

[ID number]

[name and address]

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.

It is now over a year since the RECOVERY trial first started. It is now the largest trial in the world to find effective treatments against COVID-19 for patients in hospital, with over 40,000 participants so far. Whether you participated recently, or during the very first wave of the pandemic, your contribution has played an essential role in improving the care of those who contract this devastating disease. Thanks to your involvement, patients hospitalised with COVID-19 now receive better treatment than before.

What have we learnt from RECOVERY so far?

In addition to discovering whether several drugs are effective in treating people in hospital with COVID-19 (see below for more details), we have also learnt more about how to run trials in this setting. One particular aspect we have learnt about is how we recruit patients and how they give their consent to participate.

You were recruited into RECOVERY when you were unwell with COVID-19 in hospital. If possible, the doctors and nurses at your hospital would have discussed this with you in person, but if you were too unwell then they would have sought the opinion of a 'legal representative' (either a relative or another doctor). On the basis of this consent you may have received study treatment in addition to the usual care given in the NHS (decided by a computer which allocated you at random - like rolling a dice - between the possible treatment options), and we collected some information about the care you received from your hospital and NHS records.

If a legal representative agreed for you to be in the trial because you were initially too unwell to discuss the trial yourself, you should have been informed about your participation before you left hospital.

We are aware that some participants whose consent was provided by a 'legal representative' were not given the opportunity to confirm their agreement to the study once they had recovered sufficiently to do so, for which we sincerely apologise. We have also found some evidence of other issues with the consent process for some participants (for example, consent being obtained verbally rather than in writing; the 'legal representative' not always being fully independent). The study has been inspected by the MHRA (the UK government's regulatory authority) who noted these issues in some cases. They did though recognise the extraordinary circumstances in the NHS at the time, which made it hard for trial teams to discuss the trial with participants prior to hospital discharge.

We remain committed to making sure that everyone in the study knows about their participation, what is involved for them and their rights. If you have any concerns and would like to discuss your participation please see the "Communicating with you" section below. If you would prefer to speak to the doctors at your local hospital, we can put you in touch with them.

We have also put procedures in place to minimise the chances of this happening in the future in RECOVERY. These procedures have been discussed and agreed with the independent ethics committee which oversees the trial. What we have learnt will also improve future trials that would be conducted in similar circumstances.

What is involved for me from now on?

Now that you are out of hospital, we would like to do two things. First, we wish to continue to provide you with information about the study with newsletters like this one. Second, we would like to continue to obtain information about your health from your NHS records and other research databases (if you have provided information or samples to them). This is so that the study team can get more detailed and longer-term information about the effects of the study treatments on your health.

How is my information handled?

All information about you and your health will be kept private. The only people allowed to look at the information will be the doctors who are running the study, authorised staff at Oxford University and your hospital, and the regulatory authorities who check that the study is being conducted correctly. Data from which you cannot be recognised may be shared with other research groups who are doing similar research. This 'anonymised' information will not make it possible for you to be picked out as its source, and will not be combined with other information in a way that could allow that to be done.

A privacy notice is on the study website (<https://www.recoverytrial.net/study-faq/data-privacy>). The privacy notice explains how your data are used, who can see it, and your rights, which include opting out of these newsletters and/ or opting out of providing your health information to RECOVERY.

Do I have to continue my involvement?

No. You can opt out of receiving the newsletters and/or allowing the study team access to future health information. To do so, 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 (available at the top of this letter) in any correspondence. If we don't hear from you, we will continue to send you newsletters and collect information about your health from your NHS records.

Trial results

The RECOVERY trial achieved its first major success in June 2020 when we discovered that the steroid dexamethasone is effective for hospitalised patients requiring oxygen or a mechanical ventilator. NHS guidelines were rapidly updated so that dexamethasone became part of standard care for future patients.

Since then, we have found two other treatments that are effective for severe COVID-19:

- An arthritis treatment, **tocilizumab**, adds to the benefit of dexamethasone in significantly reducing deaths from COVID-19.
- An **antibody treatment** developed specifically to treat COVID-19, now known as Ronapreve, reduces the risk of death when given to patients who have not produced their own antibodies to the virus. (Antibodies are an important part of the immune system.)

We have also found out that a number of other treatments are not effective for patients hospitalised with COVID-19. Although disappointing, these results are still very important as they might otherwise be used, taking up NHS time and money for no benefit. You can read more about these results at the end of this letter and in the news section of the RECOVERY website at www.recoverytrial.net/news.

Global impact

RECOVERY has had global impact. Given its scale, the results from the RECOVERY trial are widely regarded as providing robust and reliable evidence on COVID-19 treatments and have influenced healthcare practices across many countries. For instance, NHS England have estimated that dexamethasone saved over one million lives worldwide between July 2020 and March 2021, including 22,000 in the UK.

In February 2021, the RECOVERY trial launched internationally, with trial sites in Nepal, Indonesia, and Vietnam, and with others planned around the world. This will allow us to increase the global relevance of the trial's results, and identify affordable, effective treatments that can be used even in less well-resourced settings.

RECOVERY's first anniversary

On 23 March 2021, we marked the first anniversary of the RECOVERY trial. As part of this, BBC Radio Four dedicated an episode of the health programme, *Inside Health*, to RECOVERY and the trial's impact. You can hear the programme at <https://www.bbc.co.uk/programmes/m000tccg>.

This was a good opportunity to reflect on the ups and downs so far, and the remarkable support from scientists and clinical researchers, hospital ward teams, policy makers and of course, participants. We feel privileged to be part of RECOVERY, overwhelmed by the contribution of all involved, and proud of what this amazing trial has achieved – and hope you are too.

In the words of RECOVERY participant Kimberley Featherstone: 'Being given the opportunity to participate in the RECOVERY trial was very humbling, knowing that the information they were collecting had a direct impact on the treatment of patients, and signing on was something I did gladly.'

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 www.recoverytrial.net/patients (where you will also find information about how we use your data). You will need your study ID number shown at the top of this letter.

If you would like to discuss anything in this newsletter 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.

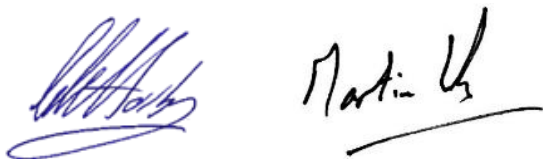
This letter was sent to you on behalf of RECOVERY by [mailing details].

Joining our advisory group

We would also like to invite you to be part of a group to advise us on future communications and other aspects of the trial. If you would be interested in hearing more about this, please contact us. We really value the involvement of former patients in our research.

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 signature on the left is 'Peter Horby' and the signature on the right is 'Martin Landray'. Both signatures are written in a cursive, flowing style.

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

Further information about the treatments tested in the RECOVERY trial

To date, twelve treatments have either been tested, or are currently being tested, in the RECOVERY trial.

The following treatments were found to be effective:

- **Dexamethasone** (a steroid treatment): 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.
- **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. Regeneron are collaborating with Roche to increase the global supply of the treatment and make it available to more people.
- **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 mortality 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 COVID-19 patients on oxygen support who are likely to benefit.

The following treatments were found not to be effective:

- **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.
- **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.

- **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.
- **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. We found no convincing evidence of the effect of convalescent plasma on clinical outcomes in 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.
- **Hydroxychloroquine** (a treatment for malaria): Hydroxychloroquine had 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): We have 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.

We are continuing to enrol patients to test these treatments:

- **Baricitinib** – an anti-inflammatory treatment for rheumatoid arthritis that may also work against the virus.
- **Dimethyl fumarate** – a treatment for multiple sclerosis that alters the immune response and has demonstrated anti-viral and anti-inflammatory effects against SARS-CoV-2 in laboratory studies.
- **Empagliflozin** – a treatment for diabetes, kidney disease and heart failure that may also protect against organ damage and improve outcomes for patients with COVID-19.

We expect that other treatments will be tested in the RECOVERY trial in the future. You can read more about the results from the trial and the treatments being tested on our website at www.recoverytrial.net.