

## COVID-19 RESEARCH



### 1. INTRODUCTION

Oxford researchers have been at the forefront of national and global efforts to tackle the COVID-19 pandemic, with many high-profile trials and studies being led by Oxford researchers. A large proportion of these are supported by the NIHR Oxford Biomedical Research Centre (BRC), which is based at Oxford University Hospitals (OUH) and run in partnership with the University of Oxford.

The Oxford BRC, whose Steering Committee is chaired by OUH's Chief Medical Officer, played a key role in the early days of the pandemic by releasing funding to kick-start key research projects, including the search of a COVID-19 vaccine.

The Oxford BRC, currently chaired by Prof Helen McShane, was one of the original five BRCs established by the National Institute for Health Research (NIHR) in 2007 to improve the translation of basic scientific developments into healthcare benefits for NHS patients. Every five years, OUH and the University bid for NIHR funding; in the last round, the BRC was awarded £114m for the period 2017 to 2022 to support ground-breaking innovation across its 20 research themes. BRC investigators have dual appointment in the Trust and the University.

Since the start of the COVID-19 pandemic, 2,897 OUH patients have participated in 21 research studies supported by the NIHR Clinical Research Network.

This briefing paper focuses on some of the key COVID-19 research being carried out in Oxford.

### 1. OXFORD COVID-19 VACCINE TRIAL

The Oxford COVID-19 vaccine trial took a major step forward in July when the results of Phase I/II of the trial showed that not only were there no early safety concerns but also the vaccine induced a strong immune response. [The results](#), published in *The Lancet*, indicate that the vaccine provoked a T cell response within 14 days of vaccination and an antibody response within 28 days.

During the study, participants who received the vaccine had detectable neutralising antibodies, and these responses were strongest after a booster dose. The next step in studying the vaccine is to confirm that it can effectively protect against SARS-CoV-2 infection.

Three leading members of the Oxford BRC's Vaccines Theme are leading the trial: Prof Sarah Gilbert and Prof Adrian Hill of the University of Oxford's Jenner Institute and Prof Andrew Pollard of the University's Oxford Vaccine Group. The BRC provided crucial funding to get the trial up and running and then helped to fund an evaluation of the safety of the vaccine. Under an agreement signed in April, AstraZeneca is responsible for the development and worldwide manufacturing and distribution of the vaccine.

Late-stage clinical trials are taking place in Brazil and South Africa, while trials are also planned for Japan and Russia. A [new arm of the trial](#) was launched in the US in early September. In late October, AstraZeneca announced that the vaccine produces an immune response in both young and old adults, and that it also triggers lower adverse responses among the elderly.

Professor Pollard gave a talk in July about the development of the Oxford vaccine candidate and the progress of the trial. [It is available on YouTube](#). The University has produced an [animation](#) explaining how they have been able to speed up the process of COVID-19 vaccine development

Health economists supported by the Oxford BRC have [published a paper](#) outlining the possible criteria governments might use to prioritise who receives a COVID-19 vaccine once one has been approved for use.

## **2. RECOVERY TRIAL (exploring potential treatments for COVID-19 symptoms)**

Oxford University researchers are leading [the RECOVERY trial](#), the world's biggest trial looking at whether existing treatments can tackle the symptoms of COVID-19. They have found that one of the drugs they were testing, dexamethasone, a cheap and widely available steroid, reduced the risk of death in COVID-19 patients on ventilators by a third, and by a fifth in those on oxygen.

The chief investigators of the trial, Professor Peter Horby and Professor Martin Landray, announced in June that the trial had found no clinical benefit from using two of the other drugs being tested on hospitalised patients with COVID-19: the anti-malaria drug [hydroxychloroquine](#) and lopinavir-ritonavir, an antiviral treatment commonly used to treat HIV.

Other treatments being tested by the RECOVERY trial are azithromycin, a commonly used antibiotic; tocilizumab, an anti-inflammatory treatment; and convalescent plasma collected from donors who have recovered from COVID-19. The trial announced in September it would evaluate the potential benefits of an anti-viral antibody cocktail, [REGN-COV2](#), developed by the pharmaceuticals company Regeneron to tackle the virus; and in early November, it was announced that [aspirin would be investigated](#) as part of the trial since patients with COVID-19 are at higher risk of developing blood clots.

Since it began in March 2020, the trial, which is supported by the BRC, has recruited more than 17,000 patients across 176 NHS hospitals.

Professor Landray, the BRC's Theme Lead for Clinical Informatics, explained the background to the RECOVERY trial in a talk that is [available on YouTube](#).

## **3. OTHER TREATMENT TRIALS**

- The [PRINCIPLE trial](#) is an urgent public health study looking at potential drug treatments for the symptoms of COVID-19, in this case in older people in primary care. The trial is being led by the University of Oxford's Nuffield Department of Primary Care Health Sciences, headed by the BRC's Theme Lead for Multimorbidity, Prof Richard Hobbs.

- Researchers at Oxford Clinical Trials Research Unit (OCTRU) are studying the effectiveness of the arthritis drug, adalimumab, as a treatment for patients with COVID-19 in the community, especially care homes. Recent studies of patients with COVID-19 have shown that patients already taking anti-tumour necrosis factor (TNF) drugs for inflammatory arthritis and inflammatory bowel disease are less likely to be admitted to hospital than those taking other anti-inflammatory drugs. [The AVID-CC trial](#), funded by the COVID-19 Therapeutics Accelerator, will enrol up to 750 patients from community care settings throughout the UK. The trial is led by Prof Duncan Richards, the Oxford BRC's Musculoskeletal Co-theme Lead. This is the first drug trial designed for Acute Hospital at Home services. Oxford Hospital at Home Service receives support from the Oxford BRC.
- University of Oxford researchers will investigate whether administering the anti-inflammatory drug infliximab to patients with COVID-19 can prevent progression to respiratory failure or death. This is one part of the multi-arm, multi-stage [CATALYST Trial](#), led from Birmingham, in collaboration with the NIHR Oxford BRC and NIHR University College London (UCL) BRC. The overall aim is to guide the selection of new drug interventions for large Phase III trials in hospitalised patients with COVID-19 infection.
- Preliminary results of a clinical trial supported by NIHR Oxford BRC researchers have suggested that a new treatment for COVID-19 dramatically reduces the number of patients needing intensive care. [The treatment](#), a protein called interferon beta, has been developed by the UK biotech company Synairgen and scientists at the University of Southampton. Interferon beta, produced naturally by the body when it gets a viral infection, is inhaled directly into the lungs of COVID-19 patients using a nebuliser, with the aim of reducing viral load and stimulating an immune response. The trial has been supported by the NIHR Respiratory Translational Research Collaboration (R-TRC), led by the NIHR Oxford BRC's Prof Ling-Pei Ho.
- The [ATOMIC2 trial](#), which is being led by NIHR Oxford Biomedical Research Centre (BRC) researcher Dr Tim Hinks, is operating across 15 sites and aims to enrol 800 people with COVID-19 who have been assessed in hospital but considered well enough to be cared for at home. It is a clinical trial for the use of Azithromycin. As well as the BRC, the trial has received funding from the University of Oxford and Pfizer. It complements the RECOVERY and PRINCIPLE trials, which are testing Azithromycin in patients in hospital and in general practice respectively.
- The [STOIC study](#) is investigating whether the early use of inhaled steroid Budesonide in adult patients in the early stages of a COVID-19 infection reduces the chance of them needing to go to hospital. In early November, the study recruited its 100th participant. It is one of two Oxford studies included in the [COVID Symptom Study App](#).

#### **4. PHOSP-COVID & C-MORE (investigating the long-term health impact of COVID-19)**

[PHOSP-COVID](#) is a major national research study investigating the long-term health impacts of COVID-19 on 10,000 hospitalised patients. Awarded £8.4 million jointly by UKRI and the NIHR and given urgent public health research status, it is led by the NIHR Leicester BRC with Oxford investigators at the forefront in providing expertise in multi-organ imaging, mental health and lung disease. It involves collaboration between OUH and Oxford Health NHS Foundation Trust and between the NIHR Oxford BRC and the Oxford Health BRC.

Oxford research leads include: Prof Ling-Pei Ho, of the Oxford BRC's Respiratory Theme, Prof Stefan Neubauer, the Oxford BRC Theme Lead for Imaging, and Prof John Geddes, Director of the NIHR Oxford Health BRC.

A key part of PHOSP-COVID is the [C-MORE study](#), led by Dr Betty Raman and Prof Neubauer, both from the University of Oxford's Radcliffe Department of Medicine. This study, which aims to recruit more than 500 patients, will use Oxford's state-of-the-art imaging facilities to assess the long-term effects of COVID-19 infection, not only on the lungs but also on the heart, liver, kidney and brain. In October, the team published their [initial findings](#), which showed that a large proportion COVID-19 patients discharged from hospital were still experiencing symptoms of breathlessness, fatigue, anxiety and depression two to three months after contracting the virus. The team detected abnormalities on MRI in multiple organs and believe that persistent or chronic inflammation may be an underlying factor for these changes among COVID-19 survivors.

A related study, C-MORE-POST, led by Prof Fergus Gleeson from the Oxford BRC's Imaging Theme, the first of its kind in Europe to use hyperpolarised Xenon gas with MRI scanning to identify the impact on lung function as patients recover from COVID-19. It has so far identified weakened lung function in all patients who have taken part in the study – damage that would not be visible on a standard MRI or CT scans.

Oxford researchers from the BRC's cardiovascular and imaging themes are playing a key role in the multi-centre COVID-HEART study, a partnership involving the NIHR and BHF. The study aims to assess the demographic, multi-morbidity and genetic impact on cardiac involvement and its recovery.

## **5. LamPORE test & population study**

Oxford scientists, led by the Oxford BRC's Theme Lead for Antimicrobial Resistance and Modernising Microbiology, Prof Derrick Crook, [published their evaluation](#) of LamPORE, a novel diagnostic platform for detecting SARS-CoV-2 RNA. This technology has the potential to analyse thousands of samples per day on a single instrument. The collaboration – which involved the university's Nuffield Department of Medicine, Public Health England Porton Down, the University of Sheffield, and the NIHR Oxford BRC - evaluated the performance of LamPORE against RT-PCR, the most commonly-used laboratory test for Covid-19, and was found to have a similar performance.

The Oxford BRC's Co-theme Lead for Antimicrobial Resistance and Modernising Microbiology, Prof Sarah Walker, is the Chief Investigator for a [major government study](#) with the Office for National Statistics to track COVID-19 in the general population. The study, which is recruiting a representative sample of the entire UK population by age and geography, aims to help improve understanding around the current rate of infection and how many people are likely to have developed antibodies to the virus. In late October, Prof Walker's team [published a pre-print paper](#) saying the study had shown a marked variation in viral load across the UK population, and that the use of cycle threshold (Ct) values could be a useful epidemiological early-warning indicator as the pandemic progresses.

The study is making use of a high-throughput assay developed in Oxford by Prof Crook with support from the BRC Gastroenterology and Mucosal Immunity theme. The test is based on a commonly used assay called enzyme-linked immunosorbent assay (ELISA).

## **6. OUH STAFF TESTING STUDY**

A study at OUH has revealed the [different levels of risk faced by healthcare workers during the COVID-19 pandemic](#) – the study, co-authored by a number of Oxford BRC and OUH researchers, was the first to comprehensively investigate all staff groups across an institution, combining data from both symptomatic and asymptomatic staff testing programmes.

Almost 10,000 OUH staff were tested both for presence of the virus responsible for COVID-19 and antibodies to the virus, giving an accurate view of who has had coronavirus infection to date in the OUH workforce. The programme was able to:

- Identify and isolate staff members who had the infection before they developed symptoms, preventing them passing infection on to other staff and patients
- Identify in which areas of the hospital staff were at greatest risk
- Identify which staff groups were at greatest risk
- Record which staff have antibodies to the virus that causes COVID-19, enabling these staff to be monitored to understand if these antibodies provide immunity against repeat infections

Based on the findings of the testing, we implemented an infection prevention and control plan at OUH to limit transmission of the virus.

A six-month [follow-up study](#) showed that antibodies to COVID-19 fall by half in less than 90 days, and antibody levels peak lower and fall faster in younger adults and those who showed no symptoms.

## **7. CURIAL (using artificial intelligence to screen for COVID-19 in Emergency Departments)**

Oxford scientists specialising in infectious disease and clinical machine learning have developed an artificial intelligence test that can rapidly screen for COVID-19 in patients arriving in Emergency Departments. [The initial findings](#) of the 'CURIAL' AI test, which was supported by the Oxford BRC, appeared in a preprint paper. The test assesses data routinely collected during the first hour in Emergency Departments, such as blood tests and vital signs, to determine in near real time the chance of a patient testing positive for COVID-19.

## **8. COVID and general practice**

Professor Trisha Greenhalgh, the NIHR Oxford BRC's Theme Lead for Partnerships for Health, Wealth and Innovation, has received [significant government funding](#) for a new study to support GPs to deliver effective remote care to their patients during the COVID-19 pandemic. She was awarded £750,000 from the Economic and Social Research Council (ESRC) for a new study entitled 'Remote-by-Default Care in the COVID-19 Pandemic' which aims to address the technological tools that GP surgeries use to interact with patients, the organisational and wider infrastructure changes that might be required to scale up and deliver better remote care, and the insights gained during the COVID-19 pandemic.

## **9. The impact of COVID-19 on sleep**

Professor Colin Espie of the Oxford BRC's Neurological Conditions Theme is the UK lead for an international study investigating the [impact of the COVID-19 pandemic on sleep](#) and daily rhythms in adults. The International COVID-19 Sleep Study (ICOSS) is looking at changes in sleep quality in relation to social confinement such as a national lockdown or self-isolation, risk of exposure to the virus, and psychological symptoms such as anxiety, depression and post-traumatic stress.

## **10. Liver disease and COVID**

An international study led by researchers at the Oxford Liver Unit, based at Oxford's John Radcliffe Hospital, has shown that patients with cirrhosis are at increased risk of dying as a result of COVID-19. [The study](#), which received support from the Oxford BRC, looked at data on more than 1,300 patients in 29 countries. It found that mortality was particularly high among patients with more advanced cirrhosis (Childs-Pugh B or C cirrhosis) and those with alcohol-related liver disease. An earlier study by the Oxford Liver Unit team found that having had a [liver transplant](#) does not increase the risk of death from COVID-19, but that other factors such as age and comorbidities do.

**Dr Bruno Holthof**

**Chief Executive Officer**

**Oxford University Hospitals NHS Foundation Trust**