

[name and address]

[ID number]

Dear Participant,

### **An update on the RECOVERY trial**

On behalf of the University of Oxford, we would like to thank you for taking part in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, and to give you an update on the study's progress.

Although COVID-19 restrictions are no longer in place, new coronavirus variants may emerge and it is important that we have treatments that are effective against many strains of the virus. So, the RECOVERY trial is continuing to investigate potential COVID-19 treatments in patients hospitalised by the disease.

To date, the trial has involved over 47,000 participants in the UK and more than 1500 from its overseas sites in Asia and Africa. It remains the largest study of COVID-19 treatments in the world, and your contribution has played a vital part in the study's impact. Thanks to the results from the study, patients hospitalised with COVID-19 now receive better treatment than before.

### **Trial results**

When we wrote to you last, RECOVERY had discovered three treatments that reduce deaths from COVID-19:

- **Dexamethasone**, an inexpensive corticosteroid treatment, reduces deaths from COVID-19 by up to a third for hospitalised patients requiring oxygen or a mechanical ventilator (June 2020).
- An arthritis treatment, **tocilizumab**, adds to the benefit of dexamethasone in reducing deaths from COVID-19 (February 2021).
- An antibody treatment developed specifically to treat COVID-19, now known as **Ronapreve**, reduced the risk of death when given to patients who had not produced their own antibodies to the virus (June 2021).

Since then, the RECOVERY trial has found an additional effective treatment against COVID-19: **baricitinib**, an anti-inflammatory drug normally used to treat rheumatoid arthritis. Treatment with baricitinib reduced deaths, shortened hospital stays, and also reduced the risk of progressing to invasive mechanical ventilation or death.

The RECOVERY trial has also found out that nine other treatments are not effective for patients hospitalised with COVID-19. We have also found that **higher doses of corticosteroids** increased the risk of death for some patients who were moderately unwell, but we are still investigating whether this treatment benefits the sickest people who require more intensive forms of respiratory support. These results are very important as the treatments might otherwise be used for patients hospitalised with COVID-19, without benefitting them but also taking up time and money.

This means that the RECOVERY trial has delivered results on 13 different treatments. Since most clinical trials take years to deliver a single result, this is an amazing achievement. You can read more about these results at the end of this letter and in the news section of the RECOVERY website at [recoverytrial.net/news](https://recoverytrial.net/news).

The RECOVERY trial is continuing to investigate two treatments: sotrovimab, an investigational monoclonal antibody that may be effective against the Omicron variant; and high dose corticosteroids in patients who need breathing support from a machine.

## **A global study**

In February 2021, the RECOVERY trial launched internationally to help identify affordable, effective treatments that can be used in less well-resourced settings. Nepal, Indonesia and Vietnam were the first countries to join. South Africa, Ghana, and India have also joined the study. Currently, RECOVERY International includes 24 hospital sites across these six countries.

## **Going ‘behind the scenes’ of the trial**

A wide range of different people have played an essential part in making the RECOVERY trial happen. You can learn more about these through a collection of interviews that go ‘behind the scenes’ of the study on the RECOVERY trial website ([recoverytrial.net/case\\_studies](https://recoverytrial.net/case_studies)). These profiles include a doctor; a participant; a research nurse; NHS Blood and Transplant; a pharmacist; the study’s international partners in Indonesia, and the communications and IT teams.

## **Other recent highlights**

- On Clinical Trials Day (20 May) this year, we launched a video featuring two members of the trial’s Coordinating Centre team; a trial participant, Elaine Bowden; a clinician, Dr Raha West; and the former Chief Scientific Adviser, Sir Patrick Vallance.
- The news section of the website also contains an article describing how RECOVERY successfully enabled the participation of pregnant women, so that we have information about treatments that are suitable for them.

- The RECOVERY trial has received several prestigious awards, all of which recognise the contribution made by participants, most recently from the Galien Foundation for 'Best Public Sector Innovation' and the Medical Research Council for 'Outstanding Team Impact'.

You can see the video and read more about these highlights in the news section of the RECOVERY website at [recoverytrial.net/news](https://recoverytrial.net/news).

## Communicating with you

We would like to write to you periodically with updates on the progress of the trial. If you would like to receive these updates via email instead, please sign up via our website at [recoverytrial.net/patients](https://recoverytrial.net/patients). You will need your study ID number shown at the top of this letter.

If you would like to discuss anything in this newsletter, or any other aspect of the study, with a member of the study team you can contact us by phone (0808 164 4060 Monday to Friday between 9am-5pm), email or post (details at the top of this letter). Please quote your participant ID number in any correspondence. If you would prefer to speak to the doctors at your local hospital, we can put you in touch with them.

This letter was sent to you on behalf of RECOVERY by NHS England via APS (an NHS-approved mailing house).

Thank you again for your participation in this remarkable effort to save the lives of patients with COVID-19.

Yours sincerely,

The image shows two handwritten signatures in blue ink. The first signature is 'Martin U' and the second is 'Peter Horby'. Both signatures are written in a cursive style.

Professor Sir Martin Landray and Professor Sir Peter Horby, Chief Investigators



## Further information about the treatments tested in the RECOVERY trial

### The following treatments were found to be effective:

- **Dexamethasone** (a steroid treatment): In June 2020, we found that this drug reduced deaths by one third in patients who received treatment with a ventilator and by one fifth in patients receiving oxygen only. That means that one death is prevented for every eight patients on ventilators who receive the treatment, and one death is prevented for every 25 patients on oxygen alone. Within hours of announcing these results, doctors started using dexamethasone to treat patients in the UK. NHS England have estimated that dexamethasone saved over a million lives worldwide between announcement of this breakthrough result in June 2020 and March 2021.
- **Tocilizumab** (an anti-inflammatory treatment given by injection): In February 2021, we found that tocilizumab, an established treatment for arthritis, added to the benefit of dexamethasone in improving outcomes of patients with COVID-19. Tocilizumab significantly reduced deaths, reduced the chance of progressing to treatment with a ventilator, and shortened hospital stays. The combination of dexamethasone and tocilizumab reduced deaths by about one third for patients requiring simple oxygen and nearly one half for those requiring invasive mechanical ventilation. Tocilizumab is now part of the standard care for those patients on oxygen support who are likely to benefit.
- **Ronapreve** (an antibody treatment developed by Regeneron Pharmaceuticals). The treatment uses a combination of two antibodies which prevent the virus from infecting cells. In June 2021, we found that this treatment reduces the risk of death when given to patients who have not produced antibodies to the virus themselves. The treatment is less effective against the Omicron variant and so it is recommended for use for other COVID-19 variants.
- **Baricitinib** (an anti-inflammatory treatment for rheumatoid arthritis): In March 2022, we found that baricitinib reduces the risk of death when given to hospitalised patients with severe COVID-19. The benefit was in addition to those of dexamethasone and tocilizumab, the two other anti-inflammatory treatments which had previously been shown to reduce the risk of death in these patients (see above).

### The following treatments were found not to be effective:

- **Hydroxychloroquine** (a treatment for malaria): Hydroxychloroquine has been used to treat COVID-19 patients despite a lack of evidence. In early June 2020, we concluded that this drug did not reduce the number of deaths or the length of time patients with COVID-19 spent in hospital, or benefit patients in any other way. As a result, hydroxychloroquine was removed from the RECOVERY trial and guidelines for doctors were updated.

- **Lopinavir-ritonavir** (an antiviral treatment commonly used to treat HIV): In June 2020, we also found that there is no beneficial (or harmful) effect of lopinavir-ritonavir in patients hospitalised with COVID-19. This treatment had been recommended in many countries, but it has now been removed from the trial and relevant guidelines have been updated.
- **Azithromycin** (an antibiotic that also reduces inflammation): In December 2020, we found that azithromycin is not an effective treatment for patients hospitalised with COVID-19. Azithromycin had been used to treat COVID patients because of its theoretical potential to reduce lung inflammation.
- **Convalescent plasma**: This is part of the donated blood from those who have recovered from COVID-19 which contains antibodies against the SARS-CoV-2 virus that causes COVID-19. In January 2021, we stopped this part of the trial because there was no convincing evidence that convalescent plasma benefitted patients admitted to hospital with COVID-19. We are grateful, however, for the generous donation of plasma by patients recovered from COVID-19, coordinated by NHS Blood and Transplant.
- **Colchicine** (a common anti-inflammatory treatment): In March 2021, we concluded that there was no convincing evidence that colchicine improved outcomes of patients with COVID-19. RECOVERY evaluated colchicine as it is used to treat various inflammatory conditions (such as gout) and had the potential to reduce symptoms of severe COVID-19.
- **Aspirin** (commonly used to thin the blood): In June 2021, we found that aspirin does not reduce the numbers of people dying from severe COVID-19 or help to prevent patients progressing to treatment with a ventilator. There was a slight reduction in the time that patients needed to stay in hospital.
- **Dimethyl fumarate** (anti-inflammatory drug usually prescribed to treat multiple sclerosis and psoriasis): We assessed dimethyl fumarate to find out whether it reduced the severity of COVID-19 after five days of treatment. It was thought that the drug might reduce the inflammation involved in the lung damage caused by COVID-19, but we have found that it does not provide any benefit in patients admitted to hospital. This was the first trial of this treatment for COVID-19, so this result helped us to understand more about lung damage in COVID-19, and to focus on other treatments that may be effective.
- **Empagliflozin** (a treatment for diabetes, kidney disease and heart failure): It had been thought that empagliflozin might protect against organ damage and improve outcomes for patients with COVID-19, but in April 2023, we announced that empagliflozin did not reduce deaths from COVID-19 or provide any other benefits to severely ill patients.

- **Higher dose corticosteroids:** RECOVERY has demonstrated that low doses of corticosteroids reduce the risk of death for patients admitted to hospital for COVID-19. There had been interest in whether using a higher dose of corticosteroids would provide additional benefits. In April 2023, we found that using higher doses of corticosteroids resulted in an increased risk of death for certain patients — adults with low blood oxygen levels or receiving simple oxygen therapy but who did not require more intensive breathing support. We are still investigating whether this treatment benefits those requiring more intensive forms of respiratory support.

### **We have stopped recruiting patients to test these treatments:**

- **Molnupiravir**, an antiviral tablet treatment originally developed for influenza; and
- **Paxlovid**, another antiviral treatment.

We are currently analysing the results ready for publication.

### **We are continuing to enrol patients to test these treatments:**

- **Sotrovimab**, a monoclonal antibody that may be effective for the Omicron variant; and
- **Higher dose corticosteroids** in the sickest patients who need mechanical breathing support.

You can read more about the results from the trial and the treatments being tested on our website at [recoverytrial.net](https://recoverytrial.net).

### **How we are using your data**

All information about you and your health is kept private. Data from which you cannot be recognised may be shared with other research groups who are doing similar research. There is more information about this in the 'For patients' section of the trial website ([recoverytrial.net/patients](https://recoverytrial.net/patients)).

We are collaborating with other research groups to generate the best possible scientific information about COVID-19 treatments. For any participants who have also entered the ISARIC4C study ([isaric4c.net](https://isaric4c.net)), we may combine your data from the two research studies, in a secure and confidential manner, to gain insights that would not be possible through either study alone.

Researchers working on other studies can now apply to access RECOVERY trial data so that they can answer new research questions using data that have already been collected. The researchers must demonstrate that their work will benefit public health and they will only be provided with the information needed to answer their specific question. You can find out more about this in an animation in the patients' section of the trial website.