Justification of substantial amendment for RECOVERY protocol V8.0

We are seeking approval for the following changes:

1. Removal of lopinavir-ritonavir from the protocol and patient information: We have now closed recruitment to this arm as the trial showed this treatment to be ineffective. Preliminary results are in the public domain and a peer-reviewed publication is in preparation.

2. Addition of intravenous immunoglobulin (IVIg) as treatment arm for children: A national Delphi survey has been conducted and IVIg has been identified as a potential treatment for COVID-19 in children (among those with the PIMS-TS variant), and its inclusion in a trial has widespread support (see supporting letter). IVIg is in widespread use already for similar conditions and paediatricians are very familiar with its use.

3. Modification of corticosteroid dose for children: The national Delphi survey referenced above has proposed testing higher dose corticosteroids for children (>44 weeks gestional age) with the PIMS-TS syndrome, so we have modified the protocol accordingly. For children >44 weeks gestional age with SARS-CoV-2 infection but not PIMS-TS (i.e. COVID-19 pneumonia), low-dose steroids are now standard care. Among children ≤44 weeks gestational age (who do not develop PIMS-TS), steroids would be included in the randomisation at previous (lower) doses as uncertainty remains about the best treatments for this group of children.

4. We seek permission to collect a sample of serum from participants in the convalescent plasma comparison which will be sent to a central laboratory for measurement of coronavirus and antibodies against it. This information will be an important characteristic when assessing the effects of convalescent plasma, which may differ depending on whether the participant had generated such antibodies themselves already at the time of presentation.