Improving and measuring the function of patients with pulmonary hypertension through rehabilitation

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Abstract

Pulmonary hypertension is a disorder of the pulmonary circulation which arises from many causes. Regardless of aetiology, pulmonary hypertension results in breathlessness and reduced functional ability, and impacts negatively on survival. There is a growing body of evidence for the benefits of rehabilitation in pulmonary hypertension, and international guidelines recommend its inclusion in patient care pathways. Despite this, access to rehabilitation programmes for patients with pulmonary hypertension in the UK is very limited.

This programme of work therefore sought to examine how existing research and knowledge of rehabilitation in patients with pulmonary hypertension could be advanced, with a particular focus on the delivery of rehabilitation in clinical practice for patients with pulmonary hypertension in the UK, and the outcomes used to assess the benefits of rehabilitation.

This goal has been achieved through a Review of Service, which described an innovative rehabilitation intervention for patients with pulmonary hypertension, and a Literature Review which highlighted the importance of selecting suitable outcome measures in the design of studies of rehabilitation. In the wake of changes to clinical practice brought about by the COVID-19 pandemic, the PERSPIRE study was undertaken which demonstrated the safety and potential of the 1-minute sit-to-stand test, an outcome which could be used in rehabilitation and in remote assessment.

The findings of the completed studies are novel and through their publication and wider dissemination across academic clinical and patient networks have an impact on research, policy and clinical practice. Plans have been made for further research which will continue to develop the findings of the research in this programme of work.

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This work is only possible because of the endeavours of those who have supported me to get here, and I would like to take this opportunity to express my profound thanks. My supervisory team of Professor Karen Sage, Professor David Kiely, Professor Janelle Yorke and Dr Molly Hashmi-Greenwood have all been overwhelmingly generous with their time, expertise and belief in me. From our first meeting Karen saw a potential in me and my work and supported me in fulfilling this, taking the care to know me well enough to recognise when I need to be pushed, nudged or left alone. David has used his vast experience and enthusiasm to inform this work and help to raise awareness of its importance. Janelle's wisdom and wide experience has helped to steer and guide us. Molly has given me professional accountability, support and friendship.

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Finally, thank you to the amazing patients with pulmonary hypertension, whose resilience and belief continually inspires me to achieve more on their behalf.

Abbreviations

All abbreviations are expanded in full in the text when first used, and are listed here for reference.

1MSTS	1-minute sit-to-stand
6MWD	6-minute walking distance
6MWT	6-minute walking test
BPA	Balloon Pulmonary Angioplasty
COPD	Chronic Obstructive Pulmonary Diseases
CPET	Cardiopulmonary Exercise Testing
CTEPH	Chromic Thromboembolic Pulmonary Hypertension
ISWT	Incremental Shuttle Walk Test
IPAH	Idiopathic Pulmonary Arterial Hypertension
mPAP	mean Pulmonary Arterial Pressure
NHS	National Health Service (UK)
NIHR	National Institute for Healthcare Research (UK)
PAH	Pulmonary Arterial Hypertension
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
PH-LHD	Pulmonary Hypertension associated with Left Heart Disease
PH-Lung	Pulmonary Hypertension associated with Lung Disease
PIFU	Patient Initiated Follow Up
PPI	Patient and Public Involvement in research
PVR	Pulmonary Vascular Resistance
RCT	Randomised Controlled Trial
RHC	Right Heart Catheter
RfPB	Research for Patient Benefit
RV	Right Ventricle
WHO	World Health Organisation
WHO-FC	World Health Organisation Functional Classification (of pulmonary hypertension)

Glossary of terms

Terms commonly used throughout the text are explained here in further detail.

1-minute sit-to-stand test	An exercise test in which patients are asked to stand up and sit down as many times as they can in one minute, without the use of arms. The measure is a count of the number of complete repetitions.
6-minute walk test	An exercise test in which patients are asked to walk as far as they can in 6 minutes over a fixed-distance track (30m). The measure is the total distance walked in the 6 minutes.
Incremental Shuttle Walk Test	An externally paced incremental walking test (beep test) over a fixed distance (10m). The measure is the total distance walked up to the point where the patient can no longer keep up with the external pace.
Pulmonary hypertension	A haemodynamic definition, including many conditions, defined by elevated pulmonary artery pressure.
Pulmonary rehabilitation	Community treatment programmes including exercise and education for patients with lung conditions (typically COPD).
Specialist Pulmonary Hypertension Referral Centre	Pulmonary hypertension centres in the UK and Ireland which care for patients with pulmonary hypertension, including 7 adult and 1 paediatric centres in the UK, which adhere to annual nationally audited standards of care.

Chapter 1 Introduction

This chapter introduces the author and the core values that underly their research practice. It outlines the background to the thesis before describing the research aims and providing an overview of the programme of work involved.

1.1 The Author

My name is Carol Keen. I work as a physiotherapist at Sheffield Teaching Hospitals NHS Foundation Trust where I have specialised for several years in rehabilitation, particularly of patients with respiratory illnesses. In 2017 I was successful in securing funding from PHA UK, the UK charity for patients with pulmonary hypertension, for an innovative role as Clinical Specialist Physiotherapist specialising in Pulmonary Hypertension at Sheffield Teaching Hospitals NHS Foundation Trust. The purpose of the role, the first of its kind in the UK, was to examine potential models of care for a rehabilitation service at the Sheffield Pulmonary Hypertension Specialist Centre, with a view to wider adoption of such a model at other Specialist Pulmonary Hypertension Referral Centres and securing long-term NHS funding for such services.

I began this PhD in 2018 following successful application for a Clinical-Academic PhD Fellowship awarded jointly by Sheffield Hallam University and Sheffield Teaching Hospital NHS Foundation Trust, before transferring my studies to Manchester Metropolitan University in 2020. I undertook this PhD part-time, continuing to work clinically alongside my studies, allowing me to fulfil a clinical-academic role that closely integrated my research and my clinical practice. The primary motivation behind my study was to generate research evidence that would drive change in clinical practice and through this bring benefits to patients with pulmonary hypertension. This ambition was supported by the publication of completed components of my research throughout the programme of work.

1.2 Philosophical assumptions

The programme of work described in this thesis is housed in the philosophy of pragmatism, first described by John Dewey, which places an emphasis on what is the goal of the research in considering research questions and the methods that are used to address them.[1]

The premise of pragmatism eschews the dualistic epistemologies of positivism and interpretivism. Instead, it considers a philosophy in which an external reality exists, and knowledge is acquired through the combination of action and reflection. Different knowledges are simply the result of different ways in which we engage with the world.[2]

Research is viewed as a process of cyclical inquiry in which beliefs are examined to generate actions, and actions are analysed to generate beliefs. Selection of methods is arrived at through a process of reflective inquiry: recognising a situation as problematic; considering the problem as a research question; developing a possible line of action or research design; reflecting on the choice of research methods; conducting the research.[1]

Inquiry occurs within a set of contexts, meaning that our prior experiences and knowledge cannot entirely reliably predict the outcomes of actions. Inquiry can be empirical but will also have an emotional element, satisfying some hope, need or desire. Choices made by researchers in relation to research questions or methods are made according to their beliefs of what is good or bad, right or wrong. According to Denzin,[3] any process of inquiry is always social in nature; any researcher's bid to generate knowledge is inevitably shaped by others, and by the politics of evidence.[1]

Methodologically, pragmatism is closely aligned with mixed-methods research. Greene and Hall[4] outline how pragmatic research has no fixed methodological requirements - it adopts a primarily problem-solving action-focussed process of inquiry. This allows the researcher to select any method, based on its appropriateness to the situation. Multiple sources of evidence can be used to

obtain and modify knowledge, which can in turn, inform potential solutions or actions.[4]

Within pragmatism, the outcomes of inquiry are considered not as truths, but as "warranted assertions".[2] That is, the assertions that come from inquiry are warranted on the basis of observation, but only in relation to the situation in which they were generated – they might not be true for all time and in all circumstances. Knowledge can be transferred between situations by guiding perception and problem solving and suggesting new ways forward. In this way the researcher can develop a body of knowledge in a field that leads to action and change by building on the findings from multiple related studies.[4]

This pragmatic approach was therefore adopted within this programme of work and is reflected in the questions asked and the methodological decisions made within each section to answer those questions.

1.3 Patient and Public Involvement

Involving patients and members of the public in research can improve its quality and relevance, by drawing from their experience to provide a perspective that might otherwise by overlooked by researchers.[5]

Patients and members of the public were actively involved in different stages of this programme of work. Access to patient groups was established in two ways:

- PHA UK is the UK patient charity for patients with pulmonary hypertension, with around 5000 members made up of patients and their kin. PHA UK support research through sharing lay summaries of proposals with selected members and discussing feedback with researchers, as well as connecting researchers with members who might be interested in further involvement.
- The Sheffield Teaching Hospitals Therapeutics and Palliative Care research panel is a Patient and Public Involvement group made up of people who have experience, either as a patient or carer, of a range of rehabilitation and

palliative care services. Researchers share their work with the panel in face-to-face or remote meetings and receive verbal and written feedback.

1.4 Research Background

1.4.1 Pulmonary hypertension

Pulmonary hypertension (PH) affects approximately 1% of the population, however forms of pulmonary hypertension for which there are specific therapies - pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) - are rare. Regardless of aetiology it impacts negatively on symptoms and survival and results in breathlessness, reduced functional ability and quality of life. For the majority of patients, it is a progressive life shortening condition.

1.4.1.1 Pathology and classification

Pulmonary hypertension arises from a progressive narrowing of the vessels of the pulmonary arterial bed. Sub-classifications of the disease are determined by shared clinical and pathophysiological characteristics (Table 1).

Table 1 - Clinical classification of pulmonary hypertension

Group	Description
Group 1	Pulmonary arterial hypertension (PAH)
Group 2	PH associated with left heart disease (PH-LHD)
Group 3	PH associated with lung diseases (PH-Lung)
Group 4	PH associated with pulmonary arterial obstructions including chromic thromboembolic disease (CTEPH)
Group 5	PH with unclear or multifactorial mechanisms
Adapted from ESC/ERS Guidelines[6]	

In PAH (Group 1), proliferation of vascular endothelial and smooth muscle cells leads to a thickening of the vessel walls and narrowing of the pulmonary arterial lumen. In patients with PH-LHD (Group 2), raised left atrial pressures result in secondary elevation of pulmonary pressures, while PH-Lung (Group 3) sees raised pulmonary arterial pressures arising from vascular damage in the lung parenchyma and hypoxic vasoconstriction. In patients with Group 4 pulmonary hypertension,

mechanical obstruction of the pulmonary vascular bed through e.g. clot is the primary process for arterial narrowing.

Irrespective of the underlying cause or mechanism, changes to the pulmonary vasculature lead to an increase in pulmonary vascular resistance (PVR) and vascular stiffness. The cumulative effect of these changes is an increase in right ventricular (RV) afterload and, in the end stages of the disease, right ventricular failure.

The ESC/ERS Guidelines on pulmonary hypertension[6] determine diagnosis through haemodynamic assessment by right heart catheterisation (RHC) where the mean pulmonary arterial pressure (mPAP) is > 20mmHg[6] (decreased to 20mmHg in the 2022 guidelines[6] from a value of 25mmHg in earlier guidelines[7]).

Common symptoms of pulmonary hypertension include increasing breathlessness, syncope and dizziness; oedema and ascites occur later in the disease. Estimates suggest a prevalence of around 1% in the global population, with PH-LHD and PH-lung as the leading causes. Prior to 2012, median survival was estimated at 2.8 years from diagnosis[8] however treatment options have advanced, and UK data from 2021 showed 5-year survival of 50% for patients with PAH.[9] It is a disease that spans all ages, with a mean age at diagnosis of 58 years for patients in Group 1.[9]

1.4.1.2 Patient perspective

Due to improvements in treatment options in the last two decades, pulmonary hypertension has evolved from a disease with poor prognosis to a long-term condition, where patients can live with the disease over many years. As such, it is important to consider patients' experiences of pulmonary hypertension and the impact it has on their lives and the lives of those close to them.

The changes to pulmonary vasculature lead to symptoms of increasing breathlessness, which in turn limits exercise capacity; patients find it harder to undertake physical activities and functional tasks. The World Health Organization classification which is used to evaluate disease severity describes its impact on physical function (Table 2).

Table 2 - World Health Organization classification of functional status of patients with pulmonary hypertension

Group	Description
WHO-FC I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC IV	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity
Adapted from ESC/ERS Guidelines[6]	

The symptoms of pulmonary hypertension have an extensive and wide-ranging impact on patients – in a 2017 survey 60% of respondents reported the disease as having a major impact on their quality of life.[10] In addition to the primary symptom of breathlessness which limit patients functional abilities, fear of symptom onset will prevent them from engaging in day to day activities,[11] consequently levels of physical activity and exercise are low in this patient population.[12,13]

Symptoms of breathlessness are often accompanied by feelings of fatigue[14] and cognitive impairment.[15] Pulmonary hypertension can have a negative impact on patients' mental health, including anxiety, low mood, isolation and suicidal ideation. Physical and psychological consequences of the disease can limit patients' ability to attend work or education, impacting on personal finances and driving feelings of insecurity. The disease and its consequences can modify patients' roles and relationships with family and friends, as well as their perceptions of themselves.[10,16]

1.4.1.3 Management of Patients with Pulmonary Hypertension

International collaborations to study pulmonary hypertension are relatively recent – the first World Health Organisation symposium on the subject was held in 1973 following an epidemic of cases attributed to a weight loss drug in the 1960's. Advances in treatment have markedly improved since the introduction of the first

intravenous drug therapy in 1995, and several targeted therapies are now available which are directed at nitric oxide, endothelin-1 and prostaglandin pathways.[17] Currently these treatments are only evidenced and available for patients in pulmonary hypertension Group 1 and Group 4. Management of patients with Group 2 and Group 3 pulmonary hypertension is based in optimising care of their underlying contributory conditions. Additionally, surgery (pulmonary endarterectomy, balloon pulmonary angioplasty) are options for some patients with chronic thromboembolic pulmonary hypertension; organ transplantation is an important treatment option for patients with very severe disease.

In the UK management of patients is based on European guidelines, the most recent version of which was published in 2022.[6] This specifies recommended diagnostic and treatment pathways, including the application of targeted drug therapies and the role of supportive therapies such as diuretics, anticoagulation or oxygen. Treatment is guided by a process of risk-assessment and stratification which places patients into categories of low, intermediate and high risk of 1-year mortality based on objective markers for disease progression; decisions to start or escalate therapies are made according to the identified level of risk.

The guidelines also recommend that patients with pulmonary hypertension are cared for in regional Specialist Pulmonary Hypertension Referral Centres, which manage the diagnosis of pulmonary hypertension as well as continued care for those patients with treatable illness (Groups 1 and 4). In the UK and Ireland there are 9 specialist centres based in London, Cambridge, Sheffield, Newcastle, Glasgow and Dublin. Over 11,000 adults with pulmonary hypertension are managed in specialist centres in the UK[9] and surveys show that patients are known to value the expert support that they provide.[10] However their regional nature means the specialist centres are often a great distance from patients, leading to long journeys with associated financial and time costs. Travel to appointments at specialist centres can be especially challenging for patients with work or caring responsibilities, as well as those more unwell patients with high impact of symptoms.

1.4.1.4 Exercise in Pulmonary Hypertension

The following section describes how the research evidence for exercise and rehabilitation in pulmonary hypertension has evolved. It is based on the findings of ERC/ERS guidelines[6,7,18–20] and the database searches established for the published Literature Review in the programme of work (Chapter 3), which continued to be monitored until July 2022.

While exercise has been widely recognised as beneficial in other respiratory conditions such as chronic obstructive pulmonary disease (COPD), early guidelines in pulmonary hypertension recommended that exercise should be limited due to its potential hazards.[19]

Two small exploratory studies in 2005[21] and 2007[22] indicated the safety and efficacy of general exercise programmes in patients with pulmonary hypertension and in 2006 Mereles et al.[23] published the first randomised controlled trial (RCT) of a supervised exercise programme including 3 weeks of inpatient rehabilitation and 12 weeks of monitored home-based exercise. They recruited 30 patients to the study and demonstrated significant improvements in 6-minute walking distance (6MWD) and quality of life, with no adverse events.

This new research was reflected in revised pulmonary hypertension guidelines of 2009[18] which advocated supervised exercise to a level of mild breathlessness to address physical deconditioning but recommended that excessive physical activity should be avoided to minimise the risk of syncope, dizziness or chest pain. The publication of subsequent rehabilitation studies and meta-analyses[24–27] led to updated guidelines in 2015[7] recommending that exercise training programmes for stable patients should be implemented by centres experienced in both care of patients with pulmonary hypertension and rehabilitation of compromised patients. These were the guidelines in place at the start of this programme of work.

A 2017 Cochrane review of evidence[28] included 6 RCTs and reported no adverse events and a change in 6MWD of 60 metres across the studies, in comparison to an estimated minimal clinically important difference of 41 metres in patients with

pulmonary hypertension.[29] A 2018 European Respiratory Society Task Force on exercise training in pulmonary hypertension called for supervised exercise in physically stable, deconditioned patients and for wider commissioning of rehabilitation programmes in this patient group.[20] The first muti-centred study of exercise in pulmonary hypertension was published in 2020 - including 129 participants across 11 sites in 10 countries it showed benefits in exercise capacity and quality of life with minimal adverse effects.[30] The 2022 guidelines for management of pulmonary hypertension[6] recommended supervised exercise for patients who are stable on treatment, and the development of specialized rehabilitation programmes for patients with pulmonary hypertension.

Studies have been published which examine the mechanisms of exercise in pulmonary hypertension[31–33] demonstrating that exercise can benefit patients by improving exercise capacity, muscular function, quality of life, peak oxygen consumption and possibly right ventricular function[20,34,35] as well as demonstrating the economic benefits of exercise interventions.[36] Barriers to exercise in patients with pulmonary hypertension can include lack of energy and motivation[37] and studies show that patients can be uncertain and fearful about undertaking exercise, while valuing interventions that would offer education, supervised and structured programmes and psychological support.[11,38]

In general, the rehabilitation model most widely used in studies of exercise in pulmonary hypertension is based on the original randomised controlled trial by Mereles,[23] named the Heidelberg model after the centre from which it originated. In this model patients undergo three weeks of intensive inpatient rehabilitation, including sessions up to three times a day, seven days per week. They are then encouraged to continue to exercise at home for a further twelve weeks, supported by weekly telephone calls. While the majority of this research is in patients with pulmonary arterial hypertension (Group 1), rehabilitation has also been demonstrated to be safe in patients with chronic thromboembolic disease (Group 4).[39]

It is recognised that delivering rehabilitation according to the Heidelberg model is not feasible in the many global health systems where specialist inpatient rehabilitation facilities do not exist; the standard of care recommended in guidelines is therefore not achievable for large numbers of patients. Preliminary studies have examined the potential for home-based exercise in this patient group,[40–42] but there is currently insufficient evidence for this to be included in guidelines. The SPHERe study[43] is a large UK RCT designed to examine rehabilitation of patients with pulmonary hypertension using existing community-based pulmonary rehabilitation services, and incorporating patients from Group 2 and Group 3, who have hitherto not been included in rehabilitation studies. Recruitment to the SPHERe study began in 2020 and is ongoing; due to the COVID-19 pandemic the study design has been modified to deliver remotely supported home-based rehabilitation.

Despite the growing evidence base, and the recommendations from guidelines in place at the start of this programme of work, access to rehabilitation programmes for patients with pulmonary hypertension has remained very limited.[30] A 2018 review of pulmonary hypertension services in the UK identified a significant gap between the research evidence in support of rehabilitation, and the rehabilitation services that were delivered to patients with pulmonary hypertension, which were limited to acute inpatient care and planning for discharge.[44]

This programme of work therefore sought to examine how existing research and knowledge of rehabilitation in patients with pulmonary hypertension could be advanced with a particular focus on the delivery of rehabilitation in clinical practice to patients with pulmonary hypertension in the UK and assessment of its impact.

1.5 Research aims, questions and programme of work

1.5.1 Research Aims

The primary aim of this programme of work was to advance the understanding of delivering rehabilitation in patients with pulmonary hypertension in clinical practice in the UK. The second aim was to examine the outcome measures that could be

used to assess patients' functional ability and the effectiveness of rehabilitation in pulmonary hypertension in research and in clinical practice.

1.5.2 Research questions

- How can rehabilitation for patients with pulmonary hypertension be delivered in the UK clinical setting?
- What outcomes can be used to assess functional ability in patients with pulmonary hypertension?

1.6 Structure of the thesis

This thesis is formed of a combination of three published papers arising from the programme of work and two study protocols as follows:

Chapter 2 Review of Service – includes the first paper published within this programme of work which described an innovative pulmonary hypertension rehabilitation service.[45]

Chapter 3 Literature Review – includes a published review of outcome measures used in studies of pulmonary hypertension rehabilitation.[46]

Chapter 4 – Feasibility Study – includes the protocol for a study which was developed in full and had obtained NHS ethical approval, but was not able to be pursued due to the COVID-19 pandemic.

Chapter 5 PERSPIRE – includes a published study of the 1-minute sit-to-stand test in patients with pulmonary hypertension.[47]

Chapter 6 – PERSPIRE 2 - outlines the next steps to be developed on completion of this programme of work.

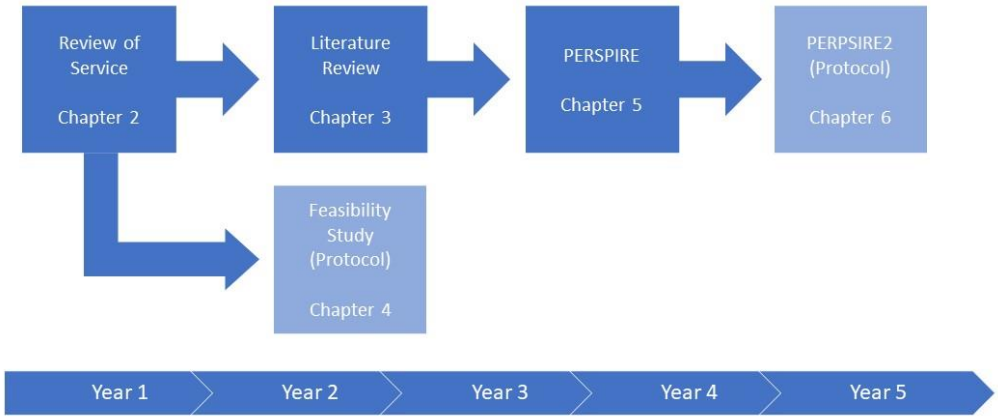
Each chapter describes the background and context to the paper or protocol therein, including further detail to the study design and methods where publication or format did not allow. Finally, a summary at the end of each chapter highlights the key findings of the chapter and its contributions to the overarching programme of work.

1.7 Programme of work

At the outset of this programme of work in 2018 there was a growing body of evidence for the benefits of rehabilitation in patients with pulmonary hypertension[28] and its provision was recommended in international guidelines.[20] There was however limited access to such services in the UK and other countries, and a mismatch between researched models of rehabilitation, which predominantly involved at least 3 weeks of inpatient rehabilitation, and care provision in the NHS which would not easily accommodate such provision.[44]

This programme of work, as described below and shown in Figure 1, sought to address understanding and approaches that might initiate change in the provision of rehabilitation for patients with pulmonary hypertension in the UK and more widely.

Figure 1 - Study Overview



1.7.1 Review of Service

The starting point for this programme of work was to examine the preliminary findings from the novel pulmonary hypertension rehabilitation service that had been established at the Sheffield Specialist Pulmonary Hypertension Referral Centre in order to develop a greater understanding of the rehabilitation needs of patients

within the service and describe the model of care that had been developed to meet these needs.

The Review of Service identified that a significant and wide-ranging rehabilitation need existed in patients with pulmonary hypertension, and that the model of care developed had the potential to address these needs for patients in the UK health system.

While the review indicated benefits of the rehabilitation delivered, it did not demonstrate effectiveness since its design did not include a control group for comparison. Furthermore, the outcome measures available to the review were those used in standard clinical practice which primarily examined measures of patient morbidity and mortality, with minimal inclusion of functional activities and participation in society, and consequently were not well suited to assessing the impact of the rehabilitation intervention. These findings therefore gave rise to two further studies: a literature review to examine the use of outcome measures in studies of rehabilitation in pulmonary hypertension, and a feasibility study of a randomised controlled trial of the rehabilitation intervention described in the Review of Service.

1.7.2 Literature Review

A review of the research literature was undertaken to examine outcome measures used in studies of rehabilitation in patients with pulmonary hypertension and identify suitable outcomes for use in this programme of work.

Relevant studies were examined, and the outcome measures used in the studies selected were mapped to the World Health Organisation model of functioning, disability and health.[48] The findings showed that outcomes used in rehabilitation studies predominantly measure aspects of patient morbidity and mortality. Alternative outcomes were identified that place a greater emphasis on patient function and participation in society, and are therefore more suited to capturing the benefits of rehabilitation.

1.7.3 Feasibility Study

A mixed-methods study was designed and planned to identify whether it was feasible to conduct a randomised controlled trial of a rehabilitation intervention in patients with pulmonary hypertension, in order to assess its effectiveness. The study was in two parts:

- A qualitative study of patients who had previously undergone rehabilitation, capturing their experiences and perspectives on its outcomes.
- A feasibility study for a randomised controlled trial of a rehabilitation intervention for patients with pulmonary hypertension.

The outcome measures used the in second part of the study would be informed by the initial qualitative stage as well as by the findings of the preceding literature review.

This study protocol was submitted for NHS ethical review, receiving approval in April 2020.

1.7.4 COVID and its impact

The COVID-19 pandemic led to a UK-wide lockdown in March 2020, with wide-ranging and long-lasting consequences for health provision and for this programme of work. The researcher was redeployed from pulmonary hypertension services to support the delivery of inpatient COVID physiotherapy services from March-June 2020 and consequently took a six-month pause from this study, returning in October 2020.

At the same time, community rehabilitation services such as those described in the Review of Service and Feasibility Study were either suspended or operating at very limited capacity. Patients with pulmonary hypertension were required to shield or minimise personal contact. It was therefore evident that it would not be possible to undertake the Feasibility Study at this time.

The pandemic also saw a shift in the delivery of outpatient clinical services, including pulmonary hypertension, from face-to-face to non-face-to-face

assessments. This indicated a requirement to review the outcome measures hitherto used in objective patient assessment, particularly those with the potential to be used in non-face-to-face settings and of value to rehabilitation.

1.7.5 PERSPIRE

The Review of Service and the Literature Review had examined the outcome measures used in pulmonary hypertension clinical and research practice, with a focus on their value in assessing the benefits of rehabilitation. Walking exercise tests are widely used in this context, however there are challenges in performing these remotely. They have not been validated for patients in the home and therefore are not available for use in non-face-to-face clinical assessments that became more commonplace following the COVID-19 pandemic.

The PERSPIRE study examined the 1-minute sit-to-stand test (1MSTS) as a possible alternative to walking exercise tests. The 1MSTS has the potential to be conducted by patients at home and might therefore offer an objective measure which could be included in non-face-to-face assessments. The study established the safety of the 1-minute sit-to-stand test in patients with pulmonary hypertension in the hospital setting and demonstrated significant correlation in comparison to existing walking exercise tests.

1.7.6 PERSPIRE2

Having shown the 1-minute sit-to-stand test to be safe in hospital, with good comparability to existing walking exercise tests, PERSPIRE2 is the protocol for a feasibility study designed to demonstrate its safety in the home, as well as examination of a larger data set, collected over a longer period of time and inclusion of mortality data to evaluate potential use in risk- assessment. The study would also examine patients' and clinicians' perspectives on the wider use of remote assessment.

The protocol for this study has been developed for submission for funding as a continuation of the body of this programme of work.

1.8 Summary

This chapter has introduced the author and the philosophy of research underpinning this programme of work. It has described the nature of pulmonary hypertension and its management, including the evidence concerning rehabilitation in managing the condition.

The research aims have been described and an overview has been given of the programme of work. The following chapters will describe each of the published papers and protocols that make up this programme of work, before summarising the learning from this programme of work, its contribution to knowledge and influence on clinical practice and patient care.

Chapter 2 Review of Service

This chapter describes the background to the Review of Service, the first study undertaken in this programme of work. It outlines the methods selected in designing the study before presenting the Review of Service and its findings as published in a peer reviewed journal, before summarising the implications of the study within this programme of work.

2.1 Background

The first study undertaken in this programme of work was a review of the newly established pulmonary hypertension rehabilitation service at the Sheffield Specialist Pulmonary Hypertension Referral Centre. At this point in time, previously published research evidence and international guidelines had established that exercise in pulmonary hypertension was safe and beneficial. However, the bulk of this evidence was based on a single model of rehabilitation – 3 weeks of intensive inpatient rehabilitation followed by 12-weeks supported homed-based exercise – which is not universally replicable, therefore the standard of care recommended in guidelines was not achievable for large numbers of patients with pulmonary hypertension, including patients in the UK.[44]

The aim of the novel service, established in July 2017, was therefore to identify a model of rehabilitation for patients with pulmonary hypertension that was deliverable within the UK health setting, while closely incorporating the existing research evidence. If this service proved to be effective then the model could be adopted by other UK Specialist Pulmonary Hypertension Referral Centres and possibly other healthcare settings.

The goal of the Review of Service was therefore to understand and describe the new pulmonary hypertension rehabilitation service as it had developed and evolved; this understanding would then set the scene and underpin the design of a further study that would assess its effectiveness (Chapter 4).

2.2 Methods

The Review of Service was designed to evaluate and describe an existing clinical service, therefore no comparator control group was possible; a prospective single cohort design was therefore indicated.

Quantitative data was taken from measures routinely collected in clinical assessment and from operational service data. Without a comparator group, data analysis was limited to descriptive statistics.

2.3 Citation

Keen, C., Hashmi-Greenwood, M., Yorke, J., Armstrong, I. J., Sage, K., & Kiely, D. (2019). Exploring a physiotherapy well-being review to deliver community-based rehabilitation in patients with pulmonary hypertension. *Pulmonary Circulation*, *9*(4), 1–9. https://doi.org/10.1177/2045894019885356

Note on the publication: Figure 3 was generated by the researcher within the development of this publication and is therefore original.

2.4 Published work

2.4.1 Abstract

Background: Highly structured, supervised exercise training has been shown to be beneficial in patients with pulmonary hypertension. Despite evidence of the effectiveness of community-based rehabilitation in other cardiopulmonary diseases there are limited data in patients with pulmonary hypertension.

Method: This prospective study evaluated the intervention of a physiotherapist well-being review in patients with pulmonary hypertension who had been established on targeted drug therapy for between 3 and 12 months. The intervention included a detailed consultation assessing functional, social and motivational status to identify individual patient rehabilitation goals and facilitate tailored referrals to community-based services.

Results: One hundred and thirty-eight patients (79% pulmonary arterial hypertension, 17% chronic thromboembolic disease), age 67±14 years, diagnosed over a one year period were evaluated between July 2017 and January 2018. Fifty-two per cent of patients were referred to community-based pulmonary rehabilitation programmes, 19% received other forms of community rehabilitation, 17% were given exercise advice, 5% had an assessment of social support and 7% declined any intervention. At the end of the study 32% of patients were undertaking independent exercise.

Conclusion: This study has identified that the majority of patients with pulmonary hypertension who are optimised on targeted drug therapy have rehabilitation needs. The use of a physiotherapy well-being review can identify this need and facilitate access to community-based rehabilitation. Further research is required to evaluate the efficacy of such interventions in pulmonary hypertension.

2.4.2 Introduction

Pulmonary hypertension is a life-shortening condition, varying from rare forms such as pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) for which specific interventions exist to, usually milder, elevations of pulmonary artery pressure seen in cardiac and respiratory disease.[7,8] With the development of advanced drug therapies,[49] more people than ever are living with pulmonary hypertension and for longer.[50] However improvements in symptoms and / or survival do not necessarily reflect the physical, emotional and psychological burdens of living with pulmonary hypertension.[51] This suggests the need to consider wider rehabilitative approaches in what is now a chronic condition.

There has been increasing interest and a growing evidence base for exercise training in patients with pulmonary hypertension since the first randomised controlled trial in 2006.[23] It has now been established that exercise in patients with pulmonary hypertension is safe and leads to improvements in functional ability and quality of life.[52,53] While further work is required to fully understand the

physiological effects of exercise training in patients with pulmonary hypertension,[54] change in skeletal muscle function and cardiac function as well as reversal of pre-existing deconditioning are potential mechanisms.[31,55] In a systematic review of studies of exercise therapy in pulmonary hypertension, Morris et al.[28] demonstrated improvements in six-minute walk distance of 60 metres as well as significant improvements in quality of life and only a single adverse event (light-headedness during exercise) across 206 study participants. The recent European Respiratory Society Task Force on exercise training in pulmonary hypertension called for supervised exercise in physically stable, deconditioned patients and for wider commissioning of rehabilitation programmes in this patient group.[20]

To date, exercise studies have focused on rehabilitation conducted in specialist pulmonary hypertension centres, including a high number of inpatient rehabilitation programmes[34,56,57] which are not universally available and which potentially exclude patients whose lifestyles are unable to accommodate this approach. Consequently provision of rehabilitation for patients with pulmonary hypertension is not yet universal standard care.[44] Establishing new in-patient rehabilitation programmes where they do not exist would have considerable cost implications. Community-based rehabilitation programmes, including pulmonary rehabilitation, are widely and successfully used in the care of patients with other respiratory conditions.[58] The potential for out-patient and home-based exercise training in pulmonary hypertension has been reported.[40,59] However while such programmes can offer greater ease of access for patients, they are likely to be delivered by staff who lack specialist knowledge of pulmonary hypertension and may provide rehabilitation which is sub-optimal.

The aim of this study was to examine whether a specialist physiotherapist well-being review can identify the individual rehabilitation needs and goals of patients with pulmonary hypertension and investigate whether these needs can be addressed by referral to community-based services.

2.4.3 Methods

2.4.3.1 Setting

This was a prospective study of a new service that consisted of physiotherapy well-being reviews of patients with pulmonary hypertension under the care of a UK regional pulmonary hypertension specialist centre which serves a referral population of in excess of 15 million, with more than 1600 patients receiving targeted drug therapies for pulmonary hypertension. Patients supported by the centre live in a mix of rural and urban areas, travelling up to 200 miles (approximately 6 hour commute) to attend appointments.

2.4.3.2 Study population

Patients who were commenced on targeted pulmonary hypertension drug therapy between October 2016 and October 2017 were considered for inclusion in the study. Patients underwent the initial physiotherapy well-being review between July 2017 and January 2018. Follow-up continued until the end of January 2019, twelve months after the last patient was enrolled.

2.4.3.3 Inclusion and Exclusion Criteria

Patient records were reviewed to identify patients suitable for physiotherapy assessment.

Patients included in the study were adults > 18 years diagnosed with pulmonary hypertension[60] who had been commenced on targeted pulmonary hypertension drug therapy within the study time period and had been established on treatment for at least 3 months but less than 12 months and attended clinic within the recruitment window. Patients were excluded from the study if they were on a pathway for pulmonary endarterectomy surgery, had recently undergone surgery, had uncorrected congenital heart disease or were seen by a shared care centre during the follow-up period (shared care arrangements exist between the specialist centre and nationally designated congenital heart disease centres). Patients who were identified, on screening, as not being stable were excluded i.e. patients who had deteriorated since their last review or required change in their targeted

pulmonary hypertension therapies. Disease severity or functional ability was not used as an inclusion or exclusion criteria.

2.4.3.4 Intervention

2.4.3.4.1 Physiotherapy Well-being Review

Patients meeting the inclusion criteria were approached by a physiotherapist specialising in pulmonary hypertension while they attended routine out-patient / day-case clinics at a pulmonary hypertension specialist centre.

Patients underwent a well-being[61] review conducted by the physiotherapist. This is a novel intervention newly devised for this study based on the clinical experience of the physiotherapist and other members of the multi-disciplinary team. The physiotherapist conducted a well-being review which took the form of an individualised one-to-one clinical assessment capturing objective and subjective information to identify the patients' current functional ability and exercise activity. The information was assimilated to identify rehabilitation needs and functional and rehabilitation goals before discussing and agreeing with the patient, suitable options for onward rehabilitation referral. Well-being reviews typically lasted between 15-45 minutes depending on the individual patient.

The physiotherapist captured a detailed history including the presence or absence of comorbidities; social and economic status; functional ability, limitations and independence; weight and diet behaviour; current and previous levels of physical activity and exercise; emotional well-being; participation in work, education, training or recreation; experiences, beliefs and attitudes to exercise and physical activity; motivation for rehabilitation and change. Where available, information was also captured from carers to gain further detail and insight into the patients' experience of living with pulmonary hypertension and its impact on the lives of the patient and those around them.

Physical examination included height, weight, body-mass index, oxygen saturations, heart rate, blood pressure and assessment for the presence or absence of heart failure. WHO functional class,[7] emPHasis-10 quality of life score,[62] Incremental

Shuttle Walking Test distance (ISWT)[63,64] and right heart catheter results were also noted.

All of the objective markers were selected as they are clinical measures routinely used in the specialist centre in which the study was conducted. No additional assessments, beyond those which are routinely used in clinical assessment, were carried out for the study.

The well-being review offer and structured content was common for each patient, regardless of their diagnosis or WHO functional class. A universal structure was followed for every review; however the detailed content of each individual's review and their expected outcomes, varied in response to each patient's status and needs which were identified for each individual during the well-being review.

2.4.3.4.2 Community Referral

The physiotherapist drew on the findings of the well-being review to identify primary patient characteristics and establish functional priorities and goals for rehabilitation. From this, discussions were held with patients to identify the most suitable method to address their rehabilitation needs and goals (Figure 2). This could include onward referral to community rehabilitation (pulmonary rehabilitation, community or domiciliary therapy, musculo-skeletal (MSK) physiotherapy), exercise advice or an assessment for social support. Full details of rehabilitation services used in the study are given in Table 3. Where patients declined support, advice or referral to rehabilitation, they were given written information on ways to increase levels of physical activity.

2.4.3.4.3 Safety and Specialist Support

To address the potential lack of knowledge of pulmonary hypertension in local rehabilitation programmes, detailed information concerning the patient and the condition were provided within referrals. This included information on the characteristics of pulmonary hypertension and specific guidance on any limitations to exercise for each patient. Additionally, each patient was advised on safe exercise practice for them. Community rehabilitation services have their own risk

assessment and safety procedures in place which will be applied to all patients taking part in rehabilitation. The pulmonary hypertension specialist physiotherapist was available to service providers and patients for any queries during the rehabilitation period, including those relating to patient safety during exercise. Data were not formally collected on the number and nature of these queries. Details of contacts with third parties were recorded in contemporaneous clinical patient notes.

2.4.3.5 Follow-up outcomes

Patients were seen on their return to clinic (typically between 3 and 6 months after their initial physiotherapy well-being review) and reassessed by the physiotherapist. Repeat measures for ISWT and emPHasis10 were extracted from routine clinical data. Current levels of patient activity were subjectively assessed (Table 4) through clinical interview by the physiotherapist along with information regarding whether the patient had attended or completed any rehabilitation programmes and the reasons behind this. Where indicated by clinical assessment and discussion with the patient, referral to further rehabilitation services or targeted exercise advice was provided (Figure 2). The physiotherapy goal was to continue to support patients until they were exercising independently or with the support of a long-term community rehabilitation programme, or until the physiotherapist judged that the patient was as active as they were likely to be within the constraints of their functional ability and motivation.

2.4.3.6 Additional data

Information was logged throughout the project to capture practical or process issues that limited or facilitated the smooth administration of the intervention. This was obtained through contemporaneous clinical notes which were taken at each patient clinic visit and also on any patient related activity e.g. patient phone calls, referral correspondence and contact with third parties involved in the patient care or provision of rehabilitation services.

Table 3 - Referral options offered to patients during the study

Referral Options	Details
Pulmonary rehabilitation	Pulmonary rehabilitation is an interdisciplinary programme of care for patients with chronic respiratory impairment comprised of individualised exercise programmes and education.[65]
Community or domiciliary therapy	Patients with poor mobility, history of falls or with limited functional independence can benefit from a therapy assessment at home by physiotherapy or occupational therapy. This may result in e.g. home adaptations or equipment provision; improved functional ability; referral to care services which can help to prolong independence and avoid hospital admission.
Musculo-skeletal (MSK) physiotherapy	Some patients, while limited by breathlessness, cite other comorbidities which are the limiting factors in their physical activity e.g. knee or back pain, which can be addressed through specialist physiotherapy assessment.
Other community rehabilitation	A wide range of rehabilitation programmes are provided by local authorities and charities which provide exercise, activity and social activity in a variety of community settings. Examples include exercise-on-prescription schemes, community walking groups, singing for health; tai chi groups etc..
Exercise advice - low level exercise	Patients with very sedentary lifestyles were offered advice on small incremental steps to becoming more active and supported to develop confidence in their physical capabilities, with a view to engaging them in other future rehabilitation activities.
Exercise advice - high level exercise	Patients who were already exercising regularly were given advice on guidelines regarding the amount and type of exercise recommended (NHS England 2018) and approaches to staying motivated and adapting exercise routines to change in circumstances.
Assessment of social support	Where patients were too unwell to undertake any form of rehabilitation, levels of home social and functional support were identified and addressed as needed

Figure 2 - Diagnostic Process Map

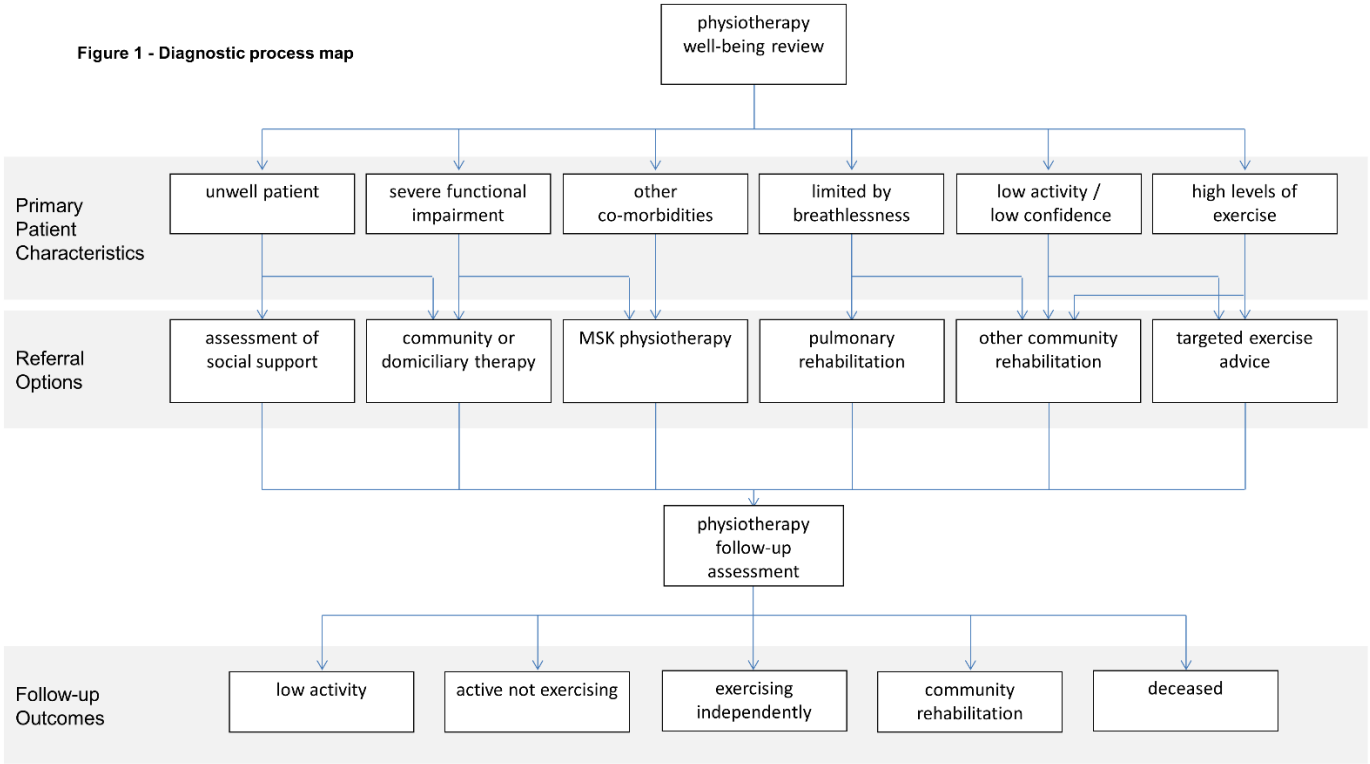


Table 4 - Levels of patient activity

Activity Levels	Details
Low activity	These patients would be largely based at home, rarely going out. They might perhaps be supported by carers and live on a single level or have a stair lift
Active not exercising	Patients who are able to get about and participate in domestic activities of daily living, social or work activities
Community rehabilitation	Regularly engaging in a community rehabilitation programme
Exercising independently	Going to the gym, carrying out a home exercise programme, regular walks for exercise

2.4.3.7 Statistical analysis

Descriptive statistics including mean, standard deviation and range were used to analyse patient demographic and outcomes from the physiotherapy well-being review.

2.4.4 Results

2.4.4.1 Study population

Of 310 patients screened for entry into the study 172 were excluded (see Table 5 for reasons) leaving a total of 138 patients who received a physiotherapy well-being review. Patient demographics are shown in Table 6. The majority of patients had PAH (79%) while 17% had a diagnosis of CTEPH, comprising either inoperable disease or residual disease following surgery and 4% had Group 5 pulmonary hypertension.[8]

Table 5 - Reasons for exclusion from study

Reason for exclusion n=172	Number of patients (%)
Not reviewed /did not attend a clinic appointment within study time period	68 (39.5)
Seen by shared care centre (congenital heart disease)	59 (34.3)
On a pathway for pulmonary endarterectomy	33 (19.2)
Not stable on current PH treatment	6 (3.5)
Uncorrected congenital heart disease under local follow-up	4 (2.3)
Recently undergone surgery	1 (0.6)
Pregnancy	1 (0.6)

The study population included patients with a wide range of disease severity and functional ability as shown by the variation in values at diagnosis for mPAP (25-81 mmHg), ISWT (0-720 metres) and emPHasis10 (score of 2-50) as shown in Table 6.

Table 6 - Patient demographics at diagnosis

Characteristics	PAH (n=109)	CTEPH (n=23)	Other (n-6)	All (n=138)
Age, mean (SD), y	66.4 (14.3)	73.3 (10.2)	63.7 (10.1)	67.5 (13.8)
Female, no. (%)	77 (70.1)	9 (39.1)	2 (33.3)	88 (63.8)
WHO FC, no. (%)				
Class II	1 (0.9)	1 (4.3)	0 (0)	2 (1.4)
Class III	85 (78.0)	21 (91.3)	6 (100.0)	112 (81.2)
Class IV	23 (21.1)	1 (4.3)	0 (0.0)	24 (17.4)
ISWT, mean (range), m	124 (0-590)	190 (0-720)	163 (40-320)	137 (0-720)
Haemodynamics				
mPAP, mean (SD),	49 (±12)	45 (±11)	42 (±5)	48 (±12)
mRAP, mean (SD),	11 (±6)	10 (±4)	9 (±8)	11 (±6)
PAWP, mean (SD),	11 (±5)	11 (±4)	10 (±4)	11 (±5)
CO (l/min)	3.85 (±1.69)	3.87 (±1.21)	3.5 (±1.07)	3.84 (±1.58)
CI (l/min/m^2)	2.09 (±0.83)	2.04 (±0.57)	1.64 (±0.39)	2.06 (±0.78)
PVR (dynes/m^2)	896 (±486)	672 (±306)	806 (±313)	855 (±459)
emPHasis10, mean (SD), score out of 50	31 (±11)	28 (±11)	29 (±5)	31 (±11)

WHO FC = World Health Organisation functional class, PAH = pulmonary arterial hypertension, CTEPH = chronic thromboembolic pulmonary hypertension. Haemodynamics measure at right heart catheterisation: mRAP = mean right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, CO = cardiac output, CI = cardiac index, PVR = pulmonary vascular resistance.

2.4.4.2 Community Referrals

The most common outcome from the physiotherapy well-being review was referral to local pulmonary rehabilitation programmes (52%). Referrals to other forms of community-based rehabilitation were made for 19% of patients; this included one patient who was initially referred for pulmonary rehabilitation but transferred to cardiac rehabilitation by the service provider and another who was referred to cardiac rehabilitation due to a myocardical infarction in the preceding three months. A further 17% of patients were given exercise advice and the 5% who

were identified as being too unwell to benefit from rehabilitation had an assessment of their social support at home (Table 7). Seven percent of patients had an identified rehabilitation need, but declined the opportunity of a referral and were instead given written advice on increasing their levels of physical activity.

During email or phone call contact regarding referrals or advice, clinicians in local services reported that they valued the triage of patients by a physiotherapist specialising in pulmonary hypertension prior to referral as well as acknowledging that easy access to the expertise of the physiotherapist increased their understanding and confidence in rehabilitation of this patient group. Challenges arose when making referrals for 6 patients where pulmonary rehabilitation was the preferred referral option but was not commissioned for patients with pulmonary hypertension within their area. In three instances this was resolved through discussion with service providers; where this was not possible, alternative rehabilitation arrangements were made.

Patients in the study lived in a wide geographical area, covering the centre of the UK, with the furthest patient living over 150 miles away. Reflective of this geographical spread, referrals were made to 69 rehabilitation services across the region.

Table 7 - Physiotherapy well-being review results

Well-being review outcome n=138	Number of patients
Pulmonary rehabilitation	72 (52.2)
Exercise advice given - high level function	17 (12.3)
Community or domiciliary therapy	16 (11.6)
Patient declined support	9 (6.5)
Exercise advice given - low level function	7 (5.1)
Other community rehabilitation	9 (6.5)
Assessment of social support	7 (5,1)
MSK Physiotherapy referral	1 (0.7)

2.4.4.3 Safety and Specialist Support

No safety issues were reported by patients during clinical assessments or by rehabilitation service providers during discussions of referrals or requests for advice, although information on adverse events was not actively sought. In some instances, providers of services contacted the referring physiotherapist to clarify guidance on rehabilitation protocols for individual patients or in general for patients with pulmonary hypertension.

2.4.4.4 Follow-Up Outcomes

Of the 74 patients referred to pulmonary or cardiac rehabilitation programmes, 36 (48%) completed the full rehabilitation programme, 14 (19%) started rehabilitation and did not complete, while 24 (32%) did not start. At follow-up assessment common reasons given by patients for non-completion included other health problems, difficulty travelling to rehabilitation and lengthy waiting times to commence rehabilitation. Some patients with work or caring responsibilities reported that the timing of pulmonary rehabilitation classes (which tend to be during the working day) did not meet their needs, while others found the programmes to be targeted at patients with COPD and therefore not well suited to them.

Measurements for ISWT and emPHasis10 were taken for 104 patients before and after rehabilitation. These data were collected at routine clinic appointments and therefore do not directly coincide with start and end of rehabilitation; the time period between measures varied from 3 to 12 months. Fifty-eight (42%) patients showed an improvement in functional ability (increase in ISWT of >=40 metres) or an improvement in quality of life (increase in emPHasis10 of 6 or more (out of 50)).

At follow-up, clinical assessment was made by the physiotherapist of the patients' current level of activity (Table 8). The largest group (38%) were considered to be active, but not exercising, while 32% were exercising independently. Low levels of activity were identified in 21% of patients while 4% were engaged in community rehabilitation.

Table 8 - Follow-up Outcomes

Follow-up outcome n=138	Number of patients (%)
Active, not exercising	52 (37.7)
Exercising independently	44 (31.9)
Low levels of activity	29 (21.0)
Community rehabilitation	6 (4.3)
Deceased	7 (5.1)

2.4.5 Discussion

2.4.5.1 Need for rehabilitation

This study has shown that the majority of patients with pulmonary hypertension receiving targeted drug therapy within the first year of diagnosis have rehabilitation needs. The use of a well-being review delivered by a physiotherapist specialising in pulmonary hypertension can identify this need and facilitate access to community-based rehabilitation.

To our knowledge this is the first study to establish the extent of the need for rehabilitation in newly diagnosed patients with pulmonary hypertension who are optimised on targeted drug therapy. With 88% of patients receiving either referral for exercise rehabilitation or targeted exercise advice the study results demonstrate a clear need for the provision of rehabilitation for patients with pulmonary hypertension to enhance their well-being. By engaging patients in rehabilitation once they are optimised on drug therapy there is an opportunity to build on the functional gains that might be achieved through pharmaceutical support to achieve further improvements in well-being. Further work is required to identify optimal timing of these interventions and the nature and extent of change that can be made to patient well-being however Figure 3 is an illustration which indicates the potential gains achievable through timely rehabilitation interventions.[25,28]

2.4.5.2 Uptake of rehabilitation

Along with high levels of need there were high levels of engagement with rehabilitation in the study. Referrals to pulmonary rehabilitation were accepted by 54% of patients and to other community-based rehabilitation by 17% of patients.

Despite reports from some patients that they found their pulmonary rehabilitation to be focused on COPD and therefore not always entirely suited to them, commencement and completion rates for pulmonary rehabilitation at 68% and 48% respectively are comparable with data for pulmonary rehabilitation in patients with COPD where 67% commenced and 46% completed rehabilitation.[66] Further research into the effectiveness and cost-effectiveness of pulmonary rehabilitation in patients with pulmonary hypertension is currently underway.[43]

The levels of physical activity at follow-up, with 32% of patients exercising independently and 6% participating in community rehabilitation programmes, are indicative of the potential for rehabilitation in patients with pulmonary hypertension. In studies of exercise training in patients with pulmonary hypertension, Chan et al[67] and Weinstein et al[68] both demonstrate significant increases in levels of physical activity in patients undergoing rehabilitation as measured by physical activity questionnaires. Further work is required to explore outcomes relating to physical activity, which might include patient reported outcome measures or wearable devices,[69] to determine their potential use in pulmonary hypertension rehabilitation.

The current study was universal in its inclusion, assessing and treating patients with even the most severe disease whose outcomes might be expected to be poor. Despite this, and despite the progressive nature of the disease, our data show some positive indications that the intervention can improve function and quality of life.

2.4.5.3 Inclusive Rehabilitation

The intervention in this study was able to meet the diverse rehabilitation needs of this complex patient group. Patients with pulmonary hypertension vary significantly in terms of age, functional ability, disease history and severity. While some patients with pulmonary hypertension are significantly limited functionally, others might be in work or have caring responsibilities. This, combined with the wide geographical spread of patients from their regional specialist centres, can make delivery of rehabilitation challenging. Patients will have preferences for the

time, location and nature of the rehabilitation in which they are prepared to engage. The physiotherapy well-being review and onward referral to community rehabilitation is able to accommodate this wider rehabilitation and thus suggests the requirement for rehabilitation solutions tailored to the individual rather than one-size-fits-all solutions.

This study was pragmatic in design and shows that it is feasible to deliver community-based rehabilitation to patients with pulmonary hypertension within existing healthcare service provision. Participants were not required to attend any additional appointments; instead their well-being review took place around the normal clinical activity of a standard clinical visit. The rehabilitation services accessed by patients in this study were pre-existing and widely available in community settings, without the need to establish bespoke and potentially expensive services for patients with pulmonary hypertension.

2.4.5.4 Role of the Physiotherapist

The expertise of the specialist physiotherapist was important in ensuring that the community-based rehabilitation met the needs of patients with pulmonary hypertension. Professionals delivering rehabilitation in community settings will be experts in rehabilitation, but may have limited knowledge of its application in this rare disease. The specialist physiotherapist role offers a combined expertise in pulmonary hypertension and rehabilitation along with access to the resources of a specialist pulmonary hypertension referral centre. They share a professional language and framework of understanding of rehabilitation with community providers. By delivering detailed expert referrals and being easily available for questions or concerns, the specialist physiotherapist has facilitated the provision of effective community-based rehabilitation to a complex patient group with a rare disease.

The specialist physiotherapist also had an important role to play in supporting the safety of the intervention. Within the physiotherapy well-being review patients who were identified as higher risk for exercise were directed towards more closely

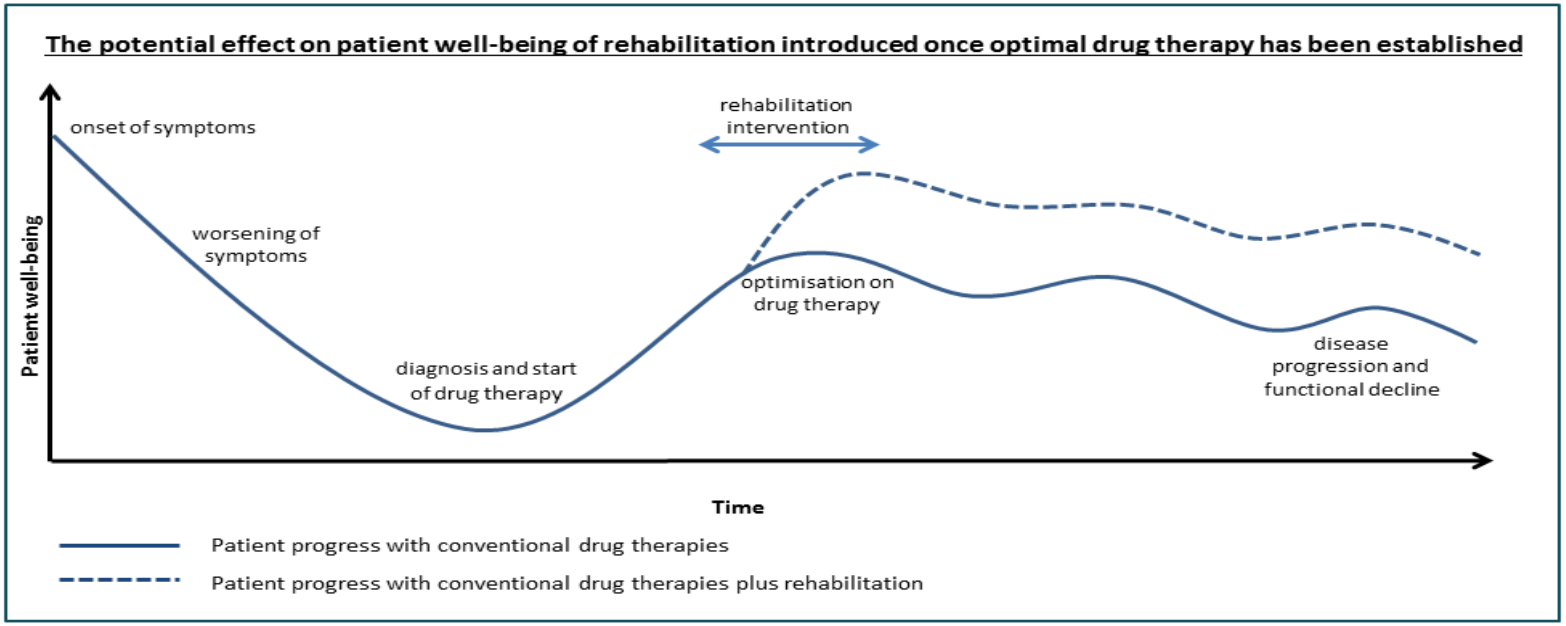
supervised rehabilitation programmes, e.g. pulmonary rehabilitation which offers physiotherapy and nursing support to patients. Detailed information concerning the patient and the condition were provided in referrals and patients were advised on safe exercise practice.

The optimal model of rehabilitation in pulmonary hypertension has yet to be determined and may vary according to country or setting[55] but it is likely that any sustainable expansion of rehabilitation in pulmonary hypertension will require an associated expansion of physiotherapy provision for patients with pulmonary hypertension and in education and access to resources for community-based rehabilitation services. This study demonstrates a model of care for rehabilitation which allows patients to access a community rehabilitation service local to them while maintaining the support and access to the expertise of their specialist centre. The tailored, individualised approach allows the best rehabilitation solution to be delivered to patients based on their needs, rather than offering a one-size-fits-all solution. Physiotherapy skills and knowledge have been at the core of the intervention and its outcomes.

2.4.5.5 Next steps

The positive indication for the outcomes of functional ability and quality of life and the practical success of the study suggests that more work should be done to establish its effectiveness in comparison to a control group. The next step would be to undertake a feasibility study of a randomised controlled trial of the intervention to establish efficacy of the intervention and benefit to patients. The acceptability of the intervention to patients and clinicians would also need to be examined along with the outcome measures best-suited to capturing the impact of such interventions. It is important to explore the importance of patient well-being and rehabilitation in the commissioning of pulmonary hypertension specialist services.

Figure 3 - The potential effect on patient well-being of rehabilitation



2.4.5.6 Limitations

The pragmatic nature of this study leads to limitations which are manifest in the variable timeframes over which follow-up outcomes were collected. Outcomes were not uniformly separated by time, nor specifically aligned with the start and finish of patient rehabilitation which may detract from their effectiveness in detecting change. Levels of physical activity were not captured at the outset of the study and therefore it was not possible to compare values before and after the intervention, which would have enhanced the study results. Reflective of the real world nature of the study, there is no control of the content or quality of the rehabilitation undertaken by patients. While no major adverse events were reported by rehabilitation providers or patients, we cannot rule out the occurrence of minor events; this would be better addressed in a controlled trial.

2.4.6 Conclusion

The study has identified an unmet need in the provision of rehabilitation to patients with pulmonary hypertension who are optimised on targeted drug therapy. The use of a physiotherapy well-being review can identify this need and facilitate access to community-based rehabilitation. Further research is required to evaluate the efficacy of such interventions in pulmonary hypertension.

2.5 Summary

On completion of this Review of Service it was evident that the novel model of service that had been developed and evaluated had the potential to be delivered within the existing structures and services of the UK health system, and to bring benefits to patients with pulmonary hypertension.

One identified next step was therefore to explore the design of a study that would examine the effectiveness of the intervention in comparison to a control group undergoing usual care. Understanding the views of patients with regards to the service was considered to be beneficial to optimising the design of the service, and to making the case for its wider adoption. The study that arose from this is described in Chapter 4.

The Review of Service also raised questions for the researcher about the outcome measures that would be best suited to capture the impact of rehabilitation on patients with pulmonary hypertension, whether they were already typically captured in existing clinical data or if alternatives needed to be sought. For this reason, a review of the literature was also undertaken at this point which considered the use of outcome measures in studies of rehabilitation in patients with pulmonary hypertension, as described in Chapter 3.

Chapter 3 Literature Review

Based on the findings of the Review of Service (Chapter 2), a review of the literature was undertaken to examine outcome measures used in studies of rehabilitation in pulmonary hypertension. This chapter describes the background to the Literature Review, and methods selected in its design. It then presents the review and its findings as published in a peer reviewed journal, before summarising the implications of the study within this programme of work.

3.1 Background

The first randomised controlled trial of a drug therapy in pulmonary hypertension began in 1990. The 6-minute walk test (6MWT) was selected as the primary outcome measure to meet the needs of the Food and Drug Administration, who required a measure of patients' symptoms, exercise tolerance, or survival; the study sponsor, who sought to avoid the prolonged study that would be necessitated by the use of survival as a measure; and clinicians in the study steering group who preferred the practicality of the 6MWT over other exercise tests.[70] The 6MWT then became the chosen the primary endpoint for almost every subsequent drug study in pulmonary hypertension, until the introduction of composite and other outcomes in the mid-2000s.[71]

As the primary endpoint in most preceding pharmaceutical clinical trials, the 6MWT was selected as the primary outcome of the first randomised controlled trial of rehabilitation in pulmonary hypertension in 2006, thereby allowing for comparison with other studies. Subsequent studies of exercise appear likewise to have used the 6MWT as a primary outcome, along with secondary outcomes linked to measurements of quality of life, and physiological markers which are used to identify the specific effects of exercise on patients and the disease process.

The Review of Service (Chapter 2) drew attention to the complexity of rehabilitation in this patient group, the multiple factors that might underlie the success of a rehabilitation intervention and raised questions regarding the most suitable

outcomes to measure its success. The goal of the Literature Review was therefore to develop a clear understanding of the outcome measures used in previous studies of rehabilitation in pulmonary hypertension, in order to support the selection of the optimal measures for assessment of the rehabilitation intervention in the next stage of this work (Chapter 4).

3.2 Method

Alongside the goal of the study, four key attributes of literature reviews[72] – search, appraisal, synthesis, analysis - were considered in selecting the method, as follows:

- Search – to evaluate the outcome measures used in studies of pulmonary hypertension rehabilitation required an exhaustive and comprehensive search of the literature
- Appraisal – as this review was solely of the outcome measures used in the studies identified, an appraisal of the quality of the studies selected was not required
- Synthesis – describing the outcome measures used in the studies selected was best suited to a tabular and narrative synthesis
- Analysis – the study sought to identify patterns in existing usage of outcome measures and potential suitable outcome measures for use in future studies, therefore the analysis included components of what was already known along with recommendations for best practice based on a conceptual model.

Within this framework the review conducted meets the description of a *systematized review* including components, but stopping short of, a systematic review.[72]

3.3 Citation

Keen, C., Harrop, D., Hashmi-Greenwood, M. N., Kiely, D. G., Yorke, J., & Sage, K. (2020). Outcome Measures Used in Studies of Rehabilitation in Pulmonary

Hypertension: A Systematic Review. *Annals of the American Thoracic Society*, *5*, 321–335. https://doi.org/10.1513/annalsats.202005-541oc

3.4 Published work

3.4.1 Abstract

Rationale: The evidence base for rehabilitation in pulmonary hypertension is expanding, but adoption in clinical practice is limited.

Objectives: The World Health Organization International Classification for Functioning, Disability and Health identifies three health domains: Body Functions/Structures, Activity and Participation in society. To ensure that the wider impact of rehabilitation in pulmonary hypertension is accurately assessed, it is important that study endpoints reflect all three domains.

Methods: A systematic review of the literature was conducted to identify studies of rehabilitation in patients with pulmonary hypertension from 2006 to 2019.

Results: Searches across five databases yielded 2,564 articles, of which 34 met eligibility criteria; 50 different outcome measures (mean = 5, minimum = 1, maximum = 9) were identified. When mapped onto the World Health Organization International Classification for Functioning, Disability and Health, 48% of instances of outcome usage were measures of Body Functions/Structure, 33% were measures of Activity, and 18% were measures of Participation. Measures of Participation were not included in seven studies (21%).

Conclusions: Studies of rehabilitation in pulmonary hypertension have focused primarily on measures of Body Functions/Structure; the impact in other health domains is not well characterized. Greater inclusion of outcome measures reflecting Activity and Participation in society is needed to allow assessment of the wider impact of rehabilitation in patients with pulmonary hypertension.

3.4.2 Introduction

Pulmonary hypertension (PH) is a condition with many causes which results in breathlessness, reduced functional ability and diminished quality of life. Once viewed as an untreatable condition, advances in medical and surgical treatment have resulted in more people living with the disease and for longer.[8]

While exercise rehabilitation was first shown to improve exercise capacity and quality of life in patients with PH in 2006,[23] greater understanding of the benefits of rehabilitation in patients with pulmonary hypertension is still required.[20,45] Effective rehabilitation is a complex, multi-faceted intervention with the potential to impact not just the underlying health condition, but also the daily life of patients, their independence and community connections[73]. It is important that this wider potential impact is given due consideration in studies of rehabilitation.

The World Health Organisation International Classification for Functioning, Disability and Health[48] (ICF) is a dynamic multi-dimensional classification of health and health-related domains. It is designed to support clinicians and health policy makers to examine and understand the health of individuals and populations, not simply in terms of diagnoses, but also reflecting the impact of disease on individuals and the lives that they are able to live. The ICF considers: i) Body Functions/Structures i.e. aspects of physiology and anatomy, ii) Activity i.e. actions and tasks undertaken by individuals, iii) Participation i.e. involvement in life situations, and iv) the environmental and personal factors which affect these experiences.

To understand the impact of rehabilitation on patients with PH, outcomes used in studies of rehabilitation need to capture the influence of those interventions across all domains of health. This study uses the WHO ICF model as a framework to examine the literature of rehabilitation interventions in patients with PH.

3.4.3 Methods

This systematic review comprised comprehensive searching of the literature and combined tabular and narrative synthesis.[72] It was prospectively registered on the PROSPERO database (CRD42019127590).

3.4.3.1 Research Aim

Characterisation and clinical meaning of outcome measures in studies of rehabilitation in patients with pulmonary hypertension.

3.4.3.2 Search Strategy

A comprehensive search was conducted of the following electronic databases: MEDLINE (EBSCO); CINAHL Complete (EBSCO); Cochrane Central Register of Controlled Trials (Wiley); Scopus (Elsevier); ASSIA (Proquest). Searches were conducted in February 2019 and databases were monitored for updates until September 2019. The strategy included searches for words and phrases relating to pulmonary hypertension and exercise or rehabilitation. The Boolean operators AND and OR were used, alongside phrase, proximity and truncation operators. The search syntax was adapted accordingly for each information source and controlled vocabulary terms used where available. Examples of search string or list of key words/phrases can be found in Appendix 1.

Where indicated, author and citation searches were undertaken of papers included in the review. Searches were conducted for conference proceedings to identify full articles if they had been published. Search strategies for each database are detailed in Appendix 1.

3.4.3.3 Study selection

Selection of studies was undertaken by one author (CK) and a sample was checked at each stage of selection by a second author (MHG). Disagreement was resolved by discussion and consensus involving a third author (KS) as necessary.

Articles from all databases were combined and duplicates removed before title and abstract were screened; if studies were considered to be eligible, then full-text was

reviewed. Studies were included if they met the following criteria; quantitative studies of any design, which included primary data; peer reviewed protocols of planned studies; originating from any time period. Studies were excluded if they were: abstract-only papers; single case studies (case series were included); review papers (although references were checked for primary data sources); non-English language papers.

Study populations had to include adults (age≥18 years) with a diagnosis of pulmonary hypertension.[7] Studies were excluded if subjects were: animals; patients with exercise-induced pulmonary hypertension; patients undergoing post-operative rehabilitation.

3.4.3.4 Data Extraction

Data were extracted from all articles which met the inclusion criteria after full-text review. Data extraction focused on identifying study design details for each article including the rehabilitation interventions, plus detailed examination of the outcome measures used.

As the purpose of the study was to evaluate the outcome measures used in studies of rehabilitation, a risk of bias assessment of the studies was not carried out.

3.4.3.5 Data Synthesis

Data were examined to identify the characteristics of the studies, number and type of outcomes used and their frequency of use.

Outcomes were categorised according to type, and the number of times each outcome was used across studies was collated. A single outcome capturing several parameters was counted only once e.g. cardiopulmonary exercise testing or echocardiographic assessment.

To develop a clear understanding of what is being measured in studies of rehabilitation in PH, the outcomes used in the studies identified in this review were analysed against the ICF classification, to identify whether the outcomes were measures of the ICF domains of Body Function/Structure, Activity or

Participation. Details of each outcome were examined and items were compared to the ICF Checklist[74] to determine which domain or sub-domain they represented. Initial classification was carried out by CK before being checked and verified by DGK and KS. Disagreement was resolved by discussion and consensus.

As pulmonary hypertension is a haemodynamic state arising from a number of causes, there is no single measure of the disease itself; all clinical or physiological outcome measures were classified as measures of body function or structure. Delineation between Activity and Participation was based on ICF guidelines[75] adopting distinct non-overlapping sets of Activities (domains 1-4: learning and applying knowledge; general tasks and demands; communication; mobility) and Participation (domains 5-9: self-care; domestic life; interpersonal interactions and relationships; major life areas; community, social and civic life). Measures of survival and time to clinical worsening were determined to be measures of Body Functions/Structures, as were outcomes related to use of healthcare resources. Outcomes which encompassed more than one of the domains e.g. Activity and Participation were counted in both categories.

The ICF model considers health in the context of environmental and personal factors which may be barriers or facilitators to patients' performance. Environmental factors might include access to supportive equipment or the building or health system in which the individual lives; personal factors may include age, gender, education or profession. While these are important aspects in understanding the health of an individual, they are not factors which will be influenced by rehabilitation interventions and therefore were not included in this analysis.

3.4.4 Results

Searches across five databases yielded 2564 articles after removal of duplicates. These were screened on title and abstract, leaving 62 articles which underwent full review and 34 articles which were included in the final data

synthesis, as show in the Flow Diagram (Figure 4). Details of the studies included in this review are in Table 9.

Studies were published between 2006 and 2019, with the majority of publications (94%) in the last 10 years (Table 10) reflecting a growing number of randomised controlled trials over that time period. Studies were most commonly of patient populations with pulmonary arterial hypertension (56%) or with pulmonary hypertension of a non-specified cause (29%). Rehabilitation interventions varied in content and length but were most frequently a form of whole-body exercise training involving a mix of cardiovascular, resistance and respiratory training alongside education around disease and symptom management.

Figure 4 - Search Flow Diagram

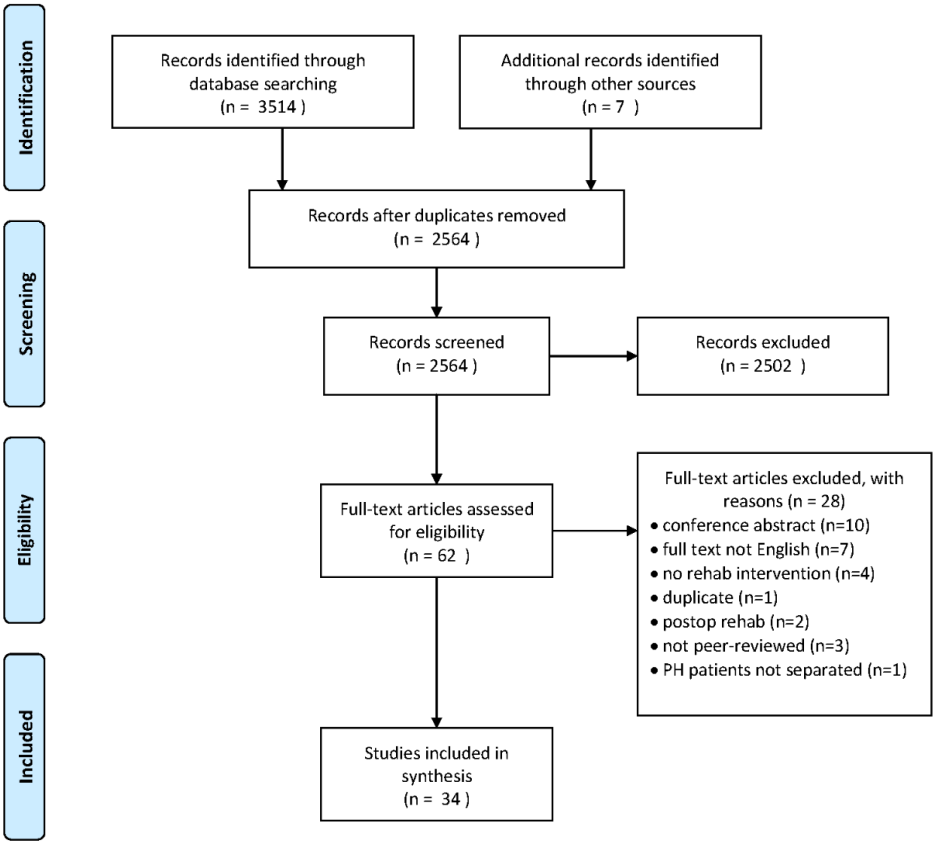


Table 9 - Full Text Studies

Study	Cohort	Study Design	Sample size (intervention/control)	Exercise Intervention	Control	Outcomes used
Awdish[76] (2015)	Pulmonary hypertension	Case series	3	Hatha yoga program designed for patients with pulmonary hypertension	NA	Health Promoting Lifestyle Questionnaire; 6MWD; oxygen saturation at rest
Babu[40] (2019)	Pulmonary hypertension	RCT, non-blinded	84 (42/42)	12 week home based exercise program plus patient education manual	education manual	6MWD; SF-36; WHO FC; RV function (via echo)
Becker-Grünig[77] (2013)	Congenital heart disease associated pulmonary arterial hypertension	Prospective non-randomised trial	20	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; CPET; SF-36; NT-proBNP; WHO FC; TTCW; survival
Brown[78] (2018)	Pulmonary arterial hypertension	Prospective non-randomised pilot study	12	Incremental walking programme plus arginine supplement	NA	6MWD; CPET; SF-36; cardiac function (via echo); NT-proBNP; step count; heart rate recovery
Bussotti[59] (2017)	Pulmonary arterial hypertension	Prospective non-randomised trial	16	4 weeks daily training combined aerobic, resistance, IMT, psychological support	NA	CPET; 6MWD; NT-proBNP; pulmonary function tests; EQ-5D; HADS
Chan[67] (2013)	Pulmonary hypertension	RCT, single blinded	26 (13/13)	10 weeks treadmill exercise plus education	Education only	CPET; 6MWD; SF-36; CAMPHOR; IPAQ
Chia[79] (2017)	Pulmonary arterial hypertension	RCT, single blinded (Protocol)	NA	12 weeks of weekly group exercise (combined endurance, respiratory muscle training, strength, psychological support)	Written advice on walking program	cardiac function (via MRI); haemodynamics (via RHC); Grip strength; 6MWD; CAMPHOR; Depression and Anxiety Severity Scale; Lawton Instrumental Activities of Daily Living Scale; NT-proBNP; pulmonary function tests
de Man[80] (2009)	Idiopathic pulmonary arterial	Prospective non-randomised trial	19	12 weeks cycling and strengthening, 3 times per week	NA	CPET; quadriceps strength; pulmonary function tests; NT-proBNP; 6MWD; muscle biopsy

	hypertension					
Ehlken(a)[36] (2014)	PH and right heart insufficiency	Prospective group and age-gender matched control group	104 (58/46)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	6MWD; TTCW; WHO FC; Health and Social Care Resource Usage; EQ-5D; survival
Ehlken(b)[34] (2016)	PAH and inoperable or persistent CTEPH	RCT, single blinded	87 (46/41)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	CPET; haemodynamic (via RHC); 6MWD; SF-36; WHO FC; NT-proBNP
Fox[81] (2011)	Pulmonary arterial hypertension	RCT	22 (11/11)	12 weeks combined cardiovascular and resistance exercise plus home exercise programme	No rehabilitation input	6MWD; CPET; cardiac function (via echo); NT-proBNP
Ganderton[82] (2011)	IPAH, familial PAH, PAH associated with connective tissue disease	RCT, single blinded (Protocol)	NA	12 weeks combined cardiovascular and resistance exercise plus home exercise programme	No rehabilitation input	6MWD; CAMPHOR; SF-36; IPAQ; CPET
Gerhardt[83] (2017)	Pulmonary arterial hypertension	RCT, non-blinded	22 (11/11)	4 weeks of exercises on an oscillatory whole body vibration plate	No rehabilitation input	6MWD; RV function (via echo); CPET; single two-leg jump; SF-36; Living with Pulmonary Hypertension Questionnaire; chair raising test
González-Saiz[84] (2017)	PAH or inoperable CTEPH	RCT, single blinded	40 (20/20)	8 weeks of exercise (combined aerobic, resistance and IMT)	No rehabilitation input	upper/lower body muscle power; NP-proBNP; CPET; 6MWD; 5STS; Respiratory Muscle Strength; SF-36; Physical activity levels (via accelerometer); muscle mass
Grünig(a)[56] (2011)	pulmonary hypertension and right heart failure	prospective cohort study	58	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; SF-36; TTCW; WHO FC; CPET; survival

Grünig(b)[57] (2012)	pulmonary hypertension	prospective cohort study	183	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; SF-36; WHO FC; CPET
Grünig(c)[85] (2012)	PAH associated with connective tissue disease	prospective cohort study	21	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; CPET; WHO FC; SF-36
Ihle[86] (2014)	pulmonary hypertension	prospective cohort study	17	10 months strengthening, breathing exercises and education plus home exercise programme	NA	6MWD; SF-36; CAMPHOR
Inagaki[87] (2014)	inoperable CTEPH or persistent PH after surgery	prospective cohort study	8	12 weeks pulmonary rehabilitation classes plus home exercise programme	NA	MRC dyspnoea scale; baseline and transition dyspnoea index; peripheral muscle force; pulmonary function tests; 6MWD; Nagasaki University Respiratory ADL questionnaire; St George's Respiratory Questionnaire
Kabitz[88] (2014)	pulmonary arterial hypertension	prospective cohort study	7	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	Pulmonary function tests; NT-proBNP; 6MWD; Respiratory Muscle Strength
Karapolat[89] (2019)	2019	RCT, single blind	30 (15/15)	8 weeks of group cardio-pulmonary exercise classes	8 weeks home exercise programme	CPET; 6MWD; SF-36; Beck Depression Index; Cardiac Function (via echo)
Ley[90] (2013)	PAH or CTEPH	RCT, single blind	20 (10/10)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	6MWD; cardiac function (via MRI); pulmonary perfusion (via MRI)
Mainguy[91] (2010)	idiopathic pulmonary hypertension	prospective cohort study	5	12 weeks combined treadmill, cycling, upper and lower limb resistance	NA	6MWD; CPET; thigh muscle area; muscle biopsy; quadriceps strength

Martínez-Quintada[92] (2010)	pulmonary hypertension associated with congenital heart disease	non-randomised controlled trial	8 (4/4)	3 months progressive cycle resistance training	Education	6MWD; step count; grip strength; quadriceps strength; SF-36
Mehani[93] (2017)	pulmonary hypertension	prospective cohort study	50	5 months interval bike or treadmill training	NA	CPET; right ventricular function (via echo)
Mereles[23] (2006)	pulmonary hypertension	RCT, single blind	30 (15/15)	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	No rehabilitation input	6MWD; SF-36; WHO FC; CPET
Morris[94] (2018)	pulmonary hypertension	RCT, single blind (Protocol)	50	8 weeks outpatient supervised progressive cycling and treadmill training, followed by home walking programme	No rehabilitation input	6MWD; CPET; CAMPHOR; SF-36; cardiac function (via MRI); cardiac function (via echo); survival; TTCW
Nagel[95] (2012)	Inoperable CTEPH	prospective cohort study	35	3 week in-patient rehabilitation (cycle ergometer, walking, light weights, respiratory exercises) followed by 12 week home-based exercise program	NA	6MWD; CPET; WHO FC; NT-proBNP; SF-36; TTCW; survival
Raskin[96] (2014)	pulmonary hypertension	Retrospective	23	30-60 minutes treadmill, cycling and cross trainer 2-3 times per week	NA	6MWD; St George's Respiratory Questionnaire
Saglam[97] (2015)	pulmonary arterial hypertension	RCT	29 (15/14)	6 weeks progressive daily IMT	6 weeks sham IMT	Pulmonary function tests; respiratory muscle strength; 6MWD; MRC dyspnoea scale; Fatigue Severity Scale; Nottingham Health Profile
Souza Leão[98] (2018)	pulmonary hypertension	RCT, double blind (Protocol)	24 (12/12)	12 weeks progressive daily IMT	12 weeks sham IMT	Respiratory muscle strength; respiratory muscle endurance SF-36; 6MWD
Talwar[99] (2017)	pulmonary arterial hypertension	Retrospective	18	12 weeks group pulmonary rehabilitation	NA	Attainable treadmill speed

Tulloh[100] (2018)	pulmonary arterial hypertension	Pilot RCT	34 (18/16)	8 weeks of group mindfulness sessions including stretching and breathing exercises	No rehabilitation input	Beck Anxiety Index; Beck depression index; cardiac function (via echo); cardiac function (via ECG); WHO FC; 6MWD; Health and Social Care Resource usage; SF-36
Weinstein[68] (2013)	pulmonary arterial hypertension	RCT	28 (14/14)	Progressive treadmill walking for 10 weeks plus education	Education	Fatigue Severity Scale; Human Activity Profile; 6MWD; Incremental Treadmill Test

Abbreviations:
6MWD: 6 minute walk distance; TTCW: time to clinical worsening; CPET: cardio-pulmonary exercise testing; IMT: inspiratory muscle training; RCT: randomised controlled trial; WHO: World Health Organisation functional class; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; 5STS: five times sit-to-stand test; IPAQ: International Physical Activity Questionnaire; SF-36: 36 item quality of life survey; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; HADS: Hospital Anxiety and Depression Scale; EQ-5D:quality of life score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome review; MRC: Medical Research Council

Table 10 - Study Characteristics

	Studies n (%)			
	2006 - 2009 (n = 2)	**2010-2014 (n = 16)**	**2015-2019 (n = 16)**	**Total (n = 34)**
Study design				
Prospective single cohort	1 (50)	8 (50)	4 (25)	13 (38)
RCT	1 (50)	3 (19)	8 (50)	12 (3)
Protocol	0 (0)	1 (6)	2 (13)	3 (9)
Non-randomised two-armed	0 (0)	3 (19)	0 (0)	3 (9)
Retrospective	0 (0)	1 (6)	1 (6)	2 (6)
Case series	0 (0)	0 (0)	1 (6)	1 (3)
Patient population				
PAH	1 (50)	8 (50)	10 (63)	19 (56)
PH	1 (50)	5 (31)	4 (25)	10 (29)
PAH or CTEPH	0 (0)	1 (6)	2 (13)	3 (9)
CTEPH	0 (0)	2 (13)	0 (0)	2 (6)
Intervention				
Whole Body Exercise training	2 (100)	14 (88)	10 (63)	26 (76)
Walking Programme	0 (0)	2 (12.5)	1(6)	3 (9)
Inspiratory muscle training	0 (0)	0 (0)	2 (13)	2 (6)
Oscillation plate	0 (0)	0 (0)	1 (6)	1 (3)
Yoga	0 (0)	0 (0)	1 (6)	1 (3)
Mindfulness	0 (0)	0 (0)	1 (6)	1 (3)
Intervention period				
up to 1 month	0 (0)	0 (0)	2 (13)	2 (6)
2-4 months	2 (100)	15 (94)	13 (81)	30 (89)
5 - 12	0	1 (6)	1 (6)	2 (6)

Abbreviations
RCT - randomised controlled trial; PAH - pulmonary arterial hypertension; PH - pulmonary hypertension; CTEPH - chronic thromboembolic pulmonary hypertension
Note: Figures in brackets are percentages of the column subtotal

Across the 34 studies in the review, there were 50 distinct outcome measures used (Table 11). Studies used an average of 5 outcome measures (min=1, max=9) giving a total of 176 instances of outcome measure usage across the studies. Exercise testing (n=56), quality of life measures (n=31) and biomarkers (n=23) were the most frequently used, with several different outcomes being used within each category.

6MWD was used in 32 of the 34 studies; in the 2 studies not using 6MWD, 1 used CPET[93] and 1 attainable treadmill speed[99]. Several studies used more than one exercise test.

There was no quality of life measure used in 9 (26%) studies. Of these, two studies used symptom-specific patient reported outcomes.

Table 11 - Outcome Measures

	Category	Measure	Frequency of Use
Clinical Measure (n=128)	Exercise Test (n=56)	6MWD	32
		CPET	19
		5STS	1
		Incremental Treadmill test	1
		Single two leg jump	1
		Attainable treadmill speed	1
		Chair raising test	1
	Biomarker (n=23)	NT-proBNP	10
		Pulmonary function tests	6
		Muscle biopsy	2
		Peripheral muscle force (quads and handgrip)	1
		Muscle mass	1
		Thigh muscle area	1
		Heart rate recovery	1
		Oxygen Saturation at rest	1
	Cardiac Function (n=15)	Cardiac Function including LV and RV function (via echo)	5
		RV function (via echo)	3
		Cardiac Function (via MRI)	3
		Haemodynamics (via RHC)	2
		Cardiac Function (via ECG)	1
		Pulmonary Perfusion (via MRI)	1
	Strength (n=11)	Respiratory Muscle Strength	4
		Quadriceps strength	3
		Grip strength	2
		Upper/lower body muscle power	1
		Respiratory Muscle Endurance	1
	Long Term Outcomes (n=10)	Time to clinical worsening	5
		Survival	5
	Function (n=10)	WHO Functional Class	10
	Physical Activity (n=3)	Step count	2
		Physical activity levels (via accelerometer)	1
Patient Reported Outcome Measure (n=48)	Quality of Life (n=31)	SF-36	19
		CAMPHOR	5
		EQ-5D	2
		Health Promoting Lifestyle Profile II (HPLPII)	1
		Nottingham Health Profile	1
		The Lawton instrumental activities of daily living scale	1
		Nagasaki University Respiratory ADL questionnaire	1
		Living with Pulmonary Hypertension Questionnaire	1
	Symptom Specific measures (n=12)	St George's Respiratory Questionnaire	2
		Fatigue Severity Scale	2
		Beck Depression index	2
		Hospital Anxiety and Depression Scale	1
		Beck Anxiety Index	1
		Depression and Anxiety Severity Scale (DASS21)	1
		Baseline and transition dyspnoea index	1

		MRC dyspnoea scale	2
	Physical Activity (n=3)	International Physical Activity Questionnaire	2
		Human Activity Profile	1
	Health Resources (n=2)	Health and Social Care Resource Usage	2

Abbreviations:
6MWD: 6 minute walk distance; TTCW: time to clinical worsening; CPET: cardio-pulmonary exercise testing; IMT: inspiratory muscle training; RCT: randomised controlled trial; WHO: World Health Organisation functional class; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; 5STS: five times sit-to-stand test; IPAQ: International Physical Activity Questionnaire; SF-36: 36 item quality of life survey; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; HADS: Hospital Anxiety and Depression Scale; EQ-5D:quality of life score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome review; MRC: Medical Research Council

When mapped against the ICF domains of Body Functions/Structures, Activity and Participation the outcomes were identified as measures of a single domain (68%), two domains (14%) or all three domains (14%). It was not possible to source sufficiently detailed information to allow classification for 2 (4%) of the outcomes (Living with Pulmonary Hypertension Questionnaire and Nagasaki University Respiratory ADL questionnaire).

The most common outcomes were measures of Body Functions/Structures (n=36) followed by measures of Activity (n=20) and Participation (n=13). Figure 5 maps study outcomes to the ICF domains. When weighted according to the frequency with which the outcomes were used, 48% of instances of outcome usage were measures of Body Functions/Structure, 33% were measures of Activity and 18% were measures of Participation. Seven (21%) of the studies in this review did not include any measure of Participation in their outcomes, the remainder (34%) captured measures across all three domains.

Table 12 shows further details of the sub-domains of Activity and Participation included in each of the outcomes. Several outcomes include only 1 or 2 of the 9 possible sub-domains, including the most common 6MWD. Outcomes encompassing higher numbers of sub-domains are less frequently used - Nottingham Health Profile (n=7), CAMPHOR (n=7), St George's Respiratory Questionnaire (n=6). SF-36, the most commonly patient reported outcome measure, encompasses 5 sub-domains.

Figure 5 - International Classification for Functioning, Disability and Health classification

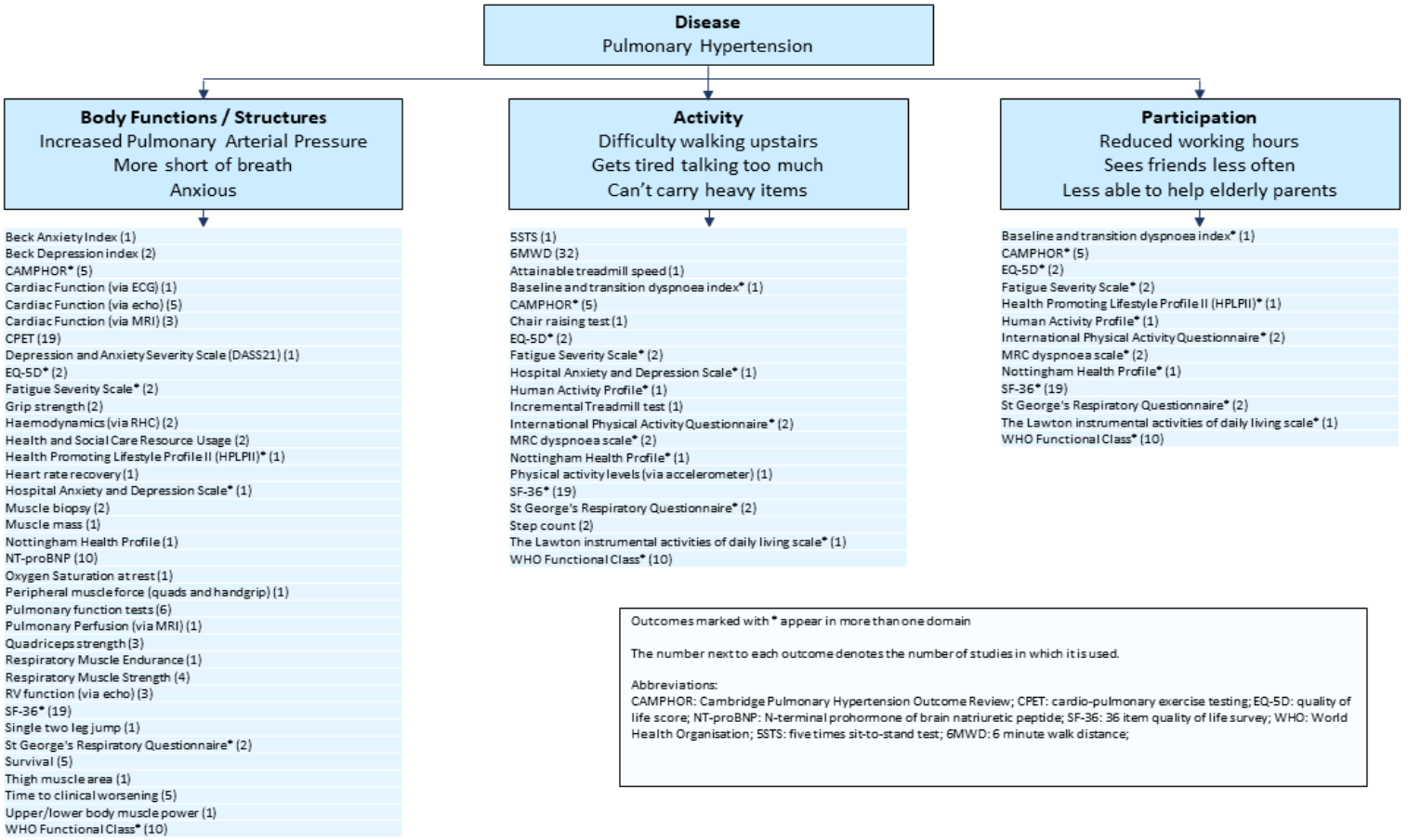


Table 12 - Outcome measures mapped to the sub-domains of ICF Activity and Participation

			Activity				Participation				
	Frequency of use	No. of domains	Learning and Applying Knowledge	General tasks and demands	Communic-ation	Mobility	Self-care	Domestic life	Interpersonal interactions and relationships	Major Life Areas	Community Social and Civic Life
Outcomes identified in the study											
5STS	1	1									
6MWD	32	1									
Attainable treadmill speed	1	1									
Baseline and transition dyspnoea index	1	2									
CAMPHOR	5	7									
Chair raising test	1	1									
EQ-5D	2	3									
Fatigue Severity Scale	2	4									
Health Promoting Lifestyle Profile II (HPLPII)	1	5									
Hospital Anxiety and Depression Scale	1	1									
Human Activity Profile	1	5									
Incremental Treadmill test	1	1									
International Physical Activity Questionnaire	2	4									
MRC dyspnoea scale	2	2									
Nottingham Health Profile	1	7									
Physical activity levels (via accelerometer)	1	1									
SF-36	19	5									
St George's Respiratory Questionnaire	2	6									
Step count	2	1									
The Lawton instrumental	1	3									

activities of daily living scale											
WHO Functional Class	10	2									
Outcomes not identified in the study											
emPHasis 10	0	5									
WHODAS 2.0	0	8									

Key:
Shaded cells denote that the outcome measures captures information relevant to this domain
Abbreviations:
6MWD: 6 minute walk distance; WHO: World Health Organisation functional class; 5STS: five times sit-to-stand test; SF-36: 36 item quality of life survey; EQ-5D:quality of life score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; MRC: Medical Research Council

3.4.5 Discussion

This review has examined outcome measures used in studies of rehabilitation in pulmonary hypertension since the first study published in 2006. The use of outcome measures is heterogenous across the studies, employing 50 different outcomes across 34 studies, with an average of 5 outcomes per study. When mapped onto the World Health Organisation International Classification for Functioning, Disability and Health,[48] it is clear that outcomes measuring changes in Body Functions/Structure predominate, with fewer measures capturing Activity and even fewer considering changes in Participation that might arise from the rehabilitation intervention. Of the studies included in this review, 21% did not use any measure of Participation.

The first randomised controlled trial of a pharmaceutical intervention in pulmonary hypertension in 1990 used 6MWD as its primary endpoint, and subsequent trials of drug therapies have tended to follow suit.[70] Reflective of the limitations of 6MWD to capture wider aspects of health, trials of drug therapies in pulmonary hypertension have incorporated patient reported outcomes to capture changes in health related quality of life, although these have been found to be less responsive to therapeutic impact.[71] Pulmonary hypertension lacks strong surrogate disease end-points; the use of invasive measures such as haemodynamics has decreased over time in pharmaceutical studies with a shift instead to composite end-points reflecting time to clinical worsening and, more recently, a focus on time to clinical improvement.[71] Studies of rehabilitation in pulmonary hypertension demonstrate a similar pattern to studies of pharmacological interventions, with initial studies focussing on 6MWD and quality of life measures also being captured, although with less frequency.

It is understandable that early studies of rehabilitation in PH chose end-points used in trials of pharmacological interventions where there was evidence for a clinically meaningful difference. The extensive use of physiological markers in earlier studies may be justified to establish the safety and mechanisms of rehabilitation as a relatively new intervention, however, the potential for rehabilitation interventions

to have wider consequences must also be considered and reflected in the outcome measures used.

3.4.5.1 Implications

It is essential that research into rehabilitation interventions in pulmonary hypertension demonstrates its impact on the issues that are most important to patients, which will include not only aspects of Body Functions/Structure but also Activity and Participation.

Pulmonary hypertension impacts the physical, practical and social aspects of the daily lives of patients and their carers. Studies show the impact of the disease on levels of anxiety and depression as well as cognitive function. Emotional and relationship issues are common, with high levels of depression and anxiety.[15,101] In living with the disease on a day-to-day basis, parameters of survival, biomarkers, exercise capacity and haemodynamics can have less relevance to patients than their concerns about employment, reliance on others for help, or loneliness.[51] Diminished quality of life[102] and reducing the burden of living with PH are priorities for organisations supporting patients.[103]

Rehabilitation is a broad term which captures an active and enabling approach to optimising function for individuals. Rehabilitation in other respiratory diseases has been shown not only to deliver on increased physical functioning, as demonstrated by changes in exercise capacity, but also to impact aspects of living with long-term conditions such as fatigue, emotional function, understanding and mastery of the disease and its management.[104]

By limiting the outcomes used to measure the impact of rehabilitation in pulmonary hypertension, focusing predominantly on clinical and physiological outcomes as seen in this review, researchers, clinicians and service providers risk overlooking the wider benefits that might arise from rehabilitation of patients in this area. The interventions in most studies in the review are multi-faceted, including psychological and educational components, yet this is not effectively reflected in the outcomes captured.

Rehabilitation is not yet embedded in clinical practice in pulmonary hypertension, despite a growing evidence base[28]. Health care resources are scarce and the case for development of new services must be compelling. The cost of caring for people with respiratory disease is significant arising both from medical care of the condition - drug therapies, hospital admissions - but also from the social costs of respiratory disease - inability to work, requirement for care and support at home, dependence on benefits. Rehabilitation interventions that can be shown to address these problems, as well as associated functional limitations on comorbidities such as mental health and obesity, are important in making the case for developing services.

3.4.5.2 Future considerations

Measures which capture aspects of Activity and Participation should be used in studies of rehabilitation in pulmonary hypertension, to assess change across a broad spectrum of patients' lives. Of the outcomes which assess Participation in this review, SF-36 is the most used, and also widely used in trials of pharmacological therapies in PH. Although a generic instrument, its measures have been shown to converge well with other physiological markers in PH and a minimally clinically important difference (MCID) has been estimated.[29] Whilst several items on the questionnaire address pain and energy levels, which fall within the domains of Body Functions/Structure, it encompasses only 5 of the 9 sub-domains of Activity and Participation (Table 12).

The Cambridge Pulmonary Hypertension Outcome Review questionnaire (CAMPHOR) is a disease specific questionnaire used in five studies in this review. It addresses issues of breathlessness, mobility, energy and the emotional consequences of living with pulmonary hypertension, encompassing 7 of the 9 sub-domains in Activity and Participation (Table 12). While it may not track other PH clinical measures over time[71] its validity, reliability and MCID have been established[105]. emPHasis10[62] is an alternative pulmonary hypertension specific patient reported outcome measure. Initially designed as a tool for use in clinical practice, it is widely used in this capacity to monitor disease progression in patients

with pulmonary hypertension. Covering 5 of the 9 domains of Activity and Participation (Table 12), it is yet to be tested in studies of rehabilitation.

The use of disease specific measures may have less relevance in rehabilitation than in the assessment of pharmacological therapies or clinical progress. Many patients with pulmonary hypertension will have significant comorbidities and complex health problems for which rehabilitation may also be beneficial. In such situations, attempting to capture outcomes which reflect the impact of rehabilitation on a single disease might overlook the wider benefits to health. The World Health Organisation Disability Assessment Schedule[106] (WHODAS 2.0) is a self-administered questionnaire which covers 8 of the 9 domains of Activity and Participation (Table 12). It is not disease specific, however its psychometric properties have been repeatedly validated in diverse populations, locations and languages. Its inclusion of items relating to relationships, intimacy, dignity, practical and financial burden, which reflect concerns frequently raised by people with pulmonary hypertension,[107] suggest it may warrant further exploration and adoption in studies exploring rehabilitation. Although its use is growing there is only a single instance of its use to date in pulmonary hypertension, in a study that uses the measure to characterise patients with the disease.[108] While used in only one study of rehabilitation, the Nottingham Health Profile covers 7 of the 9 domains (Table 12) and therefore may also warrant further investigation.

It is likely that the recent global COVID-19 pandemic will result in an increased number of non-face-to-face patient assessments taking place. Outcomes which can be used in this setting will need to be examined; there may be an increased use of questionnaires, self-administered tests or remote monitoring of patients.

There are limitations on the ability of even the most rigorous questionnaires to fully capture the outcomes of complex rehabilitation interventions. In-depth exploration through qualitative research of patients' experience of rehabilitation in pulmonary hypertension and the impact on their lives and the lives of their carers would also have a valuable role in deepening our understanding of this important topic.

Adopting the best measures to capture the outcomes of rehabilitation' will allow the design, commissioning and delivery of services which best meet the needs of patients.

3.4.5.3 Acknowledgements

The authors would like to thank the staff in Library services at Sheffield Hallam University who facilitated access to the materials used in this study.

3.4.6 Conclusion

Studies of rehabilitation in pulmonary hypertension have focussed primarily on measures of Body Functions/Structure; the impact in other domains is less well characterised. Greater inclusion of outcome measures reflecting activity and participation in society is needed to allow assessment of the wider impact of rehabilitation in patients with pulmonary hypertension.

3.5 Summary

The Literature Review gave an understanding of the wide range of outcome measures that have been used in studies of rehabilitation in pulmonary hypertension, and the frequency with which they were used. It demonstrated how the outcomes aligned with the World Health Organisation International Classification for Functioning, Disability and Health[48] and in doing so identified gaps in what is commonly measured when considered against the potential benefits of rehabilitation. Possible alternative outcomes were identified that focussed on activity and participation in society.

The review also acknowledged that prevalent considerations of outcome measures may need to be reassessed in light of the increased use of non-face-to-face patient assessments as a result of the COVID-19 pandemic.

Published literature and conceptual models are important components when considering the outcomes used to measure the success of an intervention. It is also important to incorporate the views of patients, who may for example consider that

some outcomes are better aligned to the values that they ascribe to the intervention in the context of their overall health and well-being.

Chapter 4 describes activity that was undertaken alongside to the Literature Review in this programme of work: the design of a Feasibility Study for the evaluation of a rehabilitation intervention. This study design proposes incorporating the findings of the Literature Review with the views of patients in selecting the outcomes to be used in the study.

Chapter 4 Feasibility Study

This chapter outlines the background to the Feasibility Study and describes, in greater detail than was allowed in the study protocol, the reasoning behind the methods selected in the study. It then presents the study protocol as submitted for and granted NHS ethical approval, before summarising the status of this programme of work once ethical approval had been obtained.

4.1 Background

The Review of Service (Chapter 2) examined a novel model of physiotherapy rehabilitation in pulmonary hypertension that comprised a holistic well-being assessment carried out by a specialist physiotherapist, followed by sign-posting or referral to community rehabilitation services local to the patient, with additional specialist expertise and advice available to support local services as needed. The review found a significant need for rehabilitation in the patient group, which appeared to be well met by the service design. There was an indication of benefit to patients, but without a comparator group it was not possible to comment on the efficacy of the intervention, and therefore not possible to endorse its roll out to other UK services and potentially other health settings.

A comparator study to review the outcomes of the specified rehabilitation intervention against a control group was therefore indicated as a next step in this programme of work.

The Review of Service (Chapter 2) and the Literature Review (Chapter 3) both highlighted the contrast between the understanding of rehabilitation as a broad and complex intervention which encompasses physical, emotional and behavioural components,[73] and the outcome measures used in studies of rehabilitation in pulmonary hypertension which focus on a narrow spectrum of measures of body function and structure.[75] It is also important to consider the perspective of the patient on the impact of rehabilitation and suitable measures that could be used to

capture this. The question of which outcomes should be used to assess the specified intervention was therefore yet to be determined.

The complexity of the intervention and the uncertainty regarding outcome measures suggested that, in preparation for a larger study, a preparatory study was required to examine the outstanding questions regarding design and methods. Pilot studies can be conducted to test the process and inform the calculation of sample sizes of a planned larger study.[109] However in this case there remained questions of the possibility of delivering the intervention which was reliant on community-based services, and uncertainty pertaining to the choice of outcome measures, therefore a feasibility study was determined to be the most appropriate path to take.[110]

The goal of the Feasibility Study described below was therefore to test whether it was feasible to conduct a randomised controlled trial of the rehabilitation intervention described in the Review of Service.

4.2 Methods

This was a complex study assessing a complex intervention.

The pragmatic philosophy which underpins this programme of work emphasises the *goal of the research* in considering research questions and the methods used to address them, as well as the importance of the contexts within which that inquiry occurs, and supports a mixed methods approach to inquiry.[1,4] This study was therefore designed with consideration to the overarching aim of this programme of work, which was to advance the understanding of delivering rehabilitation in patients with pulmonary hypertension in clinical practice in the UK, with a secondary aim of examining the outcome measures that could be used to evaluate rehabilitation interventions. The study was designed in the context of both the findings of the Review of Service, and the Literature Review which was conducted concurrently.

The Review of Service advanced knowledge of rehabilitation through a well-being review in patients with pulmonary hypertension. However, as a "before and after" study, it is limited in its ability to accurately depict the change in outcomes achieved by the intervention due to the influence of e.g. temporal changes between the two measurement points. A randomised controlled study design was therefore indicated to eliminate sources of bias.[111]

The findings of the review of service had raised questions about the most suitable outcome measure to be used. Key to the success of any trial is the use of outcome measures that are reliable, valid and responsive to the intervention.[112,113] It is also important, as indicated by patient and public involvement in this study and throughout this programme of work (4.5.13), that *"appropriate"* measures are selected i.e. those which capture outcomes that are of importance and relevance to participant,[112] in relation to the intervention. Therefore, before any randomised controlled trial could be conducted, inquiry into the most appropriate outcomes, with particular view to validity and relevance, was needed.

While the concurrent Literature Review explored the use of outcome measures in previous studies of pulmonary hypertension rehabilitation, the views of people with pulmonary hypertension were important to examine appropriateness and validity, which therefore indicated a component of qualitative inquiry. For data collection in this qualitative element, focus groups were considered for their potential to yield generative discussion, but ruled out on practical grounds – because of the rarity of their disease people with pulmonary hypertension are widely dispersed and travel can be challenging for them. The researcher instead made the pragmatic choice to conduct remote semi-structured interviews with patients in their own homes, thus alleviating patient burden. While this approach allows individual participants to address the research questions, enabling them to express their own views and what is important to them, it loses the opportunity for building consensus that focus groups might afford.[114]

In the presence of a defined research question to be explored, analytic induction was chosen as a preferred method (in preference to alternatives such as grounded theory).[114] The Framework approach (4.5.6.3) provides an analytic method that is both structured and robust, which supports triangulation in mixed methods approaches.[3,114,115]

Triangulation brings together the findings of multiple components in mixed methods research, which is used to augment the study findings.[114] From a pragmatic viewpoint, its purpose is also to focus the outcomes of inquiry on problem solving and action.[115] In this study design the findings of the semi-structured interviews would be cross referenced to the findings from the literature review to identify areas of concord and discord and, through this, select the outcomes most suited for use in the randomised controlled trial i.e. likely to identify genuine and appropriate change.

Many other considerations were given to the design of the study, as outlined below.

4.2.1 Selecting outcome measures

The Literature Review (Chapter 3) highlighted the challenges faced in selecting outcome measures for complex rehabilitation interventions. Primary outcome measures in studies of pulmonary hypertension rehabilitation to date predominantly use objective measures of exercise capacity and quality of life questionnaires (section 3.4.4). In contrast, patient and public involvement in the early stage of this study design suggested that outcome measures might need to include measures of carer well-being, measures of fatigue or its management and measures of anxiety and depression that capture mood.

For this reason, it was determined that selection of outcome measures in the Feasibility Study would be made through consideration of the findings of qualitative patient data collection conducted in the initial stage of the study and findings of the Literature Review, which was ongoing at time of writing the protocol.

4.2.2 Mixed methods design

The goal of this study was to assess the feasibility of a randomised controlled trial, which would include the capture and analysis of quantitative data. However, the outstanding question of selection of outcome measures would involve findings from the literature review and inclusion of patient perspectives. A mixed-methods study was therefore indicated.

There are multiple considerations in designing mixed methods research which were addressed in planning this study.[114] The design choices made were founded in both the goal of this study (to assess the feasibility of conducting a larger study) and the goal of the larger study for which it was a preparation (to assess the effectiveness of the intervention in comparison to a control group).

4.2.2.1 Order

One classification of mixed methods studies lies in the order in which the components (qualitative and quantitative) are undertaken.[114] In this Feasibility Study the order of the components was apparent from the goal and definition of the study – the qualitative element of the study would determine outcome measures to be used and refine the study intervention and was therefore required to have been completed before the quantitative component which followed (QUAL-QUANT).

4.2.2.2 Priority

Some mixed-methods studies give priority to one component over another e.g. a study involving large amounts of quantitative data collection and analysis with a small number of patient interviews might be seen to prioritise the quantitative component over the qualitative. In this study both components have equal weight – the findings of the quantitative component are required to assess whether a larger future study could be conducted, but the quantitative component was dependent upon the qualitative component to inform the design of the quantitative component.

4.2.2.3 Combination

Mixed-methods research is not simply the use of both qualitative and quantitative research methods in a single study, it also requires a combination of the two data sets with a view to augmenting the study findings. Many approaches can be taken to combining the two components of the research;[114] this study design allowed for the data to be combined in two ways.

- Triangulation – the findings of the patient interviews and the Literature Review would be triangulated for mutual corroboration. Aspects of convergence or dissonance would be identified and inform the choice of outcome measures to be used in the Feasibility Study.
- Credibility – a more credible account of the feasibility of the study being examined can be presented by combining patients' perspectives of their experience of the intervention with the objective findings of the study.

4.2.3 Intervention

The intervention used in the feasibility study is based on that used in the Review of Service, in which patients underwent a Well-being review by the physiotherapist which led to referral or signposting to community rehabilitation services. This presented challenges in study design:

- The study was dependent on the availability of community rehabilitation services and their willingness to accept referrals for patients with pulmonary hypertension.
- Once the community referral was made, there would be no direct control over the rehabilitation by the research team, including the nature of the rehabilitation, its frequency, intensity or duration. Nor would the research team have access to data on patient compliance or completion of the rehabilitation programme.

However, the goal of the research was to examine rehabilitation interventions that could be delivered to patients within the UK health service. These features are

inherent in such services, and the Review of Service had identified that use of these community services appeared to meet the needs of patients.

These aspects were given due consideration before proceeding. On balance it was determined that the nature of the study was such that it would need to reflect the real-world features of rehabilitation services available to this patient group. Therefore, for the purposes of the study design, it was decided to proceed with the intervention as specified in the Review of Service. However, included in the study design was the specification that the intervention was considered to be the Well-being review and referral or signposting to community services, and did not include the community rehabilitation intervention itself.

The protocol for this Feasibility Study, as submitted and approved by an NHS ethical review panel, is outlined below. The protocol was developed in 2019-2020 and therefore refers to funding, organisational arrangements and data that were accurate at that time, including the 2015 ESC/ERS guidelines.[7]

4.3 Citation

Investigating a Physiotherapy Well-being Review in Pulmonary Hypertension

Protocol submitted and granted favourable opinion by South Yorkshire Research Ethics Committee in April 2020 reference 20/YH/0096 (Appendix 4).

4.4 Abstract

Background: Pulmonary hypertension (PH) is a disease of the pulmonary circulation characterised by breathlessness. Evidence for the benefits of exercise in PH comes from settings which are specialist in PH and also specialist in rehabilitation. Such facilities do not exist in the UK; it is therefore necessary to explore alternatives.

Aim: To examine the potential for a physiotherapy Well-Being Review to support patients with pulmonary hypertension in engaging in community-based rehabilitation, in order to improve their well-being and quality of life.

Methods: Stage1 - Qualitative study capturing patient experiences of rehabilitation and their perspectives on its outcomes. Semi-structured interviews will be conducted with a purposive sample of participants. Framework analysis will be used to identify themes and constructs which will inform Stage 2. Stage 2 - Feasibility study for a randomised controlled trial of a physiotherapy-led Well-Being Review for patients with PH, involving holistic assessment, referral to community-based rehabilitation and monitoring. A sample of 30 participants in WHO-FC II or III, stable on PH therapy for 3 months, will be randomised to:

Treatment group: Well-being Review and referral to community-based rehabilitation

Control group: Advice on exercise and physical activity

Analysis: Triangulation of findings from Stage 1 and an ongoing literature review will determine outcome measures.

4.5 Feasibility Study Protocol

4.5.1 Aim

To examine the potential for a physiotherapy Well-Being Review to support patients with pulmonary hypertension in engaging in community-based rehabilitation, in order to improve their well-being and quality of life.

4.5.2 Objectives

- To conduct qualitative research to develop an understanding of the patient experience of the Well-Being Review and the best outcome measures to capture its impact
- To assess the feasibility of conducting a randomised controlled trial into the effectiveness of a Well-Being Review in patients with pulmonary hypertension.

4.5.3 Introduction

Pulmonary hypertension (PH) is a progressive condition which can arise from a variety of causes and is characterised by re-modelling of the pulmonary vasculature and a narrowing of the pulmonary lumen. Diagnosis is confirmed by right heart catheterisation where mean pulmonary arterial pressure is at least 25mmHg.[8] It is a rare condition with an estimated UK prevalence of 6.6 cases per million.[60] Sheffield is the largest of 7 adult specialist PH centres, caring for 1600 patients, or 30% of the PH patients treated in the UK.[116]

4.5.3.1 What is the problem being addressed?

Patients with PH experience progressively worsening breathlessness and limited exercise capacity and quality of life. Prognosis is poor; however, with advances in targeted PH drug therapies over the last 10 years, more patients are now living with the disease rather than dying from it. PH is becoming a chronic rather than an acute illness and, according to the NHS Long Term Plan,[117] patients with PH should therefore be supported to live well, age well and die well through collaborative, person-centred care, encompassing pharmaceutical and non-pharmaceutical interventions.

Due to the rare nature of PH, patients can experience a long delay from onset of symptoms to diagnosis,[118] during which time many become increasingly symptomatic and less active, leading to physical deconditioning. Once established on effective treatment, patients can see a significant improvement in their symptoms; however this is not always met by an increase in physical activity. There is currently no routine provision of rehabilitation in PH in the UK which might address this physical and functional deterioration.[44]

4.5.3.2 Why is this research important?

In the last decade, there has been a growing body of evidence for exercise in patients with PH. Morris et al.[28] conducted a systematic review of exercise interventions, reporting significant improvements in exercise capacity and quality of life, with no adverse safety signals. These trials largely focus on supervised

rehabilitation services delivered in specialist PH centres. Such services do not exist in the UK and it is therefore necessary to investigate alternative approaches to delivering rehabilitation to patients with PH in existing UK health services.

Community-based exercise rehabilitation, such as pulmonary rehabilitation, is well-evidenced for patients with chronic obstructive airway disease,[65,104] with growing evidence in support of its use in other respiratory conditions, including PH.[119,120] Additionally, the potential for out-patient and home-based exercise training in pulmonary hypertension has also been examined.[40,59]

The use of community-based rehabilitation in PH warrants further investigation.

Currently, there are no established pathways for referrals from the 7 regional specialist PH centres into community-based rehabilitation services. Furthermore, as PH is a rare condition, knowledge of the disease and how it is managed is not widespread outside of specialist centres. Therefore, in investigating the wider use of community rehabilitation services in patients with PH, it will be important to consider the interface between the specialist centres, where patients are managed for their PH, and rehabilitation services, which are delivered in localised community settings by staff who are non-specialist in PH. Specifically, where patients are undertaking exercise, it is important that local staff are knowledgeable and confident to be able to deliver safe and effective interventions.

The pathway through which patients with PH can access community-based rehabilitation resources warrants further investigation.

4.5.3.3 Study Context

This study will form part of a PhD which is underway. Work to date, due for completion before the start of funding, includes a Service Evaluation and a Literature Review.

4.5.3.4 Service Evaluation

From 2017 – 2018, we conducted a service evaluation of a physiotherapy Well-Being Review for patients with PH. Participants received a 1:1 Well-Being Review

with a specialist physiotherapist and received advice and onward referral to local rehabilitation services to best-fit their clinical and functional needs. Follow-up phone calls and face-to-face contact in routine clinical visits were provided as needed, to progress referrals and provide support to participants. Of the 138 patients seen for a Well-Being Review within the study period, 131 (95%) had a need for an onward referral. Referrals were primarily to pulmonary rehabilitation (52%) but also included referrals to e.g. musculoskeletal physiotherapy and exercise advice.

The service evaluation has been published in a peer-reviewed journal article which fully describes the Well-Being Review.[45] The results from the Service Evaluation highlight that high numbers of patients with PH had a rehabilitation need and that rehabilitation outcomes were suggestive of positive change. The study was limited however by the lack of control group without which the extent and nature of any changes cannot be determined and possible negative outcomes cannot be ruled out. Additionally, it is important to identify appropriately sensitive outcome measures that can be collected in the clinical setting. Further study of the Well-Being Review is therefore warranted.

4.5.3.5 Literature Review

A systematic review of rehabilitation in PH is in progress, examining the outcome measures used in studies of rehabilitation in pulmonary hypertension; literature searching and data extraction have been completed and data synthesis is well underway. Preliminary results from this review suggest a wide variation in the measures used to assess the impact of rehabilitation in patients with PH - a total of 49 measures have been used over 34 studies, with each study using, on average, 5 outcomes. Furthermore, in contrast to the understanding of rehabilitation as a broad and complex intervention which encompasses physical, emotional and behavioural components,[73] the outcomes in these studies focus on a narrow spectrum of measures of body function and structure.[75] The perspective of the patient on the impact of rehabilitation and suitable measures to capture this, is absent from the literature. We therefore feel it is important to examine the views

of patients on the impact of a Well-Being Review on their lives and to ask what they believe could be captured from the experience that might demonstrate its impact as an outcome that could be measured.

4.5.4 Plan of the investigation

4.5.5 Study design

This will be a sequential study, comprising 2 connected work packages. Work Package 1 (WP1) will be a qualitative study to capture in-depth experiences of participants who have undergone a Well-Being Review, and its impact on their well-being. The findings from WP1 will inform the design, content and outcomes of Work Package 2 (WP2) which will comprise a feasibility study of a randomised controlled trial to assess a Well-Being Review in patients with PH.

4.5.6 Work Package 1 (WP1) – Qualitative Study

The Service Evaluation has shown variability in the nature and outcomes from Well-Being Reviews. The patient group is widely varied, often with complex health and social issues; referrals were made to a number of different services across a large region. These features contribute to the complex nature of the intervention in this study. Furthermore, early results from the Literature Review show a lack of clarity regarding suitable outcomes to assess the impact of rehabilitation in patients with PH. A qualitative investigation is therefore required to capture patient experiences of the Well-Being Review and its impact on patients in order to identify any refinements to the Well-Being Review and study design. Additionally, the findings from WP1 will be triangulated with the outcomes from the Literature Review to identify areas of convergence or dissonance and so inform the choice of outcome measures to be used in WP2.

Aim

To develop an in-depth understanding of the patient experience of a Well-Being Review and its impact on patients.

Objectives

- conduct semi-structured interviews with a purposive sample of patients
- analyse the data to identify themes and patterns
- identify outcome measures for WP2.

4.5.6.1 Sampling

A sample of participants will be selected from patients who were involved in the Service Evaluation or who have undergone a Well-Being Review as part of their clinical care at the Specialist Centre. Purposive sampling will be used to capture participants with a range of experiences and rehabilitation outcomes; sampling strategies may also consider demographic variables, disease severity or functional ability. Sampling will continue until data saturation has occurred i.e. until no major new topics are arising in the analysis. This is likely to require approximately 15 interviews.[121]

4.5.6.2 Data Collection

Semi-structured interviews will be conducted via telephone due to the wide geographic spread of patients attending the specialist centre. A topic guide will be used to direct the interview content and structure; questions will include patients' experience of the Well-Being Review and their rehabilitation as well as the impact of their rehabilitation on themselves and their carers. Interviews will be audio recorded and transcribed verbatim for analysis.

4.5.6.3 Analysis

The qualitative interview data will be analysed using the Framework approach.[122] This method is appropriate for identifying, analysing and reporting themes and patterns within data. It is a flexible and useful research tool, which can provide a rich and detailed, yet simple account of data.

Framework analysis will consist of five key stages: familiarisation with the data through repeated reading to understand its breadth and depth; identifying a thematic framework; indexing and sorting of categories into broader themes; charting data by theme in order to allow analysis as a whole; interpretation and

write up to tell the story of each theme and the data as a whole, supported by extracts from the original data.

4.5.6.4 Expected Results – WP1

The findings from Work Package 1 will provide detailed information regarding the patient experience of taking part in the Well-Being Review and will inform the design of WP2. Information obtained concerning the impact of rehabilitation on patients and their views on how this might be measured will be triangulated with findings from the Literature Review to inform the choice of outcome measures to be used in WP2.

4.5.7 Work Package 2 – Feasibility Study

Aim

To determine whether it is feasible to conduct a randomised controlled trial of a Well-Being Review for patients with PH.

Objectives

- Assess the acceptability of the study to patients by measuring recruitment rates
- Assess the suitability of inclusion and exclusion criteria by examining recruitment data
- Assess the acceptability of the intervention
- Collect data to support sample size calculations for a larger study
- Examine the suitability of outcome measures.

4.5.7.1 Design

A feasibility study of a single centre two-armed randomised controlled trial.

4.5.7.2 Study population

Inclusion Criteria - participants must be:

- over 18 years old;
- in WHO-FC II or III;

- have a diagnosis of PH;[7]
- have started on PH drug therapy in the preceding 18 months;
- showing no signs of worsening breathlessness or heart failure;
- on an unchanged PH therapeutic regime for at least 3 months prior to inclusion.

Exclusion Criteria - participants will not be enrolled in the study

- with active infection or acute exacerbation of lung disease;
- having participated in a clinical study involving another investigation of drug, device or exercise within 6 months;
- on surgical or other pathway of care that has pre-determined physiotherapy or activity regimes or restrictions;
- with general medical conditions that may adversely affect the safety of the subject or severely limit the lifespan of the subject;
- participated in rehabilitation in the last 12 months.

4.5.7.3 Intervention

Participants will be seen for a Well-Being Review within PH outpatient clinics. This will be a 1:1, face-to-face meeting with the physiotherapist. Prior to the Well-Being Review, clinical notes will be reviewed to identify patient history and current treatment plans. Full details of the Well-Being Review can be found in the published manuscript of the Service Evaluation.[14]

A subjective history will be taken which will cover relevant medical and social history, functional ability and limitations, experiences, beliefs and attitudes to exercise and physical activity.

All participants meeting the referral criteria will undergo a Well-Being Review. During that review, based on clinical reasoning and assessments, participants will be offered a referral to community rehabilitation services to best meet their needs, goals and lifestyles e.g. pulmonary rehabilitation; musculoskeletal physiotherapy; weight management services; community exercise schemes; verbal and written

advice regarding exercise. Participants who accept referrals will receive follow-up phone calls as required to ensure progress of referrals and provide necessary support or advice.

Staff delivering local rehabilitation services will be able to access support and advice from physiotherapy experts in pulmonary hypertension via phone or email throughout the intervention period.

4.5.7.4 Control

Participants in the control group will receive brief verbal and written advice on the benefits of exercise in PH. Routine follow-up phone calls will not be carried out, however additional advice will be given if sought by the participants in the control group; information on the frequency and nature of this will be captured in the study outcomes. Due to the high need for rehabilitation identified in the Service Evaluation and to assist patient recruitment, these patients will also be offered a Well-Being Review after their final assessments at 6 months (Figure 6).

4.5.7.5 Duration of Treatment

Patients will be offered follow-up support as needed through the 6-month intervention period.

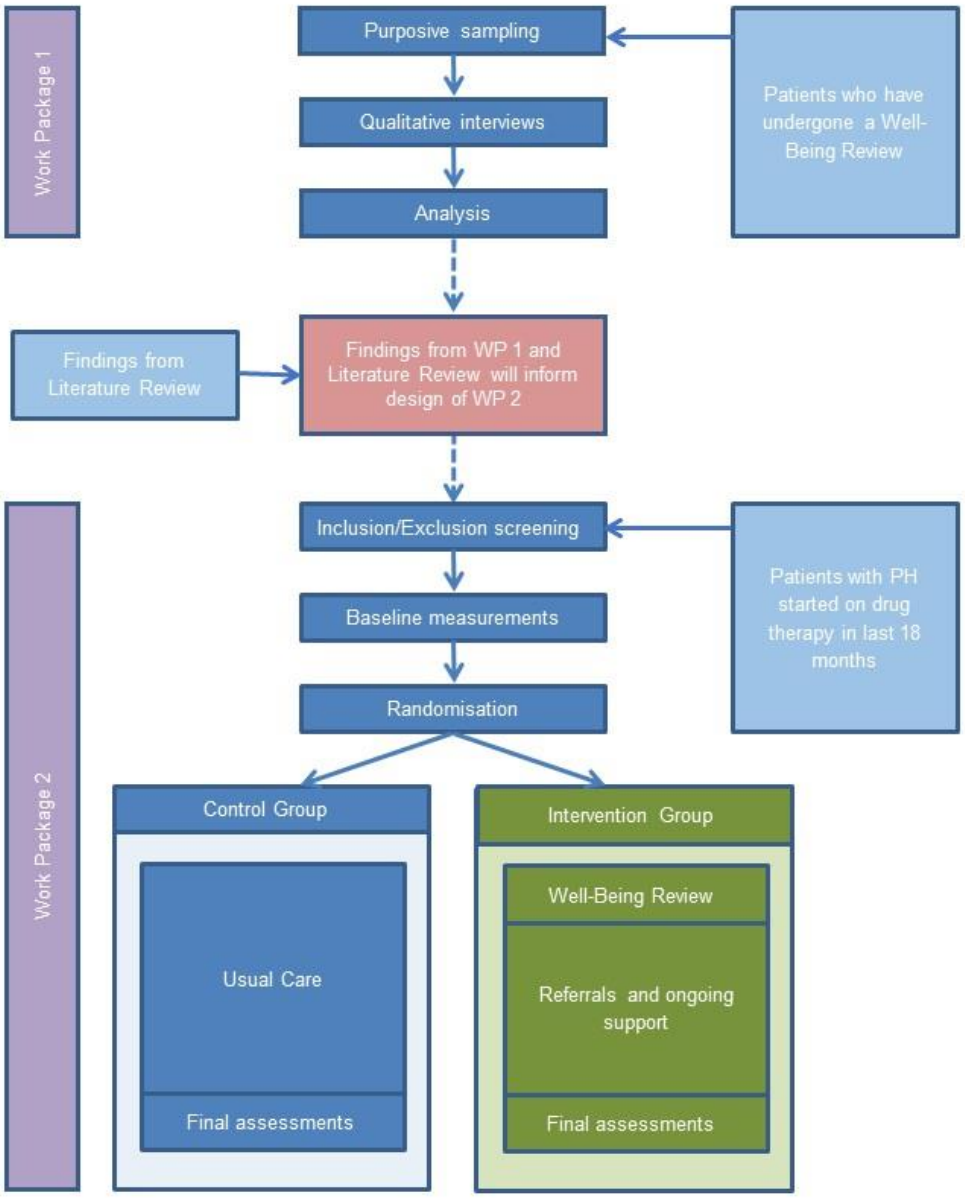
4.5.7.6 Outcome Measures

Outcome measures will be finalised on completion of WP1 based on the findings of the literature and an assessment through the qualitative interviews of what is important to patients and the potential impact of rehabilitation. A provisional list of outcomes is shown below. Deviation from this set of outcomes as a result of the findings of WP1 will require application for ethics amendment.

- Incremental Shuttle Walk Test (exercise test)
- emPHasis10 (PH quality of life measure)
- SF-36 (generic quality of life measure)
- Human Activity Profile (HAP)
- World Health Organisation Disability Assessment Schedule (WHODAS) 2.0

- MRC dyspnoea scale (measure of breathlessness).

Figure 6 - Feasibility study flow diagram



4.5.7.7 Feasibility Measures

Measures used to assess feasibility of the study will include:

- recruitment target of 5 patients per month to identify acceptability of the study
- retention rate of 75% at 6-month follow-up to assess acceptability of the intervention
- screening and recruitment data will be examined to assess suitability of inclusion and exclusion criteria
- collection of outcome data to inform sample size calculations in a larger study
- completion rates of outcome measures to identify suitability.

The research will also capture participant screening log data, drop-out rates and reasons for withdrawal. Adverse events will be monitored by the study Steering Committee and considered in the decision to proceed.

4.5.7.8 Follow Up

Outcomes will be measured at baseline and 6 months (Figure 6).

4.5.7.9 Sampling

Consecutive sampling will be used to recruit patients from PH outpatient clinics at Sheffield Teaching Hospitals. While recommendations exist for sample sizes of 24 in pilot studies,[123] patients with pulmonary hypertension can become medically unstable in a short period of time and mortality rates are relatively high (mortality rates in the Service Evaluation were 5.1%) therefore we have selected the higher sample size of 30.[124] As this is a feasibility study no power calculation is required. Study outcomes will be used to determine primary end-point and sample size of a main trial.

4.5.7.10 Power Calculations

Data from this feasibility study will be used to determine power calculations for a larger study.

4.5.7.11 Randomisation

Participants will be randomised to control or intervention groups immediately after baseline assessments. Random permuted blocks with stratification on WHO functional class will be used, to ensure balance across the groups.[125]

As this is a small feasibility study, services of a clinical trials unit will not be required; an independent randomisation service will be used.

4.5.7.12 Planned subgroup analysis

Due to the small sample size in this feasibility study, no sub-group analysis will be carried out.

4.5.7.13 Potential sources of Bias

The lack of blinding will be a potential source of bias. Additionally, patients in the control group may increase their levels of activity during the waiting period; levels of physical activity pre- and post-intervention will be included in the study outcome measures.

4.5.7.14 Statistical Analysis

This will be descriptive and focus on confidence interval estimation. We will examine: feasibility of recruitment to inform any main trial; decision on primary endpoint for main trial; number/characteristics of eligible patients approached for the study; reasons for refused consent; participant attrition rates; number of adverse incidents; data distribution across outcome measures. Analysis will also be undertaken of the variability of the intervention through review of the end rehabilitation services used for patients, as this may also inform any future study.

4.5.7.15 Expected Results – Work Package 2

The data from WP2 will inform the design of a full RCT of the intervention, including information on recruitment, power calculations and use of outcome measures.

4.5.7.16 Potential risks and hazards

Patients will undergo supervised exercise or will be given advice on safe exercise limits in PH. Adverse events and signs of clinical worsening will be monitored through the study period through clinical tracking of patient hospital admissions and follow-up phone calls, as well as any feedback provided by rehabilitation providers. Participants will be advised to contact the study team if they feel there are changes in their pulmonary hypertension.

4.5.7.17 Early stopping

Early stopping will be considered only if significant issues with recruitment or patient safety are identified by the Steering Committee through reporting of recruitment rate and adverse events.

4.5.8 Setting

The research will be based in Sheffield Pulmonary Vascular Diseases Unit, one of 7 specialist adult PH centres in the UK.

4.5.9 Recruitment

Participants for WP1 will be identified from patients who have undergone a Well-Being Review in the Specialist centre at Sheffield Teaching Hospitals either as part of the service evaluation or through other clinical care. Patients will be posted a letter of invitation to join the study including a Participant Information Sheet and a consent form. They will receive a follow-up call from a research nurse within a few days asking if they are interested in taking part in the study. If they agree, they will be advised to complete and return the consent form and a date and time will be set for their telephone interview.

Participants for WP2 will be identified from existing databases of diagnosis and treatment, with cross reference to appointment booking systems. Patients will be posted a letter of invitation to join the study and a Participant Information Sheet, giving information about the study and indicating that they might be asked to participate during their next clinic visit. Patients will then be approached during

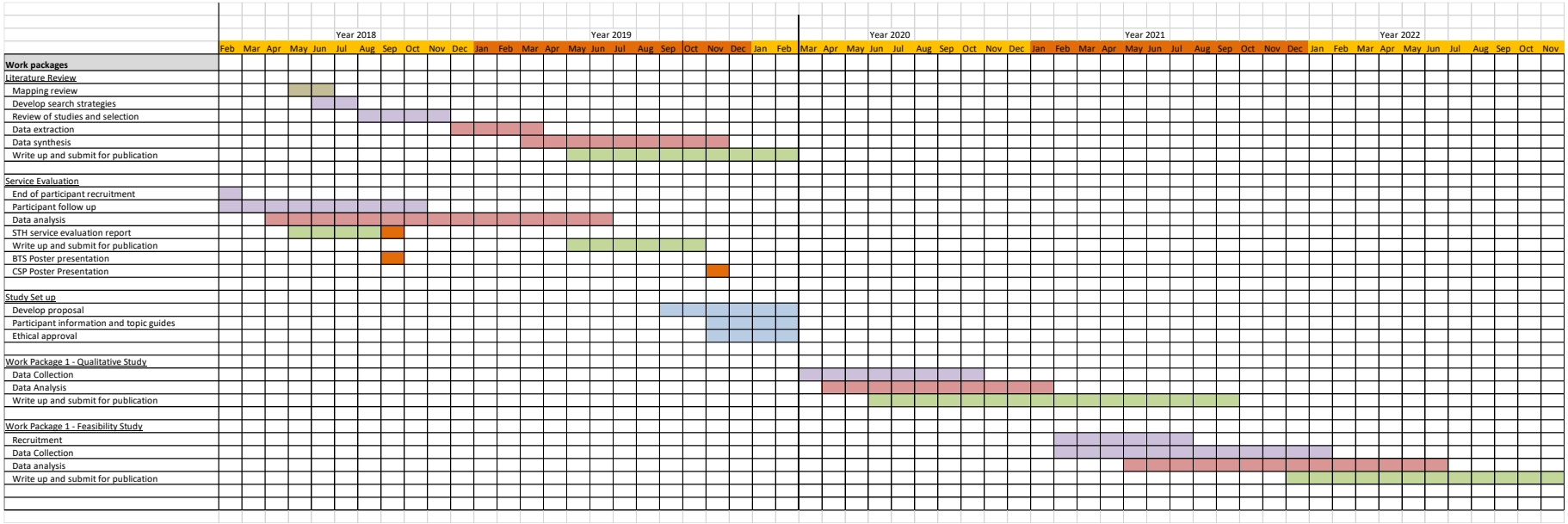
their clinic visit by a member of the nursing research team who will invite them to take part in the study. If they agree, then written consent will be obtained and they will be registered in the study. The recruitment period will continue for 4 months for WP1 and for 6 months for WP2 (see Figure 7 for details).

Around 300 new patients start on PH drug therapy in Sheffield each year. Data from the service evaluation indicate that approximately 50% would meet the inclusion criteria for WP2 i.e. 150 eligible patients per year, or 75 eligible patients during the 6-month period of recruitment to this study. On this basis, a recruitment rate of 35% would give a sample size of 26, 50% recruitment would give a sample size of 38 and recruitment at a rate of 70% would bring 52 patients to the study. The Service Evaluation recruited 138 patients in 8 months i.e. 17 patients per month; our lower target of 5 patients per months reflects the greater challenges in recruiting to a randomised study.

4.5.10 Statistical opinion

The statistical approaches in this study have been reviewed by Professor Ranjit Lall of Warwick University.

Figure 7 - Feasibility Study project timetable



4.5.11 Project management

A Steering Committee will be formed of the following members, whose expertise is outlined below:

- Professor Karen Sage is Director of Studies for Carol's PhD and will be a member of the study Steering Committee. She is Research Professor for Allied Health Professions at Sheffield Hallam University where her role is to engage therapists in research and to increase research capacity through PhD training. Her primary research interests are in rehabilitation for people after stroke and she has experience of experimental, case series, qualitative and large trial study methods. To date, Professor Sage has enabled 11 allied health professionals to successful PhD completion, 7 of whom have continued to work as clinical academics and become independent researchers. Her current PhD cohort includes 2 physiotherapists, 3 speech and language therapists and one nurse. As Director of Studies, Professor Sage currently oversees the project management and learning and development of Carol's PhD to ensure that there are completed in a timely way. She also ensures that any adaptations, changes to the timetable or additions required are adequately resourced. Professor Sage chairs the quarterly meetings of the whole supervision team and ensures the smooth running and contributions of each expert within the team as well as the 6 monthly Steering Committee meetings. As the PhD will include publications, Professor Sage will oversee the building of the articles, the submission to appropriate journals and appropriate rebuttal and resubmission for each. She will also ensure that all PhD milestones and all NHS and university governance requirements, including ethics, are met.
- Professor David Kiely (Sheffield Teaching Hospitals) is a member of Carol's PhD supervisory team and will be a member of the study Steering Committee. He is a Respiratory Consultant doctor specialising in Pulmonary Hypertension and has been Director of the Sheffield Pulmonary Vascular Disease Unit (SPVDU) since it was established in 2001. SPVDU is one of the

largest PH centres in the world and assesses and manages all forms of adult pulmonary hypertension. His external positions include: board member of International Workshop on Pulmonary Functional Imaging; Chair of the National Pulmonary Hypertension Audit Reference Group; Board member of the NHS Clinical Reference Group for Specialist Respiratory Medicine. He is the Sheffield Teaching Hospitals Pulmonary Hypertension Research Theme lead and co-director of the Donald Heath Pulmonary Hypertension translational research group. He has acted as principal investigator in multiple randomized controlled trials in pulmonary hypertension leading to the licensing of new treatments and has helped translate new imaging techniques into routine clinical practice. In 2017 he received an NIHR and Royal College of Physicians award recognizing an outstanding contribution to research in the NHS. Professor Kiely will share his expertise in pulmonary hypertension and in clinical research in the field. He will enable access to national and international research and clinical contacts in PH. His support and continued involvement in the project ensures that the work will be recognised and reach a wider medical as well rehabilitation audience.

- Professor Janelle Yorke (University of Manchester) is a member of Carol's PhD supervisory team and will be a member of the study Steering Committee. Professor Yorke is Lead of the Christie Patient Centred Research group at The Christie NHS Foundation Trust and Deputy-lead of the Supportive Palliative Care research group at University of Manchester. She holds numerous leadership roles at an international level including Chair of the European Respiratory Society Nurse Group. She has published widely and sits on the Editorial Board of many journals, including Thorax. A global leader in respiratory research Professor Yorke has an established program of research in supporting individuals living with long term conditions. She developed emPHasis10, a patient reported outcome measure (PROM) for patients with pulmonary hypertension which is now the principal measure of quality of life across the UK national service and has been translated into over 20 languages. She continues to work with the Pulmonary Hypertension

service in Sheffield and with PHA UK, the UK charity for patients with pulmonary hypertension in exploring patient symptoms in PH, particularly breathlessness. Professor Yorke will advise and support on the qualitative elements of the study, in particular underlying approaches to gathering sensitive data. She will help to develop my use of qualitative methods through review and supportive challenge of the data, ensuring that the qualitative component of this study is to an excellent standard. Drawing on her continued work and expertise in PROMs and quality of life in patients with long-term conditions she will also advise and support on my use of outcome measures linked to patients and carers.

- Professor Ranjit Lall (University of Warwick) will be a member of the study Steering Committee. She is a Professor of Clinical Trials and Biostatistics and lead of Methodology at the Warwick Clinical Trials Unit. Her expertise includes the design and analysis of accident and emergency trials and rehabilitation complex intervention clinical trials. She was a co-applicant for the Paramedic-1 (Lancet, 2015) and Paramedic 2 (NEJM, 2018) clinical trials and BEST (Lancet, 2012), DAPA (BMJ, 2018) – the latter two trials of complex interventions in rehabilitation. She is a co-applicant on the successful NIHR HTA commissioned bid for pulmonary rehabilitation in patients with PH, awarded in October 2018. Professor Lall will advise on the statistical methods in the study at all stages including sampling, sample size, randomisation, outcome measures, feasibility criteria, statistical methods, data analysis and reporting.
- Dr Molly Hashmi-Greenwood (Sheffield Hallam University) is a member of Carol's PhD supervisory team and will be a member of the study Steering Committee. She is a senior lecturer in physiotherapy at Sheffield Hallam University specialising in the care of patients with respiratory diseases will bring expertise in research methodologies and respiratory physiotherapy in other disease groups.
- Dr Gordon McGregor (University of Warwick) will be a member of the study Steering Committee. Dr McGregor is a Health and Life Sciences Clinical

Research Fellow at University of Coventry. He is PI on a recently awarded NIHR HTA commissioned bid into pulmonary rehabilitation in patients with PH. This work aligns with this study, but with clear differentiation. Both study teams are keen to progress work which is complementary and therefore to the best benefit of patients with pulmonary hypertension and research funders.

- Dr Iain Armstrong (Pulmonary Hypertension Association) will be a member of the study Steering Committee. Dr Armstrong is the chair of PHA UK (the UK patient charity for pulmonary hypertension) and a nurse consultant in PH. He has 20 years of clinical experience in nursing roles within PH: his research field is the lived experience of long-term conditions. Through his clinical role and his work in PHA UK he has been a vociferous advocate of the importance of exercise and rehabilitation in patients with PH, and of the role of physiotherapy.

In addition we will invite 2 patients with pulmonary hypertension to join the Steering Committee. We will work with PHA UK to identify and approach these patients.

The committee will meet quarterly and provide overall supervision of the study, its progress and adherence to the protocol. Patient safety will be monitored through reporting of adverse events. The Steering Committee will be responsible for decisions to proceed in light of adverse event reporting.

In addition, Professor Sage, Professor Kiely, Professor Yorke and Dr Hashmi-Greenwood form the PhD supervisory team for Carol Keen and meet regularly to provide support and review progress.

4.5.12 Ethical issues (Appendix 2)

Participants in Part 1 of the study will be required to give their time to be interviewed. They will be asked primarily about their previous experiences of rehabilitation and the changes that it may have made to them and to those around them. There is a possibility that some patients may find this an upsetting topic to

discuss - it may for example highlight to them the functional or physical limitations that they face as a result of their condition.

The use of an interview topic guide (Appendix 3) will help to ensure that interviews are not unnecessarily long, and that only topics relevant to the research are addressed by the interviewer. Participants will be informed before the interview of the topics areas that are likely to be covered. They will also be assured that the information they share will treated as confidential, and that they will not be identifiable in any outputs from this work. The interviewer will be an expert clinician with experience in the disease area and in managing difficult conversations with patients. Participants will be made aware that they can withdraw from the process at any time, including during the interview, and that they do not have to answer particular questions if they prefer not to.

In Part 2 of the study, participants will undergo additional assessments, undertake a Well-Being Review and participate in community-based rehabilitation. As far as possible we have designed the study such that study visits coincide with clinical visits, and to use routine clinical assessments.

Participants will be asked to complete additional outcome measure questionnaires. Outcome measures will be finalised on completion of WP1 based on the findings of the literature and an assessment through the qualitative interviews of what is important to patients and the potential impact of rehabilitation. A provisional list of outcomes is shown below. Deviation from this set of outcomes as a result of the findings of WP1 will require application for ethics amendment.

- Incremental Shuttle Walk Test (exercise test)
- emPHasis10 (PH quality of life measure)
- SF-36 (generic quality of life measure)
- Human Activity Profile (HAP)
- World Health Organisation Disability Assessment Schedule (WHODAS) 2
- MRC dyspnoea scale (measure of breathlessness).

The Well-Being Review will include an assessment of patients' current functional ability and their rehabilitation needs. There is a possibility that some patients may find this an upsetting topic to discuss - it may for example highlight to them the functional or physical limitations that they face as a result of their condition. Participants will be made aware in advance of the nature of this review, and that they can withdraw from the process at any time. Participants will be informed before the interview of the topics areas that likely to be covered. They will also be assured that the information they share will treated as confidential, and that they will not be identifiable in and outputs from this work. The interviewer will be an expert clinician with experience in the disease are and in managing difficult conversations with patients.

The studies to date of exercise in PH have looked closely at the safety of patients and have found that there have been only a very small number of minor incidents; for example someone becoming dizzy when they are on an exercise bike.

In the service evaluation of the Well-Being Review, we found no safety problems.

We will ensure that participants are aware that they can withdraw from the study at any time, and that this will in no way affect the care that they receive.

As part of the Well-Being Review, patients will be given information on how to exercise safely and what to do if they have any illnesses or injuries.

4.5.13 Service user involvement

Service Users have been involved in developing the study to date, and we will continue to seek their support throughout.

4.5.13.1 Identifying the Research Topic

We have worked in close collaboration with the Pulmonary Hypertension Association (PHA UK), the patient charity for pulmonary hypertension (PH) in the UK, to develop this line of clinical and research enquiry. The PHA UK identified that functional ability, physical activity and quality of life are high priorities for their

members and that exercise and rehabilitation have the potential to improve all these areas for patients.

To help address the current lack of any assistance in these areas, the PHA contributed to funding for Carol Keen from May 2017 to August 2019 to undertake an innovative clinical physiotherapy role in PH, with a focus on promoting physical activity in patients. They have collaborated actively through this work which has led to the identification of this research topic and the development of this proposal.

4.5.13.2 Developing the Application

To capture the views of patients, we presented the initial study design to two separate patient groups which were mixed in age, gender and functional ability:

- a panel of 5 Patient and Public Involvement (PPI) representatives from the Community and Acute Care Group within Sheffield Teaching Hospitals
- a focus group of 5 patients with PH and 3 carers, arranged through PHA UK.

They identified:

- The importance of this research. They are aware of significant drug research in PH but that there is little research which looks at approaches to moderate the wider burden of the disease and improve quality of life. They welcomed it as a potentially positive and optimistic intervention and did not foresee any problems with recruitment.
- The need to clearly explain in patient information the role and purpose of the control group and ensuring that participants in the control group have the opportunity to experience rehabilitation after the study end.

The views from these two groups were reflected in changes made to the study design as follows:

Updating recruitment to take place after patients have been on a stable therapeutic regime for at least 6 months (changed from 3 months). For many patients, the first few months after diagnosis can be full of anxiety and stress; it would be better to

approach patients when they have arrived at some acceptance of the disease and its consequences

Outcome measures might need to include: a measure of carer well-being; measures of fatigue to reflect the adjustments made to manage fatigue; measures of anxiety and depression that capture mood. This will be addressed in the topic guide for the qualitative interviews which aim to determine outcome measures to be used in the study.

We also discussed how best to describe the intervention and they favoured the term " Well-Being Review" as it reflected its positive and individualised nature.

4.5.13.3 Study Development

All participant information will be written in collaboration with patient representatives, who will check it is understandable and non-coercive. Patient representatives with be involved in the development of the work packages as we collect data and will help to troubleshoot any recruitment issues should they arise.

4.5.13.4 Study Management

Two patient representatives will be invited to join the study Steering Committee. We recognise the burden of the disease on patients, and that fatigue is a common symptom. To support them in participating in the Steering Committee we would seek to secure funding to allow for travel plus overnight stay for patient representatives and additional costs for a carer to travel and stay with them.

4.5.13.5 Dissemination to patients and carers

Patient representatives will be involved in review of the study findings and dissemination, particularly where this is aimed at patients and their families or carers. They will help to identify findings key to patients; suitable communication channels; appropriate language and content for communication. PHA UK has a quarterly magazine, annual patient conference and wider social media presence which would offer suitable channels for dissemination. There may be the potential

to draw on the study findings to collaboratively develop a comprehensive guide to rehabilitation for the patient group.

4.5.14 Dissemination

In addition to the dissemination to patients and carers outlined above, we will aim to share the findings of this study with physiotherapists, medical and nursing staff involved with the care of patients with Pulmonary Hypertension. We would aim to reach this audience in the following ways:

- Presentation at profession specific, disease/speciality specific and joint conferences.
- The main results would be submitted to a general open-access peer reviewed publications with the highest possible impact factor.
- Use of social media i.e. twitter, to disseminate to disease specific support groups/networks, other health professionals, educational establishments and other health care providers/commissioners of health services.
- Clinical education and MDT networking would be used to raise awareness of this work.

4.5.15 Taking the work forward

If the outcome of the study indicates that further study is feasible then we would look to undertake a pilot study or full RCT to identify the effectiveness of the intervention.

Findings from the qualitative aspect of the study may generate new knowledge around patient experience of rehabilitation and its outcomes which could generate further research questions.

Work is due to begin in the UK to review commissioning of clinical services for patients with pulmonary hypertension and we would seek to use the learning from this study and other ongoing research in pulmonary hypertension to ensure that physical activity and rehabilitation are embedded in care pathways for patients with

pulmonary hypertension. Colleagues in SPVDU and PHA UK are well placed to influence this decision-making process.

4.5.16 Costing schedule

This study will be undertaken within Carol Keen's PhD. Tuition fees are paid by Sheffield Hallam University under a fellowship awarded in 2017.

There are no additional travel or study costs for participants:

- qualitative interviews will be conducted over the telephone
- study visits will be aligned with routine clinical visits

Costs for the Steering Committee will be addressed as follows:

- there will be no costs for Steering Committee members based in Sheffield
- Steering Committee meetings will be arranged to coincide with PhD supervisory meetings to avoid travel duplication
- remote access to meetings will be arranged for members unable to travel
- resources will be sought from PHA UK, the patient charity for Pulmonary hypertension, to support patient/carer attendance at Steering Committee Meetings

These arrangements will be reviewed if our application for BHF funding is successful (see below).

4.5.17 Funding arrangements

This study will be carried out within the doctoral studies of the Chief investigator, Carol Keen.

An application has been submitted to the British Heart Foundation for fellowship funding for CK; should this application be successful the study will continue over a more condensed time period. The BHF funding panel will meet in February 2020.

4.6 Summary

The protocol for the Feasibility Study above was completed and submitted for NHS ethical review through the Integrated Research Application System (IRAS) in early 2020 and discussed with the local research ethics committee (REC) in March 2020. The minor changes they requested to the patient information were completed and a letter of HRA approval for the study to proceed was received in May 2020 (Appendix 4).

However as previously described (1.7.4) the course of this programme of work was unfortunately diverted in March 2020 by the COVID-19 pandemic.

The researcher was required to take a 6-month break from PhD studies to directly support care of COVID-19 patients. On return to study, the clinical and research landscape as it impacted on this study had significantly changed:

- The community rehabilitation services which were to be accessed in the Feasibility Study were either suspended or operating at very limited capacity. This had been highlighted as a potential risk to this study during its design (section 4.2.3), although these exceptional circumstances could not have been foreseen.
- Patients with pulmonary hypertension were required to shield or minimise personal contact with others, therefore were unable to attend any community rehabilitation services that might have been available.
- Support and approvals for research in the NHS setting were difficult to obtain, with priority being given to those studies which might directly support COVID-19 care, or which would give support to recovery of services following the restrictions of the pandemic.
- The COVID-19 pandemic brought about a shift in the delivery of outpatient clinical services, including those in pulmonary hypertension, from predominantly face-to-face to increasing non-face-to-face assessments.

In light of these circumstances the viability of the planned feasibility study was called into question.

The next chapter will describe the considerations and actions that were taken in light of these challenging circumstances.

Chapter 5 PERSPIRE

This chapter describes the background to the PERSPIRE study including its context within this programme of work. It outlines, in greater detail than was allowed in the published paper, the reasoning behind the methods selected and other considerations in designing the study. It then presents the paper as published, before summarising the implications of the study within this programme of work.

5.1 Background

As previously outlined, in March 2020 a 6-month pause from study was taken in response to the changes brought about by the COVID-19 pandemic. Return to study in October 2020 took place against a very different backdrop including COVID-19 restrictions on patient activity, clinical services and research activity. The viability of the planned Feasibility Study was therefore called into question and a reconsideration of the programme of work was required to identify how best to proceed. As described below, this required a reflection on the work completed to date, which took place within the context of the primary aim of this programme of work and the research philosophy within which it was conducted.

The findings of the completed Review of Service (Chapter 2) had demonstrated the high level of rehabilitation needs in patients with pulmonary hypertension, the challenges of delivering rehabilitation to such a complex and geographically dispersed patient group, and the potential to achieve this through accessing existing community rehabilitation services when accompanied by specialist support and expertise.

The Literature Review of outcome measures in pulmonary hypertension rehabilitation (Chapter 3) had been completed and accepted for publication at this point. Its main findings were the emphasis of previously conducted pulmonary hypertension rehabilitation studies to measures of Body Functions/Structure and the need for greater inclusion of outcome measures reflecting activity and participation in studies of rehabilitation in patients with pulmonary hypertension.

Before the events of the COVID-19 pandemic unfolded the intention had been to commence the Feasibility Study. In response to the findings of the Review of Service and the Literature Review, the Feasibility Study protocol (Chapter 4) described a study to determine the feasibility of conducting a randomised controlled trial of rehabilitation which was based on the intervention described in the Review of Service. The interventional aspect of the study was to be preceded by a piece of work which combined the findings of the Literature Review with themes identified in patient interviews to determine the most suitable outcome measures to assess the rehabilitation intervention.

The pragmatic philosophy which underpins this programme of work emphasises the *goal of the research* in considering research questions and the methods used to address them, as well as the importance of the contexts within which that inquiry occurs. In considering options to proceed it was therefore important to bear in mind the overarching aim of this programme of work, which was to advance the understanding of delivering rehabilitation in patients with pulmonary hypertension in clinical practice in the UK, with a secondary aim of examining the outcome measures that could be to evaluate rehabilitation interventions. Inevitably, the circumstances brought about by the COVID-19 pandemic were important determinants of the context within which options for progression were considered. These circumstances were:

- The community rehabilitation services which were to be accessed in the Feasibility Study were either suspended or operating at very limited capacity.
- Patients with pulmonary hypertension were required to shield or minimise personal contact with others, therefore were unable to attend any face-to-face rehabilitation services that might have been available.
- Support and approvals for NHS-based research which was not related to COVID-19 were of low priority and difficult to obtain.

Keeping in mind the findings of the work completed, the research aims and wider contextual circumstances, the following options were considered:

Option 1 – continue with the Feasibility Study

- Due to the constraints on community rehabilitation services, requirements for patients to shield, and the uncertainty of future developments in COVID-19, this option was determined not to be deliverable and was therefore excluded.

Option 2a – continue with a modified protocol of the feasibility study: remote (internet or phone-based) rehabilitation

- Questions of suitable outcome measures were still outstanding and would be further emphasised with rehabilitation conducted in the remote setting, where the use of objective measures such as exercise walking tests could be prohibitive.
- This would not meet the requirements at the time for new NHS research where priority was being given to studies supporting COVID-19 care or recovery.

Option 2b – continue with a modified protocol of the feasibility study: determining suitable outcome measures using qualitative interviews and findings of the literature review

- Preliminary discussions with PHA-UK highlighted concerns about approaching patients at that time for qualitative research which was not directly related to COVID-19.
- This would not meet the requirements at the time for new NHS research where priority was given to studies supporting COVID-19 care or recovery.

Option 3 – examination of alternative outcome measures for use in non-face-to-face assessment.

- Consideration of remote rehabilitation in Option 2a above immediately raised the question of outcome measures in that setting, particularly measures of exercise capacity that could be assessed with the patient at home.

- The COVID-19 pandemic brought about a shift in the delivery of outpatient clinical services, including those in pulmonary hypertension, from predominantly face-to-face to increasing non-face-to-face assessments.
- A study of this kind was more likely to meet the requirements at the time for new NHS research where priority was given to studies supporting COVID-19 care or recovery.

It was therefore decided to proceed with Option 3: an investigation of outcome measures that could be conducted by patients, outside the hospital setting, which would be of value to studies of rehabilitation in pulmonary hypertension, and supportive of non-face-to-face assessments used in clinical care.

5.2 Methodological Considerations

This section describes additional methodological considerations which were not included in the published manuscript of this study, due to journal word count constraints.

The pragmatic approach adopted in this programme of work[1] and contextual considerations outlined in section 5.1 determined that this study would investigate outcome measures that could be conducted by patients at home; a pragmatic approach continued to be applied throughout the detailed study design.

The literature on outcome measures identifies expected qualities of measures, which include validity, reliability and repeatability.[112,113] Additionally, as indicated by clinician experience and confirmed by patient and public involvement across this programme of work, it is important to consider whether the measure is appropriate (4.2) for the circumstances in which it will be used – in an exercise test such as the 1-minute sit-to-stand any appropriate test would need to be safe.

In the absence of previous published studies of use of the 1-minute sit-to-stand test in patients with pulmonary hypertension, it was therefore first essential to establish whether the measure was safe in this population. The 1-minute sit-to-stand test is an exercise test that can require significant cardiovascular effort, balance, leg

strength and range of movement. Pulmonary hypertension is a serious cardiovascular illness, and many patients have additional co-morbidities and, while it was not anticipated that the test would pose a significant risk to patients, it was essential to establish that the test was safe, which meant that this became the primary aim of the study.

As well as conducting the simple safety test, where patients conducted the test and safety observations were recorded, the researcher took the pragmatic opportunity to simultaneously assess the validity of the outcome. By conducting the study in the clinic where patients were already completing the ISWT, an established exercise test, as part of their clinical assessment, it was possible to compare the outcomes of the two measures. This enabled the examination of concurrent validity of the 1-minute sit-to-stand test in this patient group without use of additional research resources and with minimal patient burden.[112] This study design, comparing the 1-minute sit-to-stand test with an established gold-standard, has been widely used in previous studies in other disease areas (e.g. COPD, stroke etc).[126–128]

The use of a convenience sample reflected the study design that had been selected, with the addition of risk-stratification bands (5.3.4) to examine validity across the range of the patient population and was enabled by virtue of the study's location at one of regional Specialist Pulmonary Hypertension Referral Centres where patients with the full range of disease severity could take part if they chose. The statistical approaches adopted are common, standard techniques applied to the comparison of two outcome measures.[126–128]

Further assessment of the validity, repeatability and responsiveness of the outcome measure were planned to be examined in the PERSPIRE2 study. The inclusion of a brief survey to gather information on availability of home assessment equipment and home-testing in a sub-sample of participants in the PERSPIRE study represented another resource-efficient approach to exploring the potential for this later study.

Many additional considerations were given to details of the design of the study, as outlined below.

5.3 Methods

This section describes additional methodological considerations which were not included in the published manuscript of this study.

5.3.1 Selection of the 1-minute sit-to-stand

Having decided to pursue a study which would examine an alternative outcome measure for exercise capacity that could be conducted by patients at home, the next step was to select which outcome measure should be studied.

Similar questions were being considered in other disease areas at the time, particularly pulmonary rehabilitation services for patients with COPD which were considerably impacted by COVID-19 in their delivery. Reviews of the literature highlighted alternatives which were considered for this study.[129] The 1-minute sit-to-stand was identified as the preferable choice as it:

- was a physical test of exercise capacity (in preference to questionnaires about physical performance)
- did not require access to steps or stairs in the home which could lead to practical challenges, as well as those of balance and safety
- was easily repeatable and measurable
- was most likely to capture the wide variation in exercise capacity of the pulmonary hypertension patient population, from the least to the most severely impaired
- had a strong functional component, replicating activities of daily living such as getting in and out of a chair or on and off the toilet.

Phone-based apps which determine distance walked in 6-minutes were also considered, however their use was not supported by research evidence[130,131] or by small scale pilot testing (Appendix 5).

Contemporaneous discussions with colleagues in pulmonary rehabilitation indicated a preference for the 1-minute sit-to-stand test for their patient group and

the test was also being adopted to determine desaturation on exertion in patients with COVID-19.

5.3.2 Choice of comparator test

In addition to establishing the safety of the 1MSTS, it would be important to assess it against other commonly used walking exercise tests. While the 6-minute walk test is the most widely used of these tests in pulmonary hypertension,[46] this study was carried out at the Sheffield Specialist Pulmonary Hypertension Referral Centre, where the Incremental Shuttle Walk Test is standard care in clinical practice. The study was conducted at a time where clinical services were under significant pressure due to the COVID-19 pandemic; comparing the 1MSTS against the ISWT avoided the need to arrange an additional or alternative walking test and minimised the disruption to patients and clinical services.

5.3.3 Home testing

To assist with planning of potential future studies (Chapter 6), on completion of the 1MSTS, a subset of 11 participants was provided with written instructions and undertook a repeat 1MSTS test at home within 4 weeks of the initial test. This was conducted over video call with the researcher, with a family member or friend at home for safety purposes.

All 11 participants included in the sub-study were able to complete the test at home, and there were no safety concerns or adverse events. The video platform used to conduct the home-testing was not adequate to allow for reliable counting of repetitions of the 1MSTS, therefore this data was not collected. This sub-component of the study was omitted from the publication on advice of the reviewers.

5.3.4 Stratification bands

To ensure that the data collected in this study was reflective of the pulmonary hypertension patient population, it was necessary to ensure that sufficient data was collected from across the spectrum of patients with pulmonary hypertension, including those who were more or less impaired. To achieve this, patients were

stratified into three bands of high, intermediate and low risk based on their previous ISWT, aiming for recruitment that was balanced across the three groups.

During recruitment it was apparent that uptake was not occurring uniformly across the three bands of patients. The low-risk band recruited more rapidly than the others – this may have been because they tended to be the least affected patients, therefore felt more able to take part in the test. Following discussion with the study steering group it was decided that for practical reasons we would not pursue equal recruitment to the three groups. The statistical guidance suggested a sample size of 22 participants; it was therefore decided that recruitment would be limited to no less than 22 participants in any group, within overall recruitment target of 75 participants.

5.3.5 Ethical Approval

Ethical approval for the study protocol was obtained in April 2021 (Appendix 6, Appendix 8). The addition of home-based testing for a sub-sample of patients was approved in an amendment to the protocol in July 2021.

5.3.6 Project Management

A study steering group was established to oversee the running of the study, its terms of reference are in Appendix 9.

5.4 Citation

Keen, C., Smith, I., Hashmi-Greenwood, M., Sage, K., & Kiely, D. G. (2023). Pulmonary Hypertension and Measurement of Exercise Capacity Remotely: Evaluation of the 1-min Sit-to-Stand Test (PERSPIRE) – a cohort study. *ERJ Open Research*, *9*(1). https://doi.org/10.1183/23120541.00295-2022

5.5 Published work

5.5.1 Abstract

Background

Multiparameter risk assessment is recommended to aid treatment decisions in patients with pulmonary arterial hypertension. The 1-min sit-to-stand test (1MSTS) has been validated for use in other respiratory illnesses. The aim of this study was to evaluate its safety in the hospital setting and potential utility in remote assessment in patients with pulmonary hypertension.

Methods

In a prospective cohort study design patients performed the 1MSTS and incremental shuttle walk test (ISWT) on the same day. The primary aim of the study was to assess safety signals and correlations with other metrics used in risk assessment.

Results

60 patients with pulmonary arterial hypertension and 15 with chronic thromboembolic pulmonary hypertension were enrolled. No adverse events were recorded. Post-test change in physiological parameters was lower for the 1MSTS than for the ISWT in heart rate (mean±SD change +9.4±8.0 *versus* +38.3±25.9 beats per min, p <0.001), oxygen saturation (−3.8±4.0% *versus* −8.9±7.3%, p<0.01) and systolic blood pressure (+10.1±10.5 *versus* +17.7±19 mmHg, p<0.001). There were significant correlations between the 1MSTS and ISWT (r=0.702, p<0.01), World Health Organization functional class (r= −0.449, p<0.01), emPHAsis-10 (−0.436, p<0.001) and N-terminal pro-b-type natriuretic peptide (r= −0.270, p=0.022). 97% of patients were willing to perform the test at home.

Conclusion

This study has demonstrated the safety, sub-maximal characteristics of the 1MSTS in pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension in the hospital setting, its positive correlation with the ISWT and potential role in remote risk assessment. Further evaluation of this exercise test is now warranted.

5.5.2 Introduction

Pulmonary hypertension is a chronic, progressive life-limiting condition with a number of causes.[8] An increase in pulmonary vascular resistance and right ventricular afterload arise from re-modelling of the pulmonary arterioles in pulmonary arterial hypertension (PAH), and obstruction of the vasculature by chronic clot and a variable vasculopathy in chronic thromboembolic pulmonary hypertension (CTEPH).[8] The diagnosis of pulmonary hypertension is confirmed at right heart catheterisation and is currently defined in guidelines[7] as a mean pulmonary arterial pressure (mPAP) of at least 20mmHg.[132] Patients will typically demonstrate symptoms of breathlessness and limited exercise capacity.[8]

Drug therapies for PAH and CTEPH are focussed on slowing disease progression and minimising symptom burden. In selected patients with CTEPH, pulmonary endarterectomy (PEA) offers the prospect of cure, whilst balloon pulmonary angioplasty is also associated with significant symptomatic and haemodynamic benefits.[39] Due to the progressive nature of PAH, guidelines recommend regular multiparameter risk assessment and stratification, which may prompt change in treatment.[7] A number of risk assessments exist. All of these include measures of World Health Organisation functional class (WHO-FC), exercise capacity and right ventricular function. Hospital-based objective measures of exercise capacity used in risk assessment in PAH include the sub-maximal 6-minute walking test (6MWT)[133] and maximal tests including the incremental shuttle walk test (ISWT)[134] and cardiopulmonary exercise testing (CPET).[135] In CTEPH, data has also shown that the 6MWT can be used in the risk assessment of patients.[136]

The onset of the COVID-19 pandemic has increased the use of remote clinical consultations, and highlighted the need to develop and validate alternatives to hospital-based exercise testing to aid risk assessment and stratification.[137] The 1-minute sit-to-stand test (1MSTS) is a simple exercise test where patients are asked to stand up from a chair repeatedly for 1 minute. It has been evaluated in healthy subjects and patients with cardiorespiratory conditions including chronic obstructive pulmonary disease (COPD),[127] in whom it has been shown to correlate

with the 6MWT,[126,138] quadriceps strength[139] and levels of physical activity.[140] The 1MSTS does not rely on patients having access to equipment or infrastructure, and is therefore widely accessible and suggested for use in the home setting.[141,142]

To date, the 1MSTS has not been evaluated in patients with pulmonary hypertension. This study has investigated the safety of the 1MSTS in the hospital setting and its potential for use in remote risk assessment of patients with PAH and CTEPH.

5.5.3 Methods and Materials

In this prospective cohort study, patients with PAH and CTEPH were identified from the Sheffield Pulmonary Vascular Disease Unit between June and December 2021.

Inclusion criteria required patients to be >= 18 years of age with a diagnosis of PAH or CTEPH following multimodality testing including right heart catheterization, as defined in guidelines.[7]

Patients were excluded if they also presented with significant mobility issues, uncontrolled systemic hypertension (systolic > 220mmHg or diastolic >120mmHg) or hypotension (systolic < 90mmHg or diastolic < 60mmHg), resting tachycardia (>130 beats per minute) or cognitive impairment that would prohibit informed consent. Also excluded were patients who had experienced surgery, myocardial infarction, pneumothorax or stroke within the past 8 weeks, or chest pain, haemoptysis, or syncope within the last 2 weeks. To avoid selection bias, all patients attending on days where recruitment occurred were screened for the study.

5.5.3.1 Sample size estimation

Sample size in correlation studies can be estimated by using estimates of the effect size in t-test calculations.[143] In this study, effect sizes were estimated using comparable studies in COPD which included samples of 48 and 52 participants,[128,138] and identified correlation coefficients between 1MSTS and 6-minute walk distance (6MWD) of between r=0.57 and r=0.67. Based on these

values, assuming Type I error rate=0.05 and Type II error rate=0.2, a sample size of between n=22 (r=0.5) and n=15 (r=0.6) was indicated.[143] To capture participants with a range of exercise capabilities, a stratified sample was selected across three bands of ISWT distance: ≤ 180m, 190m – 330m, ≥ 340m.[134] To accommodate this, a total sample of 75 was sought, with a minimum of 22 participants in each of the three ISWT bands.

5.5.3.2 Exercise testing and data collection

The ISWT was conducted first, on a 10m corridor and performed using a standard protocol.[144] As per American Thoracic Society guidelines for repeat exercise testing, participants rested for at least 30 minutes before undertaking the 1MSTS test.[144]

The 1MSTS used an armless chair of 46 to 48cm height and was performed as previously described.[138] Participants were instructed to stand up and sit down as many times as they could within one minute, without using their arms. They were advised to fully stand up on each repetition, and either come fully to sitting, or tap their bottom on the chair before standing back up. They were advised to use rest periods if needed, and to stop before the end of the test if necessary. They were informed when 15s of the test time remained.[138] As the ISWT is standardly conducted in the study setting without supplemental oxygen, regardless of whether patients are on long term or ambulatory oxygen therapy,[134] the same approach was adopted for the 1MSTS.

The number of completed levels on the ISWT was recorded and expressed as metres and the number of full repetitions in the 1MSTS was recorded. Heart rate, blood pressure and oxygen saturations were captured before and after both tests, along with patient reported measures of dyspnoea.[145] Adverse events, for example, dizziness, syncope or the participant becoming unwell were also recorded. Where participants stopped the test within 1 minute, the reason for stopping was captured. Routine clinical assessments recorded on the day of testing were also captured, including N-terminal pro b-type natriuretic peptide (NT-proBNP),

emPHasis10 (patient reported outcome measure in pulmonary hypertension)[62] and WHO-FC.

5.5.3.3 Survey

On completion of testing a short survey was conducted to assess the potential for a future study assessing the 1-minute sit-to-stand performed by patients at home. Participants were asked if they would be happy to perform the test at home, and if they had access to devices to measure physiological parameters including blood pressure, weight, heart rate, oxygen saturations (Appendix 7).

5.5.3.4 Statistics

Descriptive statistics were used to describe demographics and key characteristics at diagnosis and at the time of testing. Spearman's rank correlations were used to compare the two tests. Paired t-tests were used to examine difference in physiological characteristics of the tests. Where data is normally distributed, results are presented as mean±SD; otherwise, median (interquartile range) is shown.

Patients identified and approached by PHA UK (the UK patient charity for patients with pulmonary hypertension) were consulted in the study design, involved in the development of study materials, and participated in the study steering committee.

The study protocol was approved by the National Health Service Health Research Authority (protocol reference number: 21/EE/0074). The study was registered at ClinicalTrials.gov (identifier number NCT04903704). Written informed consent was obtained.

5.5.4 Results

5.5.4.1 Participant characteristics

Of 75 participants, 60 (80%) had a diagnosis of PAH. 15 (20%) were diagnosed with CTEPH, of whom six had residual pulmonary hypertension following PEA surgery, three had residual pulmonary hypertension following BPA, three were ineligible for

PEA or BPA, and three had declined these interventions. 58 (77%) of participants were female.

At diagnosis, the mean±SD age was 52±16.8 years, 95% of participants were in WHO FC III or IV with a mPAP of 48±13.3mmHg, pulmonary arterial wedge pressure 10±5 mmHg and PVR of 764±388 dynes/m^2 (Table 13). A detailed breakdown of PAH subgroups is in the supplementary material (Appendix 10, Table 18). On the day of testing, patients were on average 4.3±4.2 years post-diagnosis. 68% were in WHO FC III or IV, with an ISWT of 281±174.4m, NT-proBNP 339 (120-723) ng/L and an emPHasis10 score of 27 (19 – 34) (Table 14).

5.5.4.2 Safety and adverse events

75 hospital-based 1MSTS tests were conducted with no adverse events. One participant reported feeling anxious at the end of the 1MSTS test, recovering after < 5 minutes of rest. Two participants terminated the test before the end of 1 minute, after 50 and 55 seconds, due to shortness of breath and leg pain (Appendix 10, Table 19).

5.5.4.3 Comparison of exercise tests

Compared to the 1MSTS, patients undergoing the ISWT had a significantly greater fall in oxygen saturation from baseline when compared to post-test measures (3.8±4.0% *versus* 8.9±7.3%, p<0.01) and a greater rise in heart rate (9.4±8.0 *versus* 38.3±25.9 beats per minute, p<0.001), systolic blood pressure (10.1±10.5 *versus* 17.7±19mHg, p<0.001), diastolic blood pressure (2.9±7.8 *versus* 10.3±15.1mmHg, p<0.01), and Borg breathlessness score (2.8±1.7 vs 3.7±2.2, p<0.001) (see

Table 15).

There were significant correlations between the 1MSTS and the ISWT (r= 0.702, p < 0.01). Correlations within the risk stratification bands were: high risk (r=0.391, p=0.044, n=27), intermediate risk (r=0.300, p=0.165, n=23), low risk (r=0.667, p<0.01, n=25). The 1MSTS correlated significantly with WHO FC (-0.503, p<0.01), emPHAsis-10 (-0.436, p<0.001) and NT-proBNP (-0.262, p=0.028). There were also

significant correlations between the ISWT and WHO FC, emPHasis-10 and NT-proBNP (Table 16). Scatterplots of 1MSTS *versus* ISWT distance, WHO FC, NT-proBNP and emPHAsis-10 scores are shown in Figure 8. Figure 9 shows box plots of 1MSTS in each of the risk stratification bands.

5.5.4.4 Survey Results

97% of participants surveyed (n=67) indicated that they would conduct a 1MSTS at home as part of a remote assessment, with 90% having access to weighing scales, 45% an oxygen saturation monitor, and 40% a sphygmomanometer at home (Appendix 10, Table 20).

Table 13 - Participant characteristics at diagnosis

Characteristics	PAH (n = 60)	CTEPH (n = 15)	All (n= 75)
Age, mean (SD), y	49.1 (16.4)	64.0 (13.8)	52 (16.8)
Female, no., (%)	47 (78.3)	11 (73.3)	58 (77.3)
BMI, mean (SD), kg/m^2	28.8 (7.3)	30.4 (8.7)	29.2 (7.6)
WHO FC, no., (%)			
Class II	4 (6.7)	0 (0)	4 (5.3)
Class III	49 (81.7)	15 (100)	64 (85.3)
Class IV	7 (11.7)	0 (0)	7 (9.3)
ISWT, mean (SD), m	222 (161)	192 (155.9)	216 (159)
Haemodynamics			
mRAP, mean (SD), mmHg	10 (6.2)	10 (5.5)	10 (6.1)
mPAP, mean (SD), mmHg	49 (13.7)	42 (11.1)	48 (13.3)
PAWP, mean (SD), mmHg	10 (4.6)	12 (6.4)	10 (5.0)
CO, mean (SD), l/min	4.49 (1.60)	4.26 (1.33)	4.44 (1.54)
CI, mean (SD), l/min/m^2	2.54 (0.94)	2.21 (0.58)	2.46 (0.87)
PVR, mean (SD), dynes/m^2	796 (401)	645 (322)	764 (388)
Mixed venous SpO_2 %	64.3 (10.7)	63.0 (7.64)	64.0 (10.0)
Pulmonary Function			
FEV_1, mean ± SD (% predicted), litres	2.09 ± 0.72 (77)	2.09 ± 0.82 (82)	2.09 ± 0.73 (78)
FVC, mean ± SD (% predicted), litres	2.82 ± 1.1 (88)	3.08 ± 1.3 (96)	2.87 ± 1.1 (90)
TL_{CO}, mean ± SD (% predicted), mmol/min/kPa	4.41 ± 1.9 (51)	4.96 ± 1.9 (64)	4.51 ± 1.8 (54)
emPHasis10, median (IQR), score out of 50	33 (25-41)	29 (22-36)	31 (23-39)
Co-morbidities			
Systemic hypertension, no., (%)	8 (13.3)	5 (33.3)	13 (17.3)
Atrial Fibrillation, no., (%)	5 (8.3)	2 (13.3)	7 (9.3)
Diabetes, no., (%)	6 (10)	2 (13.3)	8 (10.7)
Ischaemic Heart Disease, no., (%)	2 (3.3)	1 (6.7)	3 (4.0)
COPD, no., (%)	1 (1.7)	1 (6.7)	2 (2.7)
Interstitial Lung Disease, no., (%)	7 (11.7)	0 (0)	7 (9.3)
Chronic Kidney Disease, no., (%)	1 (1.7)	0 (0)	1 (1.3)

Definition of abbreviations: PAH=pulmonary arterial hypertension; CTEPH=chronic thromboembolic pulmonary hypertension; BMI=body mass index; WHO-FC = World Health Organisation Functional Classification; ISWT=Incremental Shuttle Walk Test; mRAP=mean right atrial pressure; mPAP=mean pulmonary arterial pressure; PAWP=pulmonary arterial wedge pressure; CO=cardiac output; CI=cardiac index; PVR=pulmonary vascular resistance; SpO2=oxygen saturations; FEV=forced expiratory volume; FVC=forced vital capacity; TL_{CO}=lung carbon monoxide transfer factor; emPHasis10=patient reported outcome measure; COPD=chronic obstructive pulmonary disease

Table 14 - Participant characteristics on day of testing

Characteristics	PAH (n = 60)	CTEPH (n = 15)	All (n = 75)
Age, mean (SD), years	53.9 (14.9)	68.1 (12.5)	56.7 (15.5)
Years since diagnosis, mean, (SD)	4.4 (4.4)	3.9 (3.1)	4.3 (4.2)
BMI, mean (SD), kg/m^2	29.4 (8.0)	29.7 (5.7)	29.5 (7.5)
WHO FC, no., (%)			
Class I	0 (0.0)	2 (13.3)	2 (2.7)
Class II	18 (30.0)	4 (26.7)	22 (29.3)
Class III	41 (68.3)	9 (60.0)	50 (66.7)
Class IV	1 (1.7)	0 (0.0)	1 (1.3)
ISWT mean (SD), m	278 (174)	291 (184)	281 (174)
NT-proBNP, median (IQR), pg/mL	437 (111-830)	219 (127-378)	339 (120-723)
emPHasis10, median (IQR), score out of 50	29 (20-35)	22 (9-27)	27 (19-34)

Definition of abbreviations: PAH=pulmonary arterial hypertension; CTEPH=chronic thromboembolic pulmonary hypertension; BMI=body mass index; WHO-FC = World Health Organisation Functional Classification; ISWT=Incremental Shuttle Walk Test; NT-proBNP=N-terminal pro b-type natriuretic peptide; emPHasis10=patient reported outcome measure

Table 15 - Change in physiological parameters in response to 1-minute sit-to-stand and Incremental Shuttle Walk tests

	1MSTS Mean (SD)	ISWT Mean (SD)	Mean difference	CI	p value
Oxygen Saturations SpO2 (%)					
Baseline	95 (3.4)	94 (4.1)	1.0	(0.4 - 1.8)	0.002*
Post-test	91 (6.2)	85 (8.9)	6.2	(4.6 - 7.7)	<0.001*
Change from baseline	-3.8 (4.0)	-8.9 (7.3)	5.0	(3.5 - 6.7)	<0.001*
Heart Rate (bpm)					
Baseline	79 (13.1)	80 (13.3)	-0.52	(-2.5 - 1.4)	0.593
Post-test	89 (14.9)	118 (24.3)	-29.4	(-34.9 - -23.9)	<0.001*
Change from baseline	9.4 (8.0)	38.3 (25.9)	-28.8	(-34.8 - -22.9)	<0.001*
Systolic blood pressure (mmHg)					
Baseline	126 (19.1)	119 (17.9)	7.1	(3.9 - 10.2)	<0.001*
Post-test	136 (21.4)	136 (28.2)	0.0	(-4.9 - 4.9)	0.995
Change from baseline	10.1 (10.5)	17.7 (19.0)	-7.6	(-12.0 - -3.2)	<0.001*
Diastolic blood pressure (mmHg)					
Baseline	75 (11.1)	74 (14.8)	1.4	(-1.4 - 4.3)	0.32
Post-test	78.8 (13.0)	84.4 (17.6)	-5.6	(-8.8 - -2.4)	<0.001*
Change from baseline	2.9 (7.8)	10.3 (15.1)	-7.4	(-10.7 - -4.0)	<0.001*
Borg Breathlessness (Scale 0-10)					
Baseline	0.85 (1.1)	0.92 (1.1)	-0.1	(-0.24 – 0.09)	0.34
Post-test	3.6 (1.8)	4.6 (2.0)	-1.0	(-1.37 - -0.62)	<0.001*
Change from baseline	2.8 (1.8)	3.7 (2.2)	-0.9	(-1.3 - -0.6)	<0.001*

* indicates $p < 0.05$

Table 16 - Correlation of outcomes for 1MSTS test and ISWT

	1MSTS		ISWT	
	Correlation coefficient (r)	p value	Correlation coefficient (r)	p value
1MSTS			0.702	<0.001*
High risk			0.391	0.044*
Intermediate risk			0.300	0.165
Low risk			0.667	<0.001*
WHO FC	-0.503	<0.001*	-0.592	<0.001*
NT-proBNP	-0.262	0.028*	-0.286	0.012*
emPHasis10	-0.436	<0.001*	-0.479	<0.001*
Age	-0.393	<0.001*	-0.445	<0.001*
r - Spearman's rank correlations coefficient * indicates p < 0.05				
Definition of abbreviations: 1MSTS=1-minute sit-to-stand; ISWT=Incremental Shuttle Walk Test; WHO-FC=World Health Organisation Functional Classification; NT-proBNP=N-terminal pro b-type natriuretic peptide; emPHasis10=patient reported outcome measure				

Figure 8 - Scatterplots of 1MSTS versus other test parameters

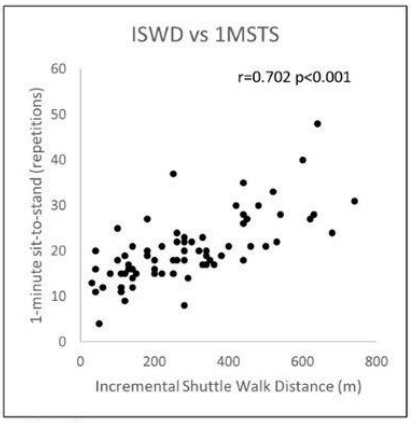


Figure 1a

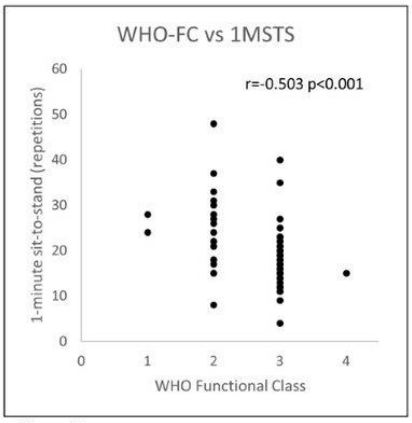


Figure 1b

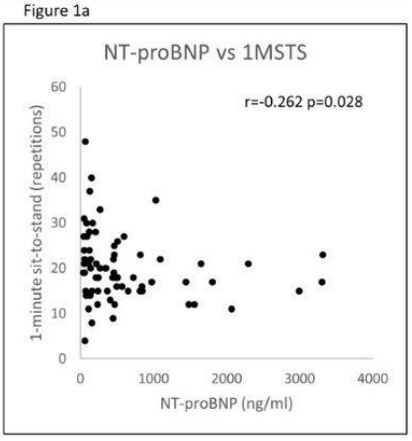


Figure 1c

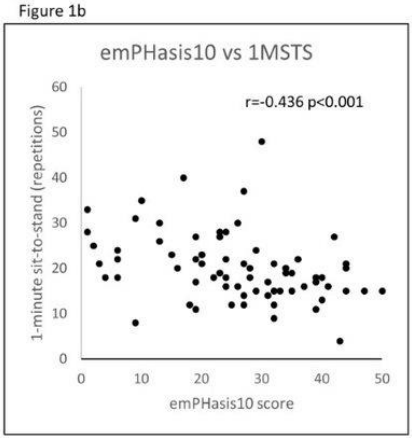
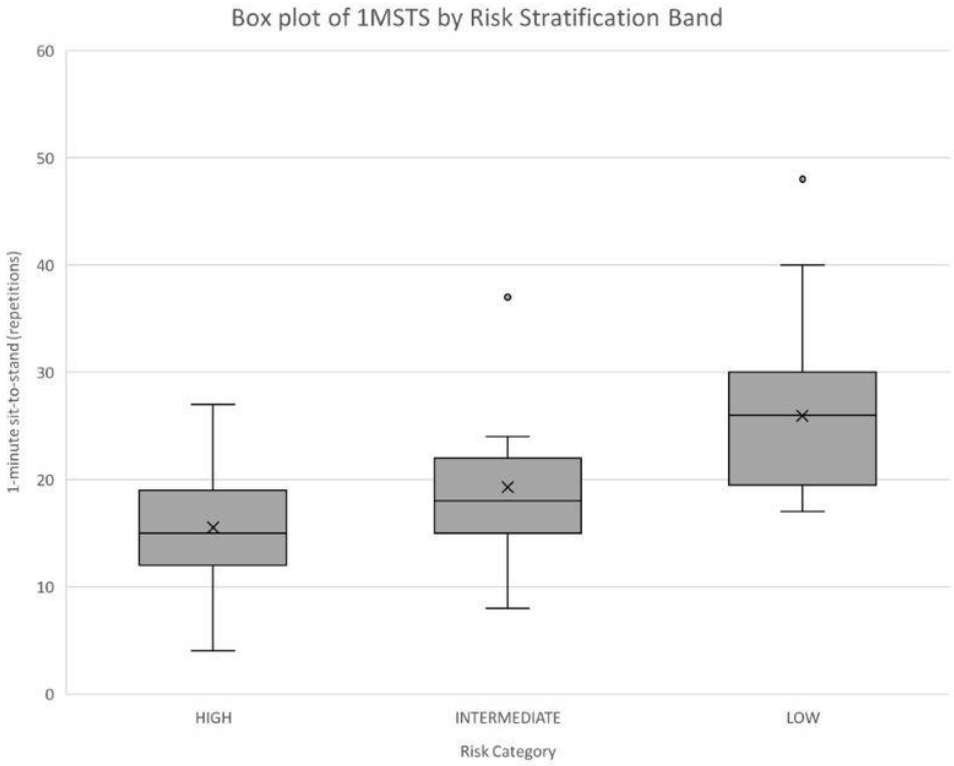


Figure 1d

Figure 9 - Box Plot of 1MSTS by Risk Stratification Band



5.5.5 Discussion

To our knowledge this is the first study to examine the 1MSTS test in patients with PAH and CTEPH. We have demonstrated that it is a safe, sub-maximal test, that correlates strongly with ISWT distance and other metrics used to assess disease severity and has the characteristics of an exercise test that could be performed by patients remotely in the home.

5.5.5.1 Safety

No adverse events occurred in 75 hospital-based 1-minute sit-to-stand. This is consistent with an acceptable safety profile, supporting further exploration of the 1MSTS for remote assessment of exercise capacity in the home setting. Two

patients undergoing hospital-based testing stopped before the end of the test due to leg pain and shortness of breath, in accordance with the test protocol.[144]

5.5.5.2 Test characteristics

Our study demonstrates the sub-maximal nature of the 1MSTS when compared to the ISWT in PAH and CTEPH, with lower post-test changes from baseline in heart rate, oxygen saturation, systolic blood pressure and Borg score when compared to changes observed with the ISWT. This is in accordance with the findings of Ozalevli et al.[126] who compared the 1MSTS to the 6MWT in patients with COPD.

This study also shows a strong correlation between the 1MSTS and ISWT ($r=0.702$, $p<0.001$). The 1MSTS also correlates significantly with other measurements used to assess patients with PAH and CTEPH, namely WHO-FC ($r=-0.449$), NT-pro BNP ($r=-0.270$) and emPHasis10 ($r=-0.436$). Furthermore, these correlations were similar to those of the ISWT with the same parameters. Comparable studies in COPD, with smaller sample sizes, identified correlation coefficients between 1MSTS and 6MWD of between 0.57 and 0.67[128,138] as well as an association with age, quality of life and muscle strength.[126,128,138]

The 1MSTS test comprises an activity commonly performed in daily life. This functional feature, along with the sub-maximal characteristics of the test, absence of adverse events in this study, its positive correlation with the ISWT, scatter and distribution of values, suggests there is potential for its use as an exercise test conducted by patients at home, as a surrogate for hospital-based exercise testing. This is an important finding in the context of the increased use of remote consultations in the management of patients with PAH and CTEPH. The advantages of remote consultation include the potential for more frequent monitoring whilst reducing patient travel, stress and fatigue, improved access for patients with disabilities and potential cost savings.[146] This approach can also empower patients to take a more active role in their own monitoring and can support patient-initiated follow-up. Increasingly, pulmonary hypertension centres are offering hybrid care

models which incorporate both remote and face-to-face clinical consultations, structured to meet the needs of patients.[137]

5.5.5.3 Risk assessment

Due to the progressive nature of PAH and the high risk for rapid deterioration, international guidelines[7] recommend regular risk assessment in PAH to aid treatment decisions. Risk assessment incorporates parameters including exercise testing, NT-proBNP, and WHO functional class. Remote consultation without exercise testing diminishes the effectiveness of risk assessment.[137]

Investigators have evaluated the of use of device-based applications to measure 6MWD as a substitute for hospital-based exercise, using smart phone or physical activity monitors; to date, these studies have been inconclusive.[130,131] Furthermore, this approach is limited to patients who own a smart phone, have reliable internet access[147] and who can confidently walk outdoors. In contrast, these restrictions do not apply in the 1MSTS.

This study was not designed to look at thresholds that could be used to risk stratify patients with PAH. Nonetheless, it has a strong correlation with the maximal exercise test that it was benchmarked against (ISWT), and strong-moderate correlations within each of the risk stratification bands, where sample sizes were lower. It also correlates with other measurements that can be used to risk stratify patients with PAH, namely WHO-FC, NT-proBNP and emPHasis 10 score.

5.5.5.4 Limitations

This pragmatic study was designed to collect data with minimal disruption to clinical services and patients during the COVID-19 pandemic. To this end, all participants conducted their ISWT before the 1MSTS, which may have contributed to fatigue in the second test. Additionally a practice test was excluded from the protocol - all participants had conducted at least one ISWT prior to their testing in this study, but none had previously completed the 1MSTS. The 1MSTS has been shown to have a learning effect in patients with COPD,[138] and this may therefore have impacted on outcomes.

5.5.5.5 Further work

While this study supports the safety of the 1MSTS in the hospital setting and illustrates its potential role in risk assessment of patients with PAH and CTEPH, further examination of this exercise test is required. Future studies should compare the 1MSTS with the 6MWT and the results of CPET testing. A larger data set collected across multiple sites with a longer period of follow-up, including testing of home-based safety, would further inform the potential for use in remote risk assessment, along with inclusion of mortality data. Test and re-test to examine the learning effect of the 1MSTS in this patient group would be of value, as would studies to establish minimal clinically important difference of 1MSTS in PAH and CTEPH and its value in measuring response to treatment.[128] The survey results in this study suggest patients would be happy to conduct the 1-minute sit-to-stand test at home, but it would be important to ascertain patients' perspectives on the wider use of remote assessment and patient initiated follow-up. It would also be of interest to explore clinicians' perceptions of patient recorded assessments, in comparison to the results of hospital-based testing.

5.5.6 Conclusion

This study has demonstrated the sub-maximal characteristics of the 1-minute sit-to-stand test in PAH and CTEPH, its safety in the hospital setting, its positive correlation with the Incremental Shuttle Walk test and potential role in remote risk assessment. Further evaluation of this exercise test is now warranted.

5.5.7 Acknowledgments

Staff and patients of Sheffield Pulmonary Vascular Diseases Unit who supported the development and fulfilment of this research; PHA UK for their support in facilitating patient involvement in the study; Mark Bunce for his contribution as patient representative on the study steering group. The Sheffield Pulmonary Vascular Disease Unit is part of the European Respiratory Network (ERN) for rare diseases.

5.6 Summary

The PERSPIRE study demonstrated the safety of the 1MSTS test and its potential for use in assessment of patients at home. While the journal publication focussed on the utility of this outcome measure in remote risk-assessment in clinical practice, it is also the case that the 1MSTS could be of value in rehabilitation of patients that might take place remotely or in face-to-face settings which have limited facilities to conduct walking exercise tests.

The study highlights further research that could be carried out to build on the findings of the PERSPIRE study and further investigate its utility as an outcome measure in this patient group. These include:

- Comparison of the 1MSTS with the 6MWT, the most widely used hospital-based exercise test in pulmonary hypertension
- Extending safety evaluation from hospital-based testing, as carried out in PERSPIRE, to home-based testing.
- Examination of a larger data set, for a longer period of time and including mortality data to evaluate potential use in clinical risk assessment.
- Test and re-test to examine the learning effect of the 1MSTS in this patient group.
- Examining patients' perspectives on the wider use of remote assessment and patient-initiated follow-up.
- Examining clinicians' perceptions of patient recorded assessments, in comparison to the results of hospital-based testing.

The next step for this programme of work was therefore to develop the protocol for a study that would address these outstanding questions. This is described in Chapter 6.

Chapter 6 PERSPIRE2

This chapter will describe the consultation and consideration that took place to determine the nature of research required to answer the further questions raised in the PERSPIRE study. It will go on to outline the protocol for a subsequent study – PERSPIRE2 – that has been developed in light of these consultations and is under consideration for submission for funding by the study team.

6.1 Background

As previously described in Chapter 5 the PERSPIRE study identified the safety of the 1-minute sit-to-stand test in patients with pulmonary hypertension in the hospital setting, its lower physiological demands in comparison to the Incremental Shuttle Walk Test and a significant correlation between the two tests. This preliminary study also identified additional questions to be addressed to further determine the potential of the 1-minute sit-to-stand test in pulmonary hypertension.

On completion of the PERSPIRE study there was a need to determine the direction of further research beyond this programme of work. The PERSPIRE study arose from changes to the programme of work that were brought about by the COVID-19 pandemic; prior to that the Feasibility Study (Chapter 4) had been proposed.

Initial consideration concerned a choice between pursuing the ongoing research questions posed by the PERSPIRE study (Chapter 5) or to returning to the Feasibility Study (Chapter 4). In reviewing this, thought was given to the aims of the programme of work - to advance the understanding of delivering rehabilitation in patients with pulmonary hypertension and to examine the outcome measures that could be used therein. Also important was the potential value of the findings of the PERSPIRE study, the interest and momentum that it had gained in the clinical and research communities in pulmonary hypertension. Furthermore, the landscape of rehabilitation research had changed since the development of the Feasibility Study protocol, with greater interest in remote and home-based rehabilitation in this patient group.[42,148,149] Therefore the decision was made to discontinue work on the

Feasibility Study, as it was no longer relevant in the current context, and focus instead on developing the work that had been carried out in the PERSPIRE study.

6.2 Consultation

Consultation for PERSPIRE2 was carried out in several forums and settings. Findings from PERSPIRE were shared with UK clinical and research colleagues in pulmonary hypertension, including discussion on potential follow-up research. Feedback was also captured from Patient and Public Involvement forums. Themes emerging from these consultations included:

- The value of continued assessment of the 1MSTS and its potential importance in home-based testing, remote risk-assessment and assessment of exercise and rehabilitation interventions
- The value of examining alternative home-based tests of exercise capacity, including apps that measure 6MWD and wearable physical activity monitors
- The potential to capture additional home-based measures which have value in the management of pulmonary hypertension e.g. weight, blood pressure
- The value of assessing the acceptability of home-based measurement for patients and clinicians
- The importance of easy-to-use processes for capturing remote data
- Considerations of digital exclusion and the impact on those patients unable to use the technology involved in remote assessment
- Potential to use 1MSTS to support Patient Initiated Follow-up.

6.2.1 Options appraisal

Taking into account these findings, two options were developed for consideration for further development of work in this area.

Figure 10 denotes the original outline of the proposal for Option 1, which focussed on the potential to use 1-minute sit-to-stand in remote assessment of patients with pulmonary hypertension for risk-assessment, rehabilitation or research purposes. It built on the PERSPIRE study to include:

- Extending safety testing from hospital-based, as carried out in PERSPIRE, to home-based.
- Comparison of the 1MSTS with the 6MWT, the most widely used hospital-based exercise test in pulmonary hypertension.
- Evaluation of the potential use of 1MSTS in risk-assessment through examination of a larger data set, across a longer time-period, with inclusion of mortality data.
- Test and re-test to examine the learning effect of the 1MSTS in this patient group.
- Examining patients' perspectives on the wider use of remote assessment.
- Examining clinicians' perceptions of patient recorded assessments, in comparison to the results of hospital-based testing.

Figure 11 presents the original outline proposal for Option 2, which considered the initial research that would be required to integrate the 1-minute sit-to-stand test into Patient Initiated Follow-up (PIFU) in pulmonary hypertension services. PIFU is an important component of NHS strategies for the management of patients with long-term conditions.[150] It helps empower patients to manage their own condition and plays a key role in enabling shared decision making and supported self-management. PIFU is an alternative to appointments with specialists at fixed-time intervals e.g. follow-up in 6-months, as is commonly the case in pulmonary hypertension services. Within PIFU patients have the tools to support them to monitor their own condition and to identify worsening, along with pathways to follow to access specialist support accordingly.

PIFU is not yet explored or established within pulmonary hypertension services, but given the distance patients are required to travel for appointments it has significant potential for patient benefit. 1MSTS is a potential tool that patients could utilise to monitor their condition within such a scheme, however preliminary work would be required with patients and clinicians to determine principles for PIFU within this patient group. Option 2 would include:

- Review of existing PIFU pathways in other health conditions
- Co-production to explore the components of PIFU – which patients to include; what measures should be used and how would they be reported; what follow up would be needed
- Small pilot study
- Evaluation, including acceptability to patients and clinicians

On balance it was felt that while both options had significant merit, Option 1 had a closer alignment with the programme of work already carried out and would therefore be pursued and developed further. Option 1 would require a large multi-centred study collecting data over an extended period of time and as such it was recognised that an initial feasibility study would address unanswered questions around possibility and uncertainty and improve the chance of success of the larger study.[151] Furthermore, a feasibility study of this kind would be eligible for consideration for funding under the NIHR Research for Patient Benefit scheme.

The protocol for this study – PERSPIRE2 – is outlined below.

Figure 10 – PERSPIRE2 Option 1

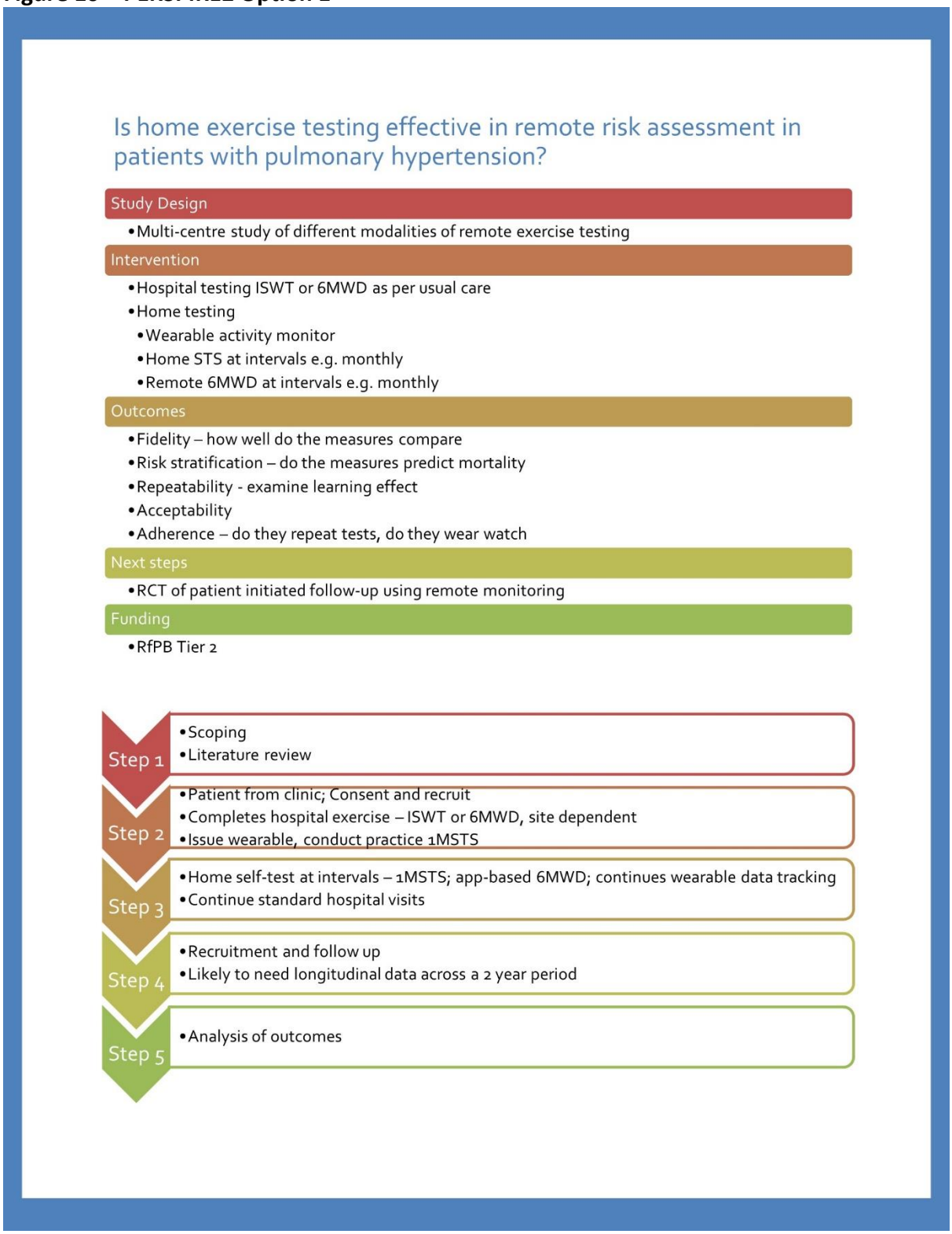
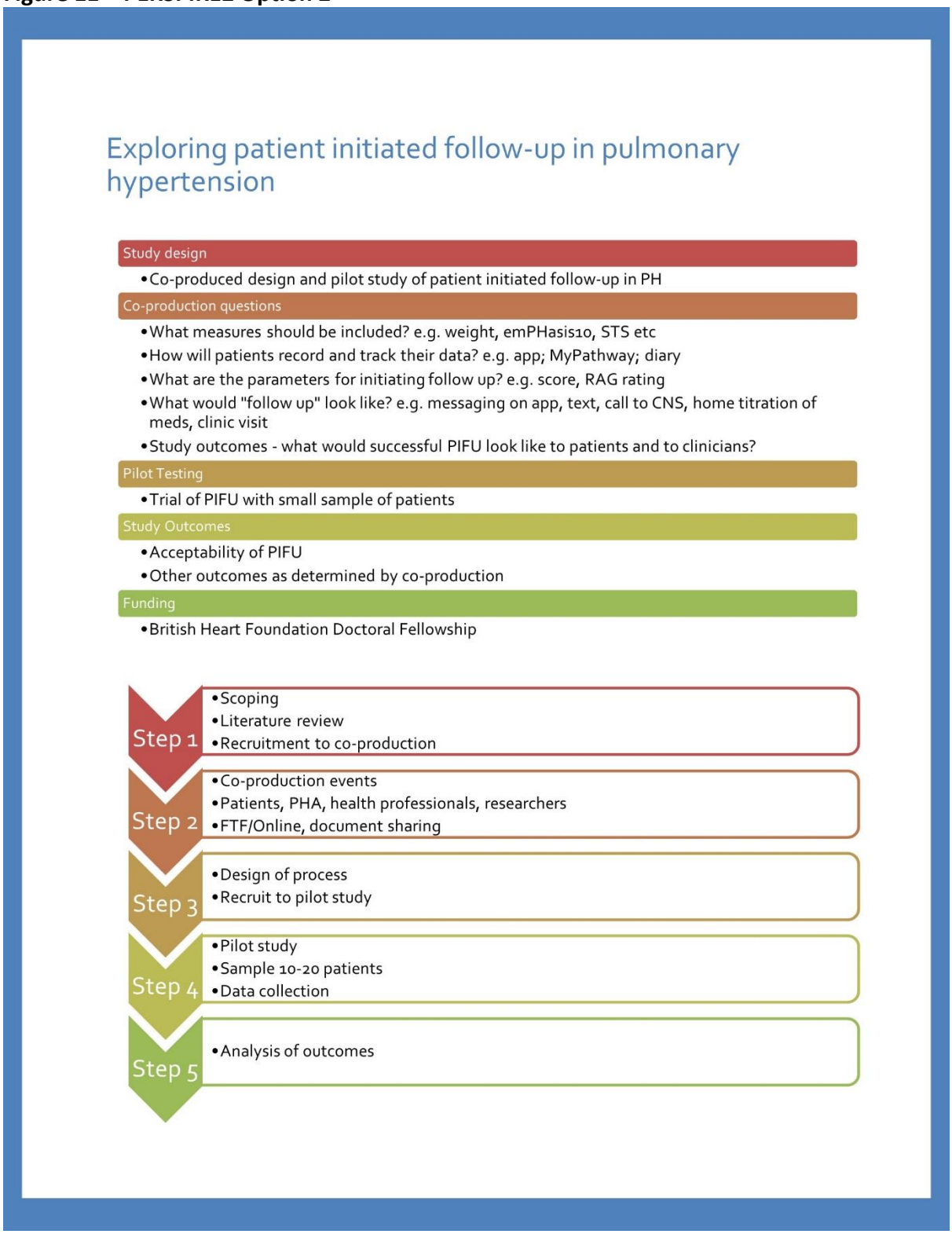


Figure 11 – PERSPIRE2 Option 2



6.3 Methodological Considerations

In keeping with the other studies in the this programme of work the underpinning theoretical principles, methodological and practical design of the PERSIRE2 study remain within pragmatism.[1] While aligning with the overall goal of this programme of work, the study builds on the questions arising from the PERSPIRE study, uses mixed methods best suited to address the problems identified and seeks to develop a tool useful to patients, while minimising research resources and patient burden.

Having established the safety of the 1-minute sit-to-stand test in the PERSPIRE study, and examined its concurrent validity, further work was required to examine additional properties of the measure:

- Reliability, examined through repeat testing with a single patient and comparing home to hospital assessment.
- Responsiveness, which would be examined by considering the potential of the outcome measure to predict mortality in the longer term and would therefore only be measurable within the full, not the feasibility, study.
- Acceptability, through patient and clinician feedback

6.3.1 Mixed methods design

The mixed methods research design choices were determined by a pragmatic approach and founded in both the goal of this feasibility study and the goal of the larger study for which it was a preparation (6.2).[114]

6.3.1.1 Order

In this Feasibility Study, the order of components was determined by the goal and definition of the study. The quantitative element of the study would examine the validity, reliability, and responsiveness of the outcome measure. Additionally, it would answer the feasibility outcomes (e.g. recruitment, retention). The qualitative element of the study was to consider the acceptability of the outcome measure to patients and clinicians and would naturally be conducted once the quantitative measures had been completed (QUANT-QUAL). [114]

This would allow patients and clinicians and patient to reflect on the measure having completed it, rather than being required to think forward. This was deemed appropriate at this stage of development considering patient and public involvement at previous stages, where those involved were required to imagine the measure.

6.3.1.2 Priority

While some mixed-methods studies give priority to one component over another, in this study, both components have equal weight. The validity, reliability and responsiveness of the outcome measure do not indicate its usefulness unless it is acceptable to patients, and vice versa.

6.3.1.3 Combination

Mixed-methods research is not simply the use of both qualitative and quantitative research methods in a single study. It also requires a combining of the two data sets with a view to augmenting the study findings. In this study, the combining of the two elements of the study delivers completeness,[114] where the combined qualitative and quantitative data sets give a more comprehensive picture of the utility of the outcome measure (i.e. determining whether it is valid, reliable, responsive and acceptable).

The design of the quantitative element of this study was developed from the hospital and home-based testing in the earlier PERSPIRE study, with protocols and procedures able to be transferred. The elements where participants repeat the 1-minute sit-to-stand test at different time points are designed to assess the reliability of the test (Figure 12).

An existing validated questionnaire tool was proposed for use to assess acceptability.[152] However because validated questionnaires might restrict the full and free expression of patient views the questionnaire would be supplemented by semi-structured interviews for a sub-set of patients.

6.4 PERSPIRE2 Proposal

The Research for Patient Benefit Programme (RfPB) programme of The National Institute for Healthcare Research funds research into the provision and use of NHS services, including feasibility research to support applications for major awards to other funders. Feasibility studies sit within Tier 2 of RfPB funding and are expected to cost less than £250,000.[110]

The following protocol meets the requirements of Stage 1 of a Tier 2 RfPB funding application, and follows the format – headings, content and word limit - laid out in the RfPB guidance.

6.4.1 What is the problem being addressed?

Pulmonary hypertension is a progressive condition which can arise from a variety of causes and is characterised by re-modelling of the pulmonary vasculature and a narrowing of the pulmonary lumen. Diagnosis is confirmed by right heart catheterisation where mean pulmonary arterial pressure is at least 20mmHg.[6] It is a rare condition with an estimated UK prevalence of 6.6 cases per million.[60] Patients in the UK are cared for at 7 adult specialist pulmonary hypertension centres in London, Cambridge, Sheffield, Newcastle and Glasgow.

Drug therapies in pulmonary hypertension are focussed on slowing disease progression and minimising symptom burden. Due to the progressive nature of the disease, guidelines recommend regular multi-parameter risk assessment and stratification, which may prompt changes in treatment. Risk-assessment at follow-up (conducted at intervals of 3-6 months) should include World Health Organisation functional class (WHO-FC), 6-minute walk test (6MWD) and right ventricular function as measured by a blood test.[6] With the exception of WHO-FC, the tests included in the recommended risk-assessment are hospital-based.

The onset of the COVID-19 pandemic has increased use of remote clinical consultations however home-based alternatives to hospital-based exercise testing, which would aid remote risk-assessment and contribute to the assessment of exercise and rehabilitation interventions and research have yet to be validated.[137]

6.4.2 Review of existing evidence

The 1-minute sit-to-stand (1MSTS) is a simple assessment of exercise capacity in which patients are asked to stand repeatedly from a chair for 1 minute. It is a highly functional test of an activity commonly performed in daily life. It has been evaluated in healthy subjects and patients with different pathologies[127]. In patients with Chronic Obstructive Pulmonary Disease it was shown to correlate with the 6-minute walk test in terms of performance,[126,138] quadriceps strength[139] and levels of physical activity.[140] It has been used in remote assessment in pulmonary rehabilitation and COVID-19.[142]

The PERSPIRE study conducted by the study team,[47] was the first to examine the 1MSTS in patients with pulmonary hypertension, establishing safety of the test in the hospital setting and its correlation with the ISWT, and identifying the need for further research to determine its utility in remote risk-assessment in patients with pulmonary hypertension.

6.4.3 Why is this research important?

Due to the rare nature of this illness and the management of patients at a small number of specialist centres, patients with pulmonary hypertension can be required to travel great distances to their hospital appointments, often requiring an overnight stay. The onset of the COVID-19 pandemic saw increased use of remote clinical consultations - a trend which is anticipated to continue.[137] The validation of reliable home-based objective markers such as the 1MSTS will allow inclusion of remote risk-assessment in these consultations, and could also support remote rehabilitation, research and patient-initiated follow-up in pulmonary hypertension - integral to NHS plans for patients with long-term conditions.[150] At the same time patients will benefit though reduced frequency of clinic visits, thus minimising extensive travel costs and time. The PERSPIRE study[47] found that 97% of participants would be happy to conduct a 1MSTS at home as part of a remote assessment.

Patients were consulted in the design of this study. They identified the importance of research into remote assessment for patients. They also highlighted the importance of easy-to-use systems for patients to share the data collected with the study team, the potential for patients without digital access to be excluded from the study, and the need to ascertain the acceptability of home measurement to patients.

Consultation was conducted with clinicians and researchers in pulmonary hypertension, who value this work and the need to build on the PERSPIRE study to determine the utility of 1MSTS in remote risk assessment, as well as investigation into the possibility of patients collecting other physiological measures at home. They cited other tools used in clinical and research practice e.g. wearable physical activity monitors and app-based 6MWT which warrant further examination, and raised the potential for digital poverty to impact on participation.

Further assessment of the 1-minute sit-to-stand test is therefore needed to examine the safety of home-based testing, compare the 1MSTS with existing tests (6MWT and ISWT) in large patient populations and determine the potential for use in remote risk-assessment through examination of mortality data. A multi-centred study would be required to recruit a sufficient sample size to inform risk-assessment and stratification.

Before proceeding with a large study in this area, a feasibility study is proposed to address questions of possibility with regards to methods of data collection across multiple sites, and uncertainty regarding recruitment, retention and therefore sample size estimation.

6.4.4 Aim

The primary aim of this study is to determine the feasibility and acceptability of conducting a multi-centred trial to determine the utility of the 1-minute sit-to-stand test in remotely measuring exercise capacity and risk-assessment in patients with pulmonary hypertension.

This will be determined through completion of the following objectives:

6.4.5 Objectives

- Assess the willingness of patients to consent by measuring recruitment against targets
- Assess adherence to the intervention by measuring follow-up data completion rates
- Assess safety of the study design by monitoring adverse events
- Assess the acceptability of the intervention though patient and clinician questionnaires and interviews
- Assess practicality of the multi-centre intervention through documentation and process review
- Assess inclusivity of study design by measuring reasons for non-participation
- Analyse recruitment and study data to determine sample sizes for a full study.

6.4.6 Methods

Prospective multi-centred study collecting and comparing different outcome measures of exercise capacity, combined with questionnaire data and interviews to determine acceptability.

6.4.7 Design

This is a feasibility study, to identify whether it is possible to conduct a study of this type, to test methods of data collection across multiple sites, and examine uncertainty regarding recruitment, retention and therefore sample size estimation. See Figure 12 for study flow chart.

6.4.8 Setting

Hospital-based assessments will take place at two UK specialist centres for care of patients with pulmonary hypertension. Patients will complete other tests at home.

6.4.9 Sample Size

The literature on sample size justification for feasibility studies[153] primarily considers randomised controlled trials and therefore suggests numbers per arm of

the study, indicating between 43 and 50 participants per arm to be suitable. This is a single armed study, however it is conducted over two sites, therefore based on statistical advice the higher value of 50 participants (25 at each site) has been selected to provide sufficient data to evaluate the feasibility goals.

6.4.10 Recruitment

Patients will be screened and invited to join the study during routine clinic appointments at the study sites.

The PERSPIRE study recruited 75 patients over 6 months. Recognising the additional complexity of this study in requiring home data collection from patients, and multiple data points in this study, a recruitment rate of 4 participants per month at each site should be achievable.

6.4.11 Inclusion

Inclusion: adults aged >= 18 with a diagnosis of pulmonary arterial hypertension (Group 1) or chronic thromboembolic pulmonary hypertension (Group 4).[6]

Exclusion: mobility significantly impaired by musculoskeletal or neurological co-morbidities; learning difficulties or cognitive impairment that would prohibit informed consent. Recent episodes of surgery or other major health problems; generally feeling unwell. Unable to access and use a smart phone or other device to record remote data.

6.4.12 Intervention

6.4.12.1 Hospital visit

Participants will undergo their standard clinical exercise capacity test (6MWT or ISWT, depending on site). They will then be allowed to rest for at least 30 minutes[144] before conducting a practice 1MSTS test. At this point they will also be:

- issued with a physical activity wearable device and instructed in its use
- supported to download the study data collection app and shown how to upload their home data

- supported to download the 6MWT app and instructed in its use
- provided with a study diary indicating data collection points
- this will be supported by written instructions for use at home.

6.4.12.2 Home assessment

Participants will receive reminders via the study data collection app to perform their home-based tests – 1MSTS and app-based 6MWT, including health-check screening questions and reporting of adverse events. Participants with suitable home equipment will also be asked to measure weight, blood pressure, heart rate, and oxygen saturations; testing equipment will be provided to participants who do not possess their own.

6.4.13 Data Collection

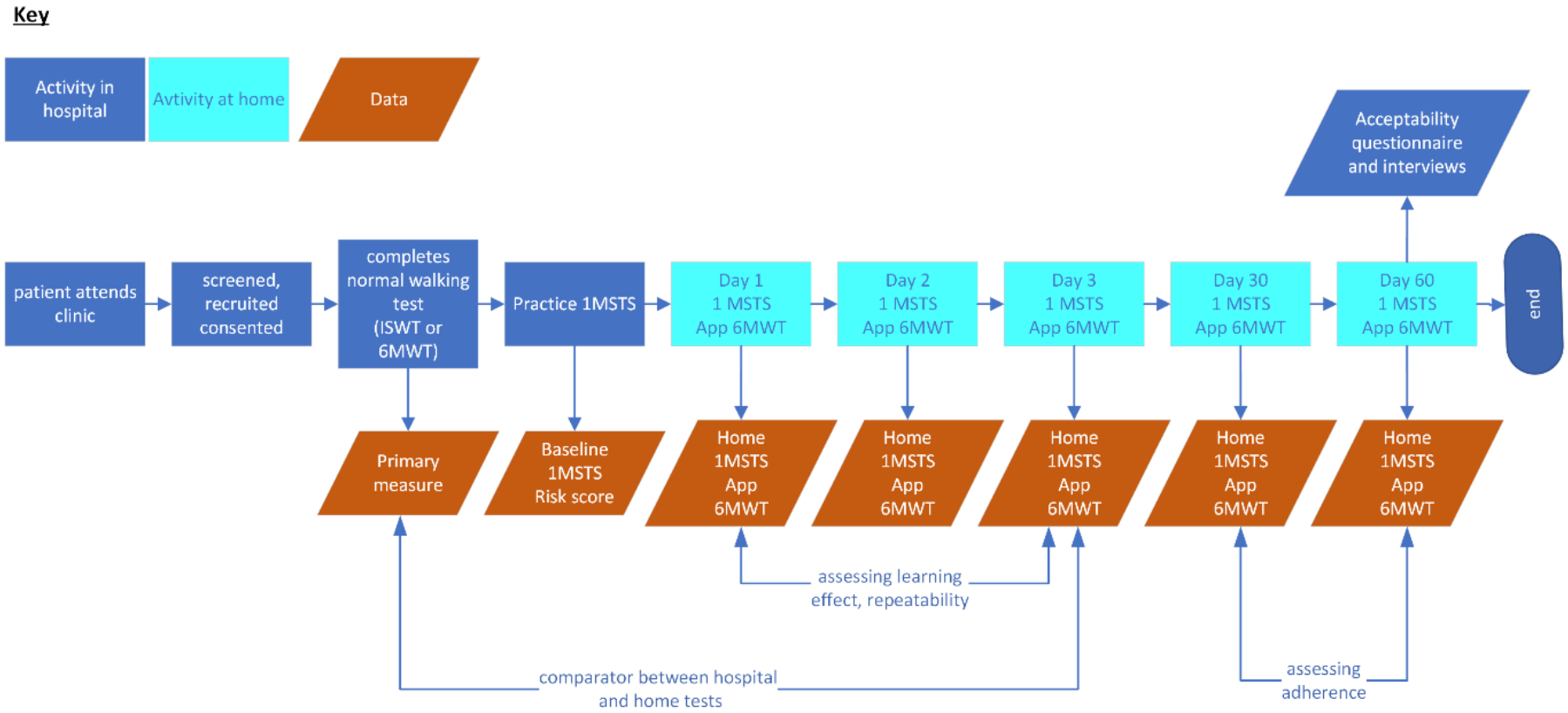
Multiple home-based data collection points are required to address the study question (See Figure 12 and Table 17).

Pulmonary hypertension services have access to digital patient portals which will be used to collect patient data and send prompts to patients to complete their testing.

Table 17 - Data Collection Points

	Recruitment	Initial Assessment	Day 1	Day 2	Day 3	Day 30	Day 60
Location	**Hospital**	**Hospital**	**Home**	**Home**	**Home**	**Home**	**Home**
Screening data	✓						
Demographic data		✓					
Weight, blood pressure, SpO2, emPHasis10		✓			✓	✓	✓
Hospital based walk test (6-minute walk/ISWT)		✓					
Home 1MSTS			✓	✓	✓	✓	✓
App-based 6MWT			✓	✓	✓	✓	✓
Acceptability							✓
Wearable data			Continuous monitoring of wear time, minutes of moderate-to-vigorous physical activity and sedentary time				

Figure 12 – PERSPIRE2 Study Flow Chart



A questionnaire designed to examine key aspects of acceptability of the study will be shared with patients at the final data collection point.[152] A subset of patients and a sample of clinicians involved in the care of patients in the study will be invited to remotely conducted semi-structured interviews which will examine questions of acceptability in greater depth.

6.4.14 Feasibility

The feasibility of the intervention is determined through the following targets:

- Recruitment: the recruitment target is 25 patients per site in a 6-month period (i.e. 4 patients per month);
- Adherence: at least 80% of data points completed
- Adverse events will be closely monitored and used to inform decisions to proceed.
- Acceptability of the intervention to patients will be determined through questionnaire responses and clinician and patient interviews
- Inclusion: less than 20% of those who decline to join the study due to digital access

6.4.15 Analysis

- Flow of participants through the study will be captured and the baseline clinical and demographic characteristics of consented participants assessed with appropriate summary and descriptive statistics.
- Reporting will determine the number and characteristics of eligible patients approached for the study and reasons for refused consent.
- The data analysis for the feasibility objectives will use descriptive statistics and focus on confidence interval estimation.
- Longitudinal plots will identify learning effect of the 1MSTS over multiple attempts.
- Linear regression will be used to compare home-based outcomes with hospital-based tests.

- Data from wearable devices will be examined to assess wear times, minutes of moderate to vigorous physical activity and sedentary time.
- Timescales and sample size of the feasibility study will not allow collection of sufficient mortality data required to examine risk stratification, however any mortality data available will be examined using a cox proportional hazards model to determine whether the home-based tests predict mortality.
- Thematic analysis will be used to examine the content of the semi-structured interviews and findings will be triangulated with questionnaire responses to identify key themes and potential modifications to future study design.

6.4.16 Patient Involvement

Patients, and the patient charity PHA UK, have been involved in developing the study to date, and we will continue to seek their support throughout.

Two patient representatives will be invited to join the Study Steering Group. We recognise the burden of the disease on patients, and that fatigue is a common symptom. To support them in participating in the steering group we will conduct meetings remotely. All participant information will be written in collaboration with patient representatives, who will check it is understandable and non-coercive. Patient representatives from the Study Steering Group will help to troubleshoot any recruitment issues that arise and will be involved in review of the study findings and dissemination, particularly where this is aimed at patients and their families or carers.

6.4.17 Ethical Considerations

Ethical issues relating to informed consent and confidentiality will be addressed throughout. Pulmonary hypertension is a progressive illness and patients may deteriorate during the study period. Due care and diligence will be taken when consenting potential participants and the option to withdraw from the study at any point will be reiterated at data collection points.

Participants will be undertaking physical activity while performing the 1MSTS test. The PERSPIRE study has established the safety of this test in patients with pulmonary hypertension. In addition, participants will be required to complete a health check questionnaire before each test, given clear instructions on stopping if they feel unwell during testing and required to report any adverse events or symptoms after testing.

Adverse events will be recorded, including patients experiencing dizziness, syncope or the participant becoming unwell. Serious adverse events would include health problems ending in hospitalisation, death or permanent injury.

6.4.18 Finances

Costings for the study are outlined in Figure 13.

6.4.19 Timings

A Gantt chart for the study is displayed in Figure 14.

6.5 Summary

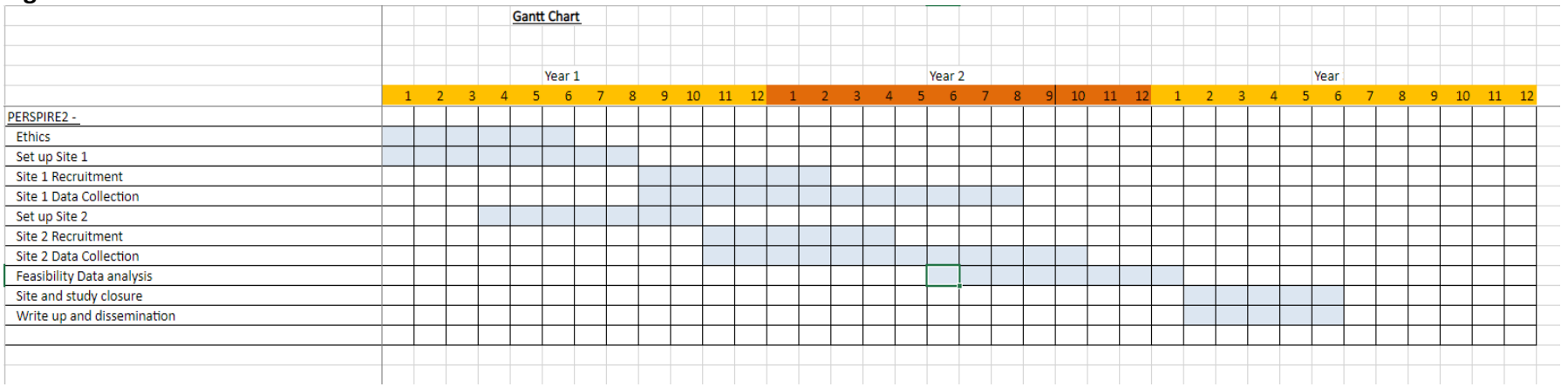
This protocol outlines the design of the PERSPRE2 study, a feasibility study which continues the work conducted in the PERSPIRE study by assessing the 1-minute sit-to-stand test in patients with pulmonary hypertension in the home setting, and thereby its potential for use in remote rehabilitation, research and risk-assessment.

The protocol has been developed for submission to the Research for Patient Benefit programme of the National Institute for Healthcare Research as an intended continuation of this programme of work.

Figure 13 - PERPSIRE2 Study costings

Finances											
								Year 1	Year 2	Year 3	
Name	Role	Grade	Employer	Wte	Y1	Y2	y3				
Carol Keen	Chief Investigator	Consultant	STH	0.10	12	12	6	7,020	7,020	3,510	17,550
David Kiely	Clinical Advisor	Consultant	STH	0.03	12	12	6	3,510	3,510	1,755	8,775
Site 1 AFC 7	Site PI and data collection	7	STH	0.50	9	12	6	20,250	27,000	13,500	60,750
Site 2 AFC 7	Site PI and data collection	7	STH	0.50	3	12	0	6,750	27,000	-	33,750
Ian Brown	Respiratory Function Support	6	STH	0.05	12	12	6	2,100	2,100	1,050	5,250
Molly Hashi-Greenwood	Academic Advisor	Senior Lecturer	MMU	0.05	12	12	6	2,700	2,700	1,350	6,750
Amy Spencer	Statistical Support	Senior Lecturer	UoS	0.10	3	6	6	1,013	2,026	2,026	5,065
Paul Sephton	PPI Lead, Acceptability Analysis		PHA UK	0.05	12	12	6	2,700	2,700	1,350	6,750
											144,640
Non Pay											
Printing, stationary, postage, storage			NHS					1500	1500	1500	4500
Equipment											
Wearable devices, weighing scales, SpO2 monitors			NHS					3,000	3,000	0	6000
Conferences		Fees	NHS	European Respiratory Society (3 days non-UK)						3000	3000
Dissemination		Open Access	NHS	2 x £1500						3000	3000
Estates								£5,006	£5,006	£2,496	£12,508
Indirect costs								£18,611	£18,611	£9,280	£46,502
Salary costs											
Non salary costs								46,043	74,056	24,541	144,640
Total costs								28,117	28,117	19,276	75,510
								74,160	**102,173**	**43,817**	**220,150**

Figure 14 - PERSPIRE2 Gantt Chart



Chapter 7 Discussion

The thesis up to this point has described the background to the programme of work (Chapter 1), the three studies that have been undertaken within it (Chapter 2, Chapter 3, Chapter 5) and the protocol for a study that was discontinued due to the circumstances of the COVID-19 pandemic (Chapter 4), before going on to describe the planned follow-up study (Chapter 6).

The next chapter will reflect on the different components of this programme of work, including contributions to knowledge and influence on clinical practice and patient care. It will also present the issues, challenges faced and learning that arose within the programme of work before indicating the future direction of research needed in this field.

7.1 Overview of the problem investigated

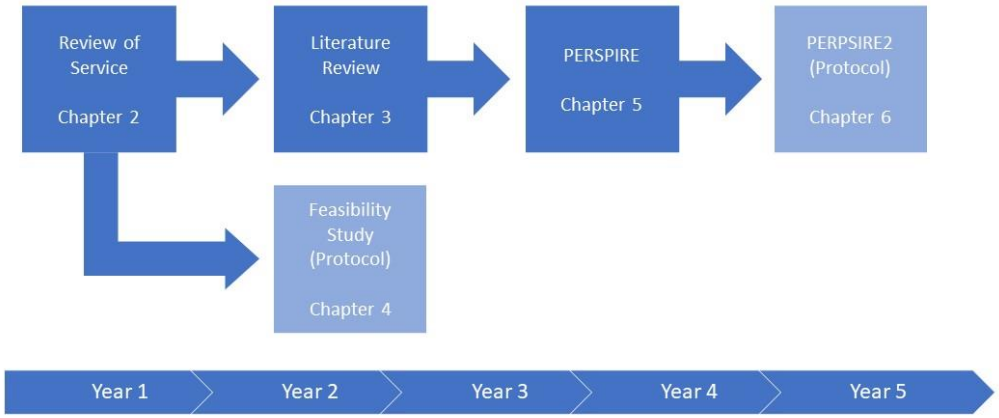
In 2018 at the outset of this programme of work there was a growing body of research evidence for the benefits of rehabilitation in patients with pulmonary hypertension, including recommendations in international guidelines for its inclusion in patient care pathways. However, access to rehabilitation programmes for patients with pulmonary hypertension, outside a handful of specialist European centres, was very limited; this included the UK.

The primary aim of this programme of research was therefore to examine how existing research and knowledge of rehabilitation in patients with pulmonary hypertension could be advanced, with a particular focus on the delivery of rehabilitation in clinical practice for patients with pulmonary hypertension in the UK. This included an examination of the outcome measures that could be used to assess patients' functional ability and the effectiveness of rehabilitation in both research and in clinical practice.

7.2 Overview of the programme of work

Against this background, the programme of work (Figure 15) began with a review of the novel rehabilitation service being provided to patients with pulmonary hypertension in the Sheffield Specialist Pulmonary Hypertension Referral Centre (Chapter 2). This study demonstrated the level of rehabilitation need in this group of patients and the potential for the intervention to fulfil this. It identified the need for a comparator study to further explore efficacy of the intervention and raised questions about suitable outcomes that could be used.

Figure 15 - Overview of the programme of work



The Literature Review (Chapter 3) was undertaken to examine the question of outcome measures in more detail, identifying the tendency for rehabilitation studies in pulmonary hypertension to capture measures of Body Structure/Function in preference to measures of Activity or of Participation which are more suited to measuring the impact of rehabilitation on patients' lives.

The protocol in Chapter 4 describes a Feasibility Study which was designed to assess whether it was feasible to conduct a randomised controlled trial of the intervention described in the Review of Service, incorporating patient perspectives on acceptability and outcome measures, as well as the learning from the Literature Review. Due to the circumstances of the COVID-19 pandemic this study was discontinued after ethical approval had been obtained.

Questions of suitable outcome measures, which had been raised in the Review of Service and Literature Review, were highlighted further by the COVID-19 pandemic where the frequency of remote clinical assessment in patients with pulmonary hypertension had significantly increased. The PERSPIRE study (Chapter 5) examined this further by testing the 1-minute sit-to-stand test in 75 patients in the hospital setting and establishing its safety and comparability to existing exercise tests.

Chapter 6 considers the steps to be taken to build on this programme of work, describing the protocol for a study – PERSPIRE2 - to further examine the 1-minute sit-to-stand test including home-based testing, data collection to inform remote risk-assessment and evaluation of acceptability to patients and clinicians.

7.3 The philosophy of pragmatism within the programme of work

As previously described, this programme of work was undertaken within the research philosophy of pragmatism (section 1.2). This philosophy places an emphasis on the goal of the research when considering selection of research questions and methods, encompasses a cyclical process of enquiry between beliefs and actions, and advocates steps of inquiry that include selecting research methods that will best answer the research problem. There are a number of ways in which this philosophy enabled the development and application of this programme of work, as described below.

While not planned or anticipated, this programme of work was subject to external influences that necessitated change in the direction of study, not least the onset of the COVID-19 pandemic. The philosophy of pragmatism provided a supportive and structured framework at key points of choice and direction. Where decisions were required, stepping back to reflect on what had been learned to date, within the framework of the overarching goals and aims of the study, enabled clear and reasoned decision making. Additionally, there was no constraint within the philosophy around selection or adaptation of methods that were required in response to changes brought about.

As a clinical-academic, the approach undertaken felt most closely aligned to identifying solutions to problems that might be encountered in clinical practice, where the controlled environments of research studies are not able to be entirely maintained or replicated.

The pragmatic philosophy underpinning this programme of work also led to challenges. The majority of research in the field of medicine is more closely aligned with different approaches, specifically the ontology of objectivism and epistemology of positivism, which tend to utilise quantitative research methodologies. This difference in approach was especially evident in feedback from reviewers for funding applications, ethical approvals and publications, where further justification, explanation or modification of methods was on occasion required to facilitate progress.

7.4 Researcher Positionality

Throughout this programme of work the researcher has worked as a clinician with patients with pulmonary hypertension. The researcher was the first, and only, physiotherapist specialising in pulmonary hypertension in the UK, which at all times brought this work into great focus within the clinical field while it was being conducted. This, along with the lack of previous work in this area, was a significant influence for the need to publish the work before the thesis was completed.

The background of the researcher's physiotherapy education, training, and clinical practice has a strong focus on measurement before and after treatment to attempt to determine cause and effect; this approach is also widely reflected in physiotherapy research. However, the researcher also recognises the highly complex and individual nature of patients receiving care, and therefore the realisation that variation in response to any intervention is unlikely to be linear, and likely to be a consequence of a range of directly and indirectly related factors. This understanding is reflected in the researcher's clinical practice, which is informed by an individualised and personalised approach to patient care. It is also reflected in

the researcher's research practice, informing the choice of pragmatism as a research philosophy and mixed methods research design.

The researcher's intention in undertaking this programme of work was to advance the case for rehabilitation in the care of patients with pulmonary hypertension by providing new evidence of its benefit and application. This thesis, and the publications within it, provide building blocks for a new paradigm in pulmonary hypertension, in which patient care is designed to meet the needs and priorities of the individual patient (7.6.4). This transcends the barriers between qualitative and qualitative methods and requires adaptive, pragmatic approaches to research.[3]

High quality research requires equipoise on the part of the researcher. In this programme of work the researcher's background and clinical role within pulmonary hypertension might be considered a challenge to that equipoise. However, the rigour embedded in the programme of work, including a diverse research supervisory team from different backgrounds, the use of ethical review and peer review in publication, as well as patient and public involvement in study design and execution, provides strong safeguards to maintain overall study equipoise.

7.5 Patient and Public Involvement

Patients and members of the public contributed throughout this programme of work. Involving patients and members of the public in research can improve its quality and relevance, providing a perspective from their experience that might otherwise by overlooked by researchers.[5]

7.5.1 Approaches to Patient and Public Involvement

Patients and members of the public were involved in this programme of work in a number of ways.

Proposals for the Feasibility, PERSPIRE and PERSPIRE2 studies were shared with PHA UK and the Sheffield Teaching Hospitals research patient panel. They were asked if they considered the research to be important, with positive responses, and their comments on the design of the studies were incorporated into final protocols.

Consent forms and patient information sheets for the Feasibility and PERSPIRE studies were shared with PHA UK; feedback from members led to modification of content to allow the documents to be more easily understood by study participants. A patient and a representative from PHA UK were included in the study steering group for the PERSPIRE study. They attended meetings throughout the study and contributed to discussions on recruitment, data collection, analysis and dissemination.

7.5.2 Learning from Patient and Public Involvement

The experience of working alongside patients in developing and delivering research has been enlightening, encouraging and a clear source of learning.

7.5.2.1 Value of research

At all points of consultation, the feedback received from patients indicated the value and importance that representatives saw in the research being carried out – they thought that what was being proposed was worthwhile and could make a difference to the lives of patients with pulmonary hypertension. This was not only a key hurdle in deciding whether to progress with aspects of the programme of work, but also an important motivational factor in maintaining focus and direction in the face of external challenges to its progress.

7.5.2.2 Patient focus

The choices that are made in research design and direction are subject to multiple and competing influences, including questions of funding, publication and organisational priorities, as well as the differing views and perspectives of team members. The involvement and contributions of patients throughout this programme of work prevented its diversion from the originally stated aim of advancing knowledge of rehabilitation in clinical practice, and thereby supported the maintenance of an appropriate clinical-academic balance throughout.

7.5.2.3 Recruitment

Recruitment targets within the PERSPIRE study were comfortably achieved within projected timescales. The influence of patients through consultation in determining the value and design of the study, and the quality of the participant information were all contributing factors to this achievement.

7.5.2.4 Patient perspective

Patient feedback highlighted limitations and improvements to study design that had not been considered by the team. The researcher and wider team involved in the programme of work have extensive and in-depth experience of work with patients with pulmonary hypertension, and those close to them. Despite this, it is impossible to anticipate the patient perspective on the processes, interventions and language of research studies, and their involvement is therefore essential to ensure optimal design and implementation.

7.5.2.5 Representative voices

The nature of PPI is such that patient representatives can offer a single, or relatively narrow, perspective of experiences; where small numbers of representatives are involved this might skew or distort the PPI contribution. The use of PPI panels such as those operated by STH, and involvement of charities such as PHA UK are approaches to broadening access and thereby alleviating aspects of this challenge. The contribution of patient representation was highly valuable in the PERSPIRE study, however including a second patient member may have afforded greater opportunity for wider reflection and discussion. This modification has been included in the PERSPIRE2 protocol.

7.6 Contributions to learning and clinical practice

Components of the programme of work have been published and shared with clinical and research colleagues and have made significant contributions to knowledge and clinical practice in the field of rehabilitation and measurement of outcomes in patients with pulmonary hypertension.

7.6.1 Review of Service

This prospective study described the outcomes of 138 patients who had undergone a physiotherapy well-being review within a newly established physiotherapy-led rehabilitation service for patients with pulmonary hypertension. Its main findings were the high levels of need for rehabilitation in this group of patients and the potential to support their needs through existing community rehabilitation services, when accompanied by specialist pulmonary hypertension expertise and advice.

The Review of Service described an entirely novel intervention in the care of patients with pulmonary hypertension. The study challenged the existing orthodoxy that rehabilitation for patients with pulmonary hypertension needed to be implemented by centres with expertise in both rehabilitation and pulmonary hypertension[7] and demonstrated the potential for safe and effective rehabilitation of these patients in alternative rehabilitation settings, when accompanied by appropriate professional support. This new evidence was an essential step for the development of clinical rehabilitation services in the UK and other countries, where specialist pulmonary hypertension rehabilitation establishments do not exist.

While there previously existed evidence of the physical limitations brought about by pulmonary hypertension, the study was the first to establish the high level of rehabilitation need that existed within the patient population. This was an important acknowledgement for patients, in allowing their needs to be recognised and heard, clinicians, in encouraging them to consider how rehabilitation might be important to support existing treatments, and for service providers, by highlighting an unmet need and prompting consideration of potential future resource allocation.

The study described “early” rehabilitation in patients with pulmonary hypertension i.e. patients who had started on targeted therapies in the previous 6-9 months. Previous studies of rehabilitation had not reported the timing of their rehabilitation in relation to diagnosis and start of treatment, therefore it is not possible to determine the heterogeneity of their populations in that respect.

The unique role of the physiotherapist as a specialist in pulmonary hypertension and in rehabilitation was highlighted by the study. This will support patients, future clinical services and research studies to identify those roles within the multi-disciplinary team which are important for the delivery of care and interventions.

The study was novel in its universal inclusion, considering all patients with pulmonary hypertension irrespective of their disease severity or level of impairment, and demonstrating that these patients can be supported by rehabilitation. This may allow future studies and services to offer inclusion to a wider patient group.

The Review of Service took place within the framework of an existing clinical service, using routinely collected clinical data to determine patient outcomes. The study highlighted the potential limitations of existing clinical data to assess how pulmonary hypertension can limit patients' levels of physical activity, functional ability and engagement and participation in society. This has implications for future research studies, particularly studies of rehabilitation, as addressed in the Literature Review.

The work was published in October 2019 in the journal Pulmonary Circulation, the official journal of the Pulmonary Vascular Research Institute (impact factor: 2.29). It was presented as a poster at the British Thoracic Society Winter Meeting in December 2018[154] and at the Annual Congress of the Chartered Society of Physiotherapists in November of 2019,[155] ensuring a wide audience of interested health professionals.

7.6.2 Literature Review

This systematized review identified the 50 outcome measures that were used in 34 studies of rehabilitation in patients with pulmonary hypertension and mapped those outcomes against the World Health Organisation International Classification for Functioning, Disability and Health. The study found a predominance of outcomes which measured changes in Body Functions/Structure, with fewer

measures capturing levels of Activity and even fewer considering changes in Participation that might arise from rehabilitation interventions.

The study draws attention to the discrepancy between the potential benefits that can be achieved from rehabilitation, and the outcome measures that are used to capture the changes it brings about. Rehabilitation can increase exercise capacity and physical functioning, but it can also impact on important aspects of living with long-term conditions such as fatigue, emotional function, understanding and mastery of the disease and interpersonal relationships, which are not assessed by measures of Body Functions/Structure or Activity.

By highlighting this issue, the Literature Review challenges researchers of future rehabilitation interventions to carefully consider their choice of outcomes to best reflect the needs and priorities of patients undertaking the interventions, alongside other research design considerations.

In addition to the research domain, the learning from the Literature Review has relevance to clinical practice. Rehabilitation is not yet embedded in clinical services in pulmonary hypertension: health care resources are scarce and the case for development of new services must be compelling. Clinical services that evaluate the wider Participation impacts of pulmonary hypertension on patients e.g. inability to work, requirement for care and support at home, dependence on benefits will be better positioned to make the case for the rehabilitation interventions that can address the issues that matter most to patients.

Morbidity and mortality, as measured by the domains of Body Functions/Structure and Activity are important to patients, however their priorities can be concerns about employment, reliance on others for help, loneliness or emotional and relationship issues. The Literature Review highlights that by limiting the outcomes used in their work researchers, clinicians and service providers risk overlooking the wider benefits that might arise from rehabilitation to meet the needs of patients with pulmonary hypertension.

The Literature Review was published in February 2020 in the journal ATS Annals, a journal of the American Thoracic Society (impact factor: 8.785), and presented as a poster at the European Respiratory Society Annual Congress in September 2020.[156]

7.6.3 PERSPIRE study

The Literature Review and Review of Service identified the need to examine alternative measures of exercise capacity that could be measured outside the hospital setting. The PERSPIRE study achieved this and in doing so was, to our knowledge, the first to examine the 1-minute sit-to-stand in patients with pulmonary hypertension.

The study demonstrated the safety of the test in the hospital setting and its strong correlation with existing measures of exercise capacity, essential first steps in the evaluation of this outcome measure which is novel to pulmonary hypertension. In doing so it has laid a foundation for future studies using the outcome in patients with pulmonary hypertension or evaluating it further.

While further work is required to validate the 1-minute sit-to-stand for use at home, the study advances the case for remote assessment in patients with pulmonary hypertension. It has demonstrated that it may be possible to support patients in capturing and sharing important physical measures without undertaking repeat hospital visits. The potential value of this to patients and clinicians in pulmonary hypertension could be transformative: regular measurement and risk-assessment are essential to optimal patient care, and yet patients can live significant distances from their specialist centres and require substantial resources to undertake regular visits. Similarly, remote assessment might also be beneficial to research studies by reducing the number of study visits required, which may aid recruitment and retention.

The use of 1-minute sit-to-stand and other remotely monitored measures could also support home-based or remote rehabilitation which may have an important role to play in the future management of patients with pulmonary hypertension.

The work was published in October 2022 in the ERJ Open Journal, the online publication of the European Respiratory Society which attracts an international readership of multi-disciplinary clinicians in respiratory medicine (impact factor: 4.2) and presented as a poster at the European Respiratory Society Annual Congress in Barcelona in September 2022.[157]

7.6.4 Unique Contribution to Knowledge

This programme of work has made a significant and unique contribution to knowledge in the field of pulmonary rehabilitation and outcome measures, in addition to the stated aims of advancing understanding of rehabilitation delivery and assessment through outcome measures as described above (7.6.1, 7.6.2, 7.6.3).

It describes a new paradigm of care in pulmonary hypertension, moving away from the current model where care for patients is entirely provided in regional specialist centres and patients travel extended distances for assessment and treatment at fixed time intervals, based on treatment guidelines which are determined by clinician-selected outcomes.

Instead, the findings of the studies in the programme of work, along with the protocols described, *open the opportunity for an alternative, innovative approach* which is better suited to meet the needs of patients. This might include:

- An approach to patient care that is underpinned by asking patients "What matters to you?",[158] and interventions aimed at addressing individual patients' priorities.
- Treatment needs identified by holistic well-being reviews - interventions focussed on meeting the *functional goals* of patients and allowing them to optimise their *participation in society*.[48]
- An increase in remote patient care, reducing the frequency of attendance at specialist centres and reducing the need for patient travel.
- Increased patient involvement in their own care – patient self-assessment of key outcomes at home, reporting to clinical teams where measures lie outside pre-determined boundaries.

- Universal access to rehabilitation based in local communities, supported by expert physiotherapists in specialist centres.
- *Appropriate* (4.2) patient and service level outcome measures that reflect this paradigm shift, where success is determined by improving and measuring things that are important to patients.

This would represent a system wide change to services which has the potential to benefit patients and to be cost effective. It would need to be accompanied by evaluative research, encompassing examination of outcomes and processes, focussing on quality of care, experience of patients, staff and other stakeholders. It may require preliminary studies, such as PERSPIRE2, to examine the necessary components for any larger system transformation.

7.6.5 Wider implications for practice

This programme of work has been carried out in close collaboration with PHA UK, the patient charity for pulmonary hypertension in the UK. PHA UK has supported this research throughout and has amplified its findings, and related topics, to its patients through articles on its website and in its quarterly magazine, audio podcasts and social media. In 2021, drawing on the research from this programme of work and other studies, they launched their "Right to Rehab" campaign advocating for access to specialist rehabilitation for all patients in the UK with pulmonary hypertension.

The findings of the Review of Service were important in securing funding for the trial of a similar rehabilitation service at a second UK Specialist Pulmonary Hypertension Referral Centre, and central to the business cases for increasing rehabilitation provision to patients with pulmonary hypertension in the UK.

On merit of the research conducted and published in this programme of work, the researcher was invited to become a member of the NIHR Research Strategy Group for Pulmonary Hypertension and through this is in a position to influence the future direction of research in this field.

7.7 Addressing the research questions

The primary and secondary aims of this programme of work were:

- to advance the understanding of delivering rehabilitation in patients with pulmonary hypertension in clinical practice in the UK.
- to examine the outcome measures that could be used to assess patients' functional ability and the effectiveness of rehabilitation in pulmonary hypertension in research and in clinical practice.

The following research questions were identified at the outset of this thesis.

- How can rehabilitation for patients with pulmonary hypertension be delivered in the UK clinical setting?
- What outcomes can be used to assess functional ability in patients with pulmonary hypertension?

Specifically, these have been addressed by the three published papers as follows.

The Review of Service (Chapter 2) has:

- established the high level of rehabilitation need in patients with pulmonary hypertension.
- examined a novel approach to delivering rehabilitation in pulmonary hypertension based on patients' needs.
- identified the potential to safely move away from the delivery of rehabilitation in specialist pulmonary hypertension centres, to supporting patients to receive care in community settings closer to their homes.
- highlighted the importance of the role of the specialist pulmonary hypertension physiotherapist in rehabilitation.
- examined the potential for inclusive rehabilitation research in pulmonary hypertension, considering patients with early disease, as well as those with any level of disease severity or impairment.

The Literature Review (Chapter 3) has:

- identified the heterogeneity of outcome measures used in pulmonary hypertension rehabilitation research.
- drawn attention to the discrepancy between the potential benefits that can be achieved from rehabilitation, and the outcome measures that are used to capture the changes it brings about.
- challenged those conducting future research and evaluation of rehabilitation to consider patients' needs and priorities in the selection of appropriate outcome measures (4.2).

The PERSPIRE study (Chapter 5) has:

- established the safety of the 1-minute sit-to-stand as an outcome measure in patients with pulmonary hypertension.
- examined the comparability of the 1-minute sit-to-stand test with an alternative exercise test already established in pulmonary hypertension.
- identified the potential use for patient benefit of the 1-minute sit-to-stand test, and the research that would be required to examine this further.

7.8 Limitations of the programme of work

It is valuable to take the opportunity to reflect on this programme of work and consider its limitations, whether through choices made or external circumstances. Key considerations in this domain are examined below.

The Review of Service (Chapter 2) offered valuable insight into a novel rehabilitation service in pulmonary hypertension. It was seen as an opportunity to use readily available clinical data to capture the current situation in clinical practice and to inform the remainder of the programme of work; with the benefit of hindsight there would have been value in including a qualitative component to this study.

Had a qualitative component been added to the Review of Service, it would have allowed examination of the perspective of patients on the intervention and its acceptability. This in turn would have contributed to the design of the Feasibility

Study (Chapter 4) and would likely have resulted in this becoming a single stage study which only examined the feasibility of conducting an RCT of the intervention. A study of this type may have been easier to conduct and communicate.

However, had the programme of work progressed in this way, questions of outcome measures would probably not have been directly examined in a qualitative component of the Review of Service, since the issue of outcome measures only emerged from the findings of this study. Instead, questions of outcomes to be used in the Feasibility Study would have needed to be addressed through the findings of the Literature Review and themes that emerged from other topics explored in the qualitative component of the Review of Service.

The impact of the findings of the PERSPIRE study could have been limited by the decision to compare the 1-minute sit-to-stand to the Incremental Shuttle Walk test, rather than the 6-minute walk test, which is almost universally used in pulmonary hypertension. This limitation was recognised during the design of the study and considered, at the time, alongside other factors of study design.

The primary aim of the study was to establish the safety of the 1-minute sit-to-stand test in patients with pulmonary hypertension; this aim would not be compromised by the choice of comparator exercise test. The Incremental Shuttle Walk test is standard in clinical care at the Sheffield Pulmonary Hypertension Specialist Referral Centre, and its use allowed the study to be carried out with minimal disruption to the clinical service and patients, at a time when COVID-19 restrictions and recovery were in operation. Additionally, it was apparent at the time that a second study would be required to test for home-based safety of the 1-minute sit-to-stand, and comparison with 6-minute walk test could be undertaken at that point, as planned in PERSPIRE2 (Chapter 6). Therefore, on balance, the decision was made to proceed with the Incremental Shuttle Walk test in the PERSPIRE study.

The acceptance of this work for publication and conference presentation shows that the decision to proceed with the ISWT has generated findings of significant

interest to researchers and clinicians and provided a platform for the next phase of work in PERSPIRE2 (Chapter 6).

7.9 Future research directions

As outlined in Chapter 6, it is proposed that the future direction of study that follows this programme of work is the PERSPIRE2 study, that will investigate in greater depth the potential of the 1-minute sit-to-stand in home-based assessment.

This programme of work reflects an area of growing research interest and as such there are other related areas of research that could also be pursued in collaboration with colleagues across the pulmonary hypertension network. These would include:

- Further exploration of patient-initiated follow-up in patients with pulmonary hypertension, including the potential role of 1-minute sit-to-stand.
- Remotely delivered and assessed rehabilitation in pulmonary hypertension,[159] including 1-minute sit-to-stand in the outcome measures.

As previously mentioned, (section 7.6.5) the researcher is a member of the NIHR Research Strategy Group for pulmonary hypertension. The group is currently undertaking an assessment of research priorities in the field,[160] which would also inform any future planning.

Chapter 8 Conclusion

This programme of work has successfully addressed its goals to advance the understanding of delivering rehabilitation for patients with pulmonary hypertension in clinical practice in the UK, and to examine the outcome measures that could potentially be used to assess patients' functional ability in pulmonary hypertension research and in clinical practice. Additionally, Covid 19 provided an opportunity to initiate an exploration of home measurement, using the 1-minute sit-to-stand measure.

The Review of Service provided the first published description of an innovative rehabilitation intervention for patients with pulmonary hypertension which has been by reviewed and referenced by clinicians and researchers (from UK, USA, Australia and Northern Europe), including 3 citations to date. The Literature Review brought together, for the first time, the range of measures used across clinical studies and by doing so, was able to highlight the importance of selecting suitable, appropriate outcome measures in the design of future studies of rehabilitation. The PERSPIRE study provided, for the first time, data showing the response to the 1-minute sit-to-stand test in patients with pulmonary hypertension and thereby enabling consideration of an alternative outcome measure which could potentially be used in remote assessment and rehabilitation. This step enables the longer-term goal of enabling patients to access assessment and rehabilitation close to home and to engage more productively and actively in their own disease management and assessment. The protocols in this thesis allow and enable further research to develop the findings of this programme of work.

The findings of the completed studies are novel and contribute significantly to learning in the field. The publication, wider dissemination and discussion of the findings from this research across clinical and patient networks has advanced thinking in clinical practice, research and policy in this field.

Importantly for the field of rare disease research, this thesis has suggested a new paradigm for patient care which pushes the envelope of scope for physiotherapy

interventions towards improving patients' quality of life and wellbeing in their community settings, and placing at its core the needs, opinions and preferences of the people with pulmonary hypertension, while appreciating the required rigour and depth of research to support this.

References

1. Morgan D. Pragmatism as a Paradigm for Social Research. *Qualitative Inquiry*. 2014;20(8):1045-1053. doi:10.1177/1077800413513733

2. Biesta G. Pragmatism and the Philosophical Foundations of Mixed Methods Research. In: Tashakkori A, Teddlie C, eds. *SAGE Handbook of Mixed Methods in Social & Behavioural Research*. 2nd ed. SAGE; 2010.

3. Denzin NK. Moments, Mixed Methods, and Paradigm Dialogs. *Qualitative Inquiry*. 2010;16(6):419-427. doi:10.1177/1077800410364608

4. Greene J, Hall J. Dialectics and Pragmatism: Being of Consequence. In: Tashakkori A, Teddlie C, eds. *Sage Handbook of Mixed Methods in Social & Behavioural Research*. 2nd ed. SAGE; 2010.

5. National Institute for Health and Care Research. Briefing notes for researchers - public involvement in NHS, health and social care research. Published March 2021. Accessed October 9, 2022. https://www.nihr.ac.uk/documents/briefing-notes-for-researchers-public-involvement-in-nhs-health-and-social-care-research/27371

6. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237

7. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *Eur Heart J*. 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317

8. Kiely DG, Elliot CA, Sabroe I, Condliffe R. Pulmonary hypertension : diagnosis and management. *Br Med J*. 2013;2028(April):1-12. doi:10.1136/bmj.f2028

9. NHS Digital. *National Audit of Pulmonary Hypertension Great Britain, 2019-2020*.; 2021. https://files.digital.nhs.uk/6F/D51252/NAPH 11AR - Main Report v1.1.pdf

10. PHA UK. *What It Means to Live with PH Today*.; 2017. Accessed November 2, 2022. https://www.phauk.org/research-survey-work/living-ph-report/

11. McCormack C, Cullivan S, Kehoe B, et al. "It is the fear of exercise that stops me" – attitudes and dimensions influencing physical activity in pulmonary hypertension patients. *Pulm Circ*. 2021;11(4):1-9. doi:10.1177/20458940211056509

12. González-Saiz L, Santos-Lozano A, Fiuza-Luces C, et al. Physical activity levels are low in patients with pulmonary hypertension. *Ann Transl Med*. 2018;6(11):205-205. doi:10.21037/atm.2018.05.37

13. Saxer S, Lichtblau M, Berlier C, Hasler ED, Schwarz EI, Ulrich S. Physical activity in incident patients with pulmonary arterial and chronic thromboembolic hypertension. *Lung*. 2019;197(5):617-625. doi:10.1007/s00408-019-00248-x

14. Tartavoulle TM, Karpinski AC, Aubin A, Kluger BM, Distler O, Saketkoo LA. Multidimensional fatigue in pulmonary hypertension: prevalence, severity and predictors. *ERJ Open Res*. 2018;4(1). doi:10.1183/23120541.00079-2017

15. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. *Respir Res*. 2006;7(1):1-10. doi:10.1186/1465-9921-7-55

16. Rawlings GH, Beail N, Armstrong I, et al. Adults' experiences of living with pulmonary hypertension: A thematic synthesis of qualitative studies. *BMJ Open*. 2020;10(12). doi:10.1136/bmjopen-2020-041428

17. Barst R. Pulmonary hypertension: Past, present and future. *Ann Thorac Med*. 2008;3(1):1. doi:10.4103/1817-1737.37832

18. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2009;30(20):2493-2537. doi:10.1093/eurheartj/ehp297

19. Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J*. 2004;25(24):2243-2278. doi:10.1016/j.ehj.2004.09.014

20. Grünig E, Eichstaedt C, Barberà JA, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *European Respiratory Journal*. 2018;53(2). doi:10.1183/13993003.00332-2018

21. Uchi M, Saji T, Harada T. Feasibility of cardiopulmonary rehabilitation in patients with idiopathic pulmonary arterial hypertension treated with intravenous prostacyclin infusion therapy. *J Cardiol*. 2005;46(5):183-193. Accessed November 2, 2022. http://europepmc.org/article/MED/16320975

22. Wilkinson A, Elliot C, Mawson S, Billings C, Kiely DG. A randomised controlled trial to investigate the effects of a physiotherapist-led rehabilitation programme on exercise capacity and quality of life measures in patients with pulmonary hypertension. *Thorax*. 2007;62(Suppl III).

23. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006;114(14):1482-1489. doi:10.1161/CIRCULATIONAHA.106.618397

24. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. *BMC Pulm Med*. 2015;15(1):40. doi:10.1186/s12890-015-0031-1

25. Pandey A, Garg SSS, Khunger M, et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. *Circ Heart Fail*. 2015;8(6):1032-1043. doi:10.1161/CIRCHEARTFAILURE.115.002130

26. Desai SA, Channick RN. Exercise in Patients With Pulmonary Arterial Hypertension. *J Cardiopulm Rehabil Prev*. 2008;28(1):12-16. doi:10.1097/01.HCR.0000311502.57022.73

27. Yuan P, Yuan XT, Sun XY, Pudasaini B, Liu JM, Hu QH. Exercise training for pulmonary hypertension: A systematic review and meta-analysis. *Int J Cardiol*. 2015;178:142-146. doi:10.1016/j.ijcard.2014.10.161

28. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database of Systematic Reviews*. 2017;(1):CD011285. doi:10.1002/14651858.CD011285.pub2

29. Gilbert C, Brown MCJ, Cappelleri JC, Carlsson M, McKenna SP. Estimating a Minimally Important Difference in Pulmonary Arterial Hypertension Following Treatment With Sildenafil. *Chest*. 2009;135(1):137-142. doi:10.1378/chest.07-0275

30. Grünig E, MacKenzie A, Peacock AJ, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. *Eur Heart J*. 2021;42(23):2284-2295. doi:10.1093/eurheartj/ehaa696

31. Nogueira-Ferreira R, Moreira-Gonçalves D, Santos M, Trindade F, Ferreira R, Henriques-Coelho T. Mechanisms underlying the impact of exercise training in pulmonary arterial hypertension. *Respir Med*. 2018;134:70-78. doi:10.1016/j.rmed.2017.11.022

32. Mackenzie A. *Exercise Pathophysiology and Exercise Therapy in Pulmonary Arterial Hypertension*. University of Glasgow; 2020. Accessed November 2, 2022. https://theses.gla.ac.uk/82012/

33. Spruijt A O, de Man FS, Groepenhoff H, et al. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. Xiao J, ed. *Am J Respir Crit Care Med*. 2015;191(1):1050-1057. doi:10.1164/rccm.201412-2271OC

34. Ehlken N, Lichtblau M, Klose H, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J*. 2016;37(1):35-44. doi:10.1093/eurheartj/ehv337 [doi]

35. de Man FS, Handoko ML, Groepenhoff H, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *European Respiratory Journal*. 2009;34(3):669-675. doi:10.1183/09031936.00027909

36. Ehlken N, Verduyn C, Tiede H, et al. Economic Evaluation of Exercise Training in Patients with Pulmonary Hypertension. *Lung*. 2014;192(3):359-366. doi:10.1007/s00408-014-9558-9

37. Cascino TM, McLaughlin V v., Richardson CR, et al. Barriers to physical activity in patients with pulmonary hypertension. *Pulm Circ*. 2019;9(2):2045894019847895. doi:10.1177/2045894019847895

38. Chia KSW, Brown K, Kotlyar E, Wong PKK, Faux SG, Shiner CT. 'Tired, afraid, breathless … .' An international survey of the exercise experience for people living with pulmonary hypertension. *Pulm Circ*. 2020;10(4):1-10. doi:10.1177/2045894020968023

39. Delcroix M, Torbicki A, Gopalan D, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *European Respiratory Journal*. 2021;57(6):2002828. doi:10.1183/13993003.02828-2020

40. Babu AS, Padmakumar R, Nayak K, Shetty R, Mohapatra AK, Maiya AG. Effects Of Home-Based Exercise Training On Functional Outcomes And Quality Of Life In Patients With Pulmonary Hypertension: A Randomized Clinical Trial. *Indian Heart J*. 2019;71(2):161-165. doi:10.1016/j.ihj.2019.03.002

41. Wojciuk M, Ciolkiewicz M, Kuryliszyn-Moskal A, et al. Effectiveness and safety of a simple home-based rehabilitation program in pulmonary arterial hypertension: an interventional pilot study. *BMC Sports Sci Med Rehabil*. 2021;13(1). doi:10.1186/s13102-021-00315-y

42. McCormack C, Kehoe B, Hardcastle SJ, et al. Pulmonary hypertension and home-based (PHAHB) exercise intervention: protocol for a feasibility study. *BMJ Open*. 2021;11(5). doi:10.1136/bmjopen-2020-045460

43. McGregor G, Bruce J, Ennis S, et al. Supervised pulmonary hypertension exercise rehabilitation (SPHERe): Study protocol for a multi-centre randomised controlled trial. *BMC Pulm Med*. 2020;20(1). doi:10.1186/s12890-020-01182-y

44. Keen C, Fowler-Davis S, McLean S, Manson J. Physiotherapy practice in pulmonary hypertension: physiotherapist and patient perspectives. *Pulm Circ*. 2018;8(3):1-9. doi:10.1177/2045894018783738

45. Keen C, Hashmi-Greenwood M, York J, Armstrong IJ, Sage K, Kiely D. Exploring a physiotherapy well-being review to deliver community-based rehabilitation in patients with pulmonary hypertension. *Pulm Circ*. 2019;9(4):1-9. doi:10.1177/2045894019885356

46. Keen C, Harrop D, Hashmi-Greenwood MN, Kiely DG, Yorke J, Sage K. Outcome Measures Used in Studies of Rehabilitation in Pulmonary Hypertension: A Systematic Review. *Ann Am Thorac Soc*. 2020;(5):321-335. doi:10.1513/annalsats.202005-541oc

47. Keen C, Smith I, Hashmi-Greenwood M, Sage K, Kiely DG. Pulmonary Hypertension and Measurement of Exercise Capacity Remotely: Evaluation of the 1-min Sit-to-Stand Test (PERSPIRE) – a cohort study. *ERJ Open Res*. 2023;9(1). doi:10.1183/23120541.00295-2022

48. World Health Organisation. *Towards a Common Language for Functioning, Disability and Health*.; 2002. Accessed February 5, 2023. https://cdn.who.int/media/docs/default-source/classification/icf/icfbeginnersguide.pdf

49. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. doi:10.1183/13993003.01913-2018

50. McGoon MD, Benza RL, Escribano-Subias P, et al. Pulmonary Arterial Hypertension: Epidemiology and Registries. *J Am Coll Cardiol*. 2013;62(25):D51-D59. doi:10.1016/j.jacc.2013.10.023

51. McGoon MD, Ferrari P, Armstrong I, et al. The importance of patient perspectives in pulmonary hypertension. *European Respiratory Journal*. 2019;53(1). doi:10.1183/13993003.01919-2018

52. Benjamin N, Marra AM, Eichstaedt C, Grünig E. Exercise Training and Rehabilitation in Pulmonary Hypertension. *Heart Fail Clin*. 2018;14(3):425-430. doi:10.1016/j.hfc.2018.03.008

53. Leggio M, Fusco A, Armeni M, et al. Pulmonary hypertension and exercise training: a synopsis on the more recent evidences. *Ann Med*. 2018;50(3):226-233. doi:10.1080/07853890.2018.1432887

54. Babu, A.S., Padmakumar, R., Maiya, A.G., Mohapatra, A.K. Kamath RL. Effects of exercise training on exercise capacity in pulmonary arterial hypertension: a systematic review of clinical trials. *Heart Lung Circ*. 2016;25(4):333-341. doi:10.1016/j.hlc.2015.10.015

55. Johnson MK, Peacock AJ. Treating Pulmonary Arterial Hypertension With Exercise: The Role of Rehabilitative Medicine. *Adv Pulm Hypertens*. 2019;18(2):56-62. doi:10.21693/1933-088X-18.2.56

56. Grünig E, Ehlken N, Ghofrani A, et al. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. *Respiration*. 2011;81(5):394-401. doi:10.1159/000322475

57. Grünig E, Lichtblau M, Ehlken N, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. *European Respiratory Journal*. 2012;40(1):84-92. doi:10.1183/09031936.00123711

58. Rochester CL, Vogiatzis I, Holland AE, et al. An official American Thoracic Society/European Respiratory Society policy statement: Enhancing implementation, use, and delivery of pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2015;192(11). doi:10.1164/rccm.201510-1966ST

59. Bussotti M, Gremigni P, Pedretti RFE, et al. Effects of an Outpatient Service Rehabilitation Programme in Patients Affected by Pulmonary

Arterial Hypertension: An Observational Study. *Cardiovasc Hematol Disord Drug Targets*. 2017;17(1):3-10. doi:10.2174/1871529X16666161130123937

60. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated Clinical Classification of Pulmonary Hypertension. *J Am Coll Cardiol*. 2013;62(25, Supplement):D34-D41. doi:10.1016/j.jacc.2013.10.029

61. Department of Health and Social Care. Care Act Statutory Guidance. Published 2014. https://www.gov.uk/government/publications/care-act-statutory-guidance/care-and-support-statutory-guidance

62. Yorke J, Corris P, Gaine S, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *European Respiratory Journal*. 2014;43(4):1106-1113. doi:10.1183/09031936.00127113

63. Billings CG, Hurdman JA, Condliffe R, et al. Incremental shuttle walk test distance and autonomic dysfunction predict survival in pulmonary arterial hypertension. *The Journal of Heart and Lung Transplantation*. 2017;36(8):871-879. doi:10.1016/j.healun.2017.04.008

64. Billings CG, Lewis R, Hurdman JA, et al. The incremental shuttle walk test predicts mortality in non-group 1 pulmonary hypertension: results from the ASPIRE Registry. *Pulm Circ*. 2019;9(2):1-9. doi:10.1177/2045894019848649

65. British Thoracic Society Pulmonary Rehabilitation Guideline Group, Society. British Thoracic Society Guideline on Pulmonary Rehabilitation in Adults. *Thorax*. 2013;68(2):ii1-31.

66. Garrod R, Marshall J, Barley E, Jones PW. Predictors of success and failure in pulmonary rehabilitation. *European Respiratory Journal*. 2006;(27):788-794. doi:10.1183/09031936.06.00130605

67. Chan L, Chin LMK, Kennedy M, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. *Chest*. 2013;143(2):333-343. doi:10.1378/chest.12-0993

68. Weinstein AA, Chin LMK, Keyser RE, et al. Effect of aerobic exercise training on fatigue and physical activity in patients with pulmonary arterial hypertension. *Respir Med*. 2013;107(5):778-784. doi:10.1016/j.rmed.2013.02.006

69. Sehgal S, Chowdhury A, Rabih F, et al. Counting Steps: A New Way to Monitor Patients with Pulmonary Arterial Hypertension. *Lung*. 2019;197(4):501-508. doi:10.1007/s00408-019-00239-y

70. Rich S. The 6-Minute Walk Test as a Primary Endpoint in Clinical Trials for Pulmonary Hypertension. *J Am Coll Cardiol*. 2012;60(13):1202-1203. doi:10.1016/j.jacc.2012.03.080

71. Sitbon O, Gomberg-Maitland M, Granton J, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. *European Respiratory Journal*. 2019;53(1):1801908. doi:10.1183/13993003.01908-2018

72. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J*. 2009;26(2):91-108. doi:10.1111/j.1471-1842.2009.00848.x

73. NHS England. *Commissioning Guidance for Rehabilitation*.; 2016. https://www.england.nhs.uk/wp-content/uploads/2016/04/rehabilitation-comms-guid-16-17.pdf

74. World Health Organisation. *ICF Checklist*.; 2003. Accessed February 5, 2023. https://www.who.int/publications/m/item/icf-checklist

75. World Health Organisation. *How to Use the ICF: A Practical Manual for Using the International Classification of Functioning, Disability and*

Health (ICF). WHO; 2013. Accessed February 5, 2023. https://www.who.int/publications/m/item/how-to-use-the-icf---a-practical-manual-for-using-the-international-classification-of-functioning-disability-and-health

76. Awdish RLA, Small Larissa B, Cajigas Flores H. Development of a modified yoga program for pulmonary hypertension: a case series. *Altern Ther Health Med*. 2015;21(2):48-52. http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=2012958845&site=ehost-live

77. Becker-Grünig T, Klose H, Ehlken N, et al. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. *Int J Cardiol*. 2013;168(1):375-381. doi:10.1016/j.ijcard.2012.09.036

78. Brown MB, Kempf A, Collins CM, et al. A prescribed walking regimen plus arginine supplementation improves function and quality of life for patients with pulmonary arterial hypertension: a pilot study. *Pulm Circ*. 2018;8(1):1-12. doi:10.1177/2045893217743966

79. Chia K, Faux S, Wong P, et al. Randomised controlled trial examining the effect of an outpatient exercise training programme on haemodynamics and cardiac MR parameters of right ventricular function in patients with pulmonary arterial hypertension: the ExPAH study protocol. *BMJ Open*. 2017;7(2):e014037. doi:10.1136/bmjopen-2016-014037

80. Provencher S, Granton JT. Current Treatment Approaches to Pulmonary Arterial Hypertension. *Canadian Journal of Cardiology*. 2015;31(4):460-477. doi:10.1016/j.cjca.2014.10.024

81. Fox BD, Kassirer M, Weiss I, et al. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. *J Card Fail*. 2011;17(3):196-200. doi:10.1016/j.cardfail.2010.10.004

82. Ganderton L, Jenkins S, Gain K, et al. Short term effects of exercise training on exercise capacity and quality of life in patients with pulmonary arterial hypertension: protocol for a randomised controlled trial. *BMC Pulm Med*. 2011;11(1):25. doi:10.1186/1471-2466-11-25

83. Gerhardt F, Dumitrescu D, Gärtner C, et al. Oscillatory whole-body vibration improves exercise capacity and physical performance in pulmonary arterial hypertension: a randomised clinical study. *Heart*. 2017;103(8):592-598. doi:10.1136/heartjnl-2016-309852

84. González-Saiz L, Fiuza-Luces C, Sanchis-Gomar F, et al. Benefits of skeletal-muscle exercise training in pulmonary arterial hypertension: The WHOLEi+12 trial. *Int J Cardiol*. 2017;231:277-283. doi:10.1016/j.ijcard.2017.03.017

85. Grünig E, Maier F, Ehlken N, et al. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. *Arthritis Res Ther*. 2012;14(3):R148-R148. doi:10.1186/ar3883

86. Ihle F NC. An Integrated Outpatient Training Program for Patients with Pulmonary Hypertension - the Munich Pilot Project. *Int J Phys Med Rehabil*. 2014;02(03). doi:10.4172/2329-9096.1000204

87. Inagaki T, Terada J, Tanabe N, et al. Home-based pulmonary rehabilitation in patients with inoperable or residual chronic thromboembolic pulmonary hypertension: A preliminary study. *Respir Investig*. 2014;52(6):357-364. doi:10.1016/j.resinv.2014.07.002

88. Kabitz HJ, Bremer HC, Schwoerer A, et al. The Combination of Exercise and Respiratory Training Improves Respiratory Muscle Function in Pulmonary Hypertension. *Lung*. 2014;192(2):321-328. doi:10.1007/s00408-013-9542-9

89. Karapolat H, Cinar ME, Tanigor G, et al. Effects of cardiopulmonary rehabilitation on pulmonary arterial hypertension: A prospective,

randomized study. *Turk J Phys Med Rehabil*. 2019;65(3):278-286. doi:10.5606/tftrd.2019.2758

90. Ley S, Fink C, Risse F, et al. Magnetic resonance imaging to assess the effect of exercise training on pulmonary perfusion and blood flow in patients with pulmonary hypertension. *Eur Radiol*. 2013;23(2):324-331. doi:10.1007/s00330-012-2606-z

91. Mainguy V, Maltais F, Saey D, et al. Effects of a Rehabilitation Program on Skeletal Muscle Function in Idiopathic Pulmonary Arterial Hypertension. *J Cardiopulm Rehabil Prev*. 2010;30(5):319-323. doi:10.1097/HCR.0b013e3181d6f962

92. Martínez-Quintana E, Miranda-Calderín G, Ugarte-lopetegui A, Rodríguez-González F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis*. 2010;5(1):44-50. doi:10.1111/j.1747-0803.2009.00370.x

93. Mehani SHM, Abdeen HAA. Cardiopulmonary rehabilitation program impact on prognostic markers in selected patients with resting and exercise-induced ventilatory inefficiency: a clinical trial. *J Phys Ther Sci*. 2017;29(10):1803-1810. doi:10.1589/jpts.29.1803

94. Morris NR, Louis M, Strugnell W, et al. Study protocol for a randomised controlled trial of exercise training in pulmonary hypertension (ExTra_PH). *BMC Pulm Med*. 2018;18:1. doi:10.1186/s12890-018-0586-8

95. Nagel C, Prange F, Guth S, et al. Exercise Training Improves Exercise Capacity and Quality of Life in Patients with Inoperable or Residual Chronic Thromboembolic Pulmonary Hypertension. Lipinski M, ed. *PLoS One*. 2012;7(7):e41603. doi:10.1371/journal.pone.0041603

96. Raskin J, Qua D, Marks T, Sulica R. A retrospective study on the effects of pulmonary rehabilitation in patients with pulmonary hypertension.

Chron Respir Dis. 2014;11(3):153-162. doi:10.1177/1479972314538980

97. Saglam M, Arikan H, Vardar-Yagli N, et al. Inspiratory Muscle Training in Pulmonary Arterial Hypertension. *J Cardiopulm Rehabil Prev*. 2015;35(3):198-206. doi:10.1097/HCR.0000000000000117

98. Souza Leão M, Bergamascki LM, Xavier VB, Jaenisch RB, Stirbulov R, Alves VL dos S. Inspiratory muscle training in pulmonary hypertension: TREMMI protocol. *Manual Therapy, Posturology & Rehabilitation Journal*. 2018;16. doi:10.17784/mtprehabjournal.2018.16.569

99. Talwar A, Sahni S, Verma S, Khan SZ, Dhar S, Kohn N. Exercise tolerance improves after pulmonary rehabilitation in pulmonary hypertension patients. *J Exerc Rehabil*. 2017;13(2):214-217. doi:10.12965/jer.1732872.436

100. Tulloh RMR, Garratt V, Tagney J, et al. A pilot randomised controlled trial investigating a mindfulness-based stress reduction (MBSR) intervention in individuals with pulmonary arterial hypertension (PAH): the PATHWAYS study. *Pilot Feasibility Stud*. 2018;4(1):11-78. doi:10.1186/s40814-018-0270-z

101. Löwe B, Gräfe K, Ufer C, et al. Anxiety and Depression in Patients With Pulmonary Hypertension. *Psychosom Med*. 2004;66(6):831-836. doi:10.1097/01.psy.0000145593.37594.39

102. Delcroix M, Howard L. Pulmonary arterial hypertension: The burden of disease and impact on quality of life. *European Respiratory Review*. 2015;24(138):621-629. doi:10.1183/16000617.0063-2015

103. Pulmonary Hypertension Association. PHocus 2021. Published 2016. Accessed February 5, 2023. https://issuu.com/phauk/docs/emphasis_summer_2017_singles/s/11136469

104. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2015;(2):CD003793. doi:10.1002/14651858.CD003793.pub3

105. Bunclark K, Doughty N, Michael A, et al. A minimal clinically important difference measured by the Cambridge Pulmonary Hypertension Outcome Review for patients with idiopathic pulmonary arterial hypertension. *Pulm Circ*. 2021;11(2):1-9. doi:10.1177/2045894021995055

106. World Health Organisation. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). Published 2018. https://www.who.int/classifications/icf/more_whodas/en/

107. Armstrong I, Billings C, Kiely DG, et al. The patient experience of pulmonary hypertension: a large cross-sectional study of UK patients. *BMC Pulm Med*. 2019;19(1):67. doi:10.1186/s12890-019-0827-5

108. Reis A, Santos M, Furtado I, et al. Disability and its clinical correlates in pulmonary hypertension measured through the World Health Organization Disability Assessment Schedule 2.0: a prospective, observational study. *Jornal Brasileiro de Pneumologia*. 2019;45(4):e20170355. doi:10.1590/1806-3713/e20170355

109. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10(2):307-312. doi:10.1111/j..2002.384.doc.x

110. National Institute for Healthcare Research. Research for Patient Benefit. Published 2022. Accessed July 14, 2022. https://www.nihr.ac.uk/explore-nihr/funding-programmes/research-for-patient-benefit.htm

111. Torgerson D, Torgerson C. *Designing Randomised Trials in Health, Education and the Social Sciences: And Introduction*. Palgrave Macmillan; 2008. doi:10.1057/9780230583993

112. de Vet HCW, Terwee CB, Mokkink LB, Knol DL. *Measurement in Medicine*. Cambridge University Press; 2011.

113. Mokkink LB, Prinsen CAC, Bouter LM, Vet HCW D, Terwee CB. The Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) and how to select an outcome measurement instrument. *Braz J Phys Ther*. 2016;20(2):105-113. doi:10.1590/bjpt-rbf.2014.0143

114. Bryman A. *Social Research Methods*. 5th ed. Oxford University Press; 2016.

115. Denzin NK. Triangulation 2.0. *J Mix Methods Res*. 2012;6(2):80-88. doi:10.1177/1558689812437186

116. NHS Digital. *Annual Report National Audit of Pulmonary Hypertension Tenth Annual Report*.; 2019. https://files.digital.nhs.uk/BA/4EF20E/NAPH 10AR - Main Report.pdf

117. Long Term Plan. NHS England. Published 2019. https://www.longtermplan.nhs.uk/

118. Pulmonary Hypertension Association. *Living with PH*.; 2006. http://www.phauk.org/living-with-pulmonary-hypertension/living-ph-report/

119. Moth L, Hogg L, McDonnell L, Patel M, Marino P. An evaluation of outcomes for patients with pulmonary hypertension (PH) incorporated into a standard UK pulmonary rehabilitation (PR) programme. *European Respiratory Journal*. 2016;48(suppl 60). doi:10.1183/13993003.congress-2016.PA2402

120. Rochester CL, Fairburn C, Crouch RH. Pulmonary rehabilitation for respiratory disorders other than chronic obstructive pulmonary disease. *Clin Chest Med*. Published online 2014. doi:10.1016/j.ccm.2014.02.016

121. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough? *Field methods*. 2006;18(1):59-82. doi:10.1177/1525822X05279903

122. Ritchie J, Spencer L. Qualitative Analysis for Applied Policy Research. In: Bryman A, Burgess R, eds. *Analysing Qualitative Data*. Routledge; 1994.

123. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005;4(4):287-291. doi:10.1002/pst.185

124. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995;14(17):1933-1940. doi:10.1002/sim.4780141709

125. Kernan W. Stratified Randomization for Clinical Trials. *J Clin Epidemiol*. 1999;52(1):19-26. doi:10.1016/S0895-4356(98)00138-3

126. Ozalevli S, Ozden A, Itil O, Akkoclu A. Comparison of the Sit-to-Stand Test with 6min walk test in patients with chronic obstructive pulmonary disease. *Respir Med*. 2007;101(2):286-293. doi:10.1016/j.rmed.2006.05.007

127. Bohannon RW, Crouch R. 1-Minute Sit-To-Stand Test: Systematic review of procedures, performance, and clinimetric properties. *J Cardiopulm Rehabil Prev*. 2019;39(1):2-8. doi:10.1097/HCR.0000000000000336

128. Vaidya T, De Bisschop C, Beaumont M, et al. Is the 1-minute sit-to-stand test a good tool for the evaluation of the impact of pulmonary rehabilitation? Determination of the minimal important difference in

COPD. *International Journal of COPD*. 2016;11:11-2609. doi:10.2147/COPD.S115439

129. Houchen-Wolloff L, Daynes E, Watt A, Chaplin E, Gardiner N, Singh S. Which functional outcome measures can we use as a surrogate for exercise capacity during remote cardiopulmonary rehabilitation assessments? A rapid narrative review. *ERJ Open Res*. 2020;6(4):00526-02020. doi:10.1183/23120541.00526-2020

130. Salvi D, Poffley E, Tarassenko L, Orchard E. App-based versus standard six-minute walk test in pulmonary hypertension: Mixed methods study. *JMIR Mhealth Uhealth*. 2021;9(6). doi:10.2196/22748

131. Poojary J, Arora E, Britto A, Polen Z, Arena R, Babu AS. Validity of Mobile-Based Technology vs Direct Observation in Measuring Number of Steps and Distance Walked in 6 Minutes. *Mayo Clin Proc*. 2018;93(12):1873-1874. doi:10.1016/j.mayocp.2018.09.003

132. Galiè N, McLaughlin V v., Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *European Respiratory Journal*. 2019;53(1). doi:10.1183/13993003.02148-2018

133. Fritz JS, Blair C, Oudiz RJ, et al. Baseline and Follow-up 6-Min Walk Distance and Brain Natriuretic Peptide Predict 2-Year Mortality in Pulmonary Arterial Hypertension. *Chest*. 2013;143(2):315-323. doi:10.1378/chest.12-0270

134. Lewis RA, Billings CG, Hurdman JA, et al. Maximal Exercise Testing Using the Incremental Shuttle Walking Test Can Be Used to Risk-Stratify Patients with Pulmonary Arterial Hypertension. *Ann Am Thorac Soc*. 2021;18(1):34-43. doi:10.1513/AnnalsATS.202005-423OC

135. Wensel R, Francis DP, Meyer FJ, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in

pulmonary arterial hypertension. *Int J Cardiol*. 2013;167(4):1193-1198. doi:10.1016/j.ijcard.2012.03.135

136. Delcroix M, Staehler G, Gall H, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. *European Respiratory Journal*. 2018;52(5). doi:10.1183/13993003.00248-2018

137. Wesley Milks M, Sahay S, Benza RL, Farber HW. Risk assessment in patients with pulmonary arterial hypertension in the era of COVID 19 pandemic and the telehealth revolution: State of the art review. *The Journal of Heart and Lung Transplantation*. 2021;40(3):172-182. doi:10.1016/j.healun.2020.12.005

138. Crook S, Büsching G, Schultz K, et al. A multicentre validation of the 1-min sit-to-stand test in patients with COPD. *European Respiratory Journal*. 2017;49(3):1-11. doi:10.1183/13993003.01871-2016

139. Rausch-Osthoff AK, Kohler M, Sievi NA, Clarenbach CF, van Gestel AJR. Association between peripheral muscle strength, exercise performance, and physical activity in daily life in patients with Chronic Obstructive Pulmonary Disease. *Multidiscip Respir Med*. 2014;9(1):1-7. doi:10.1186/2049-6958-9-37

140. van Gestel AJR, Clarenbach CF, Stöwhas AC, et al. Predicting Daily Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *PLoS One*. 2012;7(11):2-8. doi:10.1371/journal.pone.0048081

141. Holland AE, Malaguti C, Hoffman M, et al. Home-based or remote exercise testing in chronic respiratory disease, during the COVID-19 pandemic and beyond: A rapid review. *Chron Respir Dis*. 2020;17:147997312095241. doi:10.1177/1479973120952418

142. Greenhalgh T, Javid B, Knight M, Inada-Kim M. *What Is the Efficacy and Safety of Rapid Exercise Tests for Exertional Desaturation in Covid-19?*; 2020. doi:10.13140/RG.2.2.23706.80325

143. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. *Designing Clinical Research : An Epidemiologic Approach*. 4th ed. Lippincott Williams & Wilkins; 2013.

144. Holland AE, Spruit MA, Troosters T, et al. An official European respiratory society/American thoracic society technical standard: Field walking tests in chronic respiratory disease. *European Respiratory Journal*. 2014;44(6):1428-1446. doi:10.1183/09031936.00150314

145. Borg E, Borg G, Larsson K, Letzter M, Sundblad BM. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports*. 2010;20(4):644-650. doi:10.1111/j.1600-0838.2009.00985.x

146. Greenhalgh T, Wherton J, Shaw S, Morrison C. Video consultations for covid-19. *BMJ*. Published online March 12, 2020:m998. doi:10.1136/bmj.m998

147. Office for National Statistics. *Exploring the UK's Digital Divide*.; 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/householdcharacteristics/homeinternetandsocialmediausage/articles/exploringtheuksdigitaldivide/2019-03-04

148. Hemnes AR, Silverman-Loyd L, Huang S, et al. A Mobile Health Intervention to Increase Physical Activity in Pulmonary Arterial Hypertension. *Chest*. Published online April 2021. doi:10.1016/j.chest.2021.04.012

149. Wojciuk M, Ciolkiewicz M, Kuryliszyn-Moskal A, et al. Effectiveness and safety of a simple home-based rehabilitation program in pulmonary arterial hypertension: an interventional pilot study. *BMC Sports Sci Med Rehabil*. 2021;13(1). doi:10.1186/s13102-021-00315-y

150. NHS England. Patient initiated follow-up. Outpatient Recovery and Transformation Programme. Published 2022. Accessed July 14, 2022. https://www.england.nhs.uk/outpatient-transformation-programme/patient-initiated-follow-up-giving-patients-greater-control-over-their-hospital-follow-up-care/

151. National Institute for Healthcare Research. Guidance on applying for feasibility studies. Published 2022. Accessed December 29, 2022. https://www.nihr.ac.uk/documents/guidance-on-applying-for-feasibility-studies/20474

152. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res*. 2017;17(1):88. doi:10.1186/s12913-017-2031-8

153. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol*. 2013;13(1):104. doi:10.1186/1471-2288-13-104

154. Keen C, Armstrong I, Kiely D. P18 Community-based pulmonary rehabilitation in patients with pulmonary hypertension: a feasibility study. *Thorax*. 2018;73(S4):A105.2-A106. doi:10.1136/thorax-2018-212555.176

155. Keen C, Armstrong I, Kiely DG. 145 Community-based rehabilitation in patients with pulmonary hypertension: preliminary results. *Physiotherapy*. 2020;107:e95. doi:10.1016/j.physio.2020.03.133

156. Keen C, Harrop D, Kiely DG, Hashmi-Greenwood M, Sage K. Outcome measures used in studies of exercise rehabilitation in pulmonary hypertension: a systematic review. In: *European Respiratory Journal*.

Vol 56. European Respiratory Society; 2020:3236. doi:10.1183/13993003.congress-2020.3236

157. Keen C, Hashmi-Greenwood M, Sage K, Kiely D. Pulmonary Hypertension and measurement of exercise capacity remotely: the PERSPIRE study. In: *European Respiratory Society Congress*. European Respiratory Society; 2022. doi:10.1183/13993003.congress-2022.150

158. Healthcare Improvement Scotland. What Matters to You. Published 2023. Accessed July 8, 2023. https://www.whatmatterstoyou.scot/publications/

159. McCormack C, Kehoe B, Cullivan S, et al. Feasibility, acceptability, safety and efficacy of a remotely delivered home-based pulmonary hypertension exercise program. In: *European Respiratory Society Congress*. European Respiratory Society; 2022:3806. doi:10.1183/13993003.congress-2022.3806

160. Weatherald J, Iqbal H, Mielniczuk L, et al. Research priorities for future pulmonary hypertension research: a James Lind Alliance priority setting partnership. In: *European Respiratory Society Congress*. European Respiratory Society; 2022. doi:10.1183/13993003.congress-2022.2581

Appendix 1 Literature Review database search strategies

Medline (via EBSCO)

#	Query
S9	s3 and s8
S8	S4 or S5 or S6 or S7
S7	AB (social OR communit* or singing or choir or "behaviour change" or CBT or "cognitive behavioural therapy" or counselling or psychologic* or yoga or pilates or mindful* or meditat*) or TI (social OR communit* or singing or choir or "behaviour change" or CBT or "cognitive behavioural therapy" or counselling or psychologic* or yoga or pilates or mindful* or meditat*)
S6	(MM "Exercise+") OR (MM "Rehabilitation+") OR (MH "Rehabilitation, Pulmonary") OR (MM "Physical Therapy Modalities+")OR (MH "Yoga") OR (MH "Meditation") OR (MM "Mindfulness") OR (MM "Exercise Movement Techniques+")
S5	(AB ((exercise N6 interventio*) OR (exercise N6 therap*) rehabilitation OR (exercise N6 train*) OR (exercise N6 prescript*)) OR TI ((exercise N6 interventio*) OR (exercise N6 therap*) rehabilitation OR (exercise N6 train*) OR (exercise N6 prescript*)))
S4	TI (physiotherap* or "physical therap*") OR AB (physiotherap* or "physical therap*")
S3	S1 or S2
S2	AB ("pulmonary hypertension" OR "pulmonary vascular disease") OR TI ("pulmonary hypertension" OR "pulmonary vascular disease")
S1	(MM "Pulmonary Arterial Hypertension") OR (MM "Hypertension, Pulmonary+")

CINAHL (via EBSCO)

S9	S3 and S8
S8	S4 or S5 or S6 or S7
S7	AB (social OR communit* or singing or choir or "behaviour change" or CBT or "cognitive behavioural therapy" or counselling or psychologic* or yoga or pilates or mindful* or meditat*) or TI (social OR communit* or singing or choir or "behaviour change" or CBT or "cognitive behavioural therapy" or counselling or psychologic* or yoga or pilates or mindful* or meditat*)
S6	(AB ((exercise N6 interventio*) OR (exercise N6 therap*) rehabilitation OR (exercise N6 train*) OR (exercise N6 prescript*)) OR TI ((exercise N6 interventio*) OR (exercise N6 therap*) rehabilitation OR (exercise N6 train*) OR (exercise N6 prescript*)))
S5	TI (physiotherap* or "physical therap*") OR AB (physiotherap* or "physical therap*")

S4	(MM "Exercise+") OR (MM "Rehabilitation+") OR (MH "Rehabilitation, Pulmonary") OR (MM "Physical Therapy+") OR (MM "Yoga+") OR (MM "Pilates") OR (MH "Mindfulness") OR (MM "Mind Body Techniques+") OR (MM "Meditation")
S3	S1 or S2
S2	(MM "Pulmonary Arterial Hypertension") OR (MM "Hypertension, Pulmonary+")
S1	AB ("pulmonary hypertension" OR "pulmonary vascular disease") OR TI ("pulmonary hypertension" OR "pulmonary vascular disease")

Cochrane

#1	("exercise interventio*" OR "exercise therap*" OR "exercise rehabilit*" OR "exercise train*" OR "exercise prescript*"):ti,ab,kw (Word variations have been searched
#2	((exercise near (prescript* or train* or intervent* or therap*)) or rehabilitation):ti,ab,kw
#3	(physiotherap* or "physical therap*"):ti,ab,kw
#4	(social OR communit* or singing or choir or "behaviour change or "CBT or "cognitive behavioural therapy" or counselling or psychologic*):ti,ab,kw
#5	(MM "Exercise+") OR (MM "Rehabilitation+") OR (MH "Rehabilitation, Pulmonary") OR (MM "Physical Therapy Modalities+") (MH "Yoga") OR (MH "Meditation") OR (MM "Mindfulness") OR (MM "Exercise Movement Techniques+")
#6	(yoga or pilates or mindful* or meditat*); ti,ab,kw
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	(MM "Pulmonary Arterial Hypertension") OR (MM "Hypertension, Pulmonary+")
#9	("pulmonary hypertension" OR "pulmonary vascular disease"):ti,ab,kw
#10	#8 or #9
#11	#7 and #10

ASSIA

ab("pulmonary hypertension" OR "pulmonary vascular disease") OR ti("pulmonary hypertension" OR "pulmonary vascular disease")

Scopus

(TITLE-ABS-KEY("pulmonary hypertension" OR "pulmonary vascular disease")AND TITLE-ABS-KEY(physiotherap* or "physical therap*")) OR (TITLE-ABS-KEY("pulmonary hypertension" OR "pulmonary vascular disease") AND TITLE-ABS-KEY("exercise W/6 interventio*" OR "exercise W/6 therap*" OR "exercise W/6 rehabilit*" OR "exercise W/6 train*" OR "exercise W/6 prescript*")) OR (TITLE-ABS-KEY("pulmonary hypertension" OR "pulmonary vascular disease") AND TITLE-ABS-KEY(social OR communit* or singing or choir or "behaviour change" or CBT or "cognitive behavioural therapy" or counselling or psychologic* or yoga or pilates or mindful* or meditat*))

Appendix 2 Feasibility Study NHS IRAS Form

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Investigating a well-being review in Pulmonary Hypertension

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(•) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (•) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(•) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(•) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(•) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

( ) Yes (•) No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
The study is being undertaken as a PhD at Sheffield Hallam University

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Investigating a well-being review in Pulmonary Hypertension

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Investigating the feasibility of a randomised controlled trial of a physiotherapy well-being review in patients with pulmonary hypertension.

A2-1. Educational projects

Name and contact details of student(s):

Student 1

Title	Forename/Initials	Surname
Ms	Carol	Keen

Address	Room M40a, Royal Hallamshire Hospital Glossop Road Sheffield
Post Code	S10 2JF
E-mail	carol.keen@nhs.net
Telephone	01142268864
Fax	

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
Part-time PhD Fellowship for Health and Social Care Practitioners

Name of educational establishment:
Sheffield Hallam University

Name and contact details of academic supervisor(s):

Academic supervisor 1

Title	Forename/Initials	Surname
Professor	Karen	Sage

Address	F611 Robert Winston Building

	11-15 Broomhall Road
	Sheffield
Post Code	S10 2BP
E-mail	k.sage@shu.ac.uk
Telephone	01142255809
Fax	

Academic supervisor 2

	Title	Forename/Initials	Surname
	Professor	David	Kiely
Address	Ward M2		
	Royal Hallamshire Hospital, Glossop Road		
	Sheffield		
Post Code	S10 2JF		
E-mail	david.kiely1@nhs.net		
Telephone	01142712132		
Fax			

Academic supervisor 3

	Title	Forename/Initials	Surname
	Professor	Janelle	Yorke
Address	The University of Manchester		
	Room 5.320 Jean McFarlane Building, Oxford Road		
	Manchester		
Post Code	M13 9PL		
E-mail	janelle.yorke@manchester.ac.uk		
Telephone	01613067780		
Fax			

Academic supervisor 4

	Title	Forename/Initials	Surname
	Dr	Molly	Hashmi-Greenwood
Address	Department of Allied Health Professionals, Sheffield Hallam University		
	36 Collegiate Crescent		
	Sheffield		
Post Code	S10 2BP		
E-mail	m.hashmi-greenwood@shu.ac.uk		
Telephone	01142252324		
Fax			

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Ms Carol Keen	☑ Professor Karen Sage ☑ Professor David Kiely

☑ Professor Janelle Yorke

☑ Dr Molly Hashmi-Greenwood

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

◉ Student

○ Academic supervisor

○ Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Ms	Carol	Keen
Post	Clinical Specialist Physiotherapist		
Qualifications	BEngBComm, BSc, Msc		
ORCID ID	0000 0001 7803 1235		
Employer	Sheffield Teaching Hospital NHS FoundationTrust		
Work Address	Room M40a, Royal Hallamshire Hospital		
	Glossop Road		
	Sheffield		
Post Code	S10 2JF		
Work E-mail	carol.keen@nhs.net		
* Personal E-mail	carol.keen@nhs.net		
Work Telephone	01142268864		
* Personal Telephone/Mobile	01142268864		
Fax			

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Ms	Aimee	Card
Address	Clinical Research & Innovation Office, Sheffield Teaching Hospitals		
	Glossop Road		
	Sheffield		
Post Code	S10 2JF		
E-mail	aimee.card@nhs.net		
Telephone	01142265345		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	STH20898
Sponsor's/protocol number:	STH20898
Protocol Version:	1.0
Protocol Date:	18/11/2019
Funder's reference number (enter the reference number or state not applicable):	
Project website:	

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

◯ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Pulmonary Hypertension (PH) is a rare disease that makes patients easily become breathless. There is evidence that people with PH can benefit from exercise; we want to look at how they can access rehabilitation in their local community.
Aim: To see if it is feasible to study physiotherapy well-being reviews in PH. Step 1: We will interview some patients with PH who have had rehabilitation and ask questions about their experiences. We will also ask what they think we should measure to show any difference their rehabilitation has made to them. The findings from Step 1 will help us to shape the details of Step 2, where we will conduct a small study to see if it is feasible to run a full study. Participants will be divided randomly into a treatment group and a control group. The treatment group will have a physiotherapy well-being review, leading to referral to their most suitable local rehabilitation service and follow-up after 6 months. The control group will receive brief exercise advice and follow-up after 6 months. The findings will help to design a full study and be shared with patients and health professionals.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified

and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

1. Time burden to patients - patients involved in the second part of this study will be assessed and referred to community services where they will be encouraged to take part already established (mostly NHS-delivered) rehabilitation programmes that involve a regular time commitment (once or twice a week) over a period of time (up to 3 months). As part of the physiotherapy well-being review,we will work with patients to identify what form of rehabilitation will best suit them before making any referrals, so we can ensure that we are not asking them to commit to something that will feel a burden. We will make clear to patients that they can stop their rehabilitation or withdraw from the study at any point, without detriment to their care. This is a feasibility study - one purpose of it is to identify whether the burden of the intervention is acceptable to patients, so it will be important that we capture data on adherence and we plan to ask patients through a questionnaire tool at the end of the study on this topic. We have tried to minimise the time commitments to patients of all other aspects of the study by overlapping events with planned clinical activity and using clinical outcomes as much as is possible.

2. The qualitative interviews and well-being reviews may provoke an emotional response in patients as they reflect on the limitations and challenges arising from their disease. The interviews and well-review reviews will be conducted by an experienced physiotherapist who is expert in managing difficult conversations with patients. The physiotherapist also has clinical supervision with another senior physiotherapist to assist in ensuring both the patient and therapist are well supported during these conversations. We will also be able to offer patients access to a free counselling service, should they feel they would like to access it.

3. The studies, to date, of exercise in Pulmonary Hypertension have looked closely at the safety of patients and have found that there have been only a very small number of minor incidents; for example someone becoming dizzy when they are on an exercise bike. The well-being review will assess for risk of exercise in individual patients and that assessment will be considered when offering them the most suitable rehabilitation service. Community-based rehabilitation programmes will also all have their own local risk assessment processes and will be informed of any patient specific risks during the referral process. In our service evaluation of the well-being review, we found no safety problems. We will ensure that participants are aware that they can withdraw from the study at any time, and that this will in no way affect the care that they receive. As part of the well-being review, patients will be given information on how to exercise safely and what to do if they have any illnesses or injuries. We will continually monitor and review feedback from patients and adverse events and will move to stop the study prematurely if indicated by the data.

4. Participants will randomised to either intervention or control groups. Those randomised to the control group will not be offered the intervention which this study wants to explore. They may feel they are being denied a beneficial intervention. The reasons for randomisation will be explained in the PIS and during the consent process, and participants in the control group will be offered the opportunity to have a well-being review and referrals to rehabilitation once their participation in the study has ended.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply:*

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☑ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☑ Qualitative research
- ☐ Questionnaire, interview or observation study

☐ Randomised controlled trial

☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To carry out a small study of a physiotherapy well-being review in patients with pulmonary hypertension, in order to test whether it would be possible and worthwhile to run a large study.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

1. To find out more about patients' experience of taking part in rehabilitation and of having a well-being review.
2. To make sure the study we design is the best it can be.
3. To find out from people who have had rehabilitation what difference, if any, it has made to their lives and the lives of those around them.
4. To decide what types of things we should measure to see if the rehabilitation in our study has made a difference.
5. To find out if its acceptable to people with PH to be randomised into a control group where they don't receive the intervention
6. To see if it possible to recruit enough people with PH and to see how long it takes so we can estimate that for a bigger study

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Pulmonary Hypertension (PH) is a rare disease where there is poor blood flow to the lungs from the heart. This means that patients easily become breathless and extremely tired. There is no cure for PH. It is a serious illness. However, because of new drugs which have been developed in the last 10-15 years, people are now living for longer with the disease. This means that we need to think more about how we can improve their quality of life.

PH in the UK is managed through a small number of regional centres, where staff teams have a high level of specialist knowledge of management of the condition and care of the patient. Sheffield is one of 7 regional centres and covers all of the North of England and Wales.

There is evidence that people with PH can benefit from exercise to improve their quality of life. The evidence comes from research which has been carried out in Germany with patients exercising in very controlled settings, where the staff have highly specialist knowledge of PH.

There is no research that shows whether there are ways for patients with PH to take part in exercise and rehabilitation within the clinical services that already exist in the NHS and health communities in the UK. If patients are going to have rehabilitation, it makes sense for it to happen close to their home. This might be a problem if their local rehabilitation services do not know very much about PH, which could easily happen as it is a rare disease.

We believe that a well-being review by a physiotherapist specialist in PH will help patients to take part in local rehabilitation, but also provide the specialist PH support that is needed for the patient and the local services. Our study will explore, in a focused way, what difference it makes to patients with PH if they have a physiotherapy well-being review. The study will be small scale and aims to find out whether a full-sized study of this kind would be possible.

For their well-being review, patients will meet with a physiotherapist specialist in PH and discuss:
- how they are
- what they can do for themselves
- what it is challenging for them to do
- how active they are
- if they have ever exercised before

The physiotherapist will then make a referral to the most suitable rehabilitation service local to the patient e.g. rehabilitation classes, physiotherapy at home, weight-loss programmes.

We have been running a service evaluation in Sheffield for the last year, where we offer a well-being review to new PH patients. Of the 138 patients we've seen, 90% have had a problem that would potentially benefit from rehabilitation. Now that we know that the well-being review works in practice, we need to do some research to see if it makes a positive difference to patients. This study is the first step in that process.

At the moment, patients with PH typically receive no rehabilitation. Our aim is to make rehabilitation standard care for these patients. To achieve this, we need to have research evidence which shows that rehabilitation works for patients within the settings that exist in our NHS and healthcare communities. Without this evidence, we will not be able to convince commissioners, who decide where the money in the NHS is allocated, to invest money in rehabilitation for PH.
This research will help to build this evidence. If the findings are positive, we will be able to design a full-sized study and we will have a good case to ask for funding for the full-sized study which will build the evidence even further.
As well as helping us to build the research evidence in this area, this research will raise awareness with doctors and other health professionals, researchers, NHS staff, patients and their families, of the importance of rehabilitation for these patients. By doing this, we can change the way key people think about rehabilitation and its role in PH.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The study is made up of two parts:
Part 1 – to understand how it feels to take part in the well-being review, we will interview some participants who have already had this kind of treatment and ask questions about their experiences of it and how it was for them. We are also interested to know what differences they felt it made so that we can help to decide about the things we want to measure as outcomes in Part 2 of the study.
The interviews will last between about 30 and 60 minutes. We will tape-record the interviews and look carefully for common patterns and themes in what the participants have said.
Part 2 - to conduct a small study to see if it would be possible and worthwhile to then run a full study
- Participants will be divided randomly into a treatment group and a control group.
- The treatment group will have a physiotherapy well-being review and be referred for rehabilitation. They will be seen after 6 months for follow-up
- The control group will have initial assessments then receive brief advice on exercise. They will also be followed up after 6 months.

For Part 1 of the study we will aim to interview around 15 patients for interviews. These will be invited from a group of people who have undergone a similar well-being review when we did an evaluation of this in our clinic last year. For Part 2, we will recruit patients who come to Sheffield for management of their PH. We intend to recruit between 24 and 50 patients. These will be patients with pulmonary hypertension (PH) who are stable on drug treatments for their PH will be invited to join the study.

In the study we will measure:
- how many people want to join the study and how many drop out before the end
- whether what we are doing is safe
- any problems in recruiting participant

We will use the interviews in Part 1 to help us to decide on some of the other outcomes which are about what difference the rehabilitation makes to patients.
We will use all the information from the study to decide whether it will be possible to carry out a full-sized study of this type.
If so, we will use the findings to help design a full-sized study and to get funding for further research.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.

Identifying the Research Topic
In recent years, we have worked in close collaboration with the Pulmonary Hypertension Association (PHA UK), the patient charity for pulmonary hypertension (PH) in the UK, to develop this line of clinical and research enquiry. The PHA UK identified that functional ability, physical activity and quality of life are high priorities for their members and that exercise and rehabilitation have the potential to improve all these areas for patients.
To help address the current lack of any assistance in these areas, the PHA contributed to funding for a physiotherapist at the lead site working from May 2017 to August 2019 to undertake an innovative clinical physiotherapy role in PH, with a focus on promoting physical activity in patients. They have collaborated actively through this project which has led to the identification of this research topic and the development of this proposal.
Developing the Application
To capture the views of patients, we presented the initial study design to two separate patient groups which were mixed in age, gender and functional ability:
• a panel of 5 Patient and Public Involvement (PPI) representatives from the Community and Acute Care Group within Sheffield Teaching Hospitals
• a focus group of 5 patients with PH and 3 carers, arranged through PHA UK.
They identified:
• The importance of this research. They are aware of significant drug research in PH but that there is little research which looks at approaches to moderate the wider burden of the disease and improve quality of life. They welcomed it as a potentially positive and optimistic intervention and did not foresee any problems with recruitment.
• The need to clearly explain, in patient information, the role and purpose of the control group and ensure that participants in the control group have the opportunity to experience rehabilitation after the study ends.

The views from these two groups were reflected in changes made to the study design as follows:
• Updating recruitment to take place after patients have been on a stable therapeutic regime for at least 6 months (changed from 3 months). For many patients, the first few months after diagnosis can be full of anxiety and stress; it would be better to approach patients, when they have arrived at some acceptance of the disease and its consequences
• Outcome measures might need to include: a measure of carer well-being; measures of fatigue to reflect the adjustments made to manage fatigue; measures of anxiety and depression that capture mood. This will be addressed in the topic guide for the qualitative interviews which aim to determine outcome measures to be used in the study

We also discussed how best to describe the intervention and they favoured the term "well-being review" as it reflected its positive and individualised nature.

Study Development
All participant information will be written in collaboration with patient representatives, who will check it is understandable and non-coercive. Patient representatives will be involved in the development of the work packages as we collect data and will help to analyse and address any recruitment issues should they arise.
Study Management
Two patient representatives will be invited to join the study steering group. We recognise the burden of the disease on patients and that fatigue is a common symptom. To support them in participating in the steering group, we have included costs for travel plus overnight stay for patient representatives and additional costs for a carer to travel and stay with them.
Dissemination
Patient representatives will be involved in the review of the study findings and dissemination, particularly where this is aimed at patients and their families or carers. They will help to identify findings key to patients; suitable communication channels; appropriate language and content for communication. PHA UK has a quarterly magazine, annual patient conference and wider social media presence which would offer suitable channels for dissemination. There may be the potential to draw on the study findings to collaboratively develop a comprehensive guide to rehabilitation for the patient group.
We will feedback the outcome of the grant application and the study findings to the PPI panel that have supported the application and continue to involve and update the panel throughout the course of the fellowship.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☐ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☑ Respiratory
- ☐ Skin
- ☐ Stroke

Gender: Male and female participants

Lower age limit: 18 Years

Upper age limit: Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Participants must:
- be over 18 years old;
- in World Health Organisation (WHO) Functional Class II or III
- have a diagnosis of PH
- have started on PH drug therapy in the preceding 18 months
- showing no signs of worsening breathlessness or heart failure
- on an unchanged PH therapeutic regime for at least 6 months prior to inclusion.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Participants will not be enrolled in the study if they
- have an active infection or acute exacerbation of lung disease
- have participated in a clinical study involving another investigation of drug, device or exercise within the previous 6 months
- are on a surgical or other pathway of care that has pre-determined physiotherapy or activity regimes or restrictions
- have any additional medical conditions that may adversely affect the safety of the subject or severely limit the lifespan of the subject
- have participated in rehabilitation in the last 12 months.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Part 1 participants - Letter to seek consent	1	0	15 minutes	Prospective participants will be sent a letter 2 weeks prior to a routine clinic appointment informing them of the details of the study (Participant Information Sheet) and that they will be approached and invited to take part
Part 1 participants - Participation follow-up call	1	0	15 minutes	1 week after the letter to seek consent is sent, prospective participants will receive a call from a research nurse to see if they have received the letter and if they have any questions about the study that they would like to be clarified. If not they will be asked if they would like to take part. If they agree a date and time for telephone interviews will be arranged
Part 1 particpants - Consent	1	0	15 minutes	Participants agreeing to take part in telephone interviews will be asked to complete and sign the consent form and return a copy to the research team before the interview takes place
Part 1 participants - Qualitative interview	1	0	45 minutes	Telephone interview - participants can choose when the interview takes place. Interviews will be conducted with a member of the research team
Part 2 participants - Letter to seek consent	1	0	15 minutes	Prospective participants will be sent a letter 2 weeks prior to a routine clinic appointment informing them of the details of the study (Participant Information Sheet) and that they will be approached and invited to take part
Part 2 participant - Participation follow up call	1	0	15 minutes	1 week after the letter to seek consent is sent, prospective participants will receive a call from a research nurse to see if they have received the letter and if they have any questions about the study that they would like to be clarified
Part 2 participants - Consent approach	1	0	15 mintues	During their clinic visit, potential participants will be approached by a research nurse who will review the details of the study with them and ask if they would be happy to take part. Informed consent will be obtained
Part 2 participants - Final questionnaire	1	0	15 mintues	At their final assessment, participants will be asked to complete a questionnaire to capture their experiences of taking part in the study, including the acceptability of the recruitment process, the information they received, the intervention and the outcome assessments.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research,

how many of the total would be routine?

3. Average time taken per intervention/procedure (minutes, hours or days).

4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Part 2 participants - Initial assessments	4	3	60 minutes	Participants will have standard observations checked, complete an Incremental Shuttle Walk Test and a Patient Reported Outcome measure. These would all be collected as part of routine clinical care. In addition participants will be asked to complete study specific outcome measures (questionannire-based). The number and nature of these will be determined in the first stage of the study, likely to be between 3 and 5.
Part 2 participants - Physiotherapy Well-being review. A detailed 1 to 1 physiotherapy assessment of patient function and rehabilitation needs	1	0	45 minutes	Conducted by physiotherapy member of the research team. This will take place in routine Pulmonary Hypertension clinic at Sheffield Teaching Hospitals
Part 2 participants Community-based rehabilitation	1	0	estimate 20-30 hours	varied time commitment depending on the local community provision available (type, duration, frequency) e.g. twice a week for 2 hours, for as total of 6 weeks.
Part 2 participants - Follow-up call	1	0	20 minutes	call from the research physiotherapist to the participant during the period of their community rehabilitation to ensure everything is progressing and there are no questions or concerns
Part 2 participants - Final assessments	4	3	60 minutes	Participants will have standard observations checked, complete an Incremental Shuttle Walk Test and a Patient Reported Outcome measure. These would all be collected as part of routine clinical care. In addition participants will be asked to complete study specific outcome measures (questionannire-based). The number and nature of these will be determined in the first stage of the study, likely to be between 3 and 5.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

◯ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

6 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Participants in Part 1 of the study will be required to give their time to be interviewed. They will be asked primarily about their previous experiences of rehabilitation and the changes that it may have made to them and to those around them. There is a possibility that some patients may find this an upsetting topic to discuss - it may, for example, highlight to them the functional or physical limitations that they face as a result of their condition.

The use of an interview topic guide will help to ensure that interviews are not unnecessarily long and that only topics relevant to the research are addressed by the the interviewer. Participants will be informed before the interview of the topics areas that are likely to be covered. They will also be assured that the information they share will treated as confidential and that they will not be identifiable in any outputs from this work. The interviewer will be an expert clinician with experience in the disease area and in managing difficult conversations with patients. Participants will be made aware that they can withdraw from the process at any time, including during the interview and that they do not have to answer particular questions if they prefer not to. If appropriate, participants will be signposted to further counselling and to the PHA charity support network.

In Part 2 of the study, participants will undergo additional assessments, undertake a well-being review and participate in community-based rehabilitation.
As far as possible, to reduce the burden, we have designed the study so that study visits coincide with clinical visits and and to reduce potential fatigue, we will use routine clinical assessments as baseline measures. However, participants will be asked to complete additional outcome measure questionnaires: we are using Part 1 of the study to ensure these are the most relevant outcomes to the intervention. We will be mindful of fatigue and burden when working with the PPI group to select these additional measures.

The well-being review will include an assessment of patients' current functional ability and their rehabilitation needs. There is a possibility that some patients may find this an upsetting topic to discuss - it may for example highlight to them the functional or physical limitations that they face as a result of their condition. Participants will be made aware, in advance, of the nature of this review and that they can withdraw from the process at any time. Participants will be informed before the interview of the topics areas that are likely to be covered. They will also be assured that the information they share will be treated as confidential and that they will not be identifiable in any outputs from this work. The interviewer will be an expert clinician with experience in the disease area and in managing difficult conversations with patients. Again, where appropriate, participants will be signposted to further counselling and to the PHA charity support network.

To date, the studies of exercise in PH have looked closely at the safety of patients and have found that there have been only a very small number of minor incidents; for example someone becoming dizzy when they are on an exercise bike.
In our service evaluation of the well-being review, we found no safety problems.
We will ensure that participants are aware that they can withdraw from the study at any time and that this will, in no way, affect the clinical care that they receive.
As part of the well-being review, patients will be given information on how to exercise safely and what to do if they have any illnesses or injuries.

The well-being review will assess for risk of exercise in individual patients and that assessment will be considered when offering them the most suitable rehabilitation service. Community-based rehabilitation programmes also all have their own local risk assessment processes and will be informed of any patient specific risks during the referral process. We will continually monitor and review feedback from patients and adverse events and will move to stop the study
prematurely if indicated by the data.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

(●) Yes ( ) No

If Yes, please give details of procedures in place to deal with these issues:

There is a possibility that some patients may find the conversations they have in the interviews or the well-being review to be upsetting or distressing - it may for example highlight to them the functional or physical limitations that they face as a result of their condition.

Participants will be informed in advance of the topics areas that are likely to be covered. They will also be assured that the information they share will be treated as confidential, and that they will not be identifiable in any outputs from this work. The interviewer will be an expert clinician with experience in the disease area and in managing difficult conversations with patients. Participants will be made aware that they can withdraw from the process at any time, including during the interview or review, and that they do not have to answer particular questions if they prefer not to.

We have worked closely with the patient charity of PH in the UK - PHA UK - in putting together this research. They have an ongoing relationship with the charity Anxiety UK, which allows for free advice or counselling for patients with PH. Information on this service will be made available to participants in the study through the PIS, and will be reinforced to any participants who appear particularly anxious or distressed during the process. Where necessary,

the study team would ask the participant permission to contact their GP to assess for any further necessary support or intervention.

The study team will actively review any incidents or particular distress to reflect on and apply learning that might inform future interaction with participants.

A24. What is the potential for benefit to research participants?

Participants in Part 1 of the study will have the opportunity to reflect on their rehabilitation and the changes it has made for them.

Participants in Part 2 will have an assessment of their rehabilitation needs and the opportunity to participate in rehabilitation programmes selected to suit their needs and goals.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

All rehabilitation interventions will be completed by the end of the study period, or will be ongoing under the supervision of local community teams. Any participants requiring additional rehabilitation follow-up after the study closes will continue to be supported by the clinical physiotherapy service at the study site

A26. What are the potential risks for the researchers themselves? *(if any)*

There is a risk of emotional distress to the researcher in challenging encounters with participants. The researcher is an experienced clinician with expertise in this area, however it is always the case that specific patients or situations can present a challenge. Existing professional networks and clinical supervision will be used for support in these situations.
The clinical researcher is a PhD student, so will also have the support the research supervisory team to address any issues that might arise.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? *For example, identification may involve a disease register, computerised search of social care or GP records, or review of medical records. Indicate whether this will be done by the direct care team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants for the Part 1 qualitative interviews will be identified from patient tracking and may include those who took part in a service evaluation that has previously been conducted of the well-being review at the study site as well as people engaged in ongoing clinical care. Patients who have completed rehabilitation will be screened to identify those who would be potential candidates for interview before they are approached to take part.

Potential participants for the Part 2 of the study will be identified from a clinical database of patients at the study centre, looking initially at when they started on their PH drug therapy, in line with the inclusion criteria. The records of these patients will then be checked by research nurses against records of upcoming clinic visits and screened for full inclusion criteria matching.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◉ Yes ○ No

Please give details below:
Patient clinical records will be reviewed to identify potential candidates.
These will only be accessed by the research physiotherapist and research nurses in the team.

Patient clinical records will be reviewed by the research physiotherapist as part of the initial assessment and final assessment. This is to allow access to clinical outcomes and for safety purposes, to identify any changes or issues in the participants' clinical condition. The research physiotherapist is a member of the clinical care team.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants. *Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Clinical records will be reviewed and considered within the clinical area, following local Trust protocols for confidentiality.

All relevant clinical information will be transferred to research records, which will be held without identifiable personal information.

A patient log, cross referencing Study ID with personal identifiers will be held in a secured file.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

◯ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

◯ Yes ◉ No

A29. How and by whom will potential participants first be approached?

For Part 1 of the study
Prospective participants will be sent a letter informing them of the details of the study (Participant Information Sheet) and that they will be approached and invited to take part. A consent form will be included with the letter. One week after the letter is sent, prospective participants will receive a call from a research nurse to see if they have received the letter and if they have any questions about the study that they would like to be clarified. If they are happy to take part, then a date and time will be arranged for a telephone interview to take place. They will be asked to return a signed copy of the consent form, which must be received before the telephone interview can take place.

For Part 2 of the study
Prospective participants will be sent a letter 2 weeks prior to a routine clinic appointment informing them of the details of the study (Participant Information Sheet) and that they will be approached and invited to take part. One week after the letter to seek consent is sent, prospective participants will receive a call from a research nurse to see if they have received the letter and if they have any questions about the study that they would like to be clarified.

During their clinic visit, potential participants will be approached by a research nurse who review the details of the study with them and ask if they would be happy to take part. Informed consent will be obtained.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ◯ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

As described above in section A29, for Part 1 of the study, potential participants will receive a letter and telephone call from research nurses attached to the project but not directly involved in delivering the intervention. They will discuss

the PIS and study details with the potential participant and, if they are happy to participate, they will discuss the consent form with them, before advising them to complete it and return it to the study team once they consent to take part.

For Part 2 of the study, consent will be sought by the research nurses when potential participants attend clinic appointments. Potential participants will be asked if they understand the content of the PIS and have any outstanding questions clarified before informed consent is sought.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

In both Parts 1 and 2, participants will receive a letter outlining the details for the study and receive a follow up call from a research nurse 1 week later.
For participants in Part 1, they will be invited to consent to take part in the follow up phone call 1 week after receiving the initial information.
For participants in Part 2, they will attend clinic approximately 1 week after receiving the follow up phone call and will be offered the opportunity to consent to take part in this study at that point

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

○ Yes
◉ No
○ Not Known

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

An interpreter will be used, if necessary, to support the consent and research process for patients for whom English is a second language. Large text format will be provided for any person with a visual impairment.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Due to the small number of participants in this study, participants will be contacted individually by the research team, should such a need arise.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
○ The participant would continue to be included in the study.
○ Not applicable – informed consent will not be sought from any participants in this research.

○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- ☑ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☑ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☑ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:
Publication of direct quotations from interview participants will be anonymised.
University computers are encrypted.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Sheffield Hallam University computers are encrypted and the University has a dedicated Research Store that is used to store research data. Data will only be shared with the supervisory team via the University's Research Store. The University Research Store has a firewall and data are backed up to two remote locations. Other storage devices such as a USB stick will be encrypted and are supplied by the University IT Department. Audio files will be uploaded to the University Research Store and deleted from the recorder as soon as the files have been uploaded. Audio files will be transcribed and transcriptions will be anonymised. The unique code potentially linking the participant to the anonymised data will be stored on the Sheffield Teaching Hospitals NHS Foundation Trust hard drive until the end of the research project; the research physiotherapist will be responsible for its removal.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The NHS Code of Confidentiality will be followed and existing best practice. Patients will be provided with information about how their data will be used and anonymised to ensure confidentiality. Participants will be informed of the boundaries of confidentiality; that is, what will not be held as confidential, for example, if during the study the participant disclosed information which had the potential to cause risk or harm to the participant or others

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The research nurses will have access to participants' clinical records for screening and identifying of potential participants.
The research physiotherapist, will have access to the participants' clinical records for assessment at their well-being review and ongoing support and monitoring during their rehabilitation.
The Academic Supervisory Team will only have access to the anonymised data during the study.
Participants will sign a consent form which will state they have read the participant information sheet which explains how data will be accessed and by whom, and understood the information it contains.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be generated on NHS Trust premises and analysed on University Computers by the research physiotherapist. Non-identifiable patient information will be transferred by an encrypted USB stick. Data will be backed up by the University Research Store.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Professor	Karen	Sage
Post	Professor for AHP Research		
Qualifications			
Work Address	F611 Robert Winston Building		
	11-15 Broomhall Road		
	Sheffield		
Post Code	S10 2BP		
Work Email	k.sage@shu.ac.uk		
Work Telephone	01142255809		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
Sheffield Hallam University policy is to preserve primary data for 10 years (after the final publication) or as long as the external funder requires. The data stored will not be participant identifiable data.

A44. For how long will you store research data generated by the study?

Years: 10
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

Research data will be registered and stored on Sheffield Hallam University Research Data Archive (SHURDA). Access to the data will only be within the supervisory team. Data will be stored for 10 years following access by a third party including any publisher of the research. This means if someone was to request access after nine years it would be stored for another 10 years after this request. Audio files will be transcribed and anonymised transcribed data will be stored for 10 years following access by a third party.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

○ Yes ◉ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The research will be registered on the host institution Sheffield Hallam University database and clintrials.gov

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

☑ Peer reviewed scientific journals
☐ Internal report
☑ Conference presentation
☐ Publication on website
☑ Other publication
☐ Submission to regulatory authorities
☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
☐ No plans to report or disseminate the results
☐ Other (please specify)

We will work with PHA UK, the patient association for PH in the UK, to share the findings with patients in the most suitable method - they have a regular magazine, a web page, social media accounts and a patient conference.

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

All data will be anonymised before analysis and reporting take place. Where direct quotes might be used, e.g. in presentation of the qualitative data, we will ensure that they are not identifiable or attributable to any specific participant.

A53. Will you inform participants of the results?

○ Yes ◉ No

Please give details of how you will inform participants or justify if not doing so.
Participants will be able to access the results of the study through the dissemination as described in A51. We do not plan to directly inform participants of the results, however we will be happy to do so for individual participants if they specifically ask.

5. Scientific and Statistical Review

A54-1. How has the scientific quality of the research been assessed? *Tick as appropriate:*

☑ Independent external review
☐ Review within a company
☐ Review within a multi−centre research group

☐ Review within the Chief Investigator's institution or host organisation

☐ Review within the research team

☑ Review by educational supervisor

☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
This research has been developed under the review of the PhD students supervisory team.
An earlier version of the research was submitted to two external funding organisations (NIHR and BHF). Neither application was successful, however the feedback from reviewers has been incorporated into a revised protocol which forms the basis of this application.
The current application is currently under review by the British Heart Foundation for their Nursing and AHP Fellowship, pending feedback which is due in February 2020

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☐ Review by independent statistician commissioned by funder or sponsor

☐ Other review by independent statistician

☐ Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☐ Review by a statistician within the research team or multi-centre group

☑ Review by educational supervisor

☑ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Ranjit	Lall
Department	Warwick Medical School Clinical Trials Unit		
Institution	University of Warwick		
Work Address			
Post Code	CV4 7AL		
Telephone	02476574649		
Fax			
Mobile			
E-mail	R.Lall@warwick.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

As this is a feasibility study, feasibility outcomes will be used as follows:
- recruitment target of 4-8 patients per month

- retention rate to 6-month follow-up
- completion rates of outcome measures.

A58. What are the secondary outcome measures? *(if any)*

In Part 2 of the study, we will capture participant screening log data, drop-out rates and reasons for withdrawal. Patient outcomes measures will also be used in Part 2 of the study. The final set will be determined after the completion of Part 1 of the study but may include measures of fatigue, anxiety or levels of physical activity.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	34
Total international sample size (including UK):	34
Total in European Economic Area:	34

Further details:
The numbers above are for Part 2 of the study.
For Part 1, qualitative interviews, purposive sampling will be used and interviews will be conducted until data saturation has been reached. This is likely to be in the region of 10-15 interviews.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Consecutive sampling will be used to recruit patients from PH outpatient clinics at Sheffield Teaching Hospitals. We will aim for sample sizes of between 24 and 50 as recommended for feasibility studies, to support calculations for full trial sample size and recruitment rates.

A61-1. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Participants will be randomised to control or intervention groups immediately after baseline assessments. Random permuted blocks with stratification on WHO functional class will be used, to ensure balance across the groups. As this is a small feasibility study, services of a clinical trials unit will not be required; a standalone randomisation service will be used.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Part 1 - qualitative interviews. A framework approach will be used to analyse the data from the interviews conducted in Part 1. This will consist of five key stages: familiarisation with the data through repeated reading to understand its breadth and depth; identifying a thematic framework; indexing and sorting of categories into broader themes; charting data by theme in order to allow analysis as a whole; interpretation and write up to tell the story of each theme and the data as a whole, supported by extracts from the original data.

Part 2 - The analysis of data from Part 2 will be descriptive and focus on confidence interval estimation. We will examine: feasibility of recruitment to inform any main trial; decision on primary endpoint for main trial; number/characteristics of eligible patients approached for the study; reasons for refused consent; participant attrition rates; number of adverse incidents

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Professor	Ranjit	Lall
Post	Professor of Clinical Trials		
Qualifications			
Employer	University of Warwick		
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	Coventyr		
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Work Email	r.lall@warwick.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Iain	Armstrong
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Post Code	S10 2JF		
Telephone	+441142711719		
Fax			
Mobile			
Work Email	Iain.Armstrong@sth.nhs.uk		

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	Sheffield Teaching Hospitals NHS Foundation Trust
Given name	Dipak
Family name	Patel
Address	Clinical Research & Innovation Office, Room D49, D Floor, Royal Hallamshire
Town/city	Sheffield
Post code	S10 2JF
Country	UNITED KINGDOM
Telephone	01142265945
Fax	
E-mail	dipak.patel12@nhs.net

A65. Has external funding for the research been secured?

Please tick at least one check box.

- ☐ Funding secured from one or more funders
- ☑ External funding application to one or more funders in progress
- ☐ No application for external funding will be made

What type of research project is this?

- ○ Standalone project
- ○ Project that is part of a programme grant
- ○ Project that is part of a Centre grant
- ◉ Project that is part of a fellowship/ personal award/ research training award
- ○ Other

Other – please state:

Please give details of funding applications.

Organisation	British Heart Foundation
Address	Research Funds Department Greater London House 180 Hampstead Road
Post Code	NW1 7AW
Telephone	02075540434
Fax	
Mobile	
Email	research@bhf.org.uk

Funding Application Status: ○ Secured ◉ In progress

Date Funding decision expected: 14/02/2020

Amount: 134882

Duration

Years: 2
Months: 6

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
British Heart Foundation Fellowships for Nurses and Allied Health Professionals

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

◯ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

◯ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Ms	Aimee	Card
Organisation	Sheffield Teaching Hospitals NHS Foundation Trust		
Address	Clinical Research & Innovation Office, Room D49, D Floor		
	Royal Hallamshire Hospital, Glossop Road, Sheffield		
Post Code	S10 2JF		
Work Email	aimee.card@nhs.net		
Telephone	01142265945		
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 02/03/2020
Planned end date: 02/05/2022
Total duration:
Years: 2 Months: 2 Days: 1

A71-1. Is this study?

◉ Single centre
◯ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study

Does this trial involve countries outside the EU?

◯ Yes ◯ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

[x] NHS organisations in England	1
[ ] NHS organisations in Wales	
[ ] NHS organisations in Scotland	
[ ] HSC organisations in Northern Ireland	
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Joint health and social care agencies (eg community mental health teams)	
[ ] Local authorities	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent (private or voluntary sector) organisations	
[ ] Educational establishments	
[ ] Independent research units	
[ ] Other (give details)	
Total UK sites in study:	1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

◯ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

As this is a PhD study, the research will be monitored the educational supervisory team. As part of the university internal monitoring process, the researcher completes an application for approval of research programme at six months, an application for confirmation of PhD registration at end of 12 months, an interim monitoring plan at end of 36 months and Thesis Submission for examination end of 60 months.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

The study steering group will act as a data monitoring committee. They will review any adverse events or other safety issues from the trial.

Previous studies of exercise in PH have looked closely at the safety of patients and have found a small number of minor incidents; for example someone becoming dizzy when they are on an exercise bike. Such incidents will be monitored but would not be considered criteria for electively stopping the trial.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The number and frequency of adverse and serious adverse events will be monitored and used as criteria to stop the trial prematurely.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (NHS sponsors only)

☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS

sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ○ No ◉ Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email Qualification (MD...)	Carol Keen carol.keen@nhs.net BEngBComm, BSc, Msc
	Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST		
	Address	NORTHERN GENERAL HOSPITAL HERRIES ROAD SHEFFIELD SOUTH YORKSHIRE	Country	
	Post Code	S5 7AU		
	Country	ENGLAND		

Appendix 3 Feasibility Study Interview Topic Guide

- Welcome and introduction
    - > OK to record interview?
    - > Cover any practical details e.g. if you need a break, are you OK for time

- The purpose of this interview is to talk about the rehabilitation that you have had following you diagnosis and treatment for pulmonary hypertension. We would like to hear about your experience of taking part in rehabilitation to understand how you found it, whether it made any difference to you, and whether there was anything about it that went particularly well or could have been improved. We would like to hear about this from you so that we can use your information to help us in designing future research studies of rehabilitation in PH.

Q1 - You have had some rehabilitation in the past, can you tell me more about it?

Prompts:

- when did it happen
- how long for
- what kind of thing did you do
- where was it?

Q2 - How did you find your rehabilitation - can you tell me more about the experience?

Prompts:

- supportive people?
- social aspect?
- learned a lot?
- enjoyed it?
- was there a long wait
- were staff knowledgeable about PH
- did you feel safe?
- too easy or to hard?
- was it easy to get to?
- did it take up a lot of your time?

Q3 - Did it make a difference to you?

Prompts:

- did the rehab group measure your outcomes? Were there any difference?
- were you able to walk further? or do more?

- what about fatigue or tiredness?
- did it make a difference to how you feel about yourself?
- about your PH?
- confidence?
- about the future?
- are you still exercising or doing more?
- have your family noticed a difference in you?
- has it made a difference to them?

Q4 - Before your rehabilitation you had a well-being review with the physiotherapist - how did you find that?
Prompts:

- well timed
- interesting
- explorative or intrusive
- too long or too short
- felt pressurised or relaxed

Q5 - if another patient asked you about your rehabilitation, what would you tell them?

Prompts:

- any changes to recommend
- would you recommend it
- would you do it differently/
- could it be delivered differently?

- Closing

> Thank you
> Do you have any questions?
> Feel free to contact me if you have any concerns or further questions after the interview

Appendix 4 Feasibility Study Health Research Authority Favourable Opinion

NHS
Health Research Authority

Yorkshire & The Humber - South Yorkshire Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 0207 1048091

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

27 April 2020

Ms Carol Keen
Clinical Specialist Physiotherapist
Sheffield Teaching Hospital NHS Foundation Trust
Room M40a, Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear Ms Keen

Study title:	**Investigating the feasibility of a randomised controlled trial of a physiotherapy well-being review in patients with pulmonary hypertension.**
REC reference:	**20/YH/0096**
Protocol number:	**STH20898**
IRAS project ID:	**273955**

Thank you for your letter of 14 April 2020, responding to the Committee's request for further information on the above research [and submitting revised documentation].

The further information has been considered on behalf of the Committee by the Chair.

A Research Ethics Committee established by the Health Research Authority

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a **favourable ethical opinion** for the above research on the basis described in the application form, protocol and supporting documentation [as revised], subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Registration is a legal requirement for clinical trials of investigational medicinal products (CTIMPs), except for phase I trials in healthy volunteers (these must still register as a condition of the REC favourable opinion).

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We will audit these as part of the annual progress reporting process.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites listed in the application subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper		09 April 2020
GP/consultant information sheets or letters [GP Letter]	1.0	06 November 2019
Initial Assessment for REC [HRA Assessment for REC]		
Interview schedules or topic guides for participants [Interview Topic Guide]	1.0	27 November 2019
IRAS Application Form [IRAS_Form_25022020]		25 February 2020
IRAS Checklist XML [Checklist_25022020]		25 February 2020
Letters of invitation to participant [Letter of invitation stage 1]	1.0	12 February 2020
Other [Consent Form Stage 2]	1.0	06 November 2019
Other [Participant Information Stage 2]	1.0	04 December 2019

Appendix 5 Community-based field walking tests

Background

Through the COVID pandemic we have seen an increase in the number of non-face-to-face clinics. Once we are through the pandemic it is unlikely that we will return to previous levels of face to face activity, instead settling on pathways that offer a mix of FTF and NFTF appointments to best meet clinical needs.

While NFTF appointments have some clear benefits for patients and clinicians they do not provide objective clinical assessment that is used in FTF assessments.

Once aspect of this is walking tests – Incremental Shuttle Walk Test (ISWT and six-minute walking tests (6MWT) - which are widely used to determine exercise capacity in patients with PH.

Apps are available that are either specifically designed to be used to support patients in conducting their own 6MWT at home or which could be used for this function. No Apps have been identified to support ISWT in patients.

The purpose of this pilot study was to examine these Apps to determine their suitability for use with patients with PH.

Overview of Apps

An internet search was conducted for Apps which were designed to measure walking distance or to capture a timed walk. The following were identified.

	Strava	**My Heart Counts**	**Timed Walk**	**iWalkAssess**
Target Patient population	General population	Cardiovascular disease	General health use	Stroke
Intended End user	Patient	Patient	Patient	Heath Professional
Ease of Use	Account set up and login required	Account set up, login and registration to the MyHeart Counts project required	No login required	Account set up and login required

Platform	iphone, Android	iphone, Android	iphone, Android	iphone, Android
Cost	Free and subscription options	Free	Free	Free

Since the focus of this investigation was apps which could be used by patients to conduct their own 6MWT, the iWalkAssess app was not considered further as it is designed for use by health professionals in recording patient walk tests.

Home Indoor Walk Tests

I carried out a series of 6MWD at home, following the process as below:

- Identified the longest straight-line space in the house without moving furniture.
- Measured the available distance (allowing space to turn)
- Walked for 6 minutes keeping a tally of the number of laps
- Calculated the distance walked from the tally count, and also recorded App measured distance for each walk
- Conducted a 6MWD in standard conditions on 15m track, recording a distance of 582m

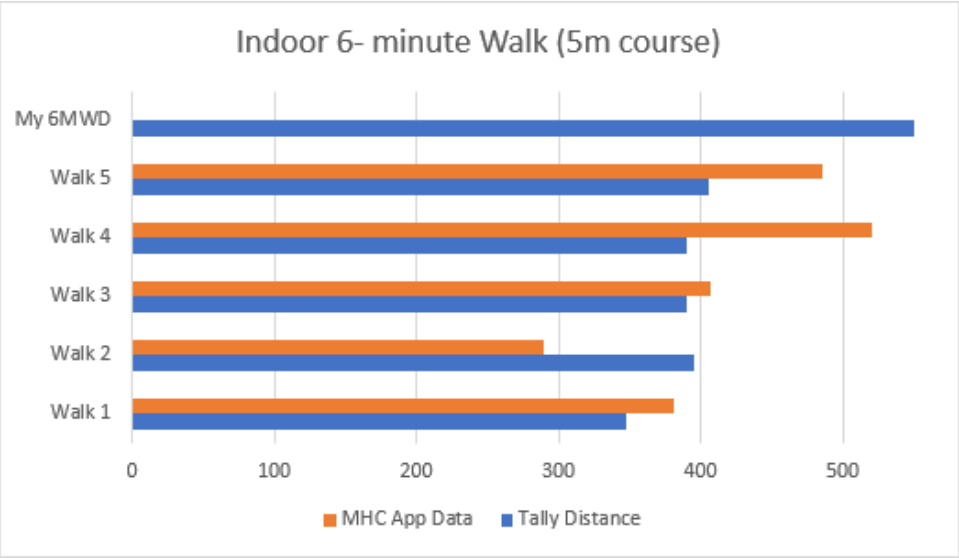
Findings

- MyHeart Counts was the only App which recorded any data while I was walking. Strava and Timed Walk were not able to detect a satellite signal in the house so did not record the walks.
- The longest distance I could use in my house was 5m – 6MWD should by standard be walked over 30m, although 15m is more commonly used
- Despite my best efforts not all of the walks were completed without general household interruptions – children, pets, postman etc
- I found it hard to keep count of the laps over 6 minutes, so used a second person for this role

- The range of values for the MHC app was considerable: 289-520m
- This is particularly significant when set against the minimum clinically important distance for 6WMD in pulmonary hypertension which is 33m

Data

	Indoor walks		
	Tally Distance	MHC App Data	Difference
Walk 1	347	381	-34
Walk 2	395	289	106
Walk 3	390	407	-17
Walk 4	390	520	-130
Walk 5	406	485	-79



Outdoor Walk Tests

The purpose of this was to determine the accuracy of the walk Apps when conducting an outdoor walk. This would be a feature of their measure of time and of distance. Since I trusted the apps to measure 6 minutes accurately, it was therefore most important to determine whether the apps could accurately measure outdoor distance.

I had no means to accurately measure a specific distance outdoors. Instead I carried out walked for 6 minutes and identified clear landmarks for the start and end of the walk (front door and lamppost) that I could use to make sure I walked the same distance each time.

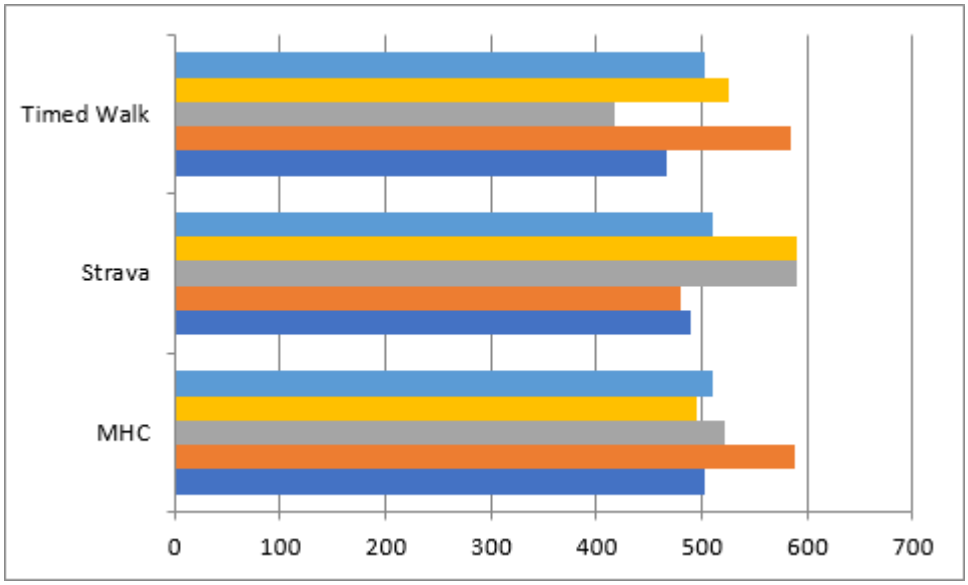
I then conducted a series of walks using the Apps, ensuring I walked from my house to the landmark on each occasion.

Findings

- All of the Apps were able to measure a distance outdoors
- The route used was on pavement in a quiet residential area, with minimal incline or decline
- While Strava was able to operate as a background app, MyHeart Counts and Timed Walk were not. This meant that they would stop measuring if another app was activated during the walk. This seemed to include notifications and messaging, so on some occasions no distance was recorded during the walk
- As with the indoor walks, variability was significant, especially when considered against the minimum clinically important distance for 6WMD in pulmonary hypertension of 41m

Data

	MHC	Strava	Timed Walk
Walk 1	502	490	466
Walk 2	588	480	585
Walk 3	522	590	417
Walk 4	496	590	525
Walk 5	510	510	502



Summary

- Repeatability
    - Variability between and within app readings
- Reliability
    - Difference from gold standard measure 6MWD
    - Apps didn't always measure the walk completed
- Accessibility
    - Need smart phone (and be able to use it)
    - Able to walk outside

Appendix 6 PERPSIRE Study NHS IRAS Form

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Pulmonary Hypertension and measurement of exercise capacity

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR Medtech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

( ) Yes (•) No

The NIHR Clinical Research Network (CRN) provides researchers with the practical support they need to make clinical studies happen in the NHS in England e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, information from your IRAS submission will automatically be shared with the NIHR CRN. ***Submission of a Portfolio Application Form (PAF) is no longer required.***

6. Do you plan to include any participants who are children?

◯ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

◯ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

◯ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ◯ No

Please describe briefly the involvement of the student(s):
The study is part of a PhD, the student will be the Chief Investigator with the support and guidance of their supervisory team

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ◯ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

◯ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

◯ Yes ◉ No

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Pulmonary Hypertension and measurement of exercise capacity

Please complete these details after you have booked the REC application for review.

REC Name:
East of England - Cambridge Central Research Ethics Committee

REC Reference Number:
21/EE/0067

Submission date:
12/03/2021

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Pulmonary Hypertension and measurement of exercise capacity remotely: the PERSPIRE study

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title	Forename/Initials	Surname
	Ms	Carol	Keen
Address	Room M40a, Royal Hallamshire Hospital		
	Glossop Road		
	Sheffield		
Post Code	S10 2JF		
E-mail	carol.keen@nhs.net		
Telephone	01142268864		
Fax			

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
PhD

Name of educational establishment:
Manchester Metropolitan University

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title	Forename/Initials	Surname
	Professor	Karen	Sage
Address	Brooks Building		
	53 Bonsall Street		
	Manchester		
Post Code	M15 6GX		
E-mail	k.sage@mmu.ac.uk		
Telephone	01612472000		
Fax			

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Ms Carol Keen	☑ Professor Karen Sage

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- (•) Student
- ( ) Academic supervisor
- ( ) Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Ms	Carol	Keen
Post	Clinical Specialist Physiotherapist		
Qualifications	MSc, Bsc (Phsyiotherapy), BEngBComm, MCSP		
ORCID ID	0000 0001 7803 1235		
Employer	Sheffield Teaching Hospital NHS FoundationTrust		
Work Address	PVDU, M Floor		
	Glossop Road		
	Sheffield		
Post Code	S10 2JF		
Work E-mail	carol.keen@nhs.net		
* Personal E-mail	carol.keen@nhs.net		
Work Telephone	01142268864		

* Personal Telephone/Mobile 07790588031

Fax

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Miss	Sarah	Birchall
Address	Clinical Research & Innovation Office		
	Glossop Road		
	Sheffield		
Post Code	S10 2JF		
E-mail	sarah.birchall4@nhs.net		
Telephone	01142713910		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	STH21477
Sponsor's/protocol number:	STH21477
Protocol Version:	1.0
Protocol Date:	15/02/2021
Funder's reference number (enter the reference number or state not applicable):	Not applicable
Project website:	Not applicable

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

(●) Yes ( ) No

Please give brief details and reference numbers.
Sheffield Teaching Hospitals holds a biobank for patients with pulmonary hypertension (REC Reference Number 18/YH/0441) which allows for data sharing with other studies.
We may request access to information from the biobank for patients in this study - we would do this through the

eastablished protocols for the biobank.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Hospital based exercise tests are routinely used in patients with pulmonary hypertension to assess functional ability and disease progression over time. We are seeing a greater emphasis on non-face-to-face clinical assessments, where such tests cannot be conducted. It is important to identify alternative test which can be used to support clinical decision making.
Aim
To test the safety and efficacy of the 1-minute sit-to-stand test in patients with pulmonary hypertension.
Methods
A sample of 75 patients attending hospital appointments will carry out an Incremental Shuttle Walk Test, followed by a 1 minute sit-to-stand test after a 30 minute rest. Data will be analysed for safety and comparability between the 2 tests.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Participants will be undertaking physical activity while performing the 1MSTS test. This will be under the supervision of the clinician performing the test, with easy access to clinical facilities in the event of the participant becoming unwell. Clinical observations (heart rate, blood pressure, oxygen saturations) will be taken before and after both tests and other relevant medical data will be reviewed from their medical records, if required.

We anticipate the likelihood of patients becoming unwell during the testing to be low. Studies to date of exercise rehabilitation in PH have looked closely at the safety of patients and have found that there have been only a very small number of minor incidents; for example someone becoming dizzy when they are on an exercise bike.

Over the last 5 years SPVDU has conducted approximately 2000 ISWT tests per year. Across that time period there have been <10 events where the assessor needed assistance, or the patient required further treatment.

This study was reviewed by the Yorkshire and the Humber - South Yorkshire Panel on 28/1/21 REC Reference REC reference 21/YH/0021 and received an Unfavourable Opinion.

This issues raised by the panel have been addressed as follows:

Comment 1
The Committee stated that Phase 2 of the study contained a number of safety monitoring issues that would not be available in the home setting, ie use of oxygen , observation of the stand test, no indication of the number of adverse events expected and issues from review by a data monitoring committee. The Committee stated that whilst the idea for the research was sound, there were too many undetermined factors for Phase 2, especially regarding safety of participants, which would have to be given before the REC could give an opinion on that aspect of the research. The Committee explained that Phase 1 of this proposal must be submitted as a separate application to Phase 2. Phase 2 could then be submitted once the results have been determined from Phase 1.

Response 1
Phase 2 of the study has been removed from the application.

Comment 2
The Committee required that consideration be given to allowing participants to have as long as possible to decide on whether to participate in the study.

Response 2
Processes and timings for consent have been revised to refelct this.

Comment 3
More information on the storage arrangements of data obtained in the study, ie clinical observations (heart rate, blood pressure, oxygen saturations) would be taken before and after both tests (for hospital sample) and that other medical data would be accessed from their medical records.security.

Response 3
The application has been revised to explain in more detail the data security processes in place at the institutions involved in the study

Comment 4
The Participant Information Sheet (Part 1) should state that

Response 4
The Participant Information Sheet has been revised as suggested.

Comment 5
It was noted that there was one Consent Form for both groups. For the home sample, a statement needed to be added regarding consenting to use of video recording.

Response 5
The removal of Part 2 of the study means that this no longer applicable.

HRA Assessment Comments
Comment 1
Please explain in Part 2 PIS on what platform the video call will take place. Will you audio or video record this call? If so, please explain in the PIS who will have access to the audio / video recordings, where they will be stored, for how long, and at what point they will be deleted and how. Audio and video recordings are by their very nature, identifiable so this information should be explained fully in the PIS to allow informed consent.

Response 1
This is no longer relevant as Part 2 has been removed from the study

Comment 2
The MMU logo is on the PIS, along with MMU specific data protection wording however Sheffield Teaching has been listed as the sponsor of the study and the application has been signed off by Sheffield Teaching's sponsor representative. Please confirm this is correct and clarify the role of MMU in this study. Or should MMU be the sponsor for the study?

Response 2
STH is the sponsor for the study. The data protection wording has been changed in the PIS to reflect this.

Comment 3
If Sheffield Teaching is the sponsor of the study, is there a contract in place for MMU to process the data on behalf of the sponsor?

Response 3
A fully executed Data Sharing Agreement will be in place prior to the sharing of data between STH (Sponsor) and Manchester Metropolitan University (Educational establishment). Only pseudo-anonymised data will be shared with the educational establishment.

Comment 4
If Sheffield Teaching Hospitals NHS Foundation Trust are the sponsor for the study, they must be classed as the data controller. Please remove from the PIS that MMU is the data controller, as well as any MMU specific GDPR wording.

Comment 4
The IRAS from has been amended to change the data controller to STH and the wording in he PIS has been amended accordingly.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply:*

- ☐ Case series/ case note review
- ☐ Case control
- ☑ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☐ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

Is the 1-minute sit-to stand test safe in patients with pulmonary hypertension and does it correlate with other tests of exercise capacity?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

NA

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Pulmonary hypertension (PH) is a progressive condition affecting the circulation to the lungs from the heart. It is a rare condition and Sheffield Pulmonary Vascular Diseases Unit (SPVDU) is the largest of 7 adult specialist pulmonary hypertension centres, caring for 1900 patients, or 30% of the pulmonary hypertension patients treated in the UK.

Measures of how well patients tolerate exercise and their functional abilities are widely established in pulmonary hypertension. This includes hospital-based assessments such as Incremental Shuttle Walk Test (ISWT - a "beep" test which requires patients to walk progressively faster until they cannot continue) and 6-minute walking test (how far patients can walk in 6 minutes), which are included in international risk guidelines for PH.

At SPVDU patients attend clinic appointments at intervals ranging from 3 -12 months; an ISWT is conducted at every clinic visit and the results are used to monitor functional progress over time.

Clinical services in all areas, including pulmonary hypertension, are being required to develop and change in response to the COVID-19 pandemic. This has already seen a significant increase in the use of non-face-to-face assessments to support and manage patients with pulmonary hypertension, while avoiding the potential virus transmission risks of hospital attendance. There are additional benefits of non-face-to-face assessments for example in terms of reduced patient travel or parking. However, non-face-to-face assessments do not allow clinicians the quality of assessment that can be achieved with a face-to-face assessment, including the physical clinical tests that are used to support patient diagnosis and assessment, such as exercise tests.

It is highly likely that future pulmonary hypertension clinical services will combine face-to-face and non-face-to-face assessments. In this case an alternative to the exercise tests which can be used in a non-face-to-face setting must be identified to replace or complement the exercise tests currently used in hospital assessments.

The 1-minute sit-to-stand is a simple assessment in which patients are asked to stand repeatedly from a chair for 1 minute. It is a highly functional test of an activity commonly performed in daily life. It has been evaluated in healthy subjects and patients with different diseases.

The 1-minute sit-to-stand does not rely on the patient having access to equipment or technology and is therefore universally accessible and suitable for use in the home setting. It has recently been suggested for use in home assessment of COVID patients and patients with COPD.

The 1MSTS has not to date been tested on patients with pulmonary hypertension; this study aims to address this. This study will investigate the safety and comparability of the 1MSTS with hospital-based walking tests: if these are established then we would plan to conduct further research to investigate the safety, feasibility, efficacy acceptability of the test in the home setting, with a view to potentially incorporating the test into non-face-to-face clinical reviews within pulmonary hypertension services

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

This study will seek to establish the safety of the 1-minute sit-to-stand test and its comparability to the Incremental Shuttle Walk Test.

Participants will be recruited as part of their standard clinic visit to SPVDU. They will undergo their standard clinical Incremental Shuttle Walk Test. This test is a standard of clinical care and its essential to the patient assessment on their clinical visit and will therefore be conducted first in all cases.

They will be allowed a 30 minute rest before undertaking the 1-minute sit-to-stand test.

It is standard at SPVDU that patients undertake the Incremental Shuttle Walk Test without supplemental oxygen – standardised protocols allow for this if repeat tests follow the same procedure. Patients are advised that they should stop the activity when they feel they can no longer continue. The same protocol will be adopted for the 1-minute sit-to-stand test.

Clinical observations (heart rate, blood pressure, oxygen saturations) will be taken before and after both tests. Heart rate and oxygen saturations will be monitored during both tests. Patient reported measures of breathlessness and perceived exertion will be recorded on completion of both tests.

Adverse events e.g. dizziness, syncope or the participant becoming unwell be recorded. Adverse event data will be monitored and analysed to determine the safety of the 1MSTS test.
To assist in the planning or potential next stages of the study, participants will be asked if they have access to equipment that would support home monitoring e.g. tape measure, BP monitor, pulse oximeter, weighing scales, video calling.

Data collected during the testing will be analysed, along with other routinely collected clinical data to determine the comparability of the 1MSTS test with with ISWT and other clinical features.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
Service Users have been involved in developing the study to date, and we will continue to seek their support throughout.

Identifying the Research Topic
This protocol has been developed in collaboration with the Pulmonary Hypertension Association (PHA UK), the patient charity for pulmonary hypertension (PH) in the UK. PHA UK is working with clinical providers to represent patient views through service redevelopment following the COVID-19 pandemic. They recognise the need for increased NFTF consultations, but are keen to ensure excellent patient experience.

Study Development
All participant information has been written in collaboration with patient representatives, who have checked it is understandable and non-coercive. Patient representatives from the Steering Group will help to troubleshoot any recruitment issues should they arise.

Study Management
Two patient representatives will be invited to join the study steering group. We recognise the burden of the disease on patients, and that fatigue is a common symptom. To support them in participating in the steering group we will conduct meetings remotely.

Dissemination
Patient representatives will be involved in review of the study findings and dissemination, particularly where this is aimed at patients and their families or carers. They will help to identify findings key to patients; suitable communication channels; appropriate language and content for communication. PHA UK has a quarterly magazine, annual patient conference and wider social media presence which would offer suitable channels for dissemination. There may be the potential to draw on the study findings to collaboratively develop a comprehensive guide to rehabilitation for the patient group.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☐ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal

☐ Paediatrics
☐ Renal and Urogenital
☐ Reproductive Health and Childbirth
☑ Respiratory
☐ Skin
☐ Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Adults aged >= 18 with a diagnosis of pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH)

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Mobility significantly impaired by musculoskeletal or neurological co-morbidities; learning difficulties or cognitive impairment that would prohibit informed consent.

Recent episodes of Surgery (Abdominal, Thoracic, Eye, Neuro) <2months; Heart Attack/Stroke <8weeks; Chest Pain/Haemoptysis (cough up blood) <2weeks; Pneumothorax <8weeks; Pulmonary Embolism (blood clot) within the last 2 weeks;
Generally feeling unwell: vomiting/diarrhoea; Recent syncope (fainting/blackouts) <4weeks; Significant mobility issues causing pain or severely limiting mobility; Severe Hypertension - Resting BP > 220/120 (either or both values); Hypotension (low BP) <90/60 with symptoms (dizziness/lightheaded); Significant resting tachycardia > 130bpm

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Consent approach	1	0	15 minutes	During their clinic visit to Sheffield Pulmonary Vascular Diseases Unit, potential participants will be approached by a member of the research team (who is also a member of the clinical care team) who will inform them about the study and give them a Participant Information Sheet. Participants will be given as long as required to read the PIS, to ensure they feel they have sufficient information and have asked all questions relating to the research. If they determine that they would like to join the study they will be supported in completing the study consent form.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
1 minute sit-to-stand test	1	0	30 minutes	Conducted by a member of the research team (who is also a member of the clinical care team) in the SPVDU clinical setting

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

◯ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

This is a single event study so the participant will be in the study for only one day

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Participants will be undertaking physical activity while performing the 1MSTS test. This will be under the supervision of the clinician performing the test, with easy access to clinical facilities in the event of the participant becoming unwell.

It is standard at SPVDU that patients undertake the Incremental Shuttle Walk Test without supplemental oxygen – standardised protocols allow for this if repeat tests follow the same procedure. Patients are advised that they should stop the activity when they feel they can no longer continue. The same protocol will be adopted for the 1-minute sit-to-stand test.

Clinical observations (heart rate, blood pressure, oxygen saturations) will be taken before and after both tests. Heart rate and oxygen saturations will be monitored during both tests. Patient reported measures of breathlessness and perceived exertion will be recorded on completion of both tests.

We anticipate the likelihood of patients becoming unwell during the testing to be low. Studies to date of exercise rehabilitation in PH have looked closely at the safety of patients and have found that there have been only a very small number of minor incidents; for example someone becoming dizzy when they are on an exercise bike.
Over the last 5 years SPVDU has conducted approximately 2000 ISWT tests per year. Across that time period there have been <10 events where the assessor needed assistance, or the patient required further treatment.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◯ Yes ◉ No

A24. What is the potential for benefit to research participants?

There are no benefits to the participant from taking part in this study.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Not applicable

A26. What are the potential risks for the researchers themselves? *(if any)*

Not applicable

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified from lists of patients due to attend PH clinics at SPVDU. The clinical records of these patients will be checked by the research physiotherapist and screened for inclusion and exclusion criteria matching.

The research physiotherapist is also a member of the direct care team.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
Patient clinical records will be reviewed to identify potential candidates and extract relevant clinical information.

These will only be accessed by the research physiotherapist who is also a member of the direct care team.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Clinical records will be reviewed and considered within the clinical area, or via secure electronic clinical records. Local Trust protocols for confidentiality will be followed.

All relevant clinical information will be transferred to research records, which will be held without identifiable personal information. Each research record will be allocated a Study ID.

A patient log, cross referencing Study ID with personal identifiers will be held in a secured site file within STH. This will be the only record which links personally identifiable information to the anonymised study data.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

Potential participants will be approached and invited to join the study during their routine clinic visit to SPVDU. The approach will be by the research physiotherapist, a member of the research team (who is also a member of the direct care team).

Patients under the care of the research physiotherapist during the period of recruitment to the study will not be approached for recruitment, to ensure there is no element of coercion.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

During their clinic visit to Sheffield Pulmonary Vascular Diseases Unit, potential participants will be approached by a member of the research team (who is also a member of the direct care team) who will inform them about the study and give them a Participant Information Sheet.

Participants will be given as long as required to read the PIS to ensure they feel they have sufficient information and have asked all questions they have relating to the research. If they determine that they would like to join the study they will be supported in completing the study consent form.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Participants will be given the Participant Information Sheet on arrival at their clinic visit. They will be given as long as possible to read the PIS, to ensure they feel they have sufficient information and have asked all questions relating to the research, before deciding whether to take part in the study.

If they feel that have insufficient time to decide whether they wold like to take part in the study then they will be offered the opportunity to take the information home with them and they would be welcome to join the study if they attend a routine clinic appointment at a later date while the study is still recruiting.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

◯ Yes

◯ No

◉ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

There are a number of ongoing studies with patients with PH at SPVDU. We do not anticipate that participation in other studies would be an obstacle to participation in this study and vice versa. Should this arise we would discuss any patient concerns on an individual basis.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

An interpreter will be used, if necessary, to support the consent and research process for patients who are unable to sufficiently comprehend the study information in English.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Involvement in this study is a single event, therefore there is no continued participation for individuals involved.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

◯ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

◯ The participant would continue to be included in the study.

◯ Not applicable – informed consent will not be sought from any participants in this research.

◯ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

As involvement in this study is a single event this situation is unlikely to arise.

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

☐ Access to medical records by those outside the direct healthcare team

☐ Access to social care records by those outside the direct social care team

☑ Electronic transfer by magnetic or optical media, email or computer networks

☐ Sharing of personal data with other organisations

- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
Clinical records (paper and electronic) within Sheffield Teaching Hospitals will be accessed by the research physiotherapist (who is also a member of the direct care team) to screen potential participants.

Each participant will be allocated an Study ID. A participant log, cross referencing Study ID with personal identifiers will be held in a secured site file within STH. This will be the only record which links personally identifiable information to the pseudo-anonymised study data.

Pseudo-anonymised study data, identifiable by only by Study ID will be collected and recorded by the research team. Relevant clinical information will be included from participants' clinical records and captured in a pseudo-anonymised manner.

The pseudo-anonymised study data will be generated and held within Sheffield Teaching Hospitals, separately to any identifiable data for the duration of the study.

Copies of the pseudo-anonymised study data will be transferred to university computers for statistical analysis and review by the PhD student's supervisory team.

A37. Please describe the physical security arrangements for storage of personal data during the study?

All paper records containing personal data will be held in a locked drawer in a lockable office at Sheffield Teaching Hospitals. These will be destroyed at the end of the study. Electronic records will be stored securely in password protected files on secure NHS servers at Sheffield Teaching Hospitals in line with local data management policies. Access to these files will be restricted to the research team. STH NHS FT will then archive the study anonymously for a minimum of 5 years after the end of the trial.

The only data that will be stored on University computers will be pseudo-anonymised study data. This will be stored in password protected files on secure university servers. This data will only be shared with members of the student's supervisory team.

No study data will be stored on USB sticks or personal devices.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The NHS Code of Confidentiality will be followed and existing best practice.

The participants' data will be pseudo-anonymised and no identifiable information will be kept with the actual study data.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Relevant sections of participants' medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to taking part in this research. Some personally identifiable information (name, address, date of birth) will be collected and may be looked at by members of the research team, direct care team or individuals from regulatory authorities, but will be kept separate from other data collected during the study. Consent will be sought for the above.

The Academic Supervisory Team will only have access to pseudo-anonymised data during the study.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Pseudo-anonymised data generated the by study will be analysed on University computers by the research physiotherapist.

Files will be transferred by secured transfer and held in password protected files on the the University's secure server. A fully executed Data Sharing Agreement will be in place prior to the sharing of data between STH (Sponsor) and Manchester Metropolitan University (Educational establishment). Only pseudo-anonymised data will be shared with the educational establishment.

Access will be limited to the student and supervisory team.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Ms	Carol	Keen
Post	Clinical Specialist Physiotherapist		
Qualifications			
Work Address	Room M40a, Royal Hallamshire Hospital		
	Glossop Road		
	Sheffield		
Post Code	S10 2JF		
Work Email	carol.keen@nhs.net		
Work Telephone	01142268864		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years
- ○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 5
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

Identifiable data will be destroyed upon the ending of the study.

Data will be archived for a minimum of 5 years in STH archiving facility in accordance with Sheffield Teaching Hospitals policy.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◯ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

◯ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

◯ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◯ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ◯ No

Please give details, or justify if not registering the research.
The research will be registered on the host University database and clintrials.gov

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [ ] Publication on website
- [x] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

We will work with PHA UK, the patient association for PH in the UK, to share the findings with patients in the most suitable method - they have a regular magazine, a web page, social media accounts and a patient conference.

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

All data will be anonymised before analysis and reporting take place.

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.
Participants will be able to access the results of the study through the dissemination as described in A51. We do not plan to directly inform participants of the results, however we will be happy to do so for individual participants if they specifically ask.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [ ] Review within the Chief Investigator's institution or host organisation
- [ ] Review within the research team
- [x] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
This research has been developed under the review of the PhD students supervisory team and by 2 independent peer reviewers as stipulated by the Sheffield Teaching Hospitals NHS Trust Research department

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor

☐ Other review by independent statistician

☐ Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☐ Review by a statistician within the research team or multi−centre group

☑ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Karen	Sage
Department			
Institution	Manchester Metropolitan University		
Work Address	Brooks Building		
	53 Bonsall Street		
	Manchester		
Post Code	M15 6GX		
Telephone	0161 247 2000		
Fax			
Mobile			
E-mail	k.sage@mmu.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The number of repetitions completed in the sit-to-stand test.

A58. What are the secondary outcome measures?*(if any)*

Walking test distance distance

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	75
Total international sample size (including UK):	75
Total in European Economic Area:	75

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Patients requiring face-to-face clinical review are attending PH clinics at SPVDU, with precautions in place to minimize COVID risks.
A stratified sample will be selected from these patients to capture patients with a range of exercise performance within three levels of ISWT: ≤ 180m, 190m – 330m, ≥ 340m.
Comparable studies of patients with COPD used a samples of 48 and 52 participants and identified correlation

coefficients with 6MWD of between 0.57 and 0.67. Based on these values, assuming Type I error rate=0.05 and Type II error rate=0.2 would indicate a sample size between n=22 (r=0.5) and n=15 (r=0.6)16.
Due to the two differing diagnostic groups in this study and the need to stratify for exercise performance, a larger sample size of 75 participants will be used.

A61. Will participants be allocated to groups at random?

◯ Yes ◉ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Descriptive statistics will be used to describe the patient population.
Scatter plots will be drawn to review the relationship between the two variables (ISWT distance and 1MSTS frequency) and regression and correlation calculations will be performed calculated to determine the nature and strength of the relationship between the two variables

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
		Ian	Smith
Post	Specialist Respiratory Physiologist		
Qualifications			
Employer	Sheffield Teaching Hospitals NHS Foundation Trust		
Work Address	Ward M2		
	Royal Hallamshire Hospital, Glossop Road		
	Sheffield		
Post Code	S10 2JF		
Telephone			
Fax			
Mobile			
Work Email	ian.smith37@nhs.net		

	Title	Forename/Initials	Surname
	Professor	David	Kiely
Post	Consultant Respiratory Physician		
Qualifications			
Employer	Sheffield Teaching Hospitals NHS Foundation Trust		
Work Address	Ward M2		
	Royal Hallamshire Hospital, Glossop Road		
	Sheffield		
Post Code	S10 2JF		
Telephone	01142712132		
Fax			
Mobile			
Work Email	david.kiely1@nhs.net		

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	Sheffield Teaching Hospitals NHS Foundation Trust
Given name	Dipak
Family name	Patel
Address	Clinical Research and innovation Office, Room D49, D Floor, Royal Hallamshire Hospital
Town/city	Sheffield
Post code	S10 2JF
Country	United Kingdom
Telephone	01142265945
Fax	
E-mail	dipak.patel12@nhs.net

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [ ] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [x] No application for external funding will be made

What type of research project is this?

- ( ) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- (●) Project that is part of a fellowship/ personal award/ research training award

◯ Other

Other – please state:

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

◯ Yes ◉ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

◉ Yes ◯ No

If Yes, please give details of each rejected application:

Name of Research Ethics Committee or ethics authority:	Yorkshire & The Humber - South Yorkshire
Decision and date taken:	Unfavourable - 28/1/21
Research ethics committee reference number:	21/YH/0021

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title	Forename/Initials	Surname
Miss	Sarah	Birchall

Organisation	Sheffield Teaching Hospitals NHS Foundation Trust
Address	Clinical Research and innovation Office, Room D49, D Floor, Royal Hallamshire Hospital Sheffield
Post Code	S10 2JF
Work Email	sarah.birchall4@nhs.net
Telephone	01142713910
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 04/05/2021
Planned end date: 25/03/2022
Total duration:
Years: 0 Months: 10 Days: 22

A71-1. Is this study?

◉ Single centre
◯ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

◯ Yes ◉ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

[x] NHS organisations in England	1
[ ] NHS organisations in Wales	
[ ] NHS organisations in Scotland	
[ ] HSC organisations in Northern Ireland	
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Joint health and social care agencies (eg community mental health teams)	
[ ] Local authorities	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent (private or voluntary sector) organisations	
[ ] Educational establishments	
[ ] Independent research units	
[ ] Other (give details)	
Total UK sites in study:	1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

◯ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

A Steering Committee will be formed of the PhD students supervisory team plus the following:
- Dr Iain Armstrong - Nurse Consultant SPVDU
- Ian Smith - respiratory function specialist SPVDU

In addition, we will invite one patient with pulmonary hypertension and one representative from the PHA to join the steering committee.

The committee will meet quarterly and provide overall supervision of the study, its progress and adherence to the protocol. Patient safety will be monitored through reporting of adverse events. The steering group will be responsible for decisions to proceed in light of adverse event reporting.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

The study steering group will act as a data monitoring committee. They will review any adverse events or other safety issues from the trial.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

We anticipate no or minimal safety issues, and that there will be adverse events in < 5% of tests completed.

Early stopping will be considered if significant issues with recruitment or patient safety are identified by the steering committee. These will be identified through reporting of recruitment rates and adverse events.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [x] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ○ No ◉ Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename	Carol
			Middle name	
			Family name	Keen
	Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST	Email	carol.keen@nhs.net
	Address	NORTHERN GENERAL HOSPITAL HERRIES ROAD SHEFFIELD	Qualification (MD...)	
			Country	United Kingdom
	Post Code	S5 7AU		
	Country	ENGLAND		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- (●) Chief Investigator
- ( ) Sponsor
- ( ) Study co-ordinator
- ( ) Student
- ( ) Other – please give details
- ( ) None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☑ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Mrs Carol Keen on 26/03/2021 10:52.

Job Title/Post:	Physiotherapist
Organisation:	Sheffield Teaching Hospitals
Email:	carol.keen@nhs.net

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Dr Dipak Patel on 30/03/2021 09:33.

Job Title/Post:	Research Manager
Organisation:	Sheffield Teaching Hospitals NHS Foundation Trust
Email:	dipak.patel12@nhs.net

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Professor Karen Sage on 29/03/2021 10:42.

Job Title/Post:	Professor for Applied Clinical Research
Organisation:	Manchester Metropolitan University
Email:	K.Sage@mmu.ac.uk

Appendix 7 PERPSIRE Study Data Collection Form

Study ID Number			
Date of Test		Time of test	

Contraindication	Present	Absent
Recent Surgery (Abdominal, Thoracic, Eye, Neuro) < 8 weeks		
Recent Heart Attack/Stroke < 8 weeks		
Recent Chest Pain/Haemoptysis < 2 weeks		
Recent Pneumothorax < 8 weeks		
Pulmonary Embolism < 12 weeks *		
Generally feeling unwell: vomiting/diarrhoea		
Recent syncope (fainting/blackouts) <4weeks		
Significant mobility issues (pain or limiting mobility)		
Severe Hypertension - Resting BP > 220/120 (either or both values)		
Hypotension <90/60 **with symptoms (dizzy or lightheaded)**		
Significant resting tachycardia > 130bpm – check with consultant before proceeding.		

	Pre		Post	
SpO2				
Borg Breathlessness				
Borg RPE				
Systolic				
Diastolic				
Heart Rate				

Number of complete Stands			
Terminated (Y/N)		Adverse Events (Y/N)	
Main effect or reason for termination		1. Leg Fatigue	2. Breathlessness
		3. Leg Pain	4. Dizzy / Unsteady
		5. Chest Pain	6. Other
ISWT			
Would you be happy to complete this test at home?			
Do you have scales at home?			
Do you have SpO2 monitor at home?			
Do you've BP monitor at home?			

Home assessment

Happy to take part	
Device and internet	
Home supervision available	
Date and time	
Emailed Attend Anywhere link	
Patient Instructions sent	

Date of Test		Time of test	

Contraindication	Present	Absent
Recent Surgery (Abdominal, Thoracic, Eye, Neuro) < 8 weeks		
Recent Heart Attack/Stroke < 8 weeks		
Recent Chest Pain/Haemoptysis < 2 weeks		
Recent Pneumothorax < 8 weeks		
Pulmonary Embolism < 12 weeks *****		
Generally feeling unwell: vomiting/diarrhoea		
Recent syncope (fainting/blackouts) <4weeks		
Significant mobility issues (pain or limiting mobility)		

	Pre	Post
Borg Breathlessness		
Borg RPE		

Number of complete Stands			
Terminated (Y/N)		Adverse Events	(Y/N)
Main effect or reason for termination		1. Leg Fatigue	2. Breathlessness
		3. Leg Pain	4. Dizzy / Unsteady
		5. Chest Pain	6. Other
Any effects or problems after the first hospital test?			
General comments			

Appendix 8 PERPSIRE Health Research Authority Favourable Opinion

NHS
Health Research Authority

East of England - Cambridge Central Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

06 April 2021

Ms Carol Keen
Clinical Specialist Physiotherapist
Sheffield Teaching Hospital NHS FoundationTrust
PVDU, M Floor
Glossop Road
Sheffield
S10 2JF

Dear Ms Keen

Study title:	**Pulmonary Hypertension and measurement of exercise capacity remotely: the PERSPIRE study**
REC reference:	**21/EE/0074**
Protocol number:	**STH21477**
IRAS project ID:	**296131**

Thank you for your letter of 30 march 2021, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of

research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Further guidance on registration is available at:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
IRAS Application Form [IRAS_Form_01032021]		01 March 2021
Other [Second Reviewer's Checklist]	1.0	02 November 2020
Other [Sit to Stand SOP]	1.0	15 February 2021

Other [Previous Ethical Review Feedback letter 1]		05 February 2021
Other [Previous Ethical Review Feedback Letter 2]		05 February 2021
Other [296131 REC Response letter]	1.0	24 March 2021
Other [Protocol v1.1 Clean]	1.1	24 March 2021
Participant consent form [Consent Form]	1.0	15 February 2021
Participant information sheet (PIS) [PIS v1.1 Tracked changes]	1.1	24 March 2021
Participant information sheet (PIS) [PIS v1.1 Clean]	1.1	24 March 2021
Referee's report or other scientific critique report [Lead Reviewer's Checklist]		02 November 2020
Research protocol or project proposal [Protocol v1.1 Tracked Changes]	1.1	24 March 2021
Summary CV for Chief Investigator (CI) [CI CV]	1.0	15 February 2021
Summary CV for supervisor (student research) [Supervisor CV]		15 February 2021
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow Chart]	1.0	15 February 2021

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 296131 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Miss Stephanie Ellis
Chair

Email: cambridgecentral.rec@hra.nhs.uk

Copy to: Miss Sarah Birchall, Sheffield Teaching Hospitals NHS Foundation Trust

Appendix 9 PERSPIRE Study Steering Group Terms of Reference

1. Role of the Study Steering Group

1.1 Provide overall supervision of the PERSPIRE study.
1.2 Maintain the rights, safety and well-being of the study participants.
1.3 Maintain confidentiality of all study information that is not already in the public domain.
1.4 Monitor recruitment rates and encourage the Chief Investigator (CI).
1.5 Review regular reports of the PERSPIRE study from the CI.
1.6 Approve any proposals by the CI concerning any change to the design of the study.
1.7 Oversee the timely reporting of study results.
1.8 Review and advise on the dissemination of findings.
1.9 Consider new information that arises as the study progresses.

2. Frequency of meetings

2.1 The Study Steering Group (SSG) will meet approximately 3 monthly until the completion of the study.
2.2 The SSG will meet either by teleconference, but may meet face to face if required.

3. Reports

3.1 The SSG will be provided with a report by the CI outlining accrual figures; data collection issues; protocol non-compliance; adverse events and any other matters that may affect the study.
3.2 The CI will provide copies of reports at least 1 week and preferably at least 2 weeks before any meetings.

4. Structure of meetings

4.1 Review and of reports as detailed on Section 3
4.2 Consideration of relevant external information identified by members of the SGG
4.3 Discussion of progress, concerns and considerations
4.4 Decision making and recommendations

5. Membership of the SSG

Role	Name
Chief Investigator	Carol Keen
Patient representative	Mark Bunce
PHA Representative	Paul Sephton
Respiratory Physiology Expertise	Ian Smith
Pulmonary Hypertension Expertise	David Kiely
Research Oversight	Karen Sage
Research Oversight	Molly Hashmi-Greenwood

6. Quorate

6.1 At least three members' of the Study Steering Group should be present including the CI to ensure the committee is quorate. This should include one of the patient representative or PHA representative unless in exceptional circumstance and where they have had the opportunity to review and comment on meeting materials.

6.2 Members who will not be able to attend the meeting may pass comments to the CI for consideration during the discussions.

6.3 The CI will be responsible for maintaining and circulating meeting minutes

7. Decision Making

Possible decisions include:

7.1 No action needed, study continues as planned.

7.2 Early stopping due, for example, to clear benefit or harm of a treatment, clear lack of benefit or external evidence.

7.3 Extending recruitment.

7.4 Proposing or commenting on proposed protocol changes / amendments.

7.5 Approving early release of study datasets in the event of early termination of the study.

7.6 Approving presentation of results during the study or soon after closure.

7.7 Approval of new strategies to improve recruitment or follow up.

8. After the study

8.1 The SSG will oversee the timely analysis, writing up and publication of the main study results.

8.2 The SSG will oversee the timely dissemination of the main study results to patient and carer groups.

Appendix 10 PERSPIRE Study online supplementary data

Table 18 - Participant characteristics separated by subgroup

Patient demographics at diagnosis for PAH patient by sub-classification				
	IPAH and HPAH (n = 28)	PAH-CTD (n = 18)	PH-CHD (n = 11)	PoPH (n=3)
Age, mean (SD), y	47.2 (17.1)	57.2 (13.0)	44.4 (16.8)	35.7 (6.0)
Female, no., (%)	21 (75.0)	16 (88.9)	9 (81.8)	1 (33.3)
BMI, mean (SD), kg/m^2	30.9 (8.1)	25.5 (5.0)	28.9 (7.67)	28.8 (3.5)
WHO FC, no., (%)				
Class II	1 (3.6)	1 (5.6)	2 (18.2)	0 (0)
Class III	21 (75.0)	16 (88.9)	9 (81.8)	3 (100)
Class IV	6 (21.4)	1 (5.6)	0 (0)	0 (0)
ISWT, mean (SD), m	218 (181)	173 (132)	310 (119)	220 (220)
Haemodynamics				
mRAP, mean (SD), mmHg	12 (6.5)	7 (4.9)	9 (5.0)	10 (13)
mPAP, mean (SD), mmHg	53 (13.0)	40 (12.1)	52 (11.7)	28 (1.4)
PAWP, mean (SD), mmHg	9 (3.8)	10 (6.0)	11 (3.1)	10 (5.0)
CO, mean (SD), l/min	4.14 (1.68)	4.60 (1.40)	5.75 (1.77)	4.5 (0.91)
CI, mean (SD), l/min/m^2	2.24 (0.88)	2.76 (0.88)	3.55 (0.82)	2.25 (0.85)
PVR, mean (SD), dynes/m^2	979 (364)	582 (355)	664 (442)	852 (111)
Mixed venous SpO_2 %	62.9 (11.9)	64.9 (6.4)	75.7 (6.33)	61.0 (15.2)
Pulmonary Function				
FEV_1, mean ± SD (% predicted), litres	2.25 ± 0.75 (81)	1.85 ± 0.61 (78)	1.99 ± 0.68 (70)	2.33 ± 1.19 (58)
FVC, mean ± SD (% predicted), litres	2.95 ± 1.03 (91)	2.45 ± 0.96 (86)	3.13 ± 1.01 (93)	3.11 ± 2.06 (65)
TL_{CO}, mean ± SD (% predicted), mmol/min/kPa	4.83 ± 1.99 (53)	3.06 ± 1.04 (41.5)	5.69 ± 1.15 (71)	4.53 ± 2.34 (41)
emPHasis10, median (IQR), score out of 50	34 (27-41)	32 (24-40)	19 (8-30)	37 (-)
Co-morbidities				
Systemic hypertension, no., (%)	4 (14.3)	3 (16.7)	1 (9.1)	0 (0)
Atrial Fibrillation, no., (%)	1 (3.6)	3 (16.7)	1 (9.1)	0 (0)
Diabetes, no., (%)	6 (21.4)	0 (0)	0 (0)	0 (0)
Ischaemic Heart Disease, no., (%)	0 (0)	2 (11.1)	0 (0)	0 (0)
COPD, no., (%)	0 (0)	0 (0)	1 (9.1)	0 (0)
Interstitial Lung Disease, no., (%)	0 (0)	7 (38.9)	0 (0)	0 (0)
Chronic Kidney Disease, no., (%)	1 (3.6)	0 (0)	0 (0)	0 (0)

Definition of abbreviations: PAH=pulmonary arterial hypertension; CTEPH=chronic thromboembolic pulmonary hypertension; BMI=body mass index; WHO-FC = World Health Organisation Functional Classification; ISWT=Incremental Shuttle Walk Test; mRAP=mean right atrial pressure; mPAP=mean pulmonary arterial pressure; PAWP=pulmonary arterial wedge pressure; CO=cardiac output; CI=cardiac index; PVR=pulmonary vascular resistance; SpO2=oxygen saturations; FEV=forced expiratory volume; FVC=forced vital capacity; TL_{CO}=lung carbon monoxide transfer factor; emPHasis10=patient reported outcome measure; COPD=chronic obstructive pulmonary disease

Table 19 - Safety outcomes

n = 75	Serious Adverse Event n, %	Adverse Event n, %	Early Termination n, %
Syncope	0 (0)	0 (0)	0 (0)
Pre-syncope	0 (0)	0 (0)	0 (0)
Chest pain	0 (0)	0 (0)	0 (0)
Elevated BP, not returning to baseline	0 (0)	0 (0)	0 (0)
Shortness of breath	0 (0)	0 (0)	1 (1.3)
Anxiety	0 (0)	1 (1.3)	0 (0)
Leg pain	0 (0)	0 (0)	1 (1.3)
Requiring treatment	0 (0)	0 (0)	0 (0)
Requiring admission	0 (0)	0 (0)	0 (0)

Table 20 - Survey results

n = 67	Y n (%)	N n (%)	Other n (%)
Would you be happy to do 1MSTS at home as part of a non-face-to-face assessment in the future?	65 (97.0)	0 (0)	2 (3.0)
Do you have weighing scales at home?	60 (89.6)	7 (10.5)	0 (0)
Do you have an oxygen saturation probe at home?	30 (44.8)	37 (55.2)	0 (0)
Do you have a blood pressure machine at home?	27 (40.3)	40 (59.7)	0 (0)