

Asthma drug budesonide shortens recovery time in non-hospitalised patients with COVID-19

- Inhaled budesonide, a common corticosteroid, is the first widely available, inexpensive drug found to shorten recovery times in COVID-19 patients aged over 50 who are treated at home and in other community settings, reports the UK's PRINCIPLE trial in 1,779 participants.
- PRINCIPLE is the world's largest Phase 3 platform randomised trial of community-based treatments for COVID-19, led by Oxford University.
- The trial findings have potential to change clinical practice globally, and follow the smaller Phase 2 STOIC pilot study of inhaled budesonide, which reported in January 2021.

Early treatment with inhaled budesonide shortens recovery time by a median of three days in patients with COVID-19 who are at higher risk of more severe illness and are treated in the community, finds Oxford University's Platform Randomised Trial of Interventions against COVID-19 in Older People (PRINCIPLE) trial.

PRINCIPLE is the world's largest Phase 3 platform randomised controlled trial to find clear evidence of an effective COVID-19 treatment for use in the community that can significantly shorten recovery time. As one of the UK Government's national priority platform trials, findings from PRINCIPLE have potential to change how COVID-19 is treated in its early stages in non-hospital, community settings in the UK and internationally.

Inhaled budesonide is a safe, relatively inexpensive and readily available corticosteroid commonly used around the world in inhalers to treat asthma and chronic obstructive pulmonary disease. It was added to the PRINCIPLE trial on 28th November 2020.

Recruitment for the inhaled budesonide arm of the trial stopped on 31st March 2021 since, in the view of the Trial Steering Committee, enough patients had been enrolled to establish whether or not the drug had any meaningful benefit on time to recovery. Obtaining further data on hospital admissions or death was unlikely due to the reducing number of cases in the UK.

For the interim report, a total of 961 patients were randomly assigned to receive inhaled budesonide at home and were compared with 1819 patients randomly assigned to the usual standard of NHS care alone. Of these, 751 people in the budesonide group and 1028 in the usual care group were SARS-CoV-2 positive and included in the primary interim analysis.

Based on the interim analysis using the latest data from 25th March 2021, the results showed the estimated median time to self-reported recovery for inhaled budesonide was 3.011 days shorter compared to usual care (95% Bayesian credible interval 1.134 to 5.410 days), with a high probability (0.999) of being superior to the usual standard of care. 32% of those taking inhaled budesonide, compared to 22% in the usual care group, recovered within the first 14 days since being randomised into the trial and subsequently have remained well until 28 days (relative risk 1.46, 95% CI 1.23 - 1.74). Participants in the budesonide group also reported greater wellbeing after two weeks (mean difference in WHO-5 Wellbeing score + 3.37, 95% CI 0.97 - 5.76, $p = 0.006$).

Among patients who had completed all 28 days of study follow up by 25th March 2021, 8.5% (59/692) in the budesonide group were hospitalised with COVID-19 compared with 10.3% (100/968) in the usual care group (estimated percentage benefit, 2.1% [95% BCI -0.7% - 4.8%], probability of superiority 0.928). Since fewer than expected people were admitted to hospital in the trial, and with COVID-19 cases and hospitalisations continuing to drop in the UK, it is not clear from this interim analysis whether budesonide reduces hospitalisations.

Patients with COVID-19 symptoms that started within 14 days and who are at higher risk of a poor outcome from the illness could join the trial and those with a positive SARS-CoV-2 result were included in the main analysis. Patients treated with inhaled budesonide were asked to inhale 800 micrograms twice a day for 14 days and were followed-up for 28 days. All patients were aged over 50

with an underlying health condition that put them at more risk of serious COVID-19 illness, or aged over 65.

Joint Chief Investigator, Professor Chris Butler, a South Wales GP and Professor of Primary Care from the University of Oxford's Nuffield Department of Primary Care Health Sciences, said: 'PRINCIPLE, the world's largest platform trial of community-based treatments for COVID-19, has found evidence that a relatively cheap, widely available drug with very few side effects helps people at higher risk of worse outcomes from COVID-19 recover quicker, stay better once they feel recovered, and improves their wellbeing. We therefore anticipate that medical practitioners around the world caring for people with COVID-19 in the community may wish to consider this evidence when making treatment decisions, as it should help people with COVID-19 recover quicker.

'This exciting finding about the beneficial effects of inhaled budesonide would not have been possible without the contribution of those patients who volunteered to participate: your gift of taking part will help doctors and nurses provide better evidence-based care for people with COVID-19 worldwide. It also stands as a monument to the far-sighted funders of PRINCIPLE, the UK-wide clinical research networks who have been absolutely key to the successful implementation of the trial, all the general practices and clinicians who support PRINCIPLE, NHS Digital, HDRUK, the Therapeutics Task Force and the hard work and dedication of our study team and oversight committees in the Primary Care Clinical Trials Unit.'

Joint Chief Investigator, Professor Richard Hobbs, Head of Oxford University's Nuffield Department of Primary Care Health Sciences, said: 'For the first time we have high-quality evidence of an effective treatment that can be rolled out across the community for people who are at most risk of developing more severe illness from COVID-19. Unlike other proven treatments, budesonide is effective as a treatment at home and during the early stages of the illness. This is a significant milestone for this pandemic and a major achievement for community-based research.'

Professor Mona Bafadhel, from Oxford University's Nuffield Department of Medicine, and a Consultant Respiratory Physician, led the earlier STOIC Phase 2 efficacy study of inhaled budesonide for early COVID-19 and led the development of the budesonide study arm for PRINCIPLE. She said: 'The news that the findings of the earlier-phase STOIC trial, which reported at the beginning of the year, have been replicated at scale here in the PRINCIPLE trial is outstanding. We are now sure that we have a treatment that will benefit patients with early COVID-19 worldwide. Inhaled budesonide is readily available worldwide and commonly used to treat asthma and chronic obstructive pulmonary disease.'

Professor Fiona Watt, Executive Chair of the Medical Research Council, which co-funded the study, said: 'Researchers involved in the PRINCIPLE trial have overcome considerable logistical hurdles to set up a world-leading rigorous drug trial in people's homes. We are now rewarded with the first inexpensive and widely available drug that can shorten recovery times for COVID-19 patients in the community. People around the world will be helped to recover faster thanks to these exciting new results.'

As soon as all remaining patients in the trial have completed their follow-up and a full analysis has been completed, detailed results on time to recovery and hospitalisations will be published. For this preliminary report, 92.8% of people randomised to the budesonide arm had the opportunity to complete 28 days of follow-up.

PRINCIPLE launched in April 2020 with the intention that drugs shown by the trial to have a clinical benefit could be rapidly introduced into routine NHS primary care. The trial is evaluating a range of potential community treatments for COVID-19 to reduce recovery time and prevent hospital admissions and deaths. It is recruiting participants who are most at risk of serious COVID-19 illness, either due to their age, symptoms, or an underlying health condition.

PRINCIPLE has pioneered an innovative methodology for community-based research that allows for many treatments to be efficiently and rapidly assessed in a single trial, resulting in this world-first finding of an effective community-based treatment during the course of a pandemic. Typically for trials of this size in the community, patient recruitment would take place opportunistically via general practices. Yet in PRINCIPLE, while general practice remains critical to delivery of the trial, everyone

across the UK, regardless of where they are registered to receive their health care, can sign-up if they are eligible. To date, more than 4,700 patients have volunteered to join PRINCIPLE, making it the world's largest platform trial of COVID-19 treatments to take place in community settings.

In January 2021, PRINCIPLE demonstrated that the antibiotics azithromycin and doxycycline are not effective treatments for COVID-19 in the early stages of the illness, changing clinical practice in the UK and internationally. PRINCIPLE continues to investigate the effects of treatment in the community with colchicine, a commonly used anti-inflammatory, and favipiravir, an antiviral used in Japan to treat influenza.

PRINCIPLE is funded by a grant to the University of Oxford from UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research as part of the UK Government's rapid research response fund.

NOTES FOR EDITORS:

For interview requests, please contact Dan Richards-Doran, Head of Communications, Nuffield Department of Primary Care Health Sciences, University of Oxford dan.richards-doran@phc.ox.ac.uk

Pre-print publication:

A pre-print paper has been submitted and will be published shortly on the medRxiv server.

<https://www.medrxiv.org/>

A link will be made available once this is published at www.principletrial.org/results

Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial.
PRINCIPLE Collaborative Group

About the PRINCIPLE Trial:

The PRINCIPLE trial is open to UK adults aged over 18 with COVID-19 symptoms or a positive test and an underlying health condition, or adults aged over 65. The trial is entirely remote and does not involve face-to-face visits in Oxford, so it can be joined online, over the telephone or with advice from a health and care professional.

PRINCIPLE is designed as a platform trial, so it is able to investigate multiple treatments for the same disease. In this instance, the trial is evaluating existing treatments that theoretically may be beneficial in COVID-19 in shortening illness, or preventing hospitalisation or death. Treatments can be dropped from the trial once an answer about its effectiveness is found. New treatments can be also added as the trial progresses.

PRINCIPLE is led from the Primary Care Clinical Trials Unit at the University of Oxford's Nuffield Department of Primary Care Health Sciences. PRINCIPLE is supported by a large network of care homes, pharmacies, NHS 111 Hubs, hospitals, and 1,401 GP practices across England, Wales, Scotland and Northern Ireland. The trial is integrated with the Oxford RCGP Research and Surveillance Centre and works closely with the NIHR Clinical Research Network, NHS DigiTrials, Public Health England, Health and Care Research Wales, NHS Research Scotland and the Health and Social Care Board in Northern Ireland.

Details of the trial, including the [study protocol](#) and related materials, can be found at www.principletrial.org

About the University of Oxford:

Oxford University has been placed number 1 in the *Times Higher Education* World University Rankings for the fifth year running, and at the heart of this success is our ground-breaking research and innovation. Oxford is world-famous for research excellence and home to some of the most talented people from across the globe. Our work helps the lives of millions, solving real-world problems through a huge network of partnerships and collaborations. The breadth and interdisciplinary nature of our research sparks imaginative and inventive insights and solutions.

Oxford University's Medical Sciences Division is one of the largest biomedical research centres in Europe, with over 2,500 people involved in research and more than 2,800 students. The University is rated the best in the world for medicine and life sciences, and it is home to the UK's top-ranked medical school. It has one of the largest clinical trial portfolios in the UK and great expertise in taking discoveries from the lab into the clinic. Partnerships with the local NHS Trusts enable patients to benefit from close links between medical research and healthcare delivery.

Within the division, the Nuffield Department of Primary Care Health Sciences is the largest, top-ranked centre for academic primary care in the UK and leads world-class research and training to rethink the way healthcare is delivered in general practice and other primary care settings. The department's main research focus on the prevention, early diagnosis and management of common illness, bringing together academics from many different backgrounds to work together to produce benefits for the NHS, for populations and for patients. www.phc.ox.ac.uk

About the National Institute for Health Research:

The National Institute for Health Research (NIHR) is the nation's largest funder of health and care research. The NIHR:

- Funds, supports and delivers high quality research that benefits the NHS, public health and social care
- Engages and involves patients, carers and the public in order to improve the reach, quality and impact of research
- Attracts, trains and supports the best researchers to tackle the complex health and care challenges of the future
- Invests in world-class infrastructure and a skilled delivery workforce to translate discoveries into improved treatments and services
- Partners with other public funders, charities and industry to maximise the value of research to patients and the economy

The NIHR was established in 2006 to improve the health and wealth of the nation through research, and is funded by the Department of Health and Social Care. In addition to its national role, the NIHR supports applied health research for the direct and primary benefit of people in low- and middle-income countries, using UK aid from the UK government.

This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care. www.nihr.ac.uk/patientdata

UK Research and Innovation works in partnership with universities, research organisations, businesses, charities, and government to create the best possible environment for research and innovation to flourish. We aim to maximise the contribution of each of our component parts, working individually and collectively. We work with our many partners to benefit everyone through knowledge, talent and ideas.

Operating across the whole of the UK with a combined budget of more than £8 billion, UK Research and Innovation brings together the seven research councils, Innovate UK and Research England.