
4. Identification of potential environmental triggers of disease from epidemiological studies

Outcomes measured at 5 years

Completion date
30/06/2023

Eligibility

Key inclusion criteria

Patient
1. Participant is willing and able to give informed consent for participation in the study.
2. Male or Female, aged 16-80 years
3. Diagnosed with idiopathic, anorexigen-induced or heritable PAH.

Relative:
1. Participant is willing and able to give informed consent for participation in the study.
2. Male or Female, aged 16-80 years
3. Has a family member diagnosed with idiopathic, anorexigen-induced, or heritable PAH

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
Patient
The participant may not enter the study if ANY of the following apply:
1. Patient is unable to give informed consent.
2. Not suffering from idiopathic, anorexigen-induced, or heritable PAH

Relative
The participant may not enter the study if ANY of the following apply:
1. Patient is unable to give informed consent

Date of first enrolment
01/09/2013

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

University of Cambridge
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (UK)

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Medical Research Council (MRC) (UK)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes