

Justification for RECOVERY Protocol V27.0

Substantial Amendment 33 (date 13-Sep-2023)

The trial steering committee wishes to extend the RECOVERY Platform to include patients with community-acquired pneumonia (CAP) caused by pathogens other than SARS-CoV-2 and influenza. The rationale is described in detail here.

Community-acquired pneumonia

In a non-pandemic context, most cases of CAP leading to hospital admission are caused by bacterial, rather than viral infection.¹ However, in routine practice the causative pathogen in patients with CAP is usually not identified, so CAP is a clinical diagnosis based on typical symptoms plus radiological evidence of acute lung infection (unlike pneumonia caused by SARS-CoV-2 and influenza, where PCR of a throat swab is a reliable way of diagnosing the cause of infection). CAP is common, and is associated with significant morbidity and mortality in the UK. Every year 0.5-1% of adults in the UK develop CAP, 22–42% of whom are admitted to hospital, where the mortality is between 5% and 14%.²

As a platform trial for patients hospitalised with pneumonia related to SARS-CoV-2 and influenza, RECOVERY is ideally suited to provide robust evidence to inform the treatment of CAP not related to these pathogens. Since March 2020, RECOVERY has evaluated twelve treatments for hospitalised patients with COVID-19, four of which were found to be life-saving, and eight of which were found to be of little or no benefit.³ Identifying the beneficial effects of dexamethasone alone is estimated to have saved over 1 million lives worldwide.⁴ The key to this success is the breadth of the RECOVERY collaboration, which includes most acute NHS hospitals in the UK, and has allowed it to recruit over 47,000 patients so far.

This amendment would add a new low-dose dexamethasone comparison for CAP caused by pathogens other than SAR-CoV-2 or influenza. The clinical syndrome being studied remains the same, so the inclusion of CAP involves relatively few changes to the protocol, principally creating a third category of pneumonia without suspected SARS-CoV-2 or influenza infection. Patients with suspected pulmonary tuberculosis or *Pneumocystis* pneumonia are excluded, as these infections are associated with distinct pathogens and have differing pathology (and corticosteroids are of proven benefit in severe *Pneumocystis* infection). Other inclusion and exclusion criteria are unchanged. The IMP and dosing are identical to the current low-dose dexamethasone comparison for patients with influenza pneumonia (dexamethasone 6mg daily, replaced with an equivalent dose of prednisolone or hydrocortisone for pregnant or breastfeeding women).

Favourable modulation of the immune response is considered to be the mechanism by which corticosteroids are beneficial in the treatment of COVID-19. Common to infection caused by COVID-19 and influenza, patients admitted to hospital with CAP frequently present with hypercytokinemia, which may progress to an acute respiratory distress syndrome.⁵⁻⁷ However, the pattern of lung involvement typically differs between COVID-19 and CAP caused by bacterial pathogens, with bacterial CAP being associated with more focal lung involvement and less prominent hypoxia.

RECOVERY and other randomised trials have demonstrated the benefit of corticosteroids in patients with COVID-19 pneumonia, but the potential role of corticosteroids in CAP caused by other pathogens remains uncertain.^{8,9} Several randomised trials have demonstrated that corticosteroids improve time to clinical stability and discharge in patients hospitalised with CAP, but this may simply relate to suppression of fever and inflammatory markers rather than a true improvement in disease

outcome.^{10,11} Previous trials have produced conflicting results on mortality in CAP, but have mostly been underpowered for this outcome, and in aggregate they are consistent with no significant effect of corticosteroids on mortality, or with a reduction of a third.¹² The recent CAPE COD trial reported a significant reduction in mortality associated with corticosteroid use in ICU patients, but no effect was observed in the similar ESCAPE trial.^{13,14} The role of corticosteroids in CAP remains unclear, use in clinical practice is variable, and corticosteroid treatment is not recommended in current US or UK CAP treatment guidelines.^{2,15} An adequately powered randomised trial is needed to resolve this uncertainty.

Other changes in protocol v27.0

1) Eligibility criteria

Some clarifications have been made to the definition of the pneumonia syndrome based on feedback from clinical teams. In particular, we make it clear that, even in the absence of clear chest X-ray changes, other objective evidence of lung disease can support a diagnosis of pneumonia (for example, hypoxia or clinical examination findings). Our previous eligibility criteria already allowed for this, stating ‘the diagnosis remains a clinical one based on the opinion of the managing doctor’, so there is no actual change in the syndrome definition. However we have received many requests for clarification, so it will help clinical teams if we can pre-empt these.

2) Drug specific contraindications

We would like to correct an oversight related to one of the corticosteroid contraindications in protocol Appendix 2. RECOVERY involves a high dose dexamethasone comparison for patients with COVID-19 (comparing 20mg daily to the standard 6mg). The current protocol excludes patients receiving a potent CYP3A inhibitor from entering corticosteroid comparisons, because of the potential for increased exposure to the corticosteroid. This was intended to apply only to the high dose dexamethasone comparison, but as ‘high dose’ was not specified in Appendix 2 it also excludes these patients from the low-dose dexamethasone comparison for influenza (at the time of the amendment, implementation of influenza comparisons had been held at the request of NIHR, so this discrepancy wasn’t apparent until later). Our actual intention was clear in the justification for changes submitted with Substantial Amendment 25 (protocol V23.0) in March 2022:

“The potential for interactions between all IMPs in the protocol has been considered (including the potential for combinations of more than two investigational medicinal products) and no significant interactions are expected with the exception of that between Paxlovid and high-dose dexamethasone (which could potentially create excessive dexamethasone plasma concentrations). This combination is described and excluded in the protocol (and enforced by the trial IT system). The combination of Paxlovid [a potent CYP3A4 inhibitor] and standard-dose dexamethasone (6mg once daily for up to 10 days) is not of concern.”

We propose to correct this contraindication, so that patients taking potent CYP3A4 inhibitors are only excluded from the *high* dose dexamethasone comparison. For patients eligible for low dose dexamethasone comparisons, we have added a caution highlighting the need to consider the possible increased risk of corticosteroid side effects, but this is not an exclusion. Low dose dexamethasone (or the equivalent) is commonly used by acute physicians for the treatment of COVID-19, exacerbations of COPD and asthma. Consequently, the risk-benefit balance for each potential participant is best determined by their managing doctor, considering both the severity of disease and their individual risk of corticosteroid side effects.

3) Addition of EU collaborators

We are collaborating with a European research network, the European Clinical Research Alliance for Infectious diseases, to launch RECOVERY at sites in three EU countries; France, Italy and the

Netherlands. We hope to open at these sites before the 2023/24 influenza season. Because of EU data protection requirements, no direct patient identifiers other than year of birth and sex can be stored outside the study site, so we have modified the baseline information section accordingly.

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