Development Safety Update Report (DSUR)

Report Number 3

Investigational drug(s)	Dexamethasone Empagliflozin Sotrovimab Molnupiravir Nirmatrelvir and ritonavir
Refers to CTIMP	Randomised Evaluation of COVID-19 Therapy (RECOVERY)
DIBD	17-Mar-2020
Reporting period	1-Apr-2022 to 31-Mar-2023
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Sponsor	University of Oxford
Address of Sponsor	Joint Research Office 1st Floor, Boundary Brook House Churchill Drive Headington Oxford OX3 7GB

This report was prepared by the Clinical Trial Service Unit (a Registered Clinical Trials Unit) on behalf of the Sponsor, and contains confidential information.

Name of Chief Investigator: Professor Peter Horby

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EXECUTIVE SUMMARY

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was established rapidly at the start of the COVID-19 pandemic in the UK. It is funded by the UK government (via UKRI and NIHR) and the regulatory sponsor is the University of Oxford. RECOVERY is being conducted at over a hundred NHS organisations in all four nations of the UK, as well as at international sites in Nepal, Indonesia, Vietnam, South Africa, India and Ghana.

RECOVERY is a platform trial, allowing multiple different IMPs to be assessed among patients hospitalised with COVID-19. Patients of any age who have been admitted to hospital with proven or suspected COVID-19 are eligible, as long as there is no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial. Pregnant women were included in the trial, but excluded from the assessment of certain IMPs for which the risks to the unborn child were considered too great.

The primary outcome is all-cause mortality within 28 days of randomisation. Secondary outcomes include the duration of admission and (among participants not on invasive mechanical ventilation at baseline) the composite of invasive mechanical ventilation or death.

IMPs

The RECOVERY Trial has assessed a number of IMPs (see Table).

IMP	Number in comparison	Number on active IMP	Recruitment period
Dexamethasone*	6425	2104	19-Mar-2020 to 8-Jun-2020
Lopinavir-ritonavir*	5040	1616	19-Mar-2020 to 29-Jun-2020
Hydroxychloroquine*	4716	1561	25-Mar-2020 to 5-Jun-2020
Azithromycin*	7763	2582	7-Apr-2020 to 27-Nov-2020
Tocilizumab	4177	2054	23-Apr-2020 to 20-Jan-2022†
Convalescent plasma*‡	11,558	5795	28-May-2020 to 15-Jan-2021
Casirivimab-imdevimab (REGN-COV2)	9785	4839	18-Sep-2020 to 22-May-2021
Aspirin*	14,892	7351	1-Nov-202 to 21-Mar-2021
Colchicine*	11,340	5610	27-Nov-2020 to 4-Mar-2021
Baricitinib*	8156	4148	2-Feb-2021 to 29-Dec-2021
Dimethyl fumarate*	713	356	2-Mar-2021 to 18-Nov-2021
Corticosteroids (children)*	133	62	20-Sep-2020 to 16-Jul-2021
Intravenous immunoglobulin*	128	73	20-Sep-2020 to 16-Jul-2021
Anakinra*	26	14	4-Jul-2021 to 20-Jan-2022
High-dose corticosteroids	1727	896	25-May-2021, recruitment ongoing§
Empagliflozin	4271	2113	28-Jul-2021 to 6-Mar-2023
Sotrovimab	1539	749	31-Dec-2021, recruitment ongoing
Molnupiravir	872	426	24-Jan-2022, recruitment ongoing
Nirmatrelvir and ritonavir (Paxlovid)	125	62	28-Mar-2022, recruitment ongoing

* Recruitment closed before the period covered by DSUR 3, so these IMPs are not included here

† Recruitment to the main tocilizumab comparison for patients with COVID-19 pneumonia ended 24-Jan-2021, but children with PIMS-TS continued to be randomised until 20-Jan-2022

‡ Convalescent plasma is not technically an IMP, but included here for completeness

§ Recruitment halted for participants not requiring ventilatory support on 13-May-2022 due to safety concerns

Note a planned comparison of infliximab was included in this table in the first DSUR, but this was abandoned before recruitment started

Safety assessment

The completed comparisons have demonstrated that dexamethasone, tocilizumab, baricitinib, and casirivimab-imdevimab all reduce the risk of death in patients admitted to hospital with COVID-19, and these treatments have subsequently been commonly used worldwide.

One comparison, of higher-dose corticosteroids versus usual care, has demonstrated that treatment is associated with an increased risk of death in patients not requiring ventilatory support at the time of trial entry. This hazard was identified during a routine review by the Data Monitoring Committee (DMC), and led to an urgent safety measure in May 2022 to stop recruitment in this group. These results have now been published, and the comparison remains open to patients who do require ventilatory support (as recommended by the DMC).

Eight comparisons have been reported that demonstrated no material benefit of the IMP, nor any conclusive hazard (hydroxychloroquine, lopinavir/ritonavir, azithromycin, convalescent plasma, aspirin, colchicine, dimethyl fumarate, and empagliflozin).

A further four comparisons have closed and are in the follow-up or analysis stage (anakinra, tocilizumab, corticosteroids, and IVIg in children).

Four comparisons are ongoing (high-dose corticosteroids in patients requiring ventilatory support, sotrovimab, molnupiravir, and nirmatrelvir-ritonavir). The unblinded interim data for these comparisons are reviewed regularly by the independent Data Monitoring Committee and no safety concerns have been identified.

Conclusion

The RECOVERY trial has demonstrated that it is possible to embed a robust randomised controlled platform trial into routine clinical care during a pandemic, which can then provide reliable information on the safety and efficacy of many treatments recommended for COVID-19.

Unblinded data from the ongoing comparisons within RECOVERY are being regularly reviewed by the independent Data Monitoring Committee who have not raised any safety concerns with these IMPs. Recruitment will continue until sufficient numbers of participants have been recruited to reliably assess the effects of the IMPs, unless the DMC recommend otherwise first.