

## Academic Directorate of Respiratory Medicine

### SUMMARY OF RESEARCH STRATEGY 2018 - 2021

#### Executive Summary

The Academic Directorate of Respiratory Medicine is at the forefront of changing lives for the better for patients with respiratory disease through research and innovation (e.g. transformative diagnostics and novel management approaches). The attached strategic summary emphasises this. It identifies a breadth of research that is internationally leading in areas including pulmonary hypertension, imaging, and health services research. Strong links with the University are driving discovery and innovation around identifying new diseases, bringing new treatments to the management of airways disease, and diagnostic and management technologies in imaging. In pulmonary hypertension, our goal is to replace invasive tests of heart function with non-invasive MR imaging. In asthma and COPD, we are starting to change the algorithms for assessment and diagnosis by incorporating novel imaging into routine practice. In health services research, the goal of Martin Wildman's team is to directly transform the lives of people with cystic fibrosis by delivering fundamental changes to their treatment algorithms, enabling better and more effective therapy. Our collaborations extend beyond traditional partners to include the Health and Safety Executive, Sheffield Hallam University, and others.

The strength of this underlying scientific approach and collaboration with the University is illustrated by three recent highly prestigious intermediate fellowship applications that were successful at consultant level: Dr Alex Rothman in cardiology, Dr Andy Swift in Radiology, and Dr Roger Thompson in Respiratory Medicine. These superb results also highlight the extent to which research in our Directorate is collaborative, spanning more than one department and more than one institution.

## **Cross-cutting themes**

### ***PPI***

There are several initiatives involving patients in the research cycle within different disease-group specialties of the Respiratory Directorate. The Cystic Fibrosis team have continuous patient involvement with their NIHR Programme Grant activity and patients are co-applicants in grant applications. In pulmonary hypertension the UK patient association originated in, and is based in Sheffield, and chaired by STH Nurse Consultant Dr Iain Armstrong. Patients are included in Study Steering Committees and assist with review of protocols and ethics applications. We aim to initiate a directorate-wide PPI group.

### ***Imaging***

The Respiratory service benefits from close association with Prof Jim Wild and the University of Sheffield POLARIS group, who are world-leading pioneers of advanced imaging using polarised gas, which enables detailed and functional magnetic resonance imaging of the lungs. They provide a clinical service for patients referred from the STH Respiratory Directorate and further afield. New scanners are now located at RHH and NGH providing increased capacity and opportunity for research, building on existing research with the Pulmonary Vascular Unit, COPD and Interstitial Lung Disease Service, and expanding into different indications such as cystic fibrosis, asthma and pulmonary embolism. The recent appointment of Dr Andy Swift, consultant radiologist, to a prestigious Wellcome Intermediate Fellowship, was a notable success and will continue to transform imaging of pulmonary hypertension.

### ***Respiratory Physiology***

The directorate hosts the STH Respiratory Physiology service providing clinical and research services to assess lung function and exercise capacity, as well as sleep diagnostic and therapeutic services, and ventilatory support for patients across the Trust. The department employs 22 staff and in the previous year supported > 40 studies in Respiratory Medicine, Specialised Cancer, Cardiology, Neurosciences and Specialised Medicine. The department is committed to supporting research and in 2017 Matthew Austin (Respiratory Physiologist) was awarded a place on the Health Education England MSc course funded for 2 years by NIHR.

### ***Clinical Research Facility***

The Respiratory Directorate has a long-standing relationship with the CRF. As of January 2018 the CRF supported 25 studies either active or in set-up, at both NGH (Orange Nursing Team) and RHH (Yellow team) At NGH the CRF team works closely with Respiratory Physiology delivering studies to test the efficacy of new interventions; at RHH the CRF team work with the Pulmonary Vascular unit, and pulmonary vascular department grant-funded studies have funded employment of two CRF nurses, for example to support the Sheffield Pulmonary Hypertension tissue bank. CRF teams at both sites work on asthma and COPD trials as well as collaborative imaging studies.

### ***Databases and Informatics***

In 2017, Consultants from different specialties (asthma, COPD, ILD, pulmonary embolism, occupational lung disease) began work with the STH Scientific Computing team to create new electronic databases to store and analyse clinical data.

### ***Fundamental science***

The academic directorate has particularly strong links with the University. Principal investigators including Ian Sabroe, Alison Condliffe, Stephen Renshaw and Jim Wild lead discovery science programmes that are seeking to identify new genetic defects underlying lung disease (Alison Condliffe), develop new therapeutic targets for lung disease (Condliffe, Sabroe, Renshaw) and new diagnostic and monitoring tools for respiratory disease (Jim Wild, working with Ian and Stephen and others). In these roles, investigators in this directorate collaborate successfully with other groups and directorates, including with cardiology (the PH team, Sabroe's work on inflammation) and endocrinology (e.g. Sabroe's work with Prof Simon Heller in Diabetes).

## Alignment with STH Research Strategy

The Respiratory research strategy is aligned with and connected to the Trust strategy in each of our specialty areas and cross-cutting themes. Through these initiatives we aim to develop our research and innovation program and improve patient care.

- Intimate association with University of Sheffield through clinical academics, honorary professorships and lectureships, particularly with the Department of Infection, Immunity and Cardiovascular Science and ScHARR.
- Links with Sheffield Hallam University for example Carol Keen Physiotherapist pursuing PhD examining rehabilitation in patients with pulmonary hypertension.
- Links with INSIGNEO in particular via Pulmonary Vascular disease modelling and imaging.
- Innovation initiatives:
  - Cystic Fibrosis Health Hub – implementing behaviour change via technology to measure and monitor adherence
  - Perfect Patient Pathways, e.g. South Yorkshire and Bassetlaw Test Bed for Asthma
  - Informatics with CREST team and industry partners e.g. development of new Research Database; and SPHINX project investigating predictors of diagnosis in PH patients.
  - trial in pulmonary embolism will implement new clinical procedures for thrombolytic intervention in STH.
  - Development and imaging for patient benefit, in programmes led by Jim Wild. Recent ethical approval has been granted to allow the expansion of analysis of real-world use of new diagnostics, which may have far-reaching impact on service development for people with asthma, COPD, interstitial lung diseases, and other airway diseases.
- Much of our research is delivered with the Clinical Research Facility.
- Industry collaboration - we collaborate with several companies in research projects including GSK, Boehringer, Novartis, Actelion, Roche, QIVIA.
- We will develop our patient and public involvement in research working with the Clinical Research and Innovation Office.

## Monitoring and Attainment of Research Objectives and NIHR Metrics

Monitoring is coordinated by the Directorate Research Coordinator in communication with the Research Lead, Principal Investigators, Clinical Research Facility and R&D. CRF studies now benefit from the CRF “BRAG” spreadsheet which relays information to research teams about study performance and recruitment trajectory. Regular team meetings are held to identify issues and trouble-shoot. We communicate with external Sponsors to resolve recruitment issues, and amend study targets if required.

Objectives and POF targets are discussed at monthly Research Executive meetings. The Research Coordinator liaises regularly with R&D to report on NIHR metrics performance, and Directorate staff participate in CRN Yorkshire & Humber Respiratory Specialty Meetings.

The Directorate strives to attain its research objectives and NIHR targets. Many of our consultants and clinical staff try where possible to facilitate research although the primary barrier to this is the high level of workload in the clinical service. We hope that a number of staff developments described below, such as appointment of new research-active staff and databases, will help to us to attain our objectives. The full-time appointment of Directorate Research Coordinator in February 2016 has facilitated research across the directorate. Other steps include:

- Close monitoring of POF metrics as described above
- Setting realistic, achievable recruitment targets
- Ensuring research teams are aware of 70 day and RTT targets
- Ensuring research teams are ready to recruit at study initiation.

## Pulmonary Vascular Disease / Pulmonary Hypertension Research

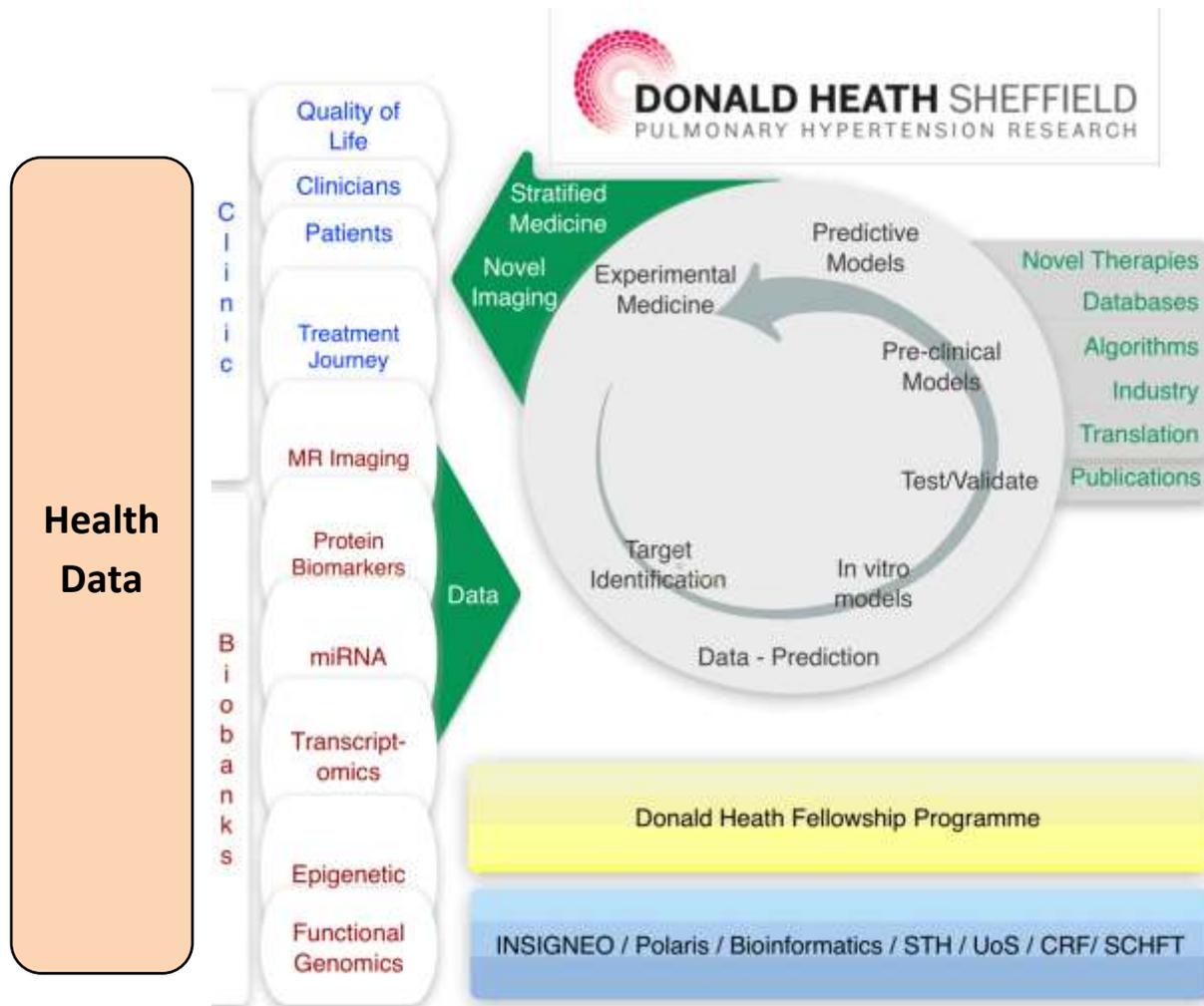
The Sheffield Pulmonary Vascular Disease Unit (SPVDU) is the largest UK centre and one of the largest pulmonary hypertension (PH) centres in the world. The clinical service is led by SPVDU Director, Prof David Kiely. Our research is intimately related to the University of Sheffield (UoS) Department of Infection, Immunity and Cardiovascular Science through pre-clinical models (including large animal models) and drug discovery (Dr Allan Lawrie, BHF Senior Research Fellow), the use of world-leading imaging (Prof Jim Wild, NIHR Professor), and the use of *in silico* approaches (Dr Andy Swift, Wellcome Trust Research Fellow). Imaging facilities are provided by the UoS POLARIS group which is supported by £7.5 million MRC funding and our research is part of the INSIGNEO programme.

Another major research strength is our close relationship with the patient pathway, the UK PH patient association which originated in Sheffield over ten years ago, the research of allied healthcare professionals (Nurse Consultant Iain Armstrong, Physiotherapist Carol Keen, and Pharmacist Neil Hamilton) and humanities research (Sabroe).

Since 2017 external funding awards of around £2 Million have been made for Sheffield PH research. There are currently 3 externally funded intermediate fellows: Dr Alex Rothman (Wellcome Intermediate Fellow), Dr Andrew Swift (Wellcome Intermediate Fellow) and Dr Roger Thompson (BHF Intermediate fellow). A number of awards have also been supporting invasive monitoring and interventional catheter studies in pulmonary hypertension (Rothman and Gunn). July 2017 saw the launch of Sheffield's **Donald Heath Pulmonary Hypertension Research Programme**. Donald Heath was a distinguished clinician scientist who put forward the first description of "hypertensive pulmonary vascular disease" in the 1950s whilst working in Sheffield. More recently the collaborations between Kiely, Lawrie, Wild and others have driven growth of PH research in Sheffield. The Donald Heath Doctoral Training Programme, jointly funded by STH, UoS and the company Actelion, will support one Clinical Lecturer, two Clinical Training Fellows and two basic science PhD students who will undertake research in Sheffield and lay foundations for future grant applications.

Another important collaboration ("SPHINX") involves Kiely / Lawrie / Wild, the STH Scientific Computing team and companies GSK and IQVIA who have analysed STH patient data alongside national Hospital Episode Statistics. We are developing a predictive algorithm for earlier diagnosis of PH based on healthcare behaviour with the potential to improve diagnostic pathways across the UK.

Fig. 1. Schematic representation of the Donald Heath PH Research Programme



Sheffield Teaching Hospitals **NHS**  
NHS Foundation Trust



## Health Services Research and Cystic Fibrosis

### Research active staff

- Dr Martin Wildman
- Dr Frank Edenborough
- Dr Zhe Hui Hoo
- Dr Rachael Curley
- Dr Sarah Thornton (Dietician)
- Dr Ailsa Milne (Dietician)

The Health Services Research (HSR) Strategy within the Respiratory Directorate at the Northern General Hospital aims to apply multidisciplinary methodologies to chronic disease management and quality improvement. In particular we aim to understand how behaviour change can support habit formation and self-management behaviours such as adherence in patients, and how behaviour change can affect clinical teams delivering care to patients. An important dimension of the programme is the equal emphasis given to changing clinician behaviour in order to support changes in patient behaviour.

Our research team including STH clinicians and the University of Sheffield Clinical Trials Research Unit works closely with the STH Service Improvement department and Sheffield Microsystems Academy.

Our research centres around the Cystic Fibrosis Health Hub which has been developed in the last 5 years through an NIHR Programme Grant award led by Dr Wildman and Prof O’Cathain with colleagues including Stephen Walters, Jon Nicholl, Daniel Hind, Paul Tappenden and Daniel Beever from SCHARR, Prof Madelynne Arden (Sheffield Hallam University) and Pauline Whelan (Farr Institute, University of Manchester).

We aim to develop and evaluate a complex behaviour change intervention to support medication adherence for adults with CF. The intervention includes a web portal (CF Health Hub) to capture adherence data (such as that from patients’ nebulisers) and display this to clinicians and patients. The programme has so far achieved its milestone objectives and the main randomised controlled trial is now underway and recruiting patients in more than 20 UK sites.

# Interstitial Lung Disease

## Research active staff

- Dr Stephen Bianchi
- Prof Stephen Renshaw
- Dr Christopher Barber
- Dr Alexander Basran
- Dr James Eaden
- Prof Jim Wild

The STH Interstitial Lung Disease team runs a nationally commissioned regional service seeing approximately 250 new patients with suspected ILD each year. We have a proven track record for delivery of patient recruitment targets for recent Portfolio studies. In 2017 we were the highest UK recruiter for the recent Boehringer INSTAGE trial in idiopathic lung fibrosis and we achieved target in the NIHR EME-TIPAC co-trimoxazole trial. In 2016 we achieved target recruitment in an observational study investigating quality of life in pulmonary fibrosis patients. The interstitial lung disease service is currently research active in pharmaceutical driven studies with Boehringer and Roche exploring the impact of potential disease modifying therapies. Currently 2 new commercial trials with a novel anti-fibrotic agent are being evaluated for feasibility.

In the last 3 years we have expanded links with Prof Wild and the University Academic Radiology team. ILD clinical service and research will be boosted by a new NGH MRI facility. A PhD student is completing his project investigating MRI methods in pulmonary fibrosis, and in 2018 a Clinical Fellow will be employed by the University to manage a Translational Imaging study through EU funding linked to the Academic Radiology and NHS ILD service. New databases are being developed by the STH CREST Computing team that will provide infrastructure to record detailed phenotypic and clinical information which will be used as a foundation to generate new research hypotheses and facilitate recruitment to upcoming trials.

## Asthma, Airway Disease and Immunodeficiency

### Research active staff

- Prof Ian Sabroe
- Prof Alison Condliffe
- Dr Shiron Saha
- Dr David Sammut
- Prof Jim Wild

Airways disease is a central component of research in the Academic Unit of Respiratory Medicine (University of Sheffield), with strong integration with the STH Academic Directorate of Respiratory Medicine. Key research themes include understanding how viral infections worsen airways inflammation in asthma and COPD, understanding how immunodeficiency affects the airways, and developing new targets and new treatments for asthma and COPD. We are funded or have been funded by Asthma UK, The British Lung Foundation, MRC, Wellcome Trust, MRC-MICA, European Society for Immunodeficiency (ESID), HC Roscoe (British Medical Association), and NC3R to meet our objectives. Many research studies are based in the fields of basic/fundamental science, and often do not directly access patients, but some have used lung cells collected after cancer surgery. We are participating in service evaluation research looking at how new technologies may support patients' use of inhaler devices.

We participate in trials of new treatments for asthma, and support other studies on asthma genetics. We are working to improve clinical imaging research through collaborations with Prof Jim Wild, including research evaluating how to use new clinical MRI scans to treat patients with airways disease. Ian Sabroe is co-founder and co-lead of the Yorkshire Asthma MDT, coordinating asthma care across the Yorkshire region, and one of the three NHS England commissioned asthma hubs in Yorkshire. Alison Condliffe has established a joint respiratory/immunology service with Dr William Egner (Clinical Immunology and Allergy Unit), and heads a BLF-funded UK consortium researching the respiratory complications of immunodeficiency (planning to establish a national MDT) as well as a European Registry. She is also working with GSK to implement clinical trials with a novel inhaled PI3Kdelta inhibitor.

Research in this area is therefore inextricably linked between the University and Trust, and goals are shared between the two organisations. Our targets include:

1. Publishing new data on mechanisms of viral-induced airways inflammation through MRC funding.
2. Establishing studies examining how best to use MRI scanning to understand asthma.
3. Continue to innovate as a leading UK centre in airways inflammation biology.
4. Develop cohesive interdisciplinary research involving people with asthma, imaging, basic research, and new models of disease.

## COPD

Clinical COPD research is led by Dr Rod Lawson. His interests include developing research imaging together with Prof Jim Wild. He is actively involved in clinical trials, particularly where these may generate opportunities to exploit novel imaging for which Sheffield is renowned.

### Participation in studies

Dr Lawson has built his research relationship with Prof Wild in academic radiology. He is PI for a two centre Portfolio study of a novel MRI imaging technique funded by the MRC over the next 3 years (**STH19050 LIFT study**). He has just completed a three centre Portfolio study as PI which was the first to use inert gas MRI as an endpoint in a commercial pharma trial (**STH19163**).

Dr Lawson is also due to commence recruitment imminently to a commercial phase II Portfolio trial in COPD (**STH19917 GSK**) and is completing a phase III trial (**STH19703 SOPHOS**). It is likely further such commercial trial work will continue.

## Occupational Lung Disease

### Centre for Workplace Health at STH, UoS and HSL

#### Research active staff

All the clinical staff below work part time at STH. Each member of staff also works, with the exception of Clare Burton, across organisation boundaries within the Centre for Workplace Health (CWH). The latter is a tripartite relationship between STH, the University of Sheffield and the Health and Safety Executive.

- David Fishwick Consultant
- Chris Barber Consultant
- Clare Burton Consultant
- Lisa Bradshaw Nurse Specialist

Despite limited resources, the occupational lung disease team continue to be very research active through the Centre for Workplace Health (CWH). The majority of our research activity is based off site at the Health and Safety laboratory (HSL, HSE), the national laboratory of HSE based in Buxton. Intermittently, we also employ research fellows through the University of Sheffield periodically to deliver specific tactical project related workplace based research.

### Pulmonary Embolism

Sheffield Teaching Hospitals offers a comprehensive Acute Pulmonary Embolism diagnostic, management and follow-up service, led by Dr Judith Hurdman. In 2018 we aim to initiate a commercial trial with the support of the CRF and Echocardiography department which will test a new intervention for treating Submassive Pulmonary Embolism cases. The trial will involve the introduction of a new clinical pathway into STH in collaboration with the departments of Critical Care and Interventional Radiology. The new intervention will use Acoustic Pulse Thrombolysis (ultrasound) to enhance distribution of thrombolytic drug to blood clots in patients with pulmonary embolism.

### Cancer

Dr Leon Lewis will continue participation in a Portfolio trial (sponsored by North Bristol NHS Trust) investigating the use of Positron Emission Tomography Computed Tomography (PET-CT) guided biopsies in patients with mesothelioma (STH19648).

The Lung Cancer Multi-Disciplinary team will continue to identify recruits for the Cancer Research UK Stratified Medicine Programme (STH18260), a Portfolio study led by the STH Cancer Clinical Trials Centre.