Development Safety Update Report (DSUR)

Report Number 5

Investigational drug(s)	Baloxavir marboxil Dexamethasone Hydrocortisone Oseltamivir Prednisolone
Refers to CTIMP	Randomised Evaluation of COVID-19 Therapy (RECOVERY)
DIBD	17-Mar-2020
Reporting period	1-Apr-2024 to 31-Mar-2025
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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.

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EXECUTIVE SUMMARY

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) platform trial was established at the start of the COVID-19 pandemic in the UK. It initially evaluated treatments for patients hospitalised with COVID-19 and children with paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), and is currently evaluating treatments for patients hospitalised with influenza and community-acquired pneumonia (CAP).

It was initially funded by the UK government (via UKRI and NIHR), with subsequent funding from the Wellcome Trust and Flu Lab (a US-based charity). The regulatory sponsor is the University of Oxford. RECOVERY is being conducted at NHS organisations in all four nations of the UK, and at sites in thirteen other countries (Nepal, Indonesia, Vietnam, South Africa, Ghana, France, the Netherlands, Italy, Belgium, Sweden, Spain, Portugal, and Romania). Children and pregnant or breastfeeding women are included in the trial, but excluded from the assessment of certain IMPs.

The primary outcome is all-cause mortality within 28 days of randomisation. Duration of admission is a co-primary outcome for influenza comparisons, and a secondary outcome for COVID-19 and CAP comparisons. The composite of invasive ventilation or death among patients not on invasive ventilation at baseline is a secondary outcome for all COVID-19, influenza and CAP comparisons.

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

IMP	Condition	Number in comparison	Number on active IMP	Recruitment period
Dexamethasone*	COVID-19	6425	2104	19-Mar-2020 to 8-Jun-2020
Lopinavir-ritonavir*	COVID-19	5040	1616	19-Mar-2020 to 29-Jun-2020
Hydroxychloroquine*	COVID-19	4716	1561	25-Mar-2020 to 5-Jun-2020
Azithromycin*	COVID-19	7763	2582	7-Apr-2020 to 27-Nov-2020
Tocilizumab*	COVID-19	4116	2022	23-Apr-2020 to 20-Jan-2022
Convalescent plasma*‡	COVID-19	11,558	5795	28-May-2020 to 15-Jan-2021
Casirivimab-imdevimab*	COVID-19	9785	4839	18-Sep-2020 to 22-May-2021
Aspirin*	COVID-19	14,892	7351	1-Nov-202 to 21-Mar-2021
Colchicine*	COVID-19	11,340	5610	27-Nov-2020 to 4-Mar-2021
Baricitinib*	COVID-19	8156	4148	2-Feb-2021 to 29-Dec-2021
Dimethyl fumarate*	COVID-19	713	356	2-Mar-2021 to 18-Nov-2021
Corticosteroids*	PIMS-TS	133	62	20-Sep-2020 to 16-Jul-2021
IV immunoglobulin*	PIMS-TS	128	73	20-Sep-2020 to 16-Jul-2021
Anakinra*	PIMS-TS	26	14	4-Jul-2021 to 20-Jan-2022
Tocilizumab*	PIMS-TS	56	28	4-Jul-2021 to 20-Jan-2022
Higher-dose corticosteroids*	COVID-19	1749	905	25-May-2021 to 31-Mar-2024§
Empagliflozin*	COVID-19	4271	2113	28-Jul-2021 to 6-Mar-2023
Sotrovimab*	COVID-19	1723	828	31-Dec-2021 to 31-Mar-2024
Molnupiravir*	COVID-19	923	445	24-Jan-2022 to 24-May-2023
Nirmatrelvir-ritonavir*	COVID-19	137	68	28-Mar-2022 to 24-May-2023
Baloxavir marboxil	Influenza	745	351	07-Mar-2023 – ongoing
Oseltamivir	Influenza	211	105	13-Oct-2023 – ongoing
Dexamethasone	Influenza	288	156	28-Dec-2023 – ongoing
Dexamethasone	CAP	587	283	08-Jan-2024 – ongoing

* Recruitment closed before the period covered by DSUR 5, so these IMPs are not reported here.

‡ 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.

Safety assessment

The completed comparisons have demonstrated that dexamethasone, tocilizumab, baricitinib, casirivimab-imdevimab, and sotrovimab all reduce the risk of death in some patients admitted to hospital with COVID-19, and these treatments have been commonly used worldwide. The RECOVERY evaluation of treatments for PIMS-TS has also shown that tocilizumab reduces the duration of hospital stay in this condition.

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.

Thirteen treatment evaluations have been reported in which there was no conclusive evidence of benefit or hazard of the IMP (hydroxychloroquine, lopinavir/ritonavir, azithromycin, convalescent plasma, aspirin, colchicine, dimethyl fumarate, empagliflozin, molnupiravir and nirmatrelvir-ritonavir for COVID-19, and corticosteroids, intravenous immunoglobulin, and anakinra for PIMS-TS).

Four comparisons are ongoing (dexamethasone, oseltamivir and baloxavir marboxil for influenza, and dexamethasone for community-acquired pneumonia). 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 demonstrated that it is possible to embed a robust randomised controlled platform trial into routine clinical care during a pandemic, and provided reliable information on the safety and efficacy of many treatments for COVID-19 and PIMS-TS. RECOVERY is now applying the same approach to evaluate treatments for influenza and CAP, both common causes of pneumonia requiring hospital admission.

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 current 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.