Development Safety Update Report (DSUR)

Report Number 6

Investigational drug(s)	Baloxavir marboxil Dexamethasone Hydrocortisone Oseltamivir Prednisolone
Refers to CTIMP	Randomised Evaluation of COVID-19 Therapy (RECOVERY)
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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

Signature of Chief Investigator:

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 either influenza pneumonia or presumed bacterial 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 fourteen other countries (Indonesia, Nepal, Vietnam, Ghana, South Africa, Belgium, Estonia, France, Italy, Netherlands, Portugal, Romania, Spain, and Sweden). 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 the CAP comparison. The composite of invasive ventilation or death among patients not on invasive ventilation at baseline is a secondary outcome for all 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-2020 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	1357	643	07-Mar-2023 – ongoing
Oseltamivir	Influenza	456	236	13-Oct-2023 – ongoing
Dexamethasone	Influenza	569	310	28-Dec-2023 – ongoing
Dexamethasone	CAP	1812	888	08-Jan-2024 – ongoing

* Recruitment closed before the period covered by DSUR 6, 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.

Based on data accrued from RECOVERY and from other studies published in the reporting period, we conclude that there is no indication of any new safety signal for the IMPs being tested, and our previous benefit-risk assessment remains unchanged.

Conclusion

The RECOVERY trial demonstrated that it is possible to embed a robust randomised controlled platform trial into routine clinical care 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.

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1. INTRODUCTION

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 either influenza pneumonia or presumed bacterial 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 fourteen other countries (Indonesia, Nepal, Vietnam, Ghana, South Africa, Belgium, Estonia, France, Italy, Netherlands, Portugal, Romania, Spain, and Sweden).

RECOVERY is a platform trial, allowing multiple different IMPs to be assessed among patients hospitalised with pneumonia. Comparisons are currently open to patients with either (i) confirmed influenza A or B infection, or (ii) CAP with planned antibiotic treatment (without suspected influenza, SARS-CoV-2, *Pneumocystis jirovecii* pneumonia, or active pulmonary tuberculosis). No comparisons for COVID-19 or PIMS-TS are currently open. Children and pregnant or breastfeeding are included in the trial, but excluded from the assessment of certain IMPs.

After confirmation of eligibility and provision of written informed consent (either from the patient or a legal representative), participants are randomised between treatments which are both available at their site and to which there is no contraindication. All comparisons are open-label and in addition to the usual care the participant would have received (and compared with usual care alone without the relevant treatment).

There has been one change to the protocol during the reporting period. Protocol V28.0 (30-Jun-2025) was introduced in Autumn 2025. This did not introduce any new treatments or trial procedures, and updated the protocol text and appendices to remove information about closed comparisons. Treatment regimens for each IMP are shown in the table below. For detailed information on dose modifications and contraindications, see the current protocol.

IMP (route)	Regimen	Notes
Baloxavir marboxil PO (influenza)	40mg (or 80mg if weight ≥80kg). Two doses, given on day 1 and day 4	Children <12y excluded
Oseltamivir PO (influenza)	75mg twice daily for 5 days (10 days if immunosuppressed)	
Dexamethasone PO/IV (same regimen for influenza and CAP)	6mg once daily for 10 days	Prednisolone/hydrocortisone used in pregnant women. Children excluded from CAP comparison.

Outcomes: For influenza and CAP comparisons 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 the CAP comparison. The composite of invasive ventilation or death among patients not on mechanical ventilation at baseline is a secondary outcome for influenza and CAP comparisons.

Subsidiary outcomes include need for any ventilation, renal replacement therapy and thrombotic events. Safety outcomes recorded in all patients include bleeding, thrombosis, new major cardiac arrhythmia, acute liver or kidney injury, hyper/hypoglycaemia, seizures, and non-pneumonia infections.

2. WORLDWIDE MARKETING APPROVAL STATUS

All IMPs currently have a marketing authorisation, but the sponsor is not the MA Holder and therefore not aware of the worldwide approval status.

3. ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

No actions were taken in the reporting period for safety reasons.

4. CHANGES TO REFERENCE SAFETY INFORMATION

All IMPs are licenced and the RSI refers to their Summary of Product Characteristics (as submitted with relevant amendment, see Section 7). All SmPCs are reviewed annually to determine whether an update to the RSI is required. The SmPCs for dexamethasone, prednisolone, hydrocortisone, and oseltamivir were updated to current versions in substantial amendment 27.0 (13-Sep-2023). The SmPC for baloxavir marboxil was updated to the current version in substantial amendment 28.0 (30-Jun-2025). SmPCs for all IMPs were last reviewed in April 2026, but there were no significant changes to the RSI compared to previous versions.

5. INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

This DSUR only relates to the RECOVERY trial. The sponsor is not conducting any other trials of these IMPs in the same patient population.

6. ESTIMATED CUMULATIVE EXPOSURE

6.1. CUMULATIVE SUBJECT EXPOSURE IN THE DEVELOPMENT PROGRAMME

The following numbers of participants have been included in the various comparisons within RECOVERY. Randomisations are factorial and participants are counted in every comparison they are included in (so may be included in more than one row in this table).

IMP	Number in comparison	Number on active IMP	Recruitment period
Oseltamivir (influenza)	456	236	13-Oct-2023 – ongoing
Baloxavir marboxil (influenza)	1357	643	7-Mar-2023 – ongoing
Dexamethasone (influenza)	569	310	28-Dec-2023 – ongoing
Dexamethasone (CAP)	1812	888	8-Jan-2024 – ongoing

The baseline characteristics of each trial cohort are shown in section 8.2.

6.2. PATIENT EXPOSURE FROM MARKETING EXPERIENCE

This is not applicable as this is an investigator-led study sponsored by a non-commercial sponsor.

7. DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

7.1. REFERENCE INFORMATION

IMP	Date of SmPC
Dexamethasone	01-Feb-2022 (PO) 23-Feb-2022 (IV)
Prednisolone	23-Mar-2023
Hydrocortisone	31-Mar-2023
Baloxavir marboxil	02-Jun-2025
Oseltamivir	25-Jan-2023

7.2. LINE LISTINGS OF SERIOUS ADVERSE REACTIONS DURING THE REPORTING PERIOD

See Appendix 1.

7.3. CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS

The RECOVERY protocol does not require collection of serious adverse events unless they are believed to be related to study treatment with reasonable probability.

8. SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

8.1. COMPLETED CLINICAL TRIALS

The primary analyses of all COVID-19 treatment comparisons, based on 28-day outcomes, were released before the reporting period. In DSUR 5 we reported analyses of the sotrovimab comparison that had been released as a preprint, and these have now been published (www.ncbi.nlm.nih.gov/pubmed/40886716).

A preprint reporting analyses of 6-month outcomes for all COVID-19 comparisons was posted by the RECOVERY investigators during the current reporting period (www.medrxiv.org/content/10.1101/2025.08.29.25334732v1). This found that for each of the treatments previously demonstrated to be effective at 28 days (dexamethasone, tocilizumab, baricitinib, casirivimab-imdevimab, and sotrovimab), the early mortality benefit was preserved up to 6 months. In line with the 28-day results, aspirin, azithromycin, colchicine, convalescent plasma, dimethyl fumarate, empagliflozin, lopinavir-ritonavir, molnupiravir, and nirmatrelvir-ritonavir did not reduce 6-month mortality. In keeping with the 28-day results, mortality at 6 months was higher with hydroxychloroquine therapy (33.3% vs. 30.2%; RR 1.14; 95% CI 1.02–1.27; p=0.018) and, among hypoxic patients not requiring ventilatory support, with higher dose dexamethasone (initial dose 20mg daily, 22.0% vs. 17.6%, RR 1.34; 95% CI 1.04–1.72; p=0.021). Allocation to dexamethasone 6mg once daily resulted in a small increase in major non-COVID infection within 6 months compared with usual care (21.4% vs. 19.1%; absolute difference 2.2%; 95% CI 0.2–4.5%). We found no evidence that any other treatments increased the risk of major non-COVID infection.

8.2. ONGOING CLINICAL TRIALS

Recruitment is ongoing for the influenza & CAP comparisons.

Baloxavir marboxil (influenza): 1357 recruited up to 31-Mar-2026, including three participants aged under 18 years and one pregnant woman.

Characteristic		Mean (SD); n (%); median (IQR)
Age (mean)		66.4 (16.3)
Male		661 (49%)
Days since symptom onset (median)		5 (3-8)
Respiratory support	No oxygen	418 (31%)
	Oxygen without non-invasive ventilation	765 (56%)
	Oxygen with non-invasive ventilation	136 (10%)
	Invasive ventilation	38 (3%)
Co-morbidity†		964 (71%)

† At least 1 of diabetes, heart disease, chronic lung disease, TB, HIV, severe liver disease, severe kidney impairment

By 31-Mar-2026, 48 participants (4%) had died. All trial staff (except the Data Monitoring Committee and those responsible for providing analyses to them) remain blind to the results.

Oseltamivir (influenza): 456 recruited to 31-Mar-2026, including 9 participants aged under 18 years and one pregnant woman.

Characteristic		Mean (SD); n (%); median (IQR)
Age (mean)		65.7 (19.2)
Male		215 (47%)
Days since symptom onset (median)		4 (3-7)
Respiratory support	No oxygen	161 (35%)
	Oxygen without non-invasive ventilation	238 (52%)
	Oxygen with non-invasive ventilation	48 (11%)
	Invasive ventilation	9 (2%)
Co-morbidity†		303 (66%)

† At least 1 of diabetes, heart disease, chronic lung disease, TB, HIV, severe liver disease, severe kidney impairment

By 31-Mar-2026, 19 participants had died (4%). All trial staff (except the Data Monitoring Committee and those responsible for providing analyses to them) remain blind to the results.

Dexamethasone (influenza): 569 recruited to 31-Mar-2026, including 15 participants aged under 18 years and no pregnant women.

Characteristic		Mean (SD); n (%); median (IQR)
Age (mean)		68.0 (18.5)
Male		289 (50%)
Days since symptom onset (median)		5 (3-7)
Respiratory support	No oxygen*	7 (1%)
	Oxygen without non-invasive ventilation	450 (79%)
	Oxygen with non-invasive ventilation	89 (16%)
	Invasive ventilation	23 (4%)
Co-morbidity†		336 (59%)

* Participants must be hypoxic to be eligible for this comparison (requiring supplemental oxygen or with peripheral oxygen saturations <92% on air).

† At least 1 of diabetes, heart disease, chronic lung disease, TB, HIV, severe liver disease, severe kidney impairment

By 31-Mar-2026, 37 participants (7%) had died. All trial staff (except the Data Monitoring Committee and those responsible for providing analyses to them) remain blind to the results.

Dexamethasone (CAP): 1812 recruited to 31-Mar-2026. No pregnant women have been recruited, and children under 18 years are excluded from this comparison.

Characteristic		Mean (SD); n (%); median (IQR)
Age (mean)		63.9 (17.6)
Male		974 (54%)
Days since symptom onset (median)		5 (3-8)
Respiratory support	No oxygen	683 (38%)
	Oxygen without non-invasive ventilation	953 (53%)
	Oxygen with non-invasive ventilation	161 (9%)
	Invasive ventilation	15 (1%)
Co-morbidity†		954 (53%)

† At least 1 of diabetes, heart disease, chronic lung disease, TB, HIV, severe liver disease, severe kidney impairment

By 31-Mar-2026, 93 participants (5%) had died. All trial staff (except the Data Monitoring Committee and those responsible for providing analyses to them) remain blind to the results.

8.3. LONG-TERM FOLLOW-UP

The trial protocol and consent materials include provision for long-term follow-up through routinely collected data.

8.4. OTHER THERAPEUTIC USE OF INVESTIGATIONAL DRUG

This section is not applicable, as the sponsor does not have expanded access or compassionate use programmes for these IMPs.

8.5. NEW SAFETY DATA RELATED TO COMBINATION THERAPIES

This section is not applicable.

9. SAFETY FINDINGS FROM NON-INTERVENTIONAL STUDIES

This is not applicable as the sponsor is not conducting any non-interventional studies.

10. OTHER CLINICAL TRIAL/STUDY SAFETY INFORMATION

Ad hoc DMC review following closure of oseltamivir comparison in the REMAP-CAP trial

On 19th March 2026 the RECOVERY team were contacted in confidence by investigators from the REMAP-CAP platform trial, which is also evaluating oseltamivir in patients admitted to hospital with influenza. They alerted us to a decision by their DSMB to suspend recruitment to the oseltamivir arms in critically ill adults. The oseltamivir arms had reached a statistical trigger for inferiority when compared to other interventions in this patient group, with a suggestion of potential for harm of oseltamivir.

This was communicated to the RECOVERY Data Monitoring Committee immediately, and the committee chair provided the following response on 27th March 2026.

"RECOVERY trial DMC report

Thank you for the note informing me about the decision by the REMAP CAP to suspend recruitment in the oseltamivir comparisons in the trial. Since I received your email, the following have occurred:

1. Meeting with REMAP CAP DSMB.

After a confidential discussion on 25th March by teleconference with the Chair and Statistician of REMAP CAP, it was agreed that, until the REMAP CAP team had completed further detailed analyses and were able to make a definitive public announcement, the available data did not support the case to suspend recruitment in RECOVERY.

2. Review of the current RECOVERY data (data freeze 23/3/26) and relevant external data.

Based on the latest information from the case report forms (but not updated record linkage), the oseltamivir vs control comparison in RECOVERY included 451 patients. The systematic review by Gao et al. Lancet 2026 provided only weak evidence on the effects of oseltamivir on mortality, based on 74 patients.

3. Decision by the DMC.

Taken together with the available external evidence, after consultation with the DMC, we agreed there was no cogent reason to suspend recruitment to oseltamivir in RECOVERY. If further information is made public by REMAP CAP, this decision may need to be reviewed. There will be a meeting of the full DMC on 28th May."

Other trial/study information relevant to safety published during the reporting period

A review of the scientific, peer-reviewed literature was conducted for the duration of the current reporting period. In the searches performed, no new relevant safety findings were identified for any of the trial IMPs that were sufficiently robust or relevant to alter the established safety profile described in the SmPCs.

Dexamethasone, prednisolone and hydrocortisone

The full peer-reviewed publication of the REMAP-CAP hydrocortisone domain (flagged as late-breaking in DSUR 5) appeared during the reporting period (REMAP-CAP Investigators, Intensive Care Med 2025; pubmed.ncbi.nlm.nih.gov/40261382/). 658 ICU patients with severe community-acquired pneumonia (CAP) were randomised to a 7-day course of intravenous hydrocortisone 50mg every 6 hours or no corticosteroid; the fixed-duration hydrocortisone arm was stopped for futility. Day 90 mortality was 15.0% and 9.8% for the hydrocortisone and control groups, respectively. The adjusted odds ratio ranged from 1.52 to 1.63, with all 95% credible intervals crossing 1. No new safety findings were identified beyond the recognised corticosteroid adverse-effect profile, and no signal of disproportionate harm in the influenza subgroup was reported.

The SONIA trial (Lucinde et al, N Engl J Med 2025; pubmed.ncbi.nlm.nih.gov/41159889/) was published during the reporting period. This pragmatic, open-label randomised controlled trial conducted in 18 Kenyan public hospitals compared 10 days of oral corticosteroid (dexamethasone, hydrocortisone, methylprednisolone, prednisolone or prednisone, at a dose equivalent to 6mg dexamethasone daily) plus standard care versus standard care alone in 2,180 adults hospitalised with CAP. 30-day all-cause mortality was 22.6% in the glucocorticoid arm versus 26.0% in the control arm (HR 0.84, 95% CI 0.73-0.97; p=0.02). Serious adverse events considered related to glucocorticoid administration occurred in 5 patients (0.5%), and no new safety findings were identified beyond the recognised corticosteroid adverse-effect profile.

The American Thoracic Society published an updated clinical practice guideline on adult CAP during the reporting period (ATS Clinical Practice Guideline, Am J Respir Crit Care Med 2025; pubmed.ncbi.nlm.nih.gov/40679934/), suggesting systemic corticosteroids for hospitalised adults with severe non-influenza CAP (conditional recommendation, low-quality evidence) and recommending against their use in non-severe CAP. Hyperglycaemia was again highlighted as the most consistent corticosteroid-related adverse effect.

A systematic review and meta-analysis of corticosteroids in adults hospitalised with non-viral CAP was published during the reporting period (Pitre et al, Intensive Care Med 2025; pubmed.ncbi.nlm.nih.gov/40323455/). The authors concluded that corticosteroids probably reduced short-term (28-30 day) mortality (RR 0.82, 95% CI 0.74-0.91; moderate certainty), while the reduction in longer-term (60-90 day) mortality was less certain (RR 0.89, 95% CI 0.76-1.03; low certainty). With respect to safety, corticosteroids probably increased hyperglycaemia requiring intervention (RR 1.32, 95% CI 1.12-1.56; moderate certainty) but probably had no effect on secondary infections (RR 0.97, 95% CI 0.85-1.11; moderate certainty). No previously unrecognised adverse drug reactions were identified. The authors explicitly noted that further research is needed to delineate the effect of corticosteroids in patients with less severe CAP and patients with viral pneumonia, and to better identify which CAP subgroups (by severity, biomarker, or microbiological aetiology) are most likely to benefit - questions the RECOVERY CAP and influenza comparisons are well-placed to inform.

Oseltamivir

A network meta-analysis of antivirals for non-severe influenza was published during the reporting period (Gao et al, JAMA Intern Med 2025; pubmed.ncbi.nlm.nih.gov/39804622/). This review was restricted to outpatients and so did not include the population studied in RECOVERY (hospitalised patients); it therefore provides only indirect evidence of safety in the trial population. In this outpatient population, oseltamivir probably increased treatment-related adverse events relative to placebo or standard care (risk difference 2.8%, 95% CI 1.2 to 4.8; moderate certainty), driven principally by the

gastrointestinal events (nausea and vomiting) that are described in the SmPC, with no novel adverse drug reactions identified. A large Canadian retrospective cohort study using target trial emulation in 11,073 adults hospitalised with seasonal influenza (Bai et al, JAMA Netw Open 2025; pubmed.ncbi.nlm.nih.gov/40493366/) reported that early oseltamivir initiation (day 0 or 1) was associated with a 1.8% absolute reduction in in-hospital mortality and earlier discharge, with no new safety signals. As an observational study of administrative data, however, these findings are at high risk of residual confounding and selection bias, so randomised evidence is needed.

A systematic review and meta-analysis of neuropsychiatric and behavioural adverse events with oseltamivir was also published (Jeong et al, J Manag Care Spec Pharm 2025; pubmed.ncbi.nlm.nih.gov/41004206/). The pooled analysis did not find an increased risk of neuropsychiatric events with oseltamivir compared with control, and reported a possible protective effect for some categories, providing further reassurance regarding a long-standing area of post-marketing concern. Several additional Food and Drug Administration Adverse Event Reporting System (FAERS)-based pharmacovigilance analyses appeared during the reporting period, but the inherent reporting biases and absence of comparator groups in spontaneous reporting data mean these do not provide robust evidence of new safety concerns.

Baloxavir marboxil

The Gao et al network meta-analysis cited above (JAMA Intern Med 2025), which evaluated outpatients rather than the hospitalised population studied in RECOVERY, found no evidence that baloxavir marboxil was associated with increased risk of treatment-related adverse effects compared with placebo or standard care (risk difference −3.2%, 95% CI −5.2 to −0.6). A paediatric systematic review and meta-analysis (Zhu et al, PLOS ONE 2025; pubmed.ncbi.nlm.nih.gov/40549724/) comparing baloxavir marboxil with oseltamivir in 3,141 children reported a lower overall incidence of adverse events with baloxavir marboxil (p=0.03) and no new safety concerns.

A pharmacovigilance disproportionality analysis of FAERS data (Lai et al, BMC Pharmacol Toxicol 2025; pubmed.ncbi.nlm.nih.gov/40420187/) flagged potential signals for haemorrhagic events, hepatic dysfunction, rhabdomyolysis and rare cardiorespiratory events. As with the oseltamivir FAERS publications, these observations are subject to substantial reporting bias and absence of denominator or comparator data, and confounding by indication is possible (influenza itself is associated with several of these outcomes); they do not in our assessment establish new safety concerns.

The protocol for the INFLUENT trial (Hosszu-Fellous et al, Trials 2025; pubmed.ncbi.nlm.nih.gov/41286959/), a placebo-controlled randomised trial of single-dose baloxavir marboxil in hospitalised adults with influenza, was also published during the reporting period but results are not yet available.

11. SAFETY FINDINGS FROM MARKETING EXPERIENCE

The sponsor is not the marketing authorisation holder for the IMPs discussed in the DSUR and hence this section is not applicable.

12. NON-CLINICAL DATA

The researchers involved in the RECOVERY trial are not involved in any non-clinical studies of these IMPs so this section is not applicable.

13. LITERATURE

See section 10.

14. OTHER DSURs

The sponsor is not assessing these treatments in other trials of hospitalised patients with influenza or CAP.

15. LACK OF EFFICACY

See section 8.1

16. OTHER INFORMATION

16.1. CUMULATIVE SUMMARY TABULATION OF SARS

See Appendix 1.

17. LATE-BREAKING INFORMATION

None

18. OVERALL SAFETY ASSESSMENT

The completed evaluations have identified five life-saving treatments for COVID-19, and ruled out meaningful benefit for many others. Evaluations of four treatments for patients hospitalised with influenza and CAP are ongoing.

The Data Monitoring Committee met on one occasion during this reporting period, on 6-Nov-2025. After review of unblinded outcome and safety data they did not raise any concerns. The next DMC meeting will occur on 28-May-2026.

Outcome letters from all DMC meetings are available at https://www.recoverytrial.net/for-site-staff/site-set-up-1/data-monitoring-committee-correspondence.

18.1. EVALUATION OF THE RISKS

The trial protocol only requires suspected serious adverse reactions to be reported, and the volume and pattern of these is not concerning. These are all provided to the DMC so they can consider them in the light of the other unblinded data that they review.

18.2. BENEFIT-RISK CONSIDERATIONS

Corticosteroids are associated with several well-recognised risks, as outlined in the SmPC. These include hyperglycaemia, gastrointestinal bleeding and secondary infection (outcomes that are routinely recorded in all patients and monitored by the DMC). Patients hospitalised with influenza or community-acquired pneumonia are at significant risk of death, and it is possible that the treatments currently being tested could reduce this risk substantially. It is important to consider this when assessing potential risks of treatment. The sponsor presents the DMC with up-to-date information on trial participants as well as relevant information from other sources on the trial IMPs so that they can consider the totality of the evidence. It is not possible to make reliable inferences about benefits and risks on solely blinded data, hence the central role of the DMC.

We conclude that the information obtained in this reporting period does not indicate any new safety signal for the IMPs being tested, nor does it alter our previous benefit-risk assessment, so justifies continuation of this investigator initiated study without any modification.

19. SUMMARY OF IMPORTANT RISKS

Risk	Clinical data	Mitigations
Secondary infection	Corticosteroids, alone or in combination with other immunomodulatory therapies, can increase risk of infection	Risk highlighted in mandatory site staff training, with instructions to anticipate and manage this as per the usual practice of the responsible clinician. Collection of data on non-COVID-19 infections from all participants, and inclusion in DMC data for unblinded monitoring. Monitoring of SSARs related to infection, which are provided for DMC monitoring.
Hyperglycaemia	Corticosteroids can increase the risk of hyperglycaemia	Risk highlighted in mandatory site staff training, with instructions to anticipate and manage this as per the usual practice of the responsible clinician. Collection of data on metabolic complications from all participants (ketoacidosis, hyperglycaemic hyperosmolar state, hyperglycaemia requiring new use of insulin), and inclusion in DMC data for unblinded monitoring. Monitoring of SSARs related to metabolic complications, which are provided for DMC monitoring.
Gastrointestinal bleeding	Corticosteroids can increase the risk of gastrointestinal bleeding	Risk highlighted in mandatory site staff training, with instructions to anticipate and manage this as per the usual practice of the responsible clinician. Collection of data on bleeding from all participants, and inclusion in DMC data for unblinded monitoring. Monitoring of SSARs related to bleeding, which are provided for DMC monitoring.
Nephrotoxicity	Acute kidney injury is common in patients hospitalised with pneumonia and concern that some IMPs may worsen it.	Collection of baseline information on kidney function, peak post-randomisation creatinine, and severe acute kidney injury during follow-up, and provision to DMC. Monitoring of SSARs related to acute kidney injury, which are provided for DMC monitoring.
Hepatotoxicity	Acute liver injury is common in patients hospitalised with pneumonia and concern that some IMPs may worsen it.	Collection of baseline information on chronic liver disease and peak post-randomisation aspartate aminotransferase and bilirubin, and provision to DMC. Monitoring of SSARs related to acute liver injury, which are provided for DMC monitoring.
Hypersensitivity	Hypersensitivity is a recognised adverse effect of all treatments being tested	Patients with known hypersensitivity to a trial treatment would be excluded from that comparison. Monitoring of SSARs related to hypersensitivity to trial treatments, which are provided for DMC monitoring.

20. CONCLUSIONS

The RECOVERY trial has demonstrated that it is possible to embed a robust randomised controlled platform trial into routine clinical care during a pandemic, and has 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 the 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.

21. APPENDICES TO THE DSUR

Table 1: Line listing of suspected serious adverse reactions (SSARs) during the study period.

21.1. TABLE 1: LINE LISTING OF SUSPECTED SERIOUS ADVERSE REACTIONS (SSARs) DURING THE STUDY PERIOD

Includes SSARs reported during DSUR 6 reporting period. None were categorised as a SUSAR.

PT ID	Event description	MedDRA code	Event date	Main randomization date	Suspect IMP(s)	Reported reason for seriousness	Outcome
[redacted]	Hyperglycaemia	10020635	[redacted]	[redacted]	Dexamethasone (CAP)	Prolonged admission	Resolved before discharge [redacted]
	Hypertension	10020772			Dexamethasone (CAP)	Prolonged admission	Resolved before discharge [redacted]
	Hyperglycaemia	10020635			Dexamethasone (CAP)	Other important medical event	Not resolved on discharge [redacted] Alive at 6 month follow up
	Hypertension	10020772			Dexamethasone (CAP)	Other important medical event	Not resolved on discharge [redacted] Alive at 6 month follow up
	Pleural empyema	10090758			Dexamethasone (CAP)	Prolonged admission	Resolving on discharge [redacted]
	Rash	10037844			Baloxavir marboxil	Prolonged admission	Resolving on discharge [redacted]
	Hyperglycaemia	10020635			Dexamethasone (Flu)	Prolonged admission	Resolving on discharge [redacted]
	Hyperglycaemia	10020635			Dexamethasone (Flu)	Other important medical event	Resolving on discharge [redacted]