RECOVERY trial investigators

13th May 2022

Dear Colleagues

Urgent communication: Recruitment to higher dose corticosteroids closed for patients with hypoxia on no oxygen or receiving simple oxygen

Thank you very much indeed for your huge contribution to the RECOVERY trial. With your support, RECOVERY remains the largest trial of treatments in patients hospitalised with COVID-19, with over 47,000 participants to date. With your help, four effective treatments for patients hospitalised for COVID-19 have been identified, substantially improving the chances of survival for these patients.

In particular, we have previously demonstrated that dexamethasone at a dose of 6mg once daily for 10 days or until discharge (if sooner) significantly reduces 28-day mortality for patients admitted to hospital for COVID-19 on oxygen (with or without non-invasive ventilation) and for patients on invasive mechanical ventilation or extra-corporeal membranous oxygenation (ECMO). As a consequence, dexamethasone 6 mg once daily is now recommended for treatment of such patients.[1]

Since February 2021 (outside the UK) and December 2021 within the UK, we have been assessing the effects of a higher dose corticosteroid regimen[2] vs. usual care (i.e. dexamethasone 6 mg once daily for up to 10 days) for adult patients admitted to hospital for COVID-19 and with clinical evidence of hypoxia (i.e. receiving oxygen or with oxygen saturations <92% on room air), including those requiring non-invasive ventilation, invasive mechanical ventilation or ECMO.

The RECOVERY Data Monitoring Committee on Wednesday 11th May and has advised:

> *"For patients being considered for treatment with high dose dexamethasone, we recommend stopping recruitment of patients who require no oxygen or simple oxygen only at the time of randomisation due to safety concerns. Follow-up of these patients should continue. However, we encourage continuing recruitment and follow-up of all those patients who, at randomisation, require either non-invasive ventilation, invasive mechanical ventilation or ECMO."*

This recommendation was made because of emerging evidence from the trial of increased 28-day mortality for those patients who, at randomisation, were hypoxic but on no oxygen or who were on simple oxygen alone and were allocated to higher dose dexamethasone compared to similar patients allocated to usual care alone.

[1] https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054

[2] Dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days followed by 10 mg once daily by mouth, nasogastric tube or intravenous infusion for 5 days. [Note: Details of the corticosteroid regimen for pregnant women are provided in the protocol (https://www.recoverytrial.net/files/recovery-protocol-v23-1-2022-03-15.pdf)].

We are making the following changes with immediate effect:

HIGHER DOSE vs STANDARD DOSE DEXAMETHASONE:

- **For patients who are on no oxygen or simple oxygen only**
  - **recruitment to this comparison should stop immediately** (and this possibility has been disabled in the randomisation system)
  - **higher dose corticosteroids should no longer be administered** as part of the trial (patients recently randomised should not be given any further doses, but should receive standard doses [6 mg once daily] if indicated).

- **For patients on non-invasive ventilation, invasive mechanical ventilation or ECMO**
  - **recruitment to this comparison remains open and is encouraged**

- **For all patients**
  - **follow-up should continue as usual** (a follow-up form should be completed for all patients following death, discharge from hospital, or 28 days).

ALL OTHER TREATMENT COMPARISONS:

- **Recruitment and follow-up for all other treatment comparisons should continue without any changes**

We have notified the relevant regulatory authorities and ethics committees. A substantial protocol amendment will be submitted shortly.

We would like to thank you and all your colleagues for continuing to support the RECOVERY trial. You are making a huge difference to patient care both all around the world.

Yours sincerely

Prof Sir Peter Horby FMedSci Prof Sir Martin Landray FMedSci

Chief Investigators for the RECOVERY trial

Attached: Letter from Chair of RECOVERY trial Data Monitoring Committee 11th May 2022

The University of Edinburgh
Edinburgh Neuroscience

CCBS
Centre for Clinical Brain Sciences

Professor Sir Peter Horby, Professor Sir Martin Landray
RECOVERY trial Co-chairs
Nuffield Department of Population Health
Oxford

11th May 2022

Dear Peter and Martin

RECOVERY trial DMC review

Following my chairman's review of the data on 6th May, I convened a meeting of the full DMC. The DMC reviewed today the RECOVERY trial safety and efficacy data that were available for the patients randomised by 2nd May 2022.

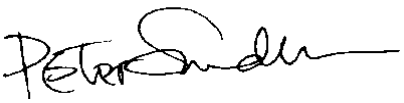
For the interventions still in active recruitment, the numbers of adults included in the comparison of each agent with its control were respectively: high dose steroids (1655), empagliflozin (3716), sotrovimab (996), molnupiravir (492) and paxlovid (19). The dataset included 4 women who were pregnant at entry and 4 children.

For patients being considered for treatment with high dose dexamethasone, we recommend stopping recruitment of patients who require no oxygen or simple oxygen only at the time of randomisation due to safety concerns. Follow-up of these patients should continue. However, we encourage continuing recruitment and follow-up of all those patients who, at randomisation, require either non-invasive ventilation, invasive mechanical ventilation or ECMO.

For all the other treatments, in the light of the available trial data and all relevant external information, we saw no cogent reason to modify the protocol or intake to those arms of the study.

The DMC will next meet to review the safety and efficacy data for all treatments on 10th June 2022.

Yours sincerely



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