Sotrovimab versus usual care in patients admitted to hospital with COVID-19: a randomised, controlled, open-label, platform trial (RECOVERY)

Running title: Sotrovimab for patients hospitalised with COVID-19

RECOVERY Collaborative Group*

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the Supplementary Appendix.

Correspondence to: Prof Peter W Horby and Prof Martin J Landray, RECOVERY Central Coordinating Office, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom.

Email: recoverytrial@ndph.ox.ac.uk

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SUMMARY

Background: Sotrovimab is a neutralising monoclonal antibody targeting the SARS-COV-2 spike protein that was evaluated in the RECOVERY trial, a randomised, controlled, open-label, platform trial testing treatments for COVID-19.

Methods: Patients hospitalised with COVID-19 pneumonia from 107 UK hospitals were randomly allocated to either usual care alone or usual care plus a single 1g infusion of sotrovimab, using web-based unstratified randomisation. Participants were retrospectively categorised as 'high-antigen' (the prespecified primary analysis population) if baseline serum SARS-CoV-2 nucleocapsid antigen was above the median concentration, and otherwise as 'low-antigen'. The primary outcome was 28-day mortality assessed by intention to treat. Recruitment closed on 31 March 2024 when funding ended. ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

Findings: From 4 January 2022 to 19 March 2024, 1723 patients were recruited, 828 allocated sotrovimab and 895 allocated usual care. 720 (42%) were classified as high-antigen, 717 (42%) as low-antigen, and 286 (17%) had unknown antigen status. 1389 (81%) patients were vaccinated, 1179/1438 with known serostatus (82%) had anti-spike antibodies at randomisation, and almost all were infected with Omicron variants. Among high-antigen patients, 82/355 (23%) allocated sotrovimab versus 106/365 (29%) allocated usual care died within 28 days (rate ratio 0.75; 95% CI 0.56-0.99; p=0.046). In an analysis of all randomised patients (regardless of antigen status), 177/828 (21%) allocated sotrovimab versus 201/895 (22%) allocated usual care died within 28 days (rate ratio 0.95; 95% CI 0.77-1.16; p=0.60).

Interpretation: In patients hospitalised with COVID-19, sotrovimab was associated with reduced mortality in the primary analysis population who had a high serum SARS-CoV-2 antigen concentration at baseline, but not in the overall population. Treatment options for hospitalised patients are limited, and mortality in those receiving current standard care was high. The emergence of high-level resistance to sotrovimab among subsequent SARS-CoV-2 variants limits its current usefulness, but these results indicate that targeted neutralising antibody therapy could potentially still benefit high-risk hospitalised patients in an era of widespread vaccination and Omicron infection.

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Keywords: COVID-19, sotrovimab, monoclonal antibody, clinical trial.

RESEARCH IN CONTEXT

Evidence before this study

We searched Medline, Embase, and MedRxiv between 1 September 2019 and 9 July 2024 for randomised controlled trials comparing the effects of neutralising monoclonal antibodies (mAbs) versus usual care or placebo in patients hospitalised with COVID-19. We used the search terms (Coronavirus infection or COVID or COVID-19 or COVID19 or 2019n-CoV or SARS-COV-2 or SARSCoV2 or SARS-Cov2) AND (sotrovimab, S309, VIR-7831, Xevudy, adintrevimab, amubarvimab, bamlanivimab, bebtelovimab, casirivimab, cilgavimab, etesevimab, imdevimab, regdanvimab, romlusevimab, tixagevimab) and validated filters to select for randomised controlled trials. No language restrictions were applied.

We identified six trials that tested mAbs in hospitalised COVID-19 patients, which recruited patients between May 2020 and July 2022 (appendix p35). In all trials a majority of patients were infected with pre-Omicron SARS-CoV-2 variants. The RECOVERY casirivimab-imdevimab comparison was the largest, and included six times as many patients who died than the other trials combined. No definite effect of mAbs was seen on mortality in analyses of all trial participants (in RECOVERY 943/4839 (19%) patients allocated mAb died versus 1029/4946 (21%) allocated usual care; rate ratio (RR) 0.94; 95% CI 0.86-1.02; p=0.14).

In RECOVERY, mAb treatment was associated with a large and definite reduction in mortality in patients who had not yet developed a SARS-CoV-2 antibody response at baseline (i.e. were seronegative); 396/1633 (24%) allocated mAb died versus 452/1520 (30%) allocated usual care; RR 0.79; 95% CI 0.69 to 0.91; p=0.0009. Two other trials

reported mortality by antibody status at baseline (ACTIV-3/TICO and COV-2066), and a similar benefit of mAb therapy was also observed in over one thousand seronegative patients in these trials. Since these three trials were reported, increasing rates of vaccination and previous infection have meant that few hospitalised patients are now antibody negative, and from 2022 most mAbs in clinical use demonstrated substantial losses of *in vitro* potency against prevalent Omicron variants.

One trial, ACTIV-3/TICO, reported outcomes among patients with high (>median) blood SARS-CoV-2 nucleocapsid antigen concentration at baseline, although it was not powered to detect or rule out a clinically meaningful benefit of treatment in this group. 90-day mortality was 43/340 (13%) in patients with high blood antigen allocated tixagevimab-cilgavimab, versus 51/342 (15%) allocated placebo; hazard ratio 0.84; 95%CI 0.56 to 1.26).

Added value of this study

This is the second largest trial of mAb therapy for patients hospitalised with COVID-19, the first directed at patients with Omicron infection, and the first performed in a predominantly vaccinated population. This RECOVERY comparison evaluated sotrovimab, a mAb that retained some in vitro neutralization activity against Omicron variants dominant in 2022-23, but which has minimal *in vitro* neutralization activity against several variants dominant from 2024.

Because most hospitalised patients had antibodies from previous vaccination or infection, serum antigen levels were used to identify high risk patients who might benefit from treatment. In the prespecified analysis population of patients with high serum

antigen at baseline, sotrovimab was associated with a reduction in the primary outcome of 28-day mortality (82/355 [23%] allocated sotrovimab vs 106/365 [29%] allocated usual care; rate ratio 0.75; 95% CI 0.56 to 0.99; p=0.046).

Implications of all the available evidence

mAb therapy could benefit current patients hospitalised with COVID-19, including those with previous vaccination and infection with Omicron variants. Efficacy appears to be limited to patients who have not yet mounted an effective immune response to their infection, in whom mortality remains high despite current treatment. However, the emergence of variants resistant to neutralisation by sotrovimab highlights the need for newer mAb therapies with reliable and durable neutralising activity against current and future SARS-CoV-2 variants. Measurement of serum viral antigen offers a promising approach to targeting treatment and could facilitate future monoclonal development, but needs further validation.

INTRODUCTION

Treatment with neutralising monoclonal antibodies (mAbs) targeting the SARS-CoV-2 spike protein has been found to substantially reduce the risk of hospitalisation or death in patients with early COVID-19 who are at high risk of complications.(1–3) nMAbs were also found to reduce the risk of death among hospitalised patients, but this benefit was restricted to those who had not yet developed their own anti-SARS-CoV-2 antibody response (i.e. who are seronegative).(4–6) The RECOVERY casirivimab-imdevimab comparison, which recruited UK patients from September 2020 to May 2021 is the largest randomised evaluation of mAb therapy in hospitalised patients. In this comparison, 28-day mortality in patients who were seronegative at randomisation was double that of seropositive patients (30% versus 15%), and mAb therapy reduced this to 24% (rate ratio 0.79; 95% confidence interval 0.69-0.91; p=0.0009; number of seronegative patients treated to save one life = 16).(4) Following this, targeted mAb therapy for seronegative patients hospitalised with COVID-19 was adopted into routine practice in the UK and elsewhere.

A major limitation of mAb therapy has been the frequent emergence of new SARS-CoV-2 variants that are not effectively neutralised by existing antibodies.(7,8) When the first Omicron variant, BA.1, became globally dominant in December 2021, it contained spike mutations conferring high-level resistance to most mAbs in clinical use.(8) This included the casirivimab-imdevimab combination, leading to its withdrawal from guidelines. Sotrovimab, a mAb originally developed from an antibody recovered from a patient who had recovered from SARS-CoV-1, targets a relatively conserved spike protein epitope,

and in the COMET-ICE trial of patients with early infection conducted in 2020-21 it reduced the risk of hospitalisation or death by 79%.(1) The neutralisation potency of sotrovimab was modestly reduced against BA.1 compared to wild-type virus (~3-5 fold in most studies), but it retained more activity than many other mAbs, which made it a promising candidate for continued use in hospitalised patients and prompted its evaluation in RECOVERY.(9,10) A further reduction in activity against BA.2 led to the withdrawal of FDA Emergency Use Authorization in the U.S. for sotrovimab in April 2022. However, it retained enough *in vitro* activity against viral variants prevalent in 2022-23 to suggest it could retain clinical benefit via direct neutralisation (as serum sotrovimab levels remained around 100 times the EC_{50} for BA.2), or via Fc-dependent effector mechanisms.(11,12) During November 2023, BA.2.86 and JN.1 SARS-CoV-2 variants became dominant in the UK and elsewhere, which have an additional spike gene mutation that confers high-level resistance to sotrovimab.(13)

The current role of therapeutic neutralising mAbs in hospitalised patients is also complicated by increasing population immunity to SARS-CoV-2, as the previous trials that identified a benefit in seronegative patients were performed before widespread vaccination and natural immunity. By the time the Omicron BA.1 variant emerged, most people hospitalised in the UK with COVID-19 had been vaccinated and many had had previous infection. In this setting, patients would be expected to have detectable anti-SARS-CoV-2 antibodies at admission, but this could reflect immune responses to previous vaccination or infection that had failed to prevent the current illness, rather than adaptive immunity to the current infection. This suggests that alternative biomarkers of

infection status may now be required to identify which, if any, hospitalised patients could benefit from mAb treatment.

One possible biomarker is SARS-CoV-2 antigenaemia. Viral nucleocapsid antigen is detectable in the blood of most hospitalised patients, and high concentrations are strongly correlated with more severe disease and worse prognosis.(14–16) In most hospitalised patients, antigen levels fall rapidly in the first few days of admission as the infection is cleared.(17) The degree of antigenaemia is inversely correlated with specific antibody responses, but, unlike antibodies, detection of viral antigen almost certainly relates only to the current infection.

Here we report the results of the sotrovimab comparison in RECOVERY, a randomised, open-label platform trial evaluating treatments for patients hospitalised with COVID-19 pneumonia. Recruitment occurred in the UK in a period in which Omicron variants were dominant and most people were vaccinated against SARS-CoV-2. The prespecified primary analysis population was patients who had serum SARS-CoV-2 nucleocapsid antigen concentration at randomisation that was above the median value of all trial participants in this comparison.

METHODS

Study design and participants

The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

Details of the trial design and results for other treatments have been published previously and are available at www.recoverytrial.net/results.(18) The trial was conducted at hospital organisations in the United Kingdom and supported by the National Institute for Health and Care Research Clinical Research Network. 107 hospitals in the UK enrolled participants in the sotrovimab comparison (appendix pp5-32). The trial is coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor, and is conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and is approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Cambridge East Research Ethics Committee (ref: 20/EE/0101). The protocol, statistical analysis plan, and additional information are available in the appendix (pp71-200) and on the study website www.recoverytrial.net.

Patients admitted to hospital were eligible for the study if they had confirmed SARS-CoV-2 infection with a pneumonia syndrome thought to be related to COVID-19, and no medical history that might, in the opinion of the managing physician, put the patient at significant risk if they were to participate in the trial. Patients were excluded if they were aged <12 years or were aged <18 years and weighed <40kg. Pregnant women were eligible. Written informed consent was obtained from all patients, or a legal representative if patients were too unwell or otherwise unable to provide informed consent.

Randomisation and masking

Eligible and consenting patients were randomly assigned in a 1:1 ratio to either usual standard of care plus sotrovimab or usual standard of care alone, using web-based simple

(unstratified) randomisation with allocation concealed until after randomisation (appendix pp42-44). Patients allocated to sotrovimab were to receive 1g in 100ml 0.9% saline or 5% glucose intravenously over 60 minutes as soon as possible after randomisation. This is double the licensed dose for early infection and was selected because of reduced neutralisation activity against Omicron BA.1 compared to wild-type virus.

As a platform trial, and in a factorial design, patients could be simultaneously included in other concurrently evaluated treatment comparisons, each having its allocation determined by an independent 1:1 randomisation: (i) empagliflozin versus usual care, (ii) higher-dose corticosteroids versus usual care, (iii) molnupiravir versus usual care, and (iv) nirmatrelvir-ritonavir versus usual care (appendix pp42-43). Participants and local study staff were not masked to allocated treatment. Other than members of the Data Monitoring Committee, all individuals involved in the trial were masked to aggregated outcome data while recruitment and 28-day follow-up were ongoing.

Procedures

Baseline data were collected using a web-based case report form that included demographics, level of respiratory support, major comorbidities, suitability of the study treatment for a particular patient, SARS-CoV-2 vaccination status, and study treatment availability at the study site (appendix p47). A serum sample and nose swab were collected at randomisation and sent to central laboratories for testing. Serum was tested for SARS-CoV-2 nucleocapsid antigen, anti-SARS-CoV-2 spike antibodies, and anti-SARS-CoV-2 nucleocapsid antibodies using Roche Elecsys assays (Roche Diagnostics, Basel, Switzerland). Patients were classified as having high- or low- serum nucleocapsid

antigen using the trial population median value (cut-off index 0.626, corresponding to a nucleocapsid protein concentration of approximately 10 pg/ml, appendix p191), and as positive or negative for anti-spike and anti-nucleocapsid antibodies using manufacturer defined thresholds (testing was retrospective, so results were not available to the patient's medical team). Nose swabs were tested for SARS-CoV-2 RNA using TaqPath COVID-19 RT-PCR (Thermo Fisher Scientific, Massachusetts, US). Samples with sufficient viral RNA were sequenced using the ONT Midnight protocol (Oxford Nanopore Technologies, Oxford, UK).(19) Sequence data were used to detect spike protein mutations associated with >5-fold reduction in sotrovimab neutralisation, which were identified from the sotrovimab summary of product characteristics and the Stanford University Coronavirus Antiviral and Resistance Database.(20) Further details of laboratory analyses and the resistance mutations included are in the appendix (pp33-34, 184-200).

Follow-up nose swabs were collected on day 3 and day 5 (counting the day of randomisation as day 1). These were analysed in the same manner as the baseline swab described above.

An online follow-up form was completed when participants were discharged, had died or at 28 days after randomisation, whichever occurred earliest (appendix pp48-56). Information was recorded on adherence to allocated study treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, major safety outcomes, and vital status (including cause of death). In addition, routine healthcare and registry data were obtained, including information on vital status (with date and cause of death), discharge from hospital, receipt of respiratory support, or renal replacement therapy.

Outcomes

Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months (not reported here). The primary outcome was all-cause mortality at 28 days. Secondary outcomes were time to discharge from hospital, and, among patients not on invasive mechanical ventilation at randomisation, invasive mechanical ventilation (including extra-corporal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were use of invasive or non-invasive ventilation (including high-flow nasal oxygen) among patients not on any ventilation at randomisation, and use of renal dialysis or haemofiltration. Prespecified safety outcomes were cause-specific mortality, major cardiac arrhythmia, thrombotic and major bleeding events, non-SARS-CoV-2 infections, hyper/hypoglycaemia, seizures, acute liver or kidney injury, and infusion reactions to sotrovimab. Virological outcomes were viral RNA copy number in nose swabs taken at day 3 and day 5, and the frequency of detection of resistance mutations. Information on suspected serious adverse reactions was collected in an expedited fashion to comply with regulatory requirements. Details of the methods used to ascertain and derive outcomes are provided in the appendix (pp160).

Sample size calculation

Because trial recruitment and event rates during the COVID-19 pandemic were unpredictable, RECOVERY treatment comparisons have not had a predetermined sample size. With high-levels of recruitment, the intention would have been to continue until enough primary outcomes had accrued for a 90% power to detect a proportional risk reduction of 20% at 2p=0.01 (approximately 5,500 participants if mortality were 20%

without treatment). Following the initial wave of Omicron infection in the UK in early 2022, the number of patients hospitalised with COVID-19 pneumonia reduced substantially in the UK, as did trial recruitment. The trial comparison closed on 31st March 2024 when funding for the trial ended.

Statistical Analysis

For all outcomes, intention-to-treat analyses compared patients randomly allocated sotrovimab with patients randomly allocated usual care. For the primary outcome of 28-day mortality, the hazard ratio from a Cox model with adjustment for age in three categories (<70 years, 70-79 years, and 80 years or older) and ventilation status at randomisation in four categories (no oxygen, simple oxygen only, non-invasive ventilation and invasive mechanical ventilation) was used to estimate the mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period (starting on the day of randomisation and ending 28 days later). We used the same Cox regression method to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right-censored on day 29. There was no evidence against the proportionality assumption for the primary outcome of 28-day mortality.

Median time to discharge was derived from Kaplan-Meier estimates. For the composite secondary outcome of progression to invasive mechanical ventilation or death within 28 days, and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and a log-binomial regression model was used to estimate the risk ratio adjusted for age and ventilation

status (in the same categories as listed above). Estimates of rate and risk ratios are shown with 95% confidence intervals. SARS-CoV-2 viral RNA levels in nose-swabs were estimated with analysis of covariance (ANCOVA) using the log transformed values after adjustment for each participant's baseline value, age and level of respiratory support at randomisation. Missing baseline and follow-up values of SARS-CoV-2 viral RNA levels were estimated using multiple imputation, with 20 replicate sets and combination of results across sets using the methods of Rubin.(21)

When the sotrovimab comparison was added to the protocol in December 2021, there was insufficient information to decide if anti-S or anti-N antibody status should define the primary analysis population, or if serum antigen status would be preferable. The statistical analysis plan stated that this would be determined at a future date (but prior to unblinding of the investigator team). Shortly after recruitment closed, but before the investigators were unblinded, high-antigen patients were selected as the primary analysis population because of low numbers of seronegative patients in the trial population and because antigen positivity best predicted mortality (described in the updated statistical analysis plan, appendix pp151-153). It was hypothesised that any beneficial effect of sotrovimab would be larger among high-antigen patients and may be negligible in low-antigen patients. Formal hypothesis-testing of the effect of allocation to sotrovimab on 28-day mortality was to be done firstly in high-antigen participants (the primary analysis population), and was to be done among all randomised participants only if a reduction in mortality in high-antigen patients was seen at $2p<0.05$. Formal testing of secondary outcomes was only to be done if a mortality reduction among all participants was seen at $2p<0.05$. A prespecified comparison of the effects of allocation to sotrovimab on 28-day

mortality in high-antigen versus low-antigen participants was done by performing a test for heterogeneity. Tests for heterogeneity according to other baseline characteristics were also prespecified (age, sex, ethnicity, level of respiratory support, days since symptom onset, use of corticosteroids, anti-SARS-CoV-2 antibody status, and immunodeficiency), and a post-hoc analysis of heterogeneity according to use of remdesivir at baseline was performed.

The full database is held by the study team which collected the data from study sites and performed the analyses at the Nuffield Department of Population Health, University of Oxford (Oxford, UK). Analyses were performed using SAS version 9.4 and R version 4.0.3. The trial is registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936).

Role of the funding source

Neither the study funders, nor the manufacturers of sotrovimab, had any role in study design, data collection, data analysis, or writing of the report. GSK and Vir Biotechnology supported the study through supply of sotrovimab and reviewed the draft publication for scientific consistency and completeness. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between 4 January 2022 and 19 March 2024, 1723/1824 (94%) patients enrolled into the RECOVERY trial at sites participating in the sotrovimab comparison were eligible and

agreed to be included in sotrovimab comparison, of whom 1448 (84%) were recruited in 2022. 828 were allocated sotrovimab and 895 were allocated usual care without sotrovimab (figure 1). The mean age of study participants was 70.7 years (SD 14.8), 1389 (81%) had received a COVID-19 vaccine, and 414 (24%) were severely immunocompromised in the opinion of the managing clinician (table 1, appendix pp59-60). At randomisation, the median time since symptom onset was 6 days (IQR 3-11 days), 1467 (85%) were receiving oxygen or ventilatory support, and 628 (36%) were receiving remdesivir. Serological results were available for 1439 (84%) of patients, among whom 720 (50%) had a serum nucleocapsid antigen concentration above the median ('high-antigen'), 1179 (82%) were anti-SARS-CoV-2 spike antibody positive, and 454 (32%) were anti-SARS-CoV-2 nucleocapsid antibody positive (table 1). Baseline serum nucleocapsid antigen was only moderately correlated with anti-spike and anti-nucleocapsid antibody levels (Pearson correlations -0.37 and -0.22, respectively, using log concentration).

The follow-up form was completed for 1710 (99%) patients, and among them 767/820 (94%) allocated sotrovimab received the treatment, compared to 14/890 (2%) allocated usual care (figure 1). Use of other treatments for COVID-19 was similar among patients allocated sotrovimab and those allocated usual care (appendix p61). Primary and secondary outcome data are known for more than 99% of randomly assigned patients.

In patients who had high-antigen at baseline, allocation to sotrovimab was associated with a reduction in the primary outcome of 28-day mortality compared with usual care alone: 82/355 (23%) patients in the sotrovimab group died versus 106/365 (29%) patients in the usual care group (rate ratio 0.75; 95% CI 0.56-0.99; p=0.046; table 2, figure 2a,

figure 3). Among all patients randomised (including those with high, low, or unknown baseline antigen status), there was no significant difference in the primary outcome of 28-day mortality between the two randomised groups: 177/828 (21%) patients in the sotrovimab group died versus 201/895 (22%) patients in the usual care group (rate ratio 0.95; 95% CI 0.77-1.16; p=0.60; figure 2b, figure 3, appendix p62). There was no evidence that the proportional effects on mortality differed in any pre-specified subgroups or in the post-hoc subgroup analysis of patients receiving remdesivir at baseline, either among high-antigen patients or among all patients (figure 4, appendix pp68-70).

Among high-antigen patients, discharge alive within 28 days did not differ between those allocated sotrovimab compared to usual care (236 [66%] versus 226 [62%]; rate ratio 1.12, 95% CI 0.93-1.34; median time to being discharged alive 13 days versus 16 days) (table 2, figure 3). There was also no difference in this outcome among the overall study population (563 [68%] versus 609 [68%]; rate ratio 0.96, 95% CI 0.85-1.08; median time to being discharged alive 11 days versus 11 days) (figure 3, appendix p62).

Among high-antigen patients not on invasive ventilation at baseline, allocation to sotrovimab was not associated with a lower risk of progressing to the composite secondary outcome of invasive ventilation or death (82/340 [24%] versus 102/354 [29%], risk ratio 0.82, 95% CI 0.64-1.03) (table 2, figure 3). There was also no difference in this outcome among the overall study population (184/799 [23%] versus 201/863 [23%], risk ratio 0.98, 95% CI 0.84 to 1.16) (figure 3, appendix p62).

We found no evidence of any difference between groups in the prespecified subsidiary outcomes among high-antigen patients, or among all patients, including in use of

ventilation in those not on ventilation at baseline, successful cessation of ventilation, or use of renal replacement therapy (table 2, appendix p62).

1479/1723 (86%) of patients had at least one nose swab available for analysis. Allocation to sotrovimab was not associated with a lower baseline-adjusted viral RNA copy number in nose swabs taken on day 3 or day 5 (table 2). 1119 (65%) patients had at least one successfully sequenced sample, and of those with at least one high quality sample (≥90% genome coverage), 1021/1026 (>99%) were identified as Omicron variants (primarily BA.1, BA.2, BA.5, and XBB). 1655/1723 (96%) patients were recruited before November 2023, and of these 14/1026 (1%) with a sequenced sample had a sotrovimab resistance mutation detected at baseline, and 3/692 (<0.5%) with sequenced baseline and follow-up samples had a new sotrovimab resistance mutation arising after trial entry, two of whom had received sotrovimab (details of these three patients are in appendix p65). Among the 68/1723 (4%) patients recruited after 1 November 2023, 14/35 (40%) with a sequenced sample were infected with BA.2.86 variants, which are known to contain the K356T spike mutation associated with high-level sotrovimab resistance.

Infusion reactions were reported for 12/781 (2%) patients receiving sotrovimab. Of these, nine were mild (no intervention required), two moderate (antihistamines or steroids required) and one severe (adrenaline required). Two serious adverse reactions to sotrovimab were reported, both of which were infusion reactions included above, one of which was in a patient with suspected anaphylaxis that resolved with treatment. We found no difference between groups in other safety outcomes, including cause-specific mortality, new cardiac arrhythmia, thrombosis, bleeding, non-coronavirus infections, hypo- or hyper-glycaemia, seizures, acute kidney injury or liver injury (appendix pp63-64).

DISCUSSION

In this randomised trial including over 1700 patients with COVID-19 pneumonia, sotrovimab was associated with a reduction in 28-day mortality in those with a high serum nucleocapsid antigen concentration, although there was substantial uncertainty about the size of this apparent benefit (RR 0.75; 95% CI 0.56-0.99; p=0.046). An analysis of all patients, regardless of antigen concentration, did not show evidence of any benefit of treatment on 28-day mortality. In contrast with our previous study of monoclonal antibody treatment in this setting, the current study was performed during a period of Omicron infection and widespread vaccination and natural immunity, making it more relevant to the treatment of current and future patients hospitalised with COVID-19.(4)

The number of patients hospitalised with COVID-19 pneumonia fell dramatically after vaccination was introduced and Omicron became dominant, so this comparison could not provide results as definitive as those of the earlier RECOVERY casirivimab-imdevimab comparison that recruited nearly 10,000 patients. However, the pattern of results from the two RECOVERY mAb comparisons are similar, despite using different markers of infection status to categorise patients. In both, a subset of patients with immune responses that were not yet adequate to clear infection were at higher risk of death than patients with more robust immune responses, and in that higher risk subset mAb therapy reduced the risk of death. During the period this comparison was recruiting, SARS-CoV-2 infection in hospitalised patients was often an incidental finding or associated with non-respiratory illness, and the benefits of antiviral therapy in these patients may be limited. In contrast, RECOVERY only included those with pneumonia thought to be related to COVID-19 and in 81% of participants this had developed despite previous COVID-19

vaccination. In keeping with this, 82% of those with known serostatus had anti-spike antibodies, although two-thirds were anti-nucleocapsid antibody negative, indicating that this was likely their first SARS-CoV-2 infection.(22) The risk of death from COVID-19 was high, despite standard supportive care and the availability of immunomodulation and antiviral treatment with remdesivir. 28-day mortality was 22% in those allocated usual care, similar to the risk among RECOVERY patients recruited in the pre-Omicron era. Since the emergence of Omicron, immunocompromised patients have made up a higher proportion of those hospitalised and dying from COVID-19 pneumonia, and in keeping with this one-quarter of the RECOVERY patients were considered severely immunocompromised.(23) Current treatment options for patients hospitalised with COVID-19 are limited, particularly for immunocompromised patients in whom immunomodulatory therapies should be used with caution.(24) Our results indicate that targeted neutralising antibody therapy could potentially still benefit high-risk patients, even when administered more than a week after symptom onset.

The benefit of mAb therapy in SARS-CoV-2 antibody negative hospitalised patients was established in previous trials, but this approach to targeting therapy was necessarily short-lived in the context of increasing population immunity.(4–6) In contrast, targeting therapy on the basis of antigenaemia remains possible for future hospitalised patients, and is practical using existing commercial assays (the one used in RECOVERY takes 20 minutes on a widely available automated clinical laboratory platform). The ACTIV-3/TICO platform trial is the only previous trial of mAb therapy reporting outcomes by baseline blood antigen status, and this evaluated four mAb therapies, although three of these were stopped early for futility.(6,14,25) In the single comparison not stopped early, 1417

hospitalised patients were randomised to receive tixagevimab-cilgavimab or placebo. Among patients with blood antigen above the median value, 90-day mortality was 43/340 (13%) in those allocated mAb versus 51/342 (15%) in those allocated placebo (hazard ratio 0.84; 95%CI 0.56-1.26; p=0.39); although inconclusive the point estimate is consistent with this RECOVERY result that is based on twice as many events. In contrast to blood antigen and antibody concentrations, the quantity of viral RNA collected when sampling the upper respiratory tract is highly variable, even in simultaneously collected swabs.(26) This limits its usefulness as a marker to predict an individual's treatment response, so subgroup analyses by nasal RNA viral copy number were not performed.

Neutralising mAbs emerged as powerful therapeutic tools during the pandemic, which highlighted their potential uses but also their limitations, particularly the loss of activity against emergent viral variants. Despite retaining potentially valuable neutralising activity against Omicron variants prevalent in 2022-23, high-level sotrovimab resistance was identified in Omicron lineages that became globally dominant in early 2024, including BA.2.86 and JN.1, and it is no longer likely to have useful activity against currently circulating variants that have retained sotrovimab resistance mutations.(27) The loss of all anti-SARS-CoV-2 mAbs that were in clinical use has led to new approaches to mAb therapy, including attempts to target more highly conserved viral epitopes, new antibody fragments or formulations that may have better potency or tissue penetration, and antibody cocktails or poly-specific antibodies that may be more robust to viral evolution.(28) The results of this comparison suggest that if new mAb therapies can be developed that effectively neutralise current and future SARS-CoV-2 variants then they could continue to benefit hospitalised patients. Viral nucleocapsid antigenaemia is a

promising biomarker to guide mAb treatment that could aid the development of future mAb therapies, but requires further validation.

Most patients in the RECOVERY sotrovimab comparison were recruited in 2022, and, other than lineage-defining Omicron mutations, there were few important sotrovimab resistance mutations identified in either baseline or follow-up samples. Because of concerns about possible reduced sotrovimab activity against BA.1, a 1g dose was used in RECOVERY rather than the 500mg dose tested previously, and this was well tolerated with no new safety concerns. The lack of any measurable effect of sotrovimab on nasal SARS-CoV-2 carriage by day 5 may be related to the early sampling timepoints used, as even in seronegative patients treated with a well-matched mAb, a reduction in carriage of viral RNA is mainly apparent from day 7 onwards.(5) In contrast to changes in viral RNA carriage, a large reduction in culturable SARS-CoV-2 can be seen as early as 24 hours after mAb therapy, but virological testing in RECOVERY did not extend to culture.(28) The emergence of new viral resistance mutations during sotrovimab treatment is well described, especially in immunocompromised patients, but there was little evidence of this in RECOVERY.(30,31) Only two treated patients had resistance mutations identified by day 5, although emergent resistance is often only identified at later timepoints, and detection of this this was not a principal aim of the trial.

Strengths of this trial include that it was randomised, had broad eligibility criteria, and a large sample size, being the second largest trial of mAb therapy performed in patients hospitalised with COVID-19. It includes baseline characterisation of markers of SARS-CoV-2 immune status and infection, and more than 99% of patients were followed up for the primary and secondary outcomes. The study has some limitations: the use of serum

antigen to define the primary analysis population was prespecified, but this is a novel therapeutic biomarker and there is little existing evidence to support the threshold used to classify patients. The distribution of serum antigen in our population was unimodal with no natural cut-point, so other thresholds could have been selected and further validation of this threshold would be needed for clinical use. In a larger trial it may have been possible to retrospectively identify an optimal antigen threshold, but this kind of sensitivity analysis would not be robust in our study given the limited number of outcome events. The trial was also not large enough to reliably exclude benefit among low antigen patients, or to exclude differences in treatment effect among specific subgroups of patients based on characteristics such as time since symptom onset, immunodeficiency, or concomitant use of remdesivir. Remdesivir was received by one-third of patients, and it is possible that sotrovimab would have had a greater effect in the absence of concomitant antiviral treatment. The RECOVERY trial is open label, so participants and local hospital staff were aware of the assigned treatment. This could potentially have affected clinical management or the recording of some trial outcomes, although we found no evidence that management differed by treatment allocation (appendix p61), and the primary and secondary outcomes are unambiguous and were ascertained without bias through linkage to routine health records. Although virological outcomes were included, this did not include viral culture or virological endpoints beyond day 5, and no information on radiological or physiological outcomes was collected. The RECOVERY trial only studied a high risk cohort of patients who had been hospitalised with COVID-19 and, therefore, the results may not be directly applicable to the safety and efficacy of treatment in other patient groups, such as low-risk hospitalised patients, or those with early infection.

In summary, the results of this randomised trial indicate that many hospitalised COVID-19 patients at high risk of death could continue to benefit from mAb therapy, and that antigen testing could help to identify these patients. Although no currently available mAbs have satisfactory activity against current SARS-Cov-2 variants, these results should inform future mAb evaluation and treatment strategies.

Contributors

This manuscript was initially drafted by LP, RH, PWH and MJL, further developed by the Writing Committee, and approved by all members of the trial steering committee. NS, JRE, PWH, MJL, RH and LP had access to the study data. NS and JRE accessed and verified the data. JRE did the statistical analysis. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan, and had final responsibility for the decision to submit for publication. PWH, NS, JRE, JKB, MB, SNF, TJ, EJ, KJ, MK, WSL, AMo, AMuk, AMum, KR, GT, MM, RH, and MJL designed the trial and study protocol. MM, MC, G P-A, LP, RS, DG, GC, NB, JM-C, PD, PH, JU, NE, JM, SB, the Data Linkage team at the RECOVERY Coordinating Centre, and the Health Records and Local Clinical Centre staff listed in the appendix collected the data. All authors contributed to data interpretation and critical review and revision of the manuscript.

Writing Committee (on behalf of the RECOVERY Collaborative Group):

Peter W Horby[*], Jonathan R Emberson[*], Leon Peto[*], Natalie Staplin, Mark Campbell, Guilherme Pessoa-Amorim, Richard Stewart, Dipansu Ghosh, Graham Cooke, Natalie Blencowe, Jeronimo Moreno-Cuesta, Purav Desai, Paul Hine, Jonathan Underwood, Nicholas Easom, Jaydip Majumdar, Sanjay Bhagani, J Kenneth Baillie, Maya H Buch, Saul N Faust, Thomas Jaki, Katie Jeffery, Edmund Juszczak, Marian Knight, Wei Shen Lim, Alan Montgomery, Aparna Mukherjee, Andrew Mumford, Kathryn Rowan, Guy Thwaites, Marion Mafham[†], Richard Haynes[†], Martin J Landray[†].

*,[†] equal contribution

Data Monitoring Committee

Peter Sandercock, Janet Darbyshire, David DeMets, Robert Fowler, David Lalloo, Mohammed Munavvar, Janet Wittes.

Declaration of interests

MJL reports research contracts with his institution (Protas) that are unrelated to the topic of this paper with GSK (the manufacturer of sotrovimab) and Regeneron (the manufacturer of casirivimab-imdevimab). SB has received honoraria from Gilead and MSD. PD has received honoraria and support for attending meetings from Pfizer. RH participates in the ACHIEVE DSMB without payment. MK receives grants to her institution from NIHR and the Healthcare Quality Improvement Partnership. NS receives grants to her institution from Boehringer Ingleheim, Eli Lilly and Novo Nordisk and was trial statistician to the RECOVERY DSMB. JU has received honoraria from GSK for

562 contribution to an advisory board. MM is a co-applicant on grants from Novartis and Novo
563 Nordisk for unrelated trials, and from Health Data Research UK, and participates in trial
564 steering committees for ASPECT, ASPIRING and STIMULATE ICP trials, and is on the
565 DSMB for the PAVE-2 trial. WSL has received a grant to his institution from Pfizer for an
566 unrelated study, and is a member of the Joint Committee on Vaccination and
567 Immunisation. PH has indirectly received support from Gilead to attend a conference (via
568 the British HIV Association). SNF has received clinical trial grants to his institution from
569 Pfizer, Sanofi, GSK, J&J, Merck, AstraZeneca, Valneva, Moderna and BioNTech, and
570 has received fees to his institution for participation in symposia from Moderna, Novavax
571 and Pfizer, and has received fees to his institution for advisory board participation from
572 AztraZeneca, MedImmune, Sanofi, Pfizer, Seqirus, Merck, J&J, and MSD, and is the chair
573 of the NICE sepsis and Lyme disease guidelines. The authors have no other potential
574 conflicts of interest or financial relationships relevant to the submitted work to disclose.
575 No form of payment was given to anyone to produce the manuscript. All authors have
576 completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
577 The Nuffield Department of Population Health at the University of Oxford has a staff policy
578 of not accepting honoraria or consultancy fees directly or indirectly from industry (see
579 https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-
580 20.pdfhttps://www.ctsu.ox.ac.uk/about/ctsu_honoraria_25june14-1.pdf).

581 **Data sharing**

582 The protocol, consent form, statistical analysis plan, definition & derivation of clinical
583 characteristics & outcomes, training materials, regulatory documents, and other relevant
584 study materials are available online at www.recoverytrial.net. As described in the protocol,

the Trial Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. Deidentified participant data and a data dictionary will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Steering Committee will have the right to review and comment on any draft manuscripts prior to publication. Data will be made available in line with the policy and procedures described at: https://www.ndph.ox.ac.uk/data-access. Those wishing to request access should complete the form at https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx and e-mailed to: data.access@ndph.ox.ac.uk

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The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the UK Department of Health and Social Care.

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Figure 1: Trial profile

ITT=intention to treat. *Number recruited to any RECOVERY comparison at sites participating in the sotrovimab comparison, during the period in which it was open. †Drug unavailability and unsuitability are not mutually exclusive.

Figure 2: Effect of allocation to sotrovimab on 28-day mortality in (a) high-antigen versus low-antigen patients, and (b) all patients

Figure 3: Primary and secondary outcomes, overall and by baseline antigen status. Subgroup-specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. Open squares represent participants with unknown status, solid squares represent participants with known status. The tests for heterogeneity compare the log RRs in high-antigen versus low-antigen patients (i.e. excluding those with unknown antigen status). All participants are included in the overall summary diamonds. RR=risk ratio for the composite outcome of invasive mechanical ventilation or death, and rate ratio for the other outcomes.

Figure 4: Effect of allocation to sotrovimab on 28-day mortality by baseline characteristics in high-antigen participants. Subgroup−specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. The ethnicity, days since onset and use of corticosteroids subgroups exclude those with missing data, but these patients are included in the overall summary diamond. * Post-hoc subgroup analysis requested during peer-review.

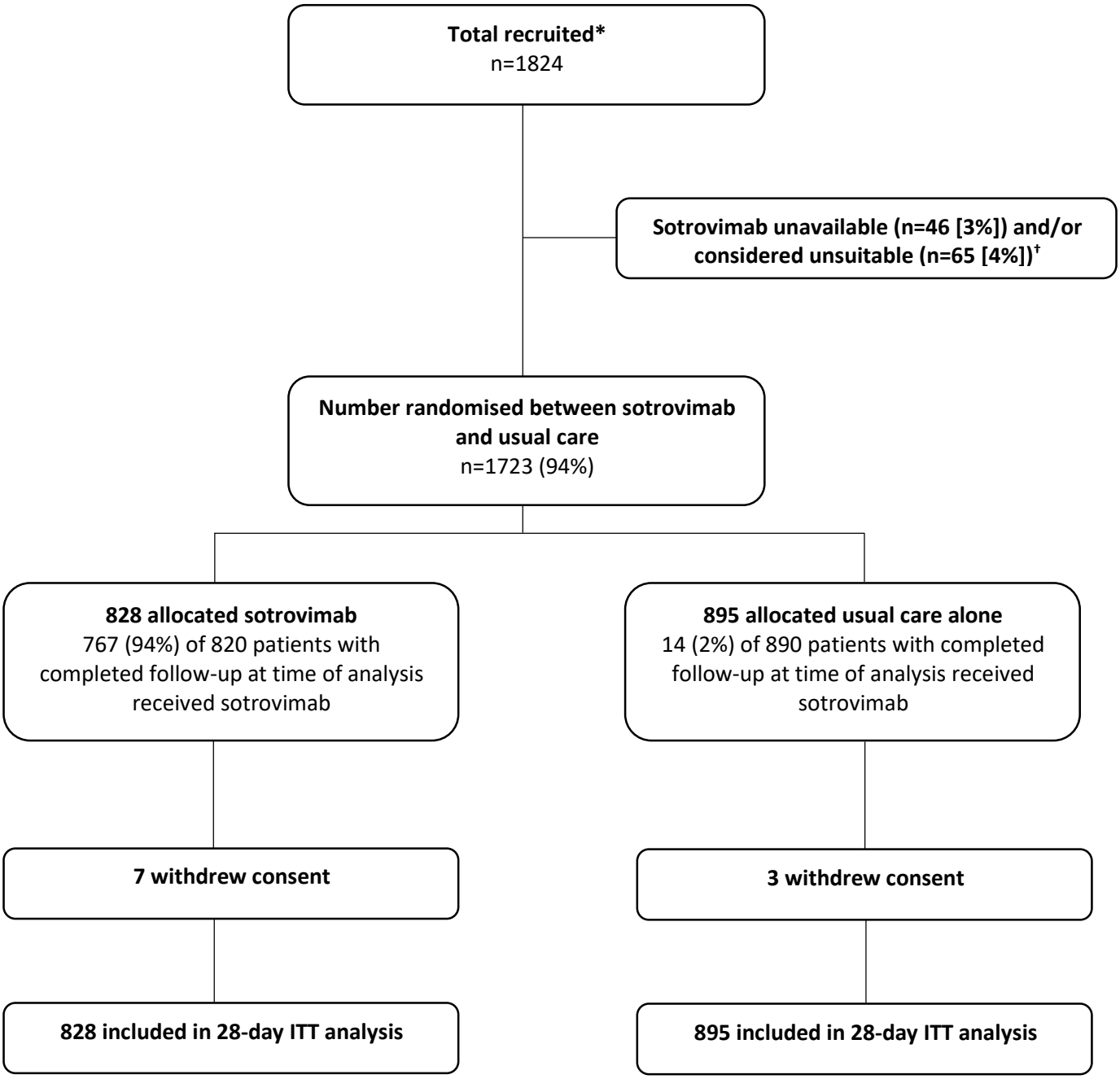
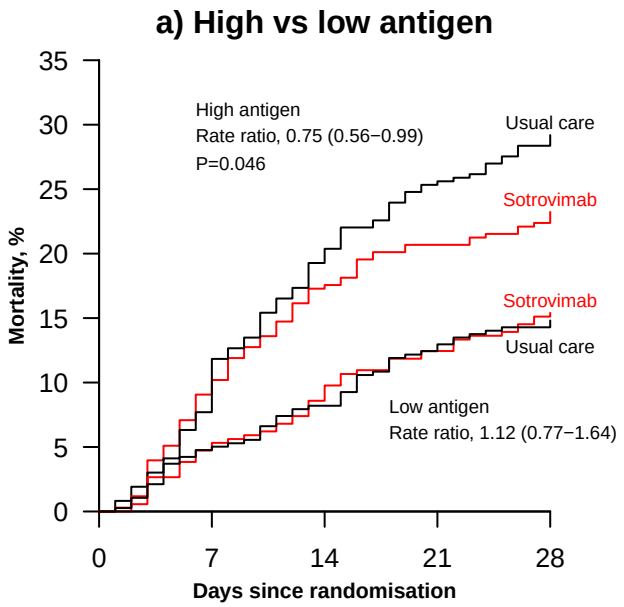


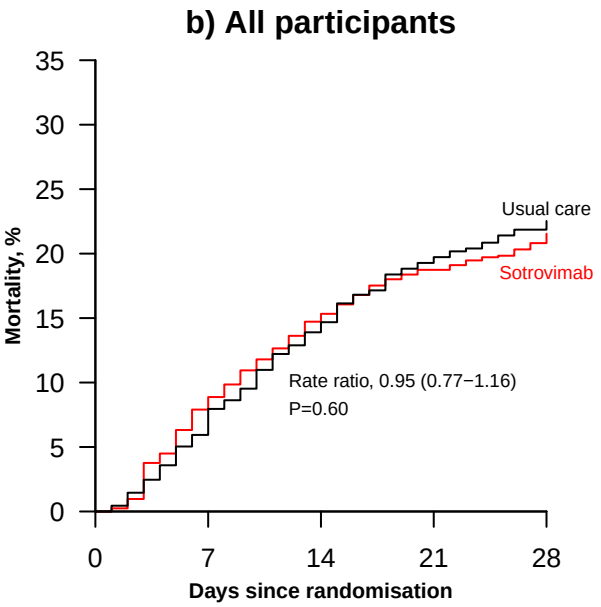
Figure 1: Trial profile

ITT=intention to treat. *Number recruited to any RECOVERY comparison at sites participating in the sotrovimab comparison, during the period in which it was open.

†Drug unavailability and unsuitability are not mutually exclusive.

Figure 2: Effect of allocation to sotrovimab on 28−day mortality in: a) participants with high vs low antigen levels; and b) all participants





No. at risk, High antigen

Sotrovimab	355	317	291	280	271
Usual care	365	320	289	270	257

No. at risk, Low antigen

Sotrovimab	339	320	304	295	285
Usual care	378	359	347	329	322

No. at risk

Sotrovimab	828	749	695	667	644
Usual care	895	821	761	716	691

Figure 3: Primary and secondary outcomes, overall and by baseline antigen status

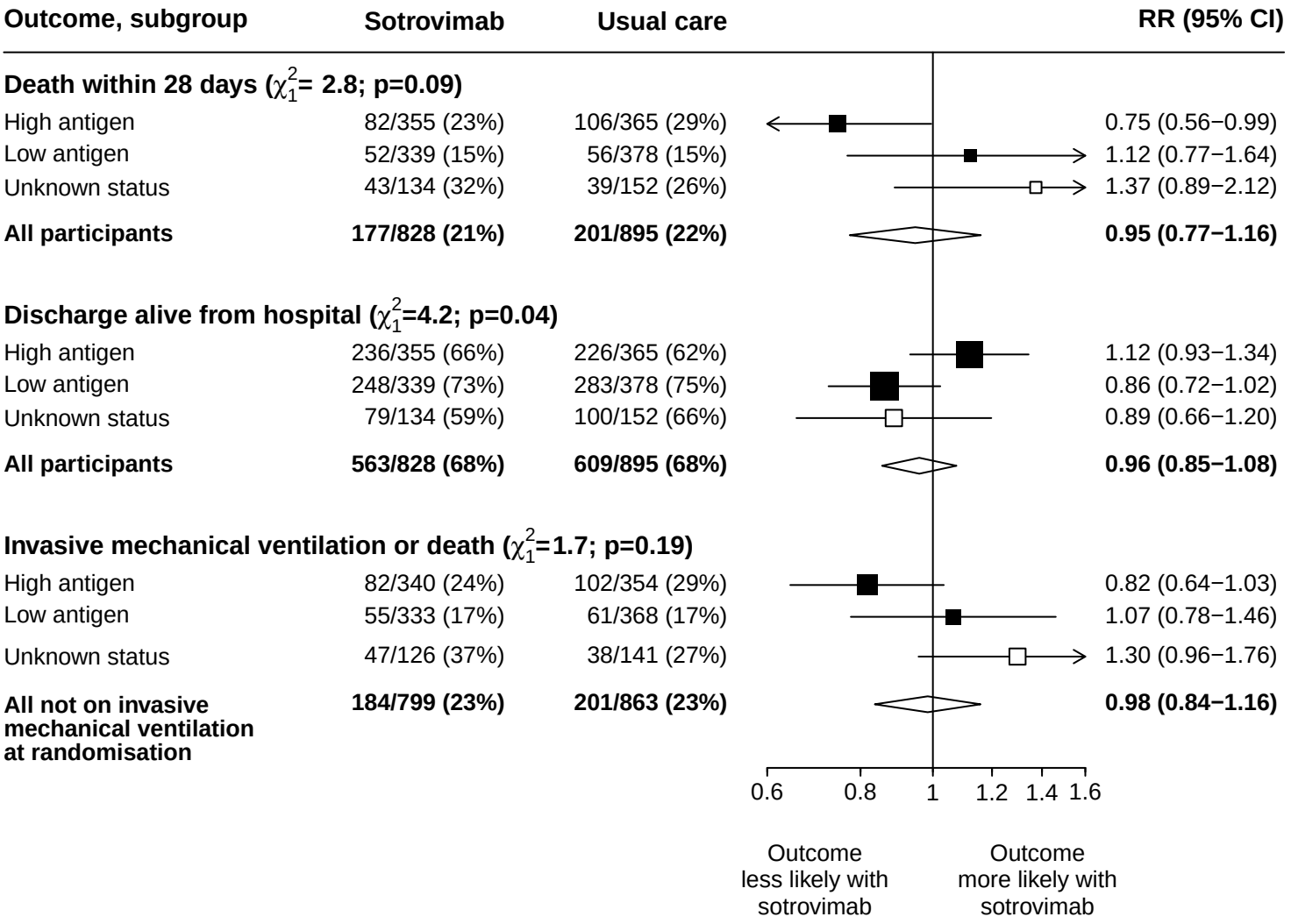
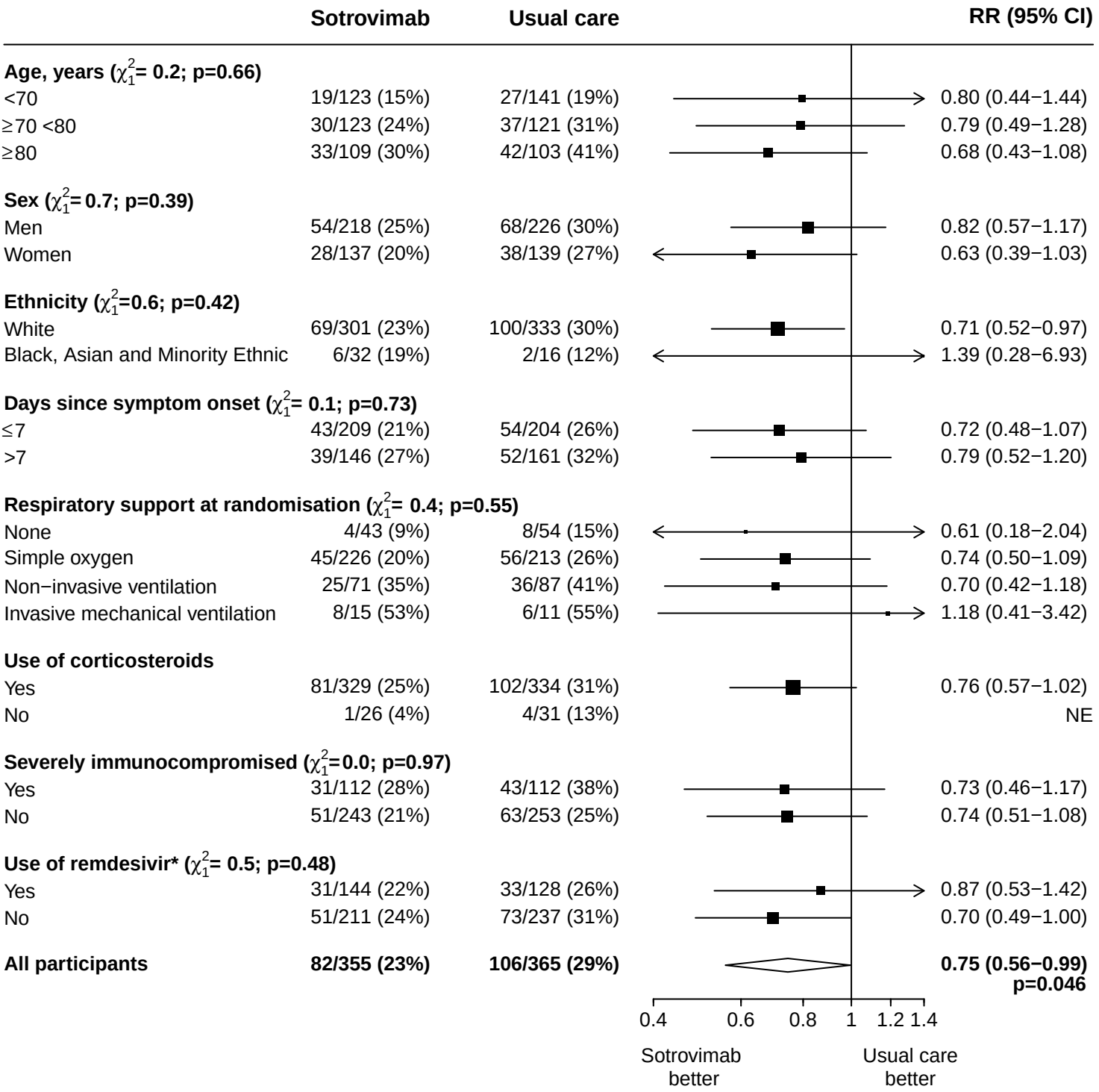


Figure 4: Effect of allocation to sotrovimab on 28−day mortality in participants with high antigen levels, by other baseline characteristics



Sotrovimab versus usual care in patients admitted to hospital with COVID-19: a randomised, controlled, open-label, platform trial (RECOVERY)

SUPPLEMENTARY APPENDIX

RECOVERY Collaborative Group

Contents

Details of the RECOVERY Collaborative Group

Writing Committee

Peter W Horby[a,b,c*], Jonathan R Emberson[d*], Leon Peto[d,e*], Natalie Staplin[d], Mark Campbell[d,e], Guilherme Pessoa-Amorim[d], Richard Stewart[f], Dipansu Ghosh[g], Graham Cooke[h], Natalie Blencowe[i], Jeronimo Moreno-Cuesta[j], Purav Desai[k], Paul Hine[l], Jonathan Underwood[m], Nicholas Easom[n,o], Jaydip Majumdar[p], Sanjay Bhagani[q], J Kenneth Baillie[r], Maya H Buch[s], Saul N Faust[t], Thomas Jaki[u,v], Katie Jeffery[e,w], Edmund Juszczak[x], Marian Knight[y], Wei Shen Lim[z], Alan Montgomery[x], Aparna Mukherjee,[za] Andrew Mumford[zb], Kathryn Rowan[zc], Guy Thwaites[a,zd], Marion Mafham[d†], Richard Haynes[d,e†], Martin J Landray[d,ze†]

[a] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

[b] International Severe Acute Respiratory and emerging Infections Consortium (ISARIC), University of Oxford, Oxford, United Kingdom

[c] Pandemic Sciences Centre, University of Oxford, Oxford, United Kingdom

[d] Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

[e] Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

[f] Milton Keynes University Hospital, Milton Keynes, United Kingdom

[g] Leeds Teaching Hospitals NHS Foundation Trust, Leeds, United Kingdom

[h] Imperial College Healthcare NHS Trust, London, United Kingdom

[i] University Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Bristol, United Kingdom

[j] North Middlesex University Hospital NHS Trust

[k] Calderdale and Huddersfield NHS Foundation Trust, Huddersfield, United Kingdom

[l] Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom

[m] Cardiff & Vale University LHB, Cardiff, United Kingdom

[n] Hull York Medical School, Hull, United Kingdom

[o] Hull University Teaching Hospitals NHS Trust, Hull, United Kingdom

[p] Mid Cheshire Hospitals NHS Foundation Trust, United Kingdom

[q] Royal Free London NHS Foundation Trust, London, United Kingdom

[r] Roslin Institute, University of Edinburgh, Edinburgh, United Kingdom

[s] Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom

[t] NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

[u] Faculty for Informatics and Data Science, University of Regensburg, Germany

[v] MRC Biostatistics Unit, University of Cambridge, UK

[w] Radcliffe Deparment of Medicine, University of Oxford, United Kingdom

[x] School of Medicine, University of Nottingham, Nottingham, United Kingdom

[y] National Perinatal Epidemiology Unit, University of Oxford, United Kingdom

[z] Respiratory Medicine Department, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

[za] Indian Council of Medical Research, New Delhi, India

[zb] School of Cellular and Molecular Medicine, University of Bristol, Bristol, United Kingdom

[zc] Intensive Care National Audit & Research Centre, London, United Kingdom

[zd] Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam

[ze] NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

*,[†] equal contribution

Steering Committee

Co-Chief Investigators PW Horby, MJ Landray, *Members* JK Baillie, M Buch, L Chappell (until August 2021), J Day (until May 2022), SN Faust, R Haynes, T Jaki, K Jeffery, E Juszczak, M Knight (from August 2021), WS Lim, M Mafham, A Montgomery, A Mukherjee, A Mumford, K Rowan, G Thwaites.

International Committee

Chair DV Dung *Regional Lead Investigators* G Thwaites, J Day *Independent members* NN Quang, Prof. Binh, E Burhan, B Alisjahbana, J Koirala, S Basnet *Other members* E Kestelyn, B Basnyat, P Gyanwali, RL Hamers, P Horby

Data Monitoring Committee

P Sandercock (chair), J Darbyshire, D DeMets, R Fowler, D Lalloo, M Munavvar (from January 2021), I Roberts (until December 2020), A Warris (from March 2021), J Wittes *Non-voting statisticians* J Emberson, N Staplin.

RECOVERY Trial Central Coordinating Office

Co-Chief Investigators P Horby, MJ Landray; *Clinical Trial Unit Lead* R Haynes; *Trial management* A Cradduck-Bamford (coordinator), J Barton, A Basoglu, R Brown, W Brudlo, E Denis, L Fletcher, S Howard, S Musini, K Taylor; *Programming and validation* G Cui, B Goodenough, A King, M Lay, D Murray, W Stevens, K Wallendszus, R Welsh; *Data linkage* C Crichton, J Davies, R Goldacre, C Harper, F Knight, M Mafham, M Nunn, H Salih, J Welch; *Clinical support* M Campbell, G Pessoa-Amorim, L Peto, M Zayed; *Quality assurance* J Wiles; *Statistics* J Emberson, E Juszczak, E Spata, N Staplin; *Communications* G Bagley, S Cameron, S Chamberlain, B Farrell, H Freeman, A Kennedy, A Whitehouse, S Wilkinson, C Wood; *Evidence synthesis (Vascular Overviews Group)* C Reith (coordinator), K Bird, K Davies, H Halls, L Holland, A Roddick, R Truell, K Wilson; *Administrative support* L Howie, M Lunn, P Rodgers

RECOVERY Trial Regional Coordinating Centres

Vietnam: *Oxford University Clinical Research Unit* G Thwaites, C Thwaites, E Kestelyn, NTH Thuong, TB Huyen, NT Thao, NB Tran, NTT Nguyen, NTP Dung, NTH Quyen, VTK Thi, NTH Trang, R van Doorn, HX Nam, PTT Hien, NY Nhi, NH Khanh

Nepal: *Nepal Health Research Council* P Gyanwali, M Dhimal, S Pant *Oxford University Clinical Research Unit* B Basnyat, A Karkey, S Rijal, S Shrestha

Indonesia: *Oxford University Clinical Research Unit Indonesia* RL Hamers, K Baird, K Puspatriani, M Rahardjani, A Rimainar, F Wulandari *Faculty of Medicine Universitas Indonesia* EJ Nelwan

India: *Indian Council for Medical Research* A Mukherjee, JJ Cherian, G Kumar

South Africa: *Wits Health Consortium* J Nel, H Rees

Ghana: *Kumasi Center for Collaborative Research in Tropic Medicine* J Amuasi, O Maiga, J Bonney, E Matey, A Afum-Adjei Awuah, H Hasford, A Amoako Adusei

Gambia: *MRC Unit The Gambia at LSHTM* B Nadjm, A Rocca, U D'Alessandro, E Usuf, M Bittaye, C Roberts, A Jagne

SARS-CoV-2 antibody and antigen testing laboratory

Emerging Pathogen Serology group, Vaccine Development and Preparedness Centre, UK Health Security Agency, Porton Down: A Otter (lead), B Hicks, T Coleman, C Rowe, J Hewson, G Hemingway, H Selman, A Lloyd, S Francis, H White, H Lewis, M Royds, E Cross, S Millward, S D'Arcangelo, S Jones, T Jones, V Summer, N Berry, K Ebisine, L Gatcombe, D Blick, C Wilson

SARS-CoV-2 PCR and sequencing laboratory

Oxford University Hospitals NHS Foundation Trust, Oxford: L Dunn (lead), J Bastable, B Constantinides, D Crook, A Justice, S Oakley, J Swann

UK National Institute for Health Research Clinical Research Network

Coordinating Centre A Barnard, J Beety, C Birch, M Brend, E Chambers, L Chappell, S Crawshaw, C Drake, H Duckles-Leech, J Graham, T Harman, H Harper, S Lock, K Lomme, N McMillan, I Nickson, U Ohia, E OKell, V Poustie**,** S Sam, P Sharratt, J Sheffield, H Slade, W Van't Hoff, S Walker, J Williamson; *Urgent Public Health Clinical Links* A De Soyza, P Dimitri, SN Faust, N Lemoine, J Minton; *East Midlands* K Gilmour, K Pearson *Eastern* C Armah, D Campbell, H Cate, A Priest, E Thomas, R Usher; *North East & North Cumbria* G Johnson, M Logan, S Pratt, A Price, K Shirley, E Walton, P Williams, F Yelnoorkar; *Kent, Surrey & Sussex* J Hanson, H Membrey, L Gill, A Oliver; *North West London* S Das, S Murphy, M Sutu; *Greater Manchester* J Collins, H Monaghan, A Unsworth, S Beddows; *North West Coast* K Barker-Williams, S Dowling, K Gibbons, K Pine; *North Thames* A Asghar, P Aubrey, D Beaumont-Jewell, K Donaldson, T Skinner; *South London* J Luo, N Mguni, N Muzengi, R Pleass, E Wayman; *South West Peninsula* A Coe, J Hicks, M Hough, C Levett, A Potter, J Taylor; *Thames Valley and South Midlands* M Dolman, L Gerdes, C Hall, T Lockett, D Porter *Wessex* J Bartholomew, L Dowden, C Rook, J Walters; *West of England* E Denton, H Tinkler; *Yorkshire & Humber* A Alexander, H Campbell, K Chapman, A Hall, A Rodgers; *West Midlands* P Boyle, M Brookes, C Callens, H Duffy, C Green, K Hampshire, S Harrison, J Kirk, M Naz, L Porter, P Ryan, J Shenton, J Warmington; *Devolved nations* M Amezaga, P Dicks, J Goodwin, H Hodgson, S Jackson, M Odam, D Williamson.

Paediatric working group

SN Faust (coordinator), A Bamford, S Bandi, J Bernatoniene, K Cathie, P Dmitri, S Drysdale, M Emonts, J Evans, A Finn, P Fleming, J Furness, C Gale, R Haynes, CE Jones, E Juszczak, D Jyotish, D Kelly, C Murray, N Pathan, L Pollock, A Ramanan, A Riordan, C Roehr, M Wan, E Whittaker.

Obstetric working group

M Knight (coordinator), K Hodson, S Pavord, C Williamson.

Clinical support

Clinical Trial Service Unit Out of Hours clinical support L Bowman, F Chen, R Clarke, M Goonasekara, R Haynes, W Herrington, P Judge, M Mafham, K Mayne, S Ng, D Preiss, C Reith, E Sammons, D Zhu.

Health records

NHS DigiTrials, Southport H Pinches, P Bowker, V Byrne-Watts, G Chapman, G Coleman, J Gray, A Rees, MJ Landray, M Mafham, N Mather, T Denwood; *Intensive Care National Audit & Research Centre, London* D Harrison; *National Records of Scotland* G Turner; *Public Health Scotland* J Bruce; *SAIL Databank, University of Swansea* C Arkley, S Rees.

Local Clinical Centre RECOVERY trial staff
(listed in descending order of the number of patients randomised per site)

Milton Keynes University Hospital NHS Foundation Trust R Stewart (PI), J Alin, L Anguvaa, J Bae, G Bega, S Bowman, A Chakraborty, E Clare, S Fox, S Franklin, S George, L How, M Kennedy, J Mead, L Mew, D Mital, L Moran, E Mwaura, M Nathvani, A Rose, D Scaletta, S Shah, L Siamia, O Spring, S Sutherland, F Teasdale, S Velankar, L Wren, F Wright.

Leeds Teaching Hospitals NHS Trust D Ghosh (PI), S Ahmed, A Ashworth, N Balatoni, M Baum, L Bonney, J Calderwood, E Carter, S Charlton, J Clarke, C Coupland, M Crow, C Favager, J Glossop, J Hemingway, S Hemphill, K Holliday, A Humphries, S James, K Johnson, A Jones, M Kacar, K Khokhar, P Lewthwaite, A Marcyniuk, G Martin, F McGill, J Minton, D Mistry, J Murira, Z Mustufvi, S O'Riordan, K Robinson, G Saalmink, R Saman (Associate PI), D Singh, B Staniforth, S Straw, A Westwood.

Imperial College Healthcare NHS Trust G Cooke (PI), L Young (Co-PI), O Adedeji, E Adewunmi, Z Al-Saadi, R Ashworth, J Barnacle, N Bohnacker, A Cann, F Cheng, J Clark, S Cooray, S Darnell, A Daunt (Associate PI), V Dave, A D'Mello, L Evison, S Fernandez Lopez, F Fitzgerald, C Gale, M Gibani, S Hamilton, S Hunter, A Jimenez Gil, S Johal, B Jones, A Kountourgioti, J Labao, V Latham, N Madeja, S Mashate, C Matthews, H McLachlan, A Mehar, J Millard (Associate PI), M Molina, A Perry, H Rafferty, S Rey, S Ryder, R Shah, E Sidebotham, R Thomas, D Thornton, J Tuff, E Whittaker, C Wignall, P Wilding, C Wong, T Yates (Associate PI), C Yu.

University Hospitals Bristol and Weston NHS Foundation Trust G Hamilton (PI), N Blencowe (Co-PI), E Stratton (Co-PI), M Abraham, D Adams, B Al-Ramadhani, B Amit, A Archer (Associate PI), G Asher (Associate PI), G Aziz, A Balcombe, K Bateman, M Baxter, L Beacham, K Beard, K Belfield (Associate PI), N Bell, M Beresford, J Bernatoniene, A Bhat, D Bhojwani, S Biggs, C Blair, J Blazeby, K Bobruk, S Brooks, N Brown, L Buckley, P Butler, A Cannon, C Caws, E Chakkarapani, K Chatar, D Chatterton, B Chivima, E Clark, C Clemente de la Torre, K Cobain, H Cooke, D Cotterill, E Courtney, S Cowman, K Coy, H Crosby, K Curtis, P Davis, O Drewett, K Druryk, R Duncan, H Dymond, K Edgerley, M Ekoi, M Elokl, B Evans, T Farmery, N Fineman, A Finn, L Gamble, F Garty, B Gibbison, L Gourbault, D Grant, K Gregory, M Griffin, R Groome, L Gurung, V Haile, M Hamdollah-Zadeh, A Hannington, R Harrison, J Heywood, A Hindmarsh, N Holling, C Horrobin, R Houlihan, J Hrycaiczuk, H Hudson, K Hurley, J Iqbal, R Jarvis, B Jeffs, A Jones, R E Jones, E King-Oakley, E Kirkham, L Kirkpatrick, R Kumar, M Kurdy, A Lagnado, S Lang, L Leandro, H Legge, F Loro, A Low, H Martin, J Mayer, T Mayo, L McCullagh, G McMahon, L Millett, K Millington, J Mok, J Moon, L

Morgan, S Mulligan, L Murray, T Nandwani, C O'Donovan, E Payne, C Penman, M Pezard-Snell, J Pickard, M Pitchford, C Plumptre, D Putensen, A Ramanan, J Ramirez, S Ratcliffe, N Redman, E Robbins, V Roberts, J Robinson, M Roderick, S Scattergood, A Schadenberg, E Schofield, R Sheppeard, C Shioi, J Shurlock, D Simpson, P Singhal, A Skorko, B Smart, N Smith, R Squires (Associate PI), V Stefania, C Stewart, M Stuttard, P Sugden, S Sundar, C Swanson-Low, T Swart, E Swift, A Tate, M Thake, K Thompson, M Trevelyan, K Turner, S Turner, A Tyer, S Vergnano, R Vincent, R Ward, A White, S Wilkinson, J Williams, S Williams, J Willis, H Winter, Z Woodward, L Woollen, R Wright, A Younes Ibrahim.

North Middlesex University Hospital NHS Trust J Moreno-Cuesta (PI), A Dhariwal (Co-PI), S Jain (Co-PI), T Amin, D Bakthavatsalam, P Brooks, M Farah, A Govind, A Haldeos, K Leigh-Ellis, T Light, S Rokadiya, C Vansomeren, R Vincent, L Walker.

Calderdale and Huddersfield NHS Foundation Trust P Desai (PI), A Abbott, K Abouelela, U Akudi, D Appleyard, L-A Bayo, D Bromley, N Chambers, M Collins, S Dale, L Gledhill, J Goddard, J Greig, K Hallas, K Hanson, K Holroyd, M Home, D Kelly, A Maharajh, L Matapure, S Mellor, E Merwaha (Associate PI), M Prior-Ong, K Rajalingam, H Riley, M Robinson, C Rourke, K Sandhu, K Schwarz, N Scriven, L Shaw, L Terrett, M Thompson (Associate PI), G Turner, M Usher, A Wilson, T Wood.

Liverpool University Hospitals NHS Foundation Trust P Hine (PI), P Albert (Co-PI), S Todd (Co-PI), I Welters (Co-PI), D Wootton (Co-PI), M Ahmed, R Ahmed, A Al Balushi, M Anderson, R Anderson, Z Ashfak, A Atomode, R Ball, P Banks, D Barr, J Bassett, A Bennett, H Bond, A Bracken, T Brankin-Frisby (Associate PI), G Bretland, P Brinksman, M Brodsky, J Brown, H Burhan, C Burston, J Byrne, F Carlin, S Casey, L Chambers, D Coey, T Cross, J Cruise, J Currie, S D'Souza, L Dobbie, R Downey, A Du Thinh, G Duncan, I Duru, J Early, T Evans, K Fenlon, J Fernandez Roman, I Fordham, H Frankland, S Glynn, J Goodall, S Gould, A Gureviciute, J Hackett, K Haigh, M Hamilton, L Hampson, A Hanson, M Harrison, L Hawker, P Hazenberg, D Heath, S Hicks, S Hope, M Howard, K Hunter, T Ingram, A Islim, K Janes, B Johnston, S Karmali, S Kavanagh, L Keogan, W Khan, S King, K Krasauskas, J Lewis, M Lofthouse, P Lopez, C Lowe, Z Mahmood, F Malein, K Martin, A Mediana, L Melling, Z Mellor, P Merron, B Metcalfe, M Middleton, K Monsell, A Morgan, H Murphy, N Nicholas, A Nuttall, L Oliver, R Osanlou, J Parsons, L Pauls, L Pilling, R Price-Eland, C Prince, S Pringle, E Richardson, L Rigby, M Riley, A Rowe, E Rybka, M Samuel, D Scanlon, J Sedano, D Shaw, F Shiham, C Smith (Associate PI), S Stevenson, A Stockdale, J Tempany, P Thu-Ta, C Toohey, I Turner-bone, S Victoria, A Waite, E Wasson, A Watkin, R Watson, V Waugh, R Westhead, L Wilding, K Williams, A Wood, A Yeoh, D Zeinali.

Cardiff & Vale University LHB M Wise (PI), J Underwood (Co-PI), A Balan, B Basker, S Bird, Z Boult, V Britten, L Broad, H Cendl, M Chakraborty, J Cole, E Davies, M Edgar, M Edwards, N Elashhar, S Elliott, J Evans, J Evans, M Evans, E Evans, C Fegan, M Forester, J Forton, S Frayling, S Gage, F Greaves, S Harrhy, M Haynes, A Heavens, H Hill, Z Hilton, L Jones, A Kelly, L Knibbs, N Krishnapalli, D Lau, J May, E McGough, A McQueen, J Milner, M Morgan, F Muhammad, R Norman, K Nyland, C Oliver, K Paradowski, M Patal, B Phillips, M Potdar, K Rahilly, D Rigler, C Robinson, S Scourfield, A Semmens, M Starr, J Stevens, S Struik, E Thomas, R Thomas-Turner, G Thueux, G Williams, J Williams, M Williams, S Zaher.

Hull University Teaching Hospitals NHS Trust N Easom (PI), K Adams, K Ahmed, D Allsup, G Barlow, R Barton, J Batac, D Clark, L Cullen, K Drury, A Frygier, S Gribben, P Gunasekera, A Harvey, M Hayes, M Ivan, S Khan, M Kolodziej, P Lillie, V Lowthorpe, V Mathew, S Mongolu, A Morrow, I Muazzam, D Norton, K Nu, R Patmore, T Perinpanathan, C Philbey, B Pickwell-Smith, D Purchase, S Rastogi, A Richards, L Rollins, A Samson, T Sathyapalan, Y See (Associate PI), L Sherris, K Sivakumar, D Smith, T Taynton (Associate PI), G Walker, A Wolstencroft, H Yates.

Mid Cheshire Hospitals NHS Foundation Trust J Majumdar (PI), T Adeyemo, K Best, G Bridgwood, R Broadhurst, C Brockelsby, T Brockley, J Brown, R Bujazia, A Burton, S Clarke, J Cremona, C Dixon, S Dowson, H Drogan, F Duncan, M Emms, H Farooq, D Fullerton, N G, C Gabriel, S Hammersley, R Hum, T Jones, S Kay, E Kelly, M Kidd, D Lees, R Lowsby, D Maren, D Maseda, E Matovu, K McIntyre, H Moulton, K Nourein, K Pagett, A Ritchings, S Smith, J Taylor, K Thomas, K Turbitt, M Williams, S Yasmin.

Royal Free London NHS Foundation Trust T Mahungu (PI), H Tahir (Co-PI), A Abdul, R Abdul-Kadir, H Aboelela, M Al-Khalil, N Allan, I Alshaer, M Anderson, M Araujo, G Badhan, A Bakhai, S Bhagani, B Bobie, A Brraka, B Caplin, A Carroll, A Carroll, H Century, E Cheung, D Cohen (Associate PI), O Coker, D Collier, V Conteh, N Cooper, J Crause, N Davies, R Davies, V Deelchand, M Dosani, L Ehiorobo, C Ellis, G Ferenando, J Franklin, P Gardiner, F Geele, J Gosai, N Handzewniak, E Hanison, S Hanson, N Holdhof, H Hughes, C Jack, C Jarvis, V Jennings, H Koo, V Krishnamurthy, A Kurani (Associate PI), Z Ladan, L Lamb, A Lang, V Le, S Lee, S Lo, A Luintel, A Maharajh, H Mahdi, T Majekdunmi, D Matila, S Melander, F Mellor, A Molloy, R Moores, J Morales, G Moray, A Nandani, S Nasa, S O'Farrell, A Oomatia, A Osadcow, J Osei-Bobie, G Pakou, P Patel, C Patterson (Associate PI), E Pyart, E Quek, S Rabinowicz, T Rampling, R Rankhelawon, A Rodger, A Scobie, S Sharma, C Singh, S Sithiravel, T Sobande, P Talbot, P Taribagil, S Veerasamy, G Wallis, J Whiteley, E Witele, A Wong, E Woodford, N Yaqoob.

Sheffield Teaching Hospitals NHS Foundation Trust P Collini (PI), A Ali, A Alli, S Anderson, A Ang, I Aslam, A Basran, J Belcher, G Benoy, S Bird, M Boothroyd, H Bowler, A Card, K Cawthorne, L Chapman, K Chin, A Clarke, S Clenton, V Clubb, L Cockayne, D Cohen, J Cole, H Colton, A Condliffe, R Condliffe, A Creaser-Myers, M Cribb, S Curran, S Darby, T Darton, D de Fonseka, T de Silva, A Dunn, C Durojaiye, P Easton, S Eggleston, A Ellwood, A Emery, E Ferriman, H Foot, A Ford, R Foster, Z Gabriel, V Goodall, J Greig, N Guthrine, J Hall, H Hanratty, S Hardman, K Harrington, J Hau, E Headon, C Holden, B Holroyd-Hind, K Housely, A Howell, L Hunt, E Hurditch, J Hurdman, Z Hussein, F Ilyas, J Jackman, Y Jackson, C Jarman, F Kibutu, B Kilner, T Kitching, S Lassa, R Lawson, C Lee, R Lenagh, L Lewis, N Lewis, T Locke, H Luke, A Lye, I Macharia, L Mair, G Margabanthu, P May, A Mbuyisha, J McNeill, S Megson, J Meirill, J Meiring, J Middle, J Middleton, L Milner, P Morris, D Mosby, A Nazir, H Newell, T Newman, L Nwafor, V Palissery, V Parkash, L Passby, R Payne, I Pernicova, P Phillips, M Plowright, A Raithatha, G Rana, P Ravencroft, S Renshaw, A Rothman, M Roycroft, D Sammut, S Sammut, R Sellars, S Sherwin, J Sidebottom, P Simpson, L Smart, M Sterrenburg, B Stone, M Surtees, A Telfer, B Thamu, R Thompson, Y Thompson, N Tinker, H Trower, K Turner, M Ul Haq, N Vethanayagam, P Wade, J Wadsley, S Walker, J G R Watson, J Wesonga, R West, R Whitham, T Williams, J Willson, A Wilson, I Wilson, T Zak, E Zincone, STH CRF COVID Nursing team.

University Hospitals Birmingham NHS Foundation Trust C Green (PI), T Whitehouse (Co-PI), I Ahmed, N Anderson, C Armstrong, A Bamford, H Bancroft, M Bates, M Bellamy, T Bellamy, C Bergin, K Bhandal, E Butler, M Carmody, N Cianci (Associate PI), K Clay (Associate PI), L Cooper, J Daglish, J Dasgin, A Desai, S Dhani, D Dosanjh, E Forster, J Gresty, E Grobovaite, N Haider, B Hopkins, D Hull, Y Hussain, A Kailey, M Lacson, M Lovell, D Lynch, C McGhee, C McNeill, F Moore, A Nilsson, J Nunnick, W Osborne (Associate PI), S Page, D Parekh, C Prest, K Price, V Price, M Sangombe, H Smith, I Storey, L Thrasyvoulou, K Tsakiridou, D Walsh, S Welch, H Willis, L Wood, J Woodford, G Wooldridge, C Zullo.

Epsom and St Helier University Hospitals NHS Trust S Winn (PI), J Evans (Co-PI), F Abbas, S Acheampong, S Ahamed Sadiq, A Aldana, B Al-Hakim, A Alipustain, P Allen, G Azzopardi, E Balogh, Z Baxter, C Bond, C Cheeld, R Chicano, I Chukwulobelu, N Colbeck, R Dogra, E Doherty, A Elradi, J Emberton, L Evans, R Ganapathy, N Hamilton, J Handford, M Haque, J Hayes, R Hayre, L Ilves, C Jagadish, S Jain, K Jian, A Johnson, L Johnson, B Kim, J Kotecha, A Kundu, D Langer, E Lester, A Lunia, Y Mashhoudi, K Mathias, T Medveczky, F

Mellor, G Mic, S Moore, M Morgan, O Mushtaq, S Nafees, A Oluwole-Ojo, V Palagiri Sai, M Phanish, H Rahimi, S Ramanna, A Ramnarine, J Ratoff, M Ridha, S Rozewicz, T Samuel, G Saxena, S Selvendran, B Shah, S Shahnazari, R Shail, A Sharif, S Singh, S Somalanka, R Suckling, P Swift, L Tarrant, V Tyagi, N Vilimiene, P Virdee, R Wake, L Walsh.

Portsmouth Hospitals NHS Trust T Brown (PI), J Andrews, R Baker, M Baker-Moffatt, A Bamgboye, D Barnes, S Baryschpolec, V Bataduwaarachchi, S Begum, L Bell, H Blackman, J Borbone, N Borman, P Braga Sardo, L Brimfield, M Broadway, F Brogan, R Bungue-Tuble, K Burrows, A Chauhan, E Cowan, M Czekaj, Z Daly, A Darbyshire, A Das, M Davey, M David, J Denham, R Duhoky, C Edwards, S Elliott, H Evison, L Fox, Z Garner, I Gedge, B Giles, S Glaysher, S Gosling, A Gribbin, J Hale, Y Harrington-Davies, L Hawes, J Hayward, A Hicks, A Holmes, S Howe, H Htet, B Jones, C Lameirinhas, E Lavington, B Longhurst, L Lopes, M Mamman, J Marshall, S McCready, L Milne, C Minnis, M Moon, J Mouland, L Murray, J Ouyang, C Pereira Dias Alves, M Rason, L Richmond, D Rodgers, S Rose, M Rowley, M Rutgers, T Scorrer, L Shayler, R Sievers, K Siggens, S Smith, C Stemp, N Szarazova, E Taylor, R Thornton, A Tiller, C Turner, L Vinall, E Walmsley, M Wands, J Warren, L Watkins, M White, L Wiffen (Associate PI), J Winter, C Wong, K Wren, Y Yang.

South Tees Hospitals NHS Foundation Trust D Chadwick (PI), A Aboagye-Odei, S Armstrong, D Athorne, A Awadelkareem, M Branch, J Brolly, S Brown, J Cheaveau, H Chen, Y Chua, N Cunningham, M Dafalla, S Davies, J Dodds, S Dorgan, D Dunn, P Dunn, M Elsayed, E Hammond, P Harper, H Harwood, K Hebbron, F Hunt, A Kala Bhushan, P Lambert, C Lawrence, D Leaning, T Linn, T Manders, B McCarron, N Miller-Biot, C Milne, W Mohammad, M Mollet, J Mulcahy, A Murad, S Ooi, M Owston, J Potts, C Proctor, S Puliyakkadi, B Puvaneswaran, S Rao, R Raw (Associate PI), M Seelarbokus, P Singh, V Srirathan, L Swithenbank, A Szekeres, L Thompson, H Wardy, L Wiblin, J Widdrington, J Williams, P Winder, C Wroe.

University College London Hospitals NHS Foundation Trust H Esmail (PI), R Heyderman (Co-PI), V Johnston (Co-PI), D Moore (Co-PI), A Andrews, F Beynon, P Bodalia, I Bokobza, X Chan, Z Chaudhry, C Chung, J Cohen, D Crilly, S Eisen, N Fard, J Gahir, L Germain, J Glanville, R Gupta, N Lack, A Last, A Luintel, M Merida Morillas, B Nadjm, N Platt, T Rampling, H Rickman, S Rokadiya, S Roy, A Samson, R Shortman, I Skorupinska, M Skorupinska, J Spillane, C Thakker, L Wellings.

NHS Fife D Dhasmana (PI), F Adam, K Aniruddhan, J Boyd, N Bulteel, P Cochrane, I Fairbairn, S Finch, K Gray, L Hogg, S Iwanikiw, M Macmahon, P Marks, A McGregor, A Morrow, J Penman, J Pickles, J Ramsay, A Scullion, H Sheridan, M Simpson, D Sloan, C Stewart, J Tait, A Timmins, M Topping.

West Suffolk NHS Foundation Trust M Moody (PI), S Barkha, H Cockerill, K Durrant, J Godden, J Kellett, T Murray, A Saraswatula, A Williams, L Wood.

Medway NHS Foundation Trust R Sarkar (PI), K Abernethy (Associate PI), C Adams, L Adams, A Addo, F Aliyuda, S Archer, A Arya, E Attubato, F Babatunde, M Bachour, P Balasingam, A Bhandari, F Brokke, R Chauhan, V Chawla, R Chineka, A Davis, N Edmond, M Elbeshy, C Ezenduka, S Ferron, C Gnanalingam, D Gotham, M Hollands, M Iqbal, A Jamal, B Josiah, S Kidney, M Kim, K Koukou, T Kyere-Diabour, L Leach, A Liao, A Maheswaran, M Mansour, N Miah, J Morilla, L Naglik, K Naicker, Z Nurgat, S Rai, I Redknap, Z Rehman, A Ryan, Y Samuel, A Shaibu, P Soor, R Squires, W Stagg, W Ul Hassan, P Vankayalapati, E Vyras, A Williams, J Wood, N Zuhra (Associate PI).

Cambridge University Hospitals NHS Foundation Trust M Knolle (PI), E Gkrania-Klotsas (Co-PI), O Abani, R Bousfield (Associate PI), T Dymond, L Eadie, K Gajewska-Knapik, J

Galloway, R Gore, K Leonard, T Mikolasch, H-P Mok, N Pathan, P Polgarova, J Sahota, K Sharrocks, R Swain.

Stockport NHS Foundation Trust R Stanciu (PI), M Afridi, M Al Dakhola, M Alafifi, S Bennett, L Brown, C Cooper, A Davison, D Eleanor, J Farthing, A Ferrera, S Gandhi, L Gomez, Z Hassan, P Haywood, C Heal, H Jackson, J Johnston, A Lloyd, S McCaughey, R Mills, R Owen, A Pemberton, F Rahim, H Robinson, N Sadiq, R Samlal, V Subramanian, D Suresh, D Tudor, H Wieringa, I Wright, B Xia.

Nottingham University Hospitals NHS Trust W S Lim (PI), M Ali, L Anderson, A Andrews, S Ashraf, D Ashton, G Babington, G Bartlett, D Batra, L Bendall, N Benetti, T Brear, A Buck, G Bugg, J Butler, R Cammack, J Cantliff, L Clark, E Connor, P Davies, M Dent, C Dobson, A Fatemi, M Fatemi, L Fleming, J Grundy, J Hallas, L Hodgen, S Hodgkinson, S Hodgson, L Howard, C Hutchinson, B Jackson, J Kaur, E Keddie-Gray, E Kendall, C Khurana, M Langley, L Lawless, L Looby, M Meredith, L Morris, H Navarra, R Nicol, J Oliver, C Peters, B Petrova, R Purdy, Z Rose, L Ryan, J Sampson, G Squires, J Squires, R Taylor, A Thomas, J Thornton, K Topham, O Vincent, S Warburton, S Wardle, H Waterfall, S Wei, T Wildsmith, L Wilson.

Dorset County Hospital NHS Foundation Trust J Chambers (PI), F Best, J Birch, L Bough, S Caddy, A Cave, J Chambers, J Colton, J Graves, S Horton, J Rees, R Thomas, W Verling, P Williams, S Williams, B Winter-Goodwin, S Wiseman, D Wixted.

East Suffolk and North Essex NHS Foundation Trust J Douse (PI), M Ramali (Co-PI), K Ahmed, S Alam, A Arumaithurai, B Atraskiewicz, J Bailey, I Balluz, D Beeby, S Bell, J Bloomfield, S Blows, N Broughton, C Buckman, M Burton, C Calver, J Campbell, P Carroll, C Chabo, R Chalmers, K Cheung, M Chowdhury, G Christoforou, K Cooke, N Deole, T H Dinh (Associate PI), C Driscoll, J Dulay, S Finbow, I Floodgate, R Francis, C Galloway, E Galloway, M Garfield, A Ghosh, G Gray, P Greenfield, A Gribble, M Gunawardena, M Hadjiandreou, H Hewer, M Hossain, R Howard-Griffin, K Howlett, C Huah, N Innes, V Inpadhas, A Islam, L James, Z Jiao, K Johannessen, J Kathirgamachelvam, M Khan Tharin, V Kushakovsky, S Lee, R Lewis, R Lloyd, LH Lui, L Mabelin, P Mallett, D Morris, S Nallapareddy, S Nishat, H C Ooi (Associate PI), R Osagie, H Patel, AK Phyo, M Pretorius, B Purewal, F Ramali, H Rawlins, P Ridley, V Rivers, J Rosier, E Rushforth, S Sethi, A Sharma, S Sharma, A Sheik, J Shoote, M Shuvo, R Skelly, R Smith, R Smith, R Sreenivasan, P Tovey, A Turner, K Turner, K Vithian, I Weichert, W Win.

Wye Valley NHS Trust I DuRand (PI), J Al-Fori, A Almahroos, J Annett, A Barclay, J Bartlett, J Birch, N Bray, A Carrasco, M Cohn, E Collins, K Crowley, A Davies, M Forkan, A Fratila, H Gashau, S Gayle, K Hammerton, A Hassan, A Hedges, R Homewood, Z Khan, S Maryosh, S Meyrick, L Moseley, B Mwale, L Myslivecek, A Phillips, J Porteous, M Qayum, P Ryan, A Salam, C Seagrave, F Suliman, A Talbot -Smith, S Turner, S Vaughan, E Wales, H Walker, J Woolley.

Blackpool Teaching Hospitals NHS Foundation Trust G Hardy (PI), A Abdullah (Associate PI), N Ahmed, O Assaf, A Barnett, A Beasley, L Benham, D Bennett, P Bradley, Z Bradshaw, M Brunton, T Capstick, M Caswell, V Cunliffe, J Cupitt, R Downes, L Elawamy, J Howard, C Jeffs, N John, N Latt, J Mason, R McDonald, A Mulla, E Mutema, J Navin, A Parker, A Potter, S Preston, N Slawson, E Stoddard, S Traynor, V Vasudevan, E Ward, S Warden, A Wignall, J Wilson, A Zmierczak.

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Liverpool Women's NHS Foundation Trust R McFarland (PI), M Dower, S Holt, A Mahdi, C Morgan, E Neary, A Smith, M Turner, E Willis.

Medical College Kolkata, Kolkata A Talukdar (PI), K Chaudhuri, D Sarkar.

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M Iman, L James, F McNeela, C Mitchell, A Rao, S Reid, B Singizi, S Smolen, M Vitaglione, S Williams, L Willsher, J Wootton.

National Hospital for Tropical Diseases, Hanoi PN Thach (PI), NT Cap, NT Ha, LNM Hoa, DTT Thuy, DQ Tung, DP Khiem, PV Phuc, TV Kien, VD Linh, DTT Hang, TV Giang, TT Hien, HTK Oanh

Nepal Police Hospital D Paudel (PI), B Rajbhandari (Co-PI), NB Chaudhary, B Gajmer, M Gartaula, J Khatri, SS Kunwar, M Maharjan, P Maskey, K Neupane, R Niroula, A Regmi, S Singh, S Singh, BJ Thakuri, S Yadav.

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NHS Ayrshire and Arran: University Hospital Crosshouse A Clark (PI), T Adams, S Allen, E Anderson, L Barker, C Burns, D Callaghan, N Connell, V Dey, A Dunleavy, F Elliott, K Gibson, D Gilmour, K Grant, M Henry, J Locke, T Massa, L McNeil, S Meehan, A Murphy, E Peggie, M Rodger, S Smith, C Turley, S Walton, D Wilkin, M Wilson, S Wood.

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NHS Highland B Sage (PI), R Acquah, L Adamu-Ikeme, C Barr, F Barrett, A Batty, W Beadles, C Bradley, R Campbell, A Cochrane, R Cooper, I Dawson, K Donald, J Finlayson, A Goh, L Heron, G Jervis, P Laidler, S Macleod, S Makin, J Matheson, D McDonald, M McKenzie, C Millar, K Monaghan, L Murray, M O'Hara, L O'Keefe, D Patience, M Peirse, S Reilly, M Robertson, N Shahzad, G Simpson, K Watson, J Wilson.

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NHS Lothian: St John's Hospital S Lynch (PI), R Anderson, S Begg, J Bentley, S Brady, M Colmar, R Frake, A Gatenby, C Geddie, F Guarino, S Guettari, C Hurley, C Kuronen-Stewart, A MacRaild, M Mancuso-Marcello, M Marecka, G McAlpine, N McCullough, A Megan, T North, O Otite, L Primrose, C Rees, L Rooney, A Saunders, A Saunderson, A Stevenson, S Stock, A Wakefield, E Walsh, J Wraight, T Wright, S Yusef.

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Pokhara Academy of Health Sciences S Baniya (PI), SA Adhikari, SC Baral, A Karki, P KC, S Pathak, KK Roka, A Thapa.

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Rumah Sakit Metropolitan Medical Centre, Jakarta E Nelwan (PI), A Abidin, M Butar, A Cahyareny, L Handayani, H Istiqomah, S Kumala Dewi, T Monika, S Prabowo, N Pratiwi, K Puspatriani, N Rika, A Saraswati, D Sari, P Suherman, T Tesha, J Wanda, K Wattimena, N Yufaniaputri.

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Sukraraj Tropical and Infectious Disease Hospital, Nepal M Rawal (PI), B Chalise, S Gyawali, A Gupta, Y Sapkota, S Paudel, J Khatri, S Pant, P Gyanwali, U Devkota, S Mandal, L Bhandari, K Paudel, N K.C., S Karki, A Chaudhary, L Chaulagain, R Kumar, R Jaiswal, M Bajracharya, S Gyawali, S Magar, J Neupane, G Shrestha, R Jaiswal, K Poudel.

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Worcestershire Acute Hospitals NHS Trust C Hooper (PI), K Austin, T Dawson, A Durie, C Hillman-Cooper, O Kelsall, M Ling, Z Parvez, D Stocker, S Stringer, J Thakrar, H Tranter, J Tyler, P Watson, B Wild, D Wilson, H Wood.

Wrightington, Wigan and Leigh NHS Foundation Trust A Ashish (PI), I Aziz, C Brown, L Claxton, D Heaton, L Hirst, S Hough, J Jeganathan Ponraj, C Moore, V Parkinson, M Regan, E Robinson, T Taylor, C Tierney, A Verma, N Waddington, J Wedlin, C Williams, C Zipitis.

York and Scarborough Teaching Hospitals NHS Foundation Trust D Yates (PI), M Abdelfattah, A Abung, J Anderson, P Antill, S Appleby, P Armtrong, J Azam, T Berriman, D Bull, K Chandler, O Clayton, A Corlett, D Crocombe, S Davies, K Elliott, L Fahel, K Freshwater, J Ghosh, N Gott, D Greenwood, T Holder, K Howard, J Ingham, P Inns, W Lea, E Lindsay, K Mack, N Marshall, S McMeekin, R Miller, R Molyneux, T Momoniat, P Nikolaos, M O'Kane, G Patrick, H Pearson, P Ponnusamy, A Poole, N Price, R Proudfoot, G Purssord, H Redfearn, S Roche, Z Scott, C Sefton, S Shahi, D Smith, B Sohail, E Suleiman, S Sutton, R Thomas, A Turnbull, L Turner, H Watchorn, E Wiafe, J Wilson.

Supplementary Methods

Study organization

The RECOVERY trial is an investigator-initiated, individually randomised, open-label, controlled trial to evaluate the efficacy and safety of a range of putative treatments in patients hospitalized with COVID-19. The protocol is available at www.recoverytrial.net. The trial is being conducted at 177 National Health Service (NHS) hospital organizations in the United Kingdom and hospitals in Vietnam, Nepal, Indonesia, South Africa, India, and Ghana. The trial is coordinated by a team drawn from the Clinical Trial Service Unit and the National Perinatal Epidemiology Clinical Trials Unit within the Nuffield Department of Population Health at University of Oxford, the trial sponsor. Support for local site activities is provided by the National Institute for Health Research Clinical Research Network.

Access to relevant routine health care and registry data is supported by NHS DigiTrials, the Intensive Care National Audit and Research Centre, Public Health Scotland, National Records Service of Scotland, and the Secure Anonymised Information Linkage (SAIL) at University of Swansea.

Regulatory and ethics approvals

Country	Regulatory body	Ethics
UK	Medicines and Healthcare products Regulatory Agency (MHRA)	Cambridge East Research Ethics Committee (ref: 20/EE/0101)
Vietnam	Vietnam Ministry of Health	Hospital for Tropical Diseases Ethics Committee*
Nepal	Government of Nepal Department of Drug Administration	Ethical Review Board, Nepal Health Research Council (NHRC)
Indonesia	Badan Pengawas Obat Dan Makanan (BPOM)	Ethics Committee of the Faculty of Medicine, University of Indonesia*
Ghana	Food and Drugs Authority	Ghana Health Service Ethics Review Committee
South Africa	South African Health Products Regulatory Authority (SAHPRA)	The University of the Witwatersrand, Human Research Ethics Committee*
India	Not required	ICMR Central Ethics Committee on Human Research (CECHR)

* For countries without a national ethics committee the name of the committee approving the first site is listed.

Laboratory analysis

Serum anti-SARS-CoV-2 antibodies and nucleocapsid antigen
Serum samples were to be collected at randomisation from all participants and analysed at the UK Health Security Agency SARS-CoV-2 Serology laboratory, Porton Down, UK. Total antibodies to SARS-CoV-2 spike protein and nucleocapsid protein were measured using the Roche Elecsys Anti-SARS-CoV-2 S and Elecsys Anti-SARS-CoV-2 assays, respectively. Patients were classified as positive or negative using manufacturer defined thresholds. Serum nucleocapsid antigen was measured using the Roche Elecsys SARS-CoV-2 Antigen assay. This assay had previously been validated only on respiratory specimens, so additional validation was performed to evaluate performance on serum samples, including repeatability, linearity, and cross reactivity (appendix pp 188-204). Samples were classified as ‘high’ or ‘low’ antigen using the median value for all participants (COI 0.626), corresponding to a

nucleocapsid protein concentration of approximately 10 pg/ml (see validation report in appendix 4 below).

Nasal SARS-CoV-2 viral PCR and sequencing
Nose (mid-turbinate) swabs were collected at randomisation (day 1), on day 3, and on day 5 from all UK patients and analysed at the Oxford University Hospitals microbiology laboratory, Oxford, UK. Swabs had RNA extraction using the Kingfisher Flex system, and SARS-CoV-2 PCR using the TaqPath COVID-19 RT-PCR assay (Thermo Fisher Scientific, Massachusetts, US). A standard curve was produced using a panel of whole virus SARS-CoV-2 standards (Qnostics SARS-CoV-2 Analytical Q Panel), which was used to quantify viral genome copy concentration in samples.

Samples with sufficient viral concentration (>2.6 log viral copies/ml) were sequenced using the Oxford Nanopore Technologies Midnight and tiling amplicon protocol, using a GridION instrument (Oxford Nanopore Technologies, Oxford, UK).[1] Sequence data was processed using the Global Pathogen Analysis System (https://gpas.global), a web-based sequence analysis pipeline that uses the Viridian assembly system and assigns viral lineage using Pangolin. Sequence data were used to detect spike protein mutations associated with >5-fold reduction in sotrovimab neutralisation, which were identified from the summary of product characteristics (https://www.medicines.org.uk/emc/product/13097/smpc) and the Stanford University Coronavirus Antiviral and Resistance Database. (https://covdb.stanford.edu/).[2] Amino acid substitutions S371F/L, which are present in all Omicron variants and are associated with moderate reduction in neutralisation (~3-5 fold in most studies), were not included. The following spike protein mutations were included:

- P337A/H/K/L/N/Q/R/S/T
- E340A/D/G/I/K/L/N/Q/R/S/V
- T345P
- K356A/E/M/N/Q/R/S/T
- L441N

1 Constantinides B, Webster H, Gentry J, et al. Rapid turnaround multiplex sequencing of SARS-CoV-2: comparing tiling amplicon protocol performance. medRxiv 2022; : 2021.12.28.21268461.

2 Tzou PL, Tao K, Pond SLK, Shafer RW. Coronavirus Resistance Database (CoV-RDB): SARS-CoV-2 susceptibility to monoclonal antibodies, convalescent plasma, and plasma from vaccinated persons. PLoS One 2022; 17: e0261045.

Systematic review methods

Search Strategy

We searched Medline, Embase and MedRxiv between 1 September 2019 and 9 July 2024 for randomised controlled trials comparing the effects of neutralising monoclonal antibodies (mAbs) versus usual care or placebo in patients hospitalised with COVID-19. We used the search terms (Coronavirus infection or COVID or COVID-19 or COVID19 or 2019n-CoV or SARS-COV-2 or SARSCoV2 or SARS-Cov2) AND (sotrovimab, S309, VIR-7831, Xevudy, adintrevimab, amubarvimab, bamlanivimab, bebtelovimab, casirivimab, cilgavimab, etesevimab, imdevimab, regdanvimab, romlusevimab, tixagevimab) and using validated filters to select for randomised controlled trials. No language restrictions were applied.

Results were screened by researchers experienced in carrying out large-scale systematic reviews and meta-analyses of randomised trials. A trial research clinician reviewed the full texts of shortlisted studies to finalise the list of included studies. The following studies were identified:

Trial	mAb(s)	published	start	end	Number of patients
RECOVERY[1]	casirivimab+imdevimab	2021	Sep-20	May-21	9785
ACTIV-3/TICO[2]	bamlanivimab	2021	Aug-20	Oct-20	314
J2W-MC-PYAA[3]	bamlanivimab	2021	May-20	Jun-20	24
ACTIV-3/TICO[4]	sotrovimab	2022	Dec-20	Mar-21	365
ACTIV-3/TICO[4]	BRII-196+BRII-198	2022	Dec-20	Mar-21	361
CCCCTG[5]	etesevimab	2022	Jan-21	Feb-21	197
ACTIV-3/TICO[6]	tixagevimab+cilgavimab	2022	Feb-21	Sep-21	1417
COV-2066[7]	casirivimab+imdevimab	2022	Jun-20	Apr-21	1197
DisCoVeRy[8]	tixagevimab+cilgavimab	2024	Apr-21	Jul-22	226

1 RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022; **399**: 665–76.

2 ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, *et al.* A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 905–14.

3 Chen P, Nirula A, Heller B, *et al.* SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N Engl J Med* 2021; **384**: 229–37.

4 ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis* 2022; **22**: 622–35.

5 Dong R, Jiang L, Yang T, *et al.* Efficacy and Safety of SARS-CoV-2 Neutralizing Antibody JS016 in Hospitalized Chinese Patients with COVID-19: a Phase 2/3, Multicenter, Randomized, Open-Label, Controlled Trial. *Antimicrob Agents Chemother* 2022; **66**: e0204521.

6 ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. *Lancet Respir Med* 2022; **10**: 972–84.

7 Somersan-Karakaya S, Mylonakis E, Menon VP, *et al.* Casirivimab and Imdevimab for the Treatment of Hospitalized Patients With COVID-19. *J Infect Dis* 2022; **227**: 23–34.

8 Hites M, Massonnaud CR, Lapique EL, *et al.* Tixagevimab-cilgavimab (AZD7442) for the treatment of patients hospitalized with COVID-19 (DisCoVeRy): A phase 3, randomized, double-blind, placebo-controlled trial. *J Infect* 2024; **88**: 106120.

Protocol changes

RECOVERY is a randomised trial among patients hospitalized for COVID-19. All eligible patients receive usual standard of care in the participating hospital and are randomly allocated between no additional treatment and one of several active treatment arms. Over time, additional treatment arms have been added (see Table).

The final protocol relevant to high dose corticosteroids are included in the supplementary material to this publication, together with summaries of the changes made.

Table. Protocol changes to COVID-19 treatment comparisons

Protocol version	Date	Randomisation	Treatment arms
1.0	13-Mar-2020	Main (part A)	No additional treatment Lopinavir-ritonavir[a] Low-dose corticosteroid[b] Nebulised Interferon-ß-1a (never activated)
2.0	23-Mar-2020	Main (part A)	No additional treatment Lopinavir-ritonavir[a] Low-dose corticosteroid[b] Hydroxychloroquine
3.0	07-Apr-2020	Main (part A)	No additional treatment Lopinavir-ritonavir[a] Low-dose corticosteroid[b] Hydroxychloroquine[c] Azithromycin[d]
4.0	14-Apr-2020	Main (part A) Second[e,f]	No additional treatment Lopinavir-ritonavir[a] Low-dose corticosteroid[b] Hydroxychloroquine[c] Azithromycin[d] No additional treatment Tocilizumab[f]
5.0	24-Apr-2020	-	(no change – extension to children <18 years old)
6.0	14-May-2020	Main (part A) Main (part B factorial) Second[e,f]	No additional treatment Lopinavir-ritonavir[a] Low-dose corticosteroid[b] Hydroxychloroquine[c] Azithromycin[d] No additional treatment Convalescent plasma No additional treatment Tocilizumab[f]
7.0	18-Jun-2020	Main (part A) Main (part B factorial) Second[e,f]	No additional treatment Lopinavir-ritonavir[a] Low-dose corticosteroid[b] Azithromycin[d] No additional treatment Convalescent plasma No additional treatment Tocilizumab[f]

Protocol version	Date	Randomisation	Treatment arms
8.0	03-Jul-2020	Main (part A)	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Azithromycin[d]
		Main (part B factorial)	No additional treatment Convalescent plasma
		Second[e,f]	No additional treatment Tocilizumab[f]
9.1	18-Sep-2020	Main (part A)	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Azithromycin[d]
		Main (part B factorial)	No additional treatment Convalescent plasma Casirivimab and imdevimab
		Second[e,f]	No additional treatment Tocilizumab[f]
10.1	01-Nov-2020	Main (part A)	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Azithromycin[d]
		Main (part B factorial)	No additional treatment Convalescent plasma Casirivimab and imdevimab
		Main (part C factorial)	No additional treatment Aspirin
		Second[e,f]	No additional treatment Tocilizumab[f]
11.1	27-Nov-2020	Main (part A)	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Colchicine
		Main (part B factorial)	No additional treatment Convalescent plasma Casirivimab and imdevimab
		Main (part C factorial)	No additional treatment Aspirin
		Second[e,f]	No additional treatment Tocilizumab[f]

Protocol version	Date	Randomisation	Treatment arms
12.1	16-Dec-2020	Main (part A)[h]	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Colchicine
		Main (part B factorial)[h]	No additional treatment Convalescent plasma Casirivimab and imdevimab
		Main (part C factorial)[h]	No additional treatment Aspirin
		Second[e,f]	No additional treatment Tocilizumab[f]
13.0	26-Jan-2021	Main (part A)[h]	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Colchicine
		Main (part B factorial)[h]	No additional treatment Casirivimab and imdevimab
		Main (part C factorial)[h]	No additional treatment Aspirin
		Main (part D factorial)	No additional treatment Baricitinib
		Second[e,f]	No additional treatment Tocilizumab[f] Anakinra
14.0	15-Feb-2021	Main (part A)[h]	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Colchicine Dimethyl fumarate
		Main (part B factorial)[h]	No additional treatment Casirivimab and imdevimab
		Main (part C factorial)[h]	No additional treatment Aspirin
		Main (part D factorial)	No additional treatment Baricitinib
		Second[e,f]	No additional treatment Tocilizumab[f] Anakinra

Protocol version	Date	Randomisation	Treatment arms
15.0	12-Apr-2021	Main (part A)[h]	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Dimethyl fumarate
		Main (part B factorial)[h]	No additional treatment Casirivimab and imdevimab
		Main (part D factorial)	No additional treatment Baricitinib Infliximab[j]
		Main (part E factorial)[i]	High-dose dexamethasone[j]
		Second[e,f]	No additional treatment Tocilizumab[f] Anakinra
16.1	08-Jul-2021	Main (part A)[h]	No additional treatment Low-dose corticosteroid[b] Intravenous immunoglobulin[g] High-dose corticosteroid[g] Dimethyl fumarate
		Main (part D factorial)	No additional treatment Baricitinib
		Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial)[l]	Empagliflozin[l]
		Second[e,f]	No additional treatment Tocilizumab[f] Anakinra
17.1	10-Aug-2021	Main (part A)[h]	No additional treatment Dimethyl fumarate
		Main (part D factorial)	No additional treatment Baricitinib
		Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial)[l]	Empagliflozin[l]
		Second[e,f]	No additional treatment Tocilizumab[f] Anakinra

Protocol version	Date	Randomisation	Treatment arms
18.1	24-Oct-2021	Main (part A)[h]	No additional treatment Dimethyl fumarate
		Main (part D factorial)	No additional treatment Baricitinib
		Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial) [l]	Empagliflozin [l]
		Second[e,f]	No additional treatment Tocilizumab[f] Anakinra
19.1	16-Nov-2021	Main (part D factorial)[k]	No additional treatment Baricitinib
		Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial) [l]	Empagliflozin [l]
		Second[e,f,h]	No additional treatment Tocilizumab[f] Anakinra
20.0	29-Nov-2021	Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial) [l]	Empagliflozin [l]
		Second[e,f,h]	No additional treatment Tocilizumab[f] Anakinra
21.0	17-Dec-2021	Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial) [l]	Empagliflozin [l]
		Main (part J factorial)	Sotrovimab
		Main (part K factorial)	Molnupiravir
		Second[e,f,h]	No additional treatment Tocilizumab[f] Anakinra
22.0	19-Jan-2022	Not implemented	
23.0	08-Mar-2022	Main (part E factorial)[i]	High-dose dexamethasone[j]
		Main (part F factorial) [l]	Empagliflozin [l]
		Main (part J factorial)	Sotrovimab
		Main (part K factorial)	Molnupiravir
		Main (part L factorial)	Nirmatrelvir-ritonavir
24.0	13-May-2022	Not implemented	

Protocol version	Date	Randomisation	Treatment arms
25.0	23-May-2022	Main (part E factorial)[i] Main (part F factorial) [l] Main (part J factorial) Main (part K factorial) Main (part L factorial)	High-dose dexamethasone[j] Empagliflozin [l] Sotrovimab Molnupiravir[m] Nirmatrelvir-ritonavir[m]
26.0	22-Jun-2023	Main (part E factorial)[i] Main (part J factorial)	High-dose dexamethasone[j] Sotrovimab
27.0	13-Sep-2023	Main (part E factorial)[i] Main (part J factorial)	High-dose dexamethasone[j,n] Sotrovimab[n]

[a] enrolment ceased 29 June 2020 when the Data Monitoring Committee advised that the Chief Investigators should review the unblinded data.
[b] enrolment of adults ceased 8 June 2020 as more than 2,000 patients had been recruited to the active arm. Enrolment of children ceased on 8 July 2021.
[c] enrolment ceased 5 June 2020 when the Data Monitoring Committee advised that the Chief Investigators should review the unblinded data.
[d] enrolment of adults ceased 27 November 2020 as more than 2,500 patients had been recruited to the active arm
[e] for patients with (a) oxygen saturation <92% on air or requiring oxygen or children with significant systemic disease with persistent pyrexia; and (b) C-reactive protein ≥75 md/L)
[f] enrolment of adults ceased 24 January 2021 as more than 2,000 patients had been recruited to the active arm.
[g] for children only. Enrolment ceased 8 July 2021.
[h] from protocol version 12.1, children could enter the second randomisation regardless of whether they were included in the main randomisation. Enrolment ceased 8 March 2022.
[i] for patients with (a) oxygen saturation <92% on air or requiring oxygen. Enrolment of patients receiving no or simple oxygen ceased on 13 May 2022.
[j] for patients outside UK (until protocol V20.0 when extended to UK)
[k] enrolment ceased 29 December 2021
[l] enrolment ceased 6 March 2023
[m] enrolment ceased 24 May 2023
[n] enrolment ceased 31 March 2024

Main and second randomisation <u>for adults</u>

All RECOVERY trial participants received usual standard of care. On study entry, adult participants initially underwent the Main Randomisation. Trial participants with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or requiring oxygen therapy, and C-reactive protein ≥75 mg/L) could be considered for the Second Randomisation at any time up to 21 days after the initial randomisation, and regardless of initial treatment allocation(s). A web-system was used to provide simple randomisation (without stratification or minimisation) with allocation concealment until randomisation had been completed.

Over time, treatment arms were added and removed from the protocol, factorial randomisations were introduced (see below), and not all treatments were available at every hospital. Similarly, not all treatments were deemed by the attending clinician to be suitable for some patients (e.g. due to comorbid conditions or concomitant medication). In any of these cases, randomisation involved fewer arms (and/or fewer factorial elements).

Main randomisation for adults

A single participant could be randomised at most to 1 arm from each of part A, B, C, D and E of the factorial randomisations (depending on location), and thus receive between 0 and 4 treatments on top of usual standard of care.

<u>Part A</u> (from 19 March 2020)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	19 March 2020	12 November 2021
Dexamethasone	19 March 2020	8 June 2020
Lopinavir-ritonavir	19 March 2020	29 June 2020
Hydroxychloroquine	23 March 2020	5 June 2020
Azithromycin	7 April 2020	27 November 2020
Colchicine	27 November 2020	5 March 2021
Dimethyl fumarate	15 February 2021	12 November 2021

<u>Part B</u> (from 14 May 2020)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	14 May 2020	21 May 2021
Convalescent plasma	14 May 2020	15 January 2021
Casirivimab and imdevimab *	18 September 2020	21 May 2021

* monoclonal neutralising antibody cocktail

<u>Part C</u> (from 1 November 2020)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	1 November 2020	21 March 2021
Aspirin	1 November 2020	21 March 2021

Part D (from 1 November 2020)

Eligible participants could be randomised to one of the following arms (UK only):

Treatment arm	Arm opened	Arm closed
No additional treatment	2 February 2021	29 December 2021
Baricitinib	2 February 2021	29 December 2021

Part E (from 25 May 2021)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	25 May 2021	31 March 2024
High-dose dexamethasone	25 May 2021	31 March 2024 (Enrolment of patients receiving no or simple oxygen ceased on 13 May 2022)

Part F (from 8 July 2021)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	8 July 2021	6 March 2023
Empagliflozin	8 July 2021	6 March 2023

Part J (from 29 December 2021)

Eligible participants could be randomised to one of the following arms (UK only):

Treatment arm	Arm opened	Arm closed
No additional treatment	30 December 2021	31 March 2024
Sotrovimab	30 December 2021	31 March 2024

Part K (from 30 December 2021)

Eligible participants could be randomised to one of the following arms:

Treatment arm	Arm opened	Arm closed
No additional treatment	30 December 2021	24 May 2023
Molnupiravir	30 December 2021	24 May 2023

Part L (from 8 March 2022)

Eligible participants could be randomised to one of the following arms (UK only):

Treatment arm	Arm opened	Arm closed
No additional treatment	8 March 2022	24 May 2023
Nirmatrelvir-ritonavir	8 March 2022	24 May 2023

Second randomisation for adults (from 14 April 2020)

From 14 April 2020, a participant could be randomised to one of the following arms and thus receive 0 or 1 treatment on top of those allocated in the initial randomisation and usual standard of care:

Treatment arm	Arm opened	Arm closed
No additional treatment	14 April 2020	24 January 2021
Tocilizumab	14 April 2020	24 January 2021

Ascertainment and classification of study outcomes

Information on baseline characteristics and study outcomes was collected through a combination of electronic case report forms (see below) completed by members of the local research team at each participating hospital and (in the UK) linkage to National Health Service, clinical audit, and other relevant health records. Full details are provided in the RECOVERY Definition and Derivation of Baseline Characteristics and Outcomes Document (see Appendix 3).

Randomisation form

The (main) Randomisation form (shown below) was completed by trained study staff. It collected baseline information about the participant (including demographics, COVID-19 history, comorbidities and suitability for the study treatments) and availability of the study treatments. Once completed and electronically signed, the treatment allocation was displayed.

The following modifications were made to the Randomisation form during the trial:

Randomisation form version	Date of release	Major modifications from previous version
1.0	19-Mar-20	Initial version (protocol V1.0)
2.0	25-Mar-20	For protocol V2.0 • Hydroxycholoroquine added as treatment • Known long QT syndrome added to comorbidities • Severe depression removed from comorbidities
3.0	09-Apr-20	For protocol V3.0 • Azithromycin added as treatment • Suspected SARS-CoV-2 infection included in eligibility criteria
[Second randomisation form introduced]	23-Apr-20	For protocol 4.0 • Eligibility criteria for second randomisation • Tocilizumab vs control as treatment allocations
5.0	09-May-20	For protocol V5.0 • Age ≥18 years removed from eligibility criteria • Additional questions on child's age and weight added
6.0	21-May-20	For protocol V6.0 • Convalescent plasma added as treatment • Baseline use of remdesivir
7.0	01-Jul-20	For protocol V7.0 • Participants eligible if convalescent plasma is only available and suitable treatment
8.0	13-Aug-20	For protocol V8.0 • Addition of low-dose and high-dose corticosteroids and intravenous immunoglobulin for children (and removal of dexamethasone for children)
9.0	24-Sep-20	For protocol V9.0 • Casirivimab and imdevimab added as treatment • Additional baseline information
10.0	06-Nov-20	For protocol V10.1 • Aspirin added as treatment
11.0	27-Nov-20	For protocol V11.1 • Colchicine added as treatment
12.0	22-Dec-20	For protocol V12.1 • Allow children to enter trial without entering main randomisation
13.0	02-Feb-21	For protocol V13.0 • Baricitinib added as treatment
14.0	24-Feb-21	For protocol V14.0 • Dimethyl fumarate added as treatment
15.0	11-May-21	For protocol V15.0 • High-dose dexamethasone added as treatment
16.0	28-Jul-21	For protocol V16.1 • Addition of empagliflozin as treatment
17.0	20-Aug-21	For protocol V17.1 • Additional warnings about eligibility for empagliflozin

Randomisation form version	Date of release	Major modifications from previous version
18.0	30-Dec-21	For protocol V21.1 • Sotrovimab and molnupiravir added as treatments • Inclusion of UK participants in high-dose dexamethasone comparison
19.0	28-Mar-22	For protocol V23.0 • Nirmatrelvir-ritonavir added as treatment
20.0	8-Jan-2024	For protocol V27.0 • Addition of non-COVID-19 community-acquired pneumonia comparison

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Sample Form (v19.00 - 28/03/22)

Randomisation Program

Call Freefone **0800 138 5451** to contact the RECOVERY team for **URGENT** problems using the Randomisation Program or for medical advice. All **NON-URGENT queries** should be emailed to **recoverytrial@ndph.ox.ac.uk**

Logged in as: **RECOVERY Site**

Section A: Baseline and Eligibility

Date and time of randomisation: 27 Mar 2022 14:00

Treating clinician

A1. Name of treating clinician

Patient details

A2. Patient surname

Patient forename

A3. NHS number ☐Tick if not available

A4. What is the patient's date of birth? 01 / January / 2000 Age: 22y 2m

A5. What is the patient's sex?

Inclusion criteria

A6. Has consent been taken in line with the protocol?
If answer is No patient cannot be enrolled in the study
NB current PIS/ICF version is V22.0 (adults) or V14.0 (children)

A6.0.1 How was consent obtained?

A6.5 Does this patient have viral pneumonia? Yes
See protocol for typical features. If answer is No patient cannot be enrolled in the study

A7.0 Does the patient have proven SARS-CoV-2 infection? Yes

A7.0.1 What was lateral flow test result?

A7.0.2 What was PCR test result?

A7.1 Does the patient have proven influenza infection?

A8. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial?

A9. Symptom onset date: / /

A10. Date of hospitalisation: / /

A11. Does the patient require oxygen?

A12. Please select one of the following to describe the current level of ventilation support

A12.1 Enter latest oxygen saturation measurement (%)

A12.2 Enter latest CRP measurement since admission to hospital (mg/L) ☐Tick if not measured
Enter 0 if below the limit of measurement ☐Tick if greater than limit of measurement

A12.3 Enter latest creatinine measurement since admission to hospital μmol/L ☐Tick if not measured

A12.4 Enter latest D-dimer measurement since admission to hospital ng/mL ☐Tick if not measured
Enter 0 if below the limit of measurement ☐Tick if greater than limit of measurement

A12.5 Has the patient received a COVID-19 vaccine?

A12.6 Has the patient received an influenza vaccine in the last 12 months?

Does the patient have any CURRENT comorbidities or other medical problems or treatments?

A13.1 Diabetes

A13.2 Heart disease

A13.3 Chronic lung disease

A13.4 Tuberculosis

A13.5 HIV

A13.6 Severe liver disease

A13.7 Severe kidney impairment (eGFR<30 or on dialysis)

A13.9.0 Does their clinician consider the patient to be severely immunocompromised?

A13.12 Has the patient received tocilizumab or sarilumab therapy during this admission?

A13.14 Current or planned treatment with neuraminidase inhibitor
eg, oseltamivir, zanamivir

A13.15 Has the patient received casirivimab+imdevimab (Ronapreve) during this illness?

A13.16 Has the patient received sotrovimab during this illness?

A13.17 Has the patient received molnupiravir during this illness?

A13.18 Has the patient received Paxlovid during this illness?

Are the following treatments UNSUITABLE for the patient?
If you answer Yes it means you think this patient should NOT receive this drug.

A14E.1 High-dose corticosteroids
NB Please carefully consider suitability of patients already on higher doses (>~7 mg/day dexamethasone or equivalent). Patients eligible for the Paxlovid comparison will be automatically marked as unsuitable for this comparison.

A14F.1 Empagliflozin
Empagliflozin is NOT suitable if patient (i) has type 1 or post-pancreatectomy diabetes mellitus; or (ii) has a history of ketoacidosis; or (iii) has blood ketones ≥1.5 mmol/L or urine ketones ≥2+; or (iv) is pregnant or breastfeeding
Empagliflozin cannot be given via an enteral feeding tube.

A14J.1 Sotrovimab

A14K.1 Molnupiravir
NB Molnupiravir is NOT suitable if patient cannot swallow capsules.

A14L.1 Paxlovid No
NB Paxlovid contains ritonavir and has many drug-drug interactions (see protocol and SmPC). Please ensure these have been checked. Paxlovid is NOT suitable if patient cannot swallow tablets. Paxlovid is not suitable for pregnant women in the first trimester.

Are the following treatments available?

A15E.1 High-dose corticosteroids

A15F.1 Empagliflozin

A15J.1 Sotrovimab

A15K.1 Molnupiravir

A15L.1 Paxlovid Yes

Current medication

A16.1 Is the patient currently prescribed remdesivir?

A16.2 Is the patient currently prescribed systemic corticosteroids (dexamethasone, prednisolone, hydrocortisone, methylprednisolone)?
Please do not include topical or inhaled treatments

A16.5 What venous thromboembolism prophylaxis is the patient receiving?
Standard = usual for hospitalised patients (not increased due to COVID-19); Higher dose = treatment dose or increased prophylaxis due to COVID-19, or oral anticoagulation (eg, warfarin/DOAC).

A16.6 Is the patient currently prescribed baricitinib (or other JAK inhibitor)?

Serum sample collection

A17.0 Please confirm that patient has had a baseline serum sample collected according to the protocol

A17.1 Please confirm that patient has had a baseline nasal swab collected according to the protocol

Please sign off this form once complete

Surname:

Forename:

Professional email:

Continue

Cancel

Home

Follow-up form

The Follow-up form (shown on the next page) collected information on study treatment adherence (including both the randomised allocation and use of other study treatments), vital status (including date and provisional cause of death if available), hospitalisation status (including date of discharge), respiratory support received during the hospitalisation, occurrence of any major cardiac arrhythmias and renal replacement therapy received. Questions on metabolic complications were added in version 16.0, after the high-dose corticosteroid comparison started.

The following modifications were made to the Follow-up form during the trial:

Follow-up form version	**Date of release**	**Modifications from previous version**
18.0	30-Dec-21	Information on sotrovimab and molnupiravir adherence Information on sample collection
19.0	25-Feb-22	Information on nirmatrelvir-ritonavir adherence
20.0	28-Mar-22	Information on liver function tests and seizures
21.0	31-Mar-22	Translations added for V19.0 and V20.0
22.0	8-Nov-22	For protocol V22
23.0	9-Jan-23	For protocol V23
24.0	17-Nov-23	Removal of closed comparisons
25.0	8-Jan-24	Addition of non-COVID-19 CAP arm
26.0	26-Feb-24	Translations added

Follow-up

Date of randomisation

Please only report events that occurred from first randomisation until 28 days later on this form (except for Q2).

Patient's date of birth *

yyyy-mm-dd

» Vital Status

0. What is the patient's vital status? *

- ◯ Alive
- ◯ Dead

0.1 What is the patient's current hospitalisation status? *

- Inpatient
- Discharged

The patient has been enrolled in the trial for **NaN** days

0.1.1 Date follow-up form completed

yyyy-mm-dd

0.1.1 What was the date of discharge? *

yyyy-mm-dd

0.1 What was the date of death? *

yyyy-mm-dd

0.2 What was the underlying cause of death? *

This can be obtained from the last entry in part 1 of the death certificate

- ◯ COVID-19
- ◯ Other infection
- ◯ Cardiovascular
- ◯ Other

Please give details

» Treatments

1. Which of the following treatment(s) did the patient definitely receive as part of their hospital admission after randomisation? *

(NB Include RECOVERY study-allocated drug, only if given, PLUS any of the other treatments if given as standard hospital care)

- ☐ No additional treatment
- ☐ Lopinavir-ritonavir

- [ ] Corticosteroid (dexamethasone, prednisolone, hydrocortisone or methylprednisolone)
- [ ] Hydroxychloroquine
- [ ] Azithromycin or other macrolide (eg, clarithromycin, erythromycin)
- [ ] Tocilizumab or sarilumab
- [ ] Remdesivir
- [ ] Intravenous immunoglobulin
- [ ] Synthetic monoclonal antibodies (REGN10933+REGN10987)
- [ ] Aspirin
- [ ] Colchicine
- [ ] Baricitinib
- [ ] Anakinra
- [ ] Favipiravir
- [ ] Empagliflozin
- [ ] Ivermectin
- [ ] Oseltamivir
- [ ] Other neuraminidase inhibitor (e.g. zanamivir, laninamivir)
- [ ] Baloxavir
- [ ] Sotrovimab
- [ ] Molnupiravir
- [ ] Paxlovid

Please select number of days the patient received corticosteroid (dexamethasone, prednisolone, hydrocortisone or methylprednisolone) (of any dose)

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Dosing information:

6 mg dexamethasone is equivalent to 40 mg prednisolone or 160 mg hydrocortisone or 32 mg methylprednisolone.

10 mg dexamethasone is equivalent to 67 mg prednisolone or 267 mg hydrocortisone or 53 mg methylprednisolone

20 mg dexamethasone is equivalent to 133 mg prednisolone or 534 mg hydrocortisone or 106 mg methylprednisolone

Please indicate the highest dose received on a single day during the 10 days after randomisation

- ○ <6 mg dexamethasone
- ○ 6 mg dexamethasone
- ○ >6 mg and <=10 mg dexamethasone
- ○ >10 mg and <20 mg dexamethasone
- ○ 20 mg dexamethasone
- ○ >20 mg dexamethasone

Please select number of doses of tocilizumab or sarilumab the patient received

○ 1 ○ >1

Please select number of days the patient received remdesivir

○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Please select number of days the patient received baricitinib

1 2 3 4 5 6 7 8 9 10

Please select number of days the patient received anakinra

1 2 3 4 5 6 7

Please select the proportion of days the patient received empagliflozin during the first 28 days after randomisation (or from randomisation to date of discharge if this is sooner)

Most days (≥90%) Some days (≥50% <90%) Few days (<50% of days, but not zero) None

Please select number of days the patient received oseltamivir

1 2 3 4 5 6 7 8 9 10

Please select number of doses of baloxavir the patient received

1 2

Did the participant experience an infusion reaction during or within 2 hours after the sotrovimab infusion? *

Yes

No

How severe was the reaction? *

Mild (no intervention required)

Moderate (eg, antihistamines or steroids required)

Severe (adrenaline required)

Was the infusion completed? *

Yes

No

Please select the number of days the patient received molnupiravir

1 2 3 4 5 6

Was the participant provided with treatment to complete the course at home?

Yes

No

Please select the number of days the patient received Paxlovid

1 2 3 4 5 6

Was the participant provided with treatment to complete the course at home?

Yes

No

Only required if Q17.0 and or Q17.1 on the Randomisation form were answered Yes

Was the baseline serum sample collected?

Yes

No

Was the baseline swab samples collected? *

Yes

No

Was the DAY 3 follow-up swab sample collected? *

Yes

No

Swab sent home with patient

Was the DAY 5 follow-up swab sample collected? *

Yes

No

Swab sent home with patient

» Ventilation

4. Did the patient require any form of assisted ventilation (ie, more than just supplementary oxygen) from day of randomisation until 28 days later? *

Yes

No

Please answer the following questions:

4.1 For how many days did the patient require assisted ventilation? *

4.2 What type of ventilation did the patient receive?

	Yes	No	Unknown
CPAP alone	◯	◯	◯
Non-invasive ventilation (eg, BiPAP)	◯	◯	◯
High-flow nasal oxygen (eg, AIRVO)	◯	◯	◯
Mechanical ventilation (intubation/tracheostomy)	◯	◯	◯
ECMO	◯	◯	◯

Total number of days the patient received invasive mechanical ventilation (intubation/tracheostomy) from randomisation until discharge/death/28 days after randomisation

» Cardiac arrhythmia

5. Has the patient been documented to have a NEW cardiac arrhythmia at any point since the main randomisation until 28 days later? *

- ◯ Yes
- ◯ No
- ◯ Unknown

5.1 Please select all of the following which apply

- ☐ Atrial flutter or atrial fibrillation
- ☐ Supraventricular tachycardia
- ☐ Ventricular tachycardia (including torsades de pointes)
- ☐ Ventricular fibrillation
- ☐ Atrioventricular block requiring intervention (eg, cardiac pacing)

» Renal outcomes

6. Did the patient require use of renal dialysis or haemofiltration from main randomisation until 28 days later? *

- ◯ Yes
- ◯ No

6.1 Please enter the highest creatinine level recorded after randomisation until 28 days later. *	Unit *	Date recorded *	Select if creatinine level not available *
.....	◯ µmol/L ◯ mg/dL	yyyy-mm-dd	◯ Not available

» Thrombosis and bleeding

7. During the first 28 days after randomisation (or until discharge if sooner), did the participant have a thrombotic event? *

- ◯ Yes
- ◯ No
- ◯ Unknown

7.1 Please indicate the type of thrombotic event

Select all that apply

- ☐ Pulmonary embolism
- ☐ Deep-vein thrombosis
- ☐ Ischaemic stroke
- ☐ Myocardial infarction
- ☐ Systemic arterial embolism
- ☐ Other

8. During the first 28 days after randomisation (or until discharge if sooner), did the participant experience clinically-significant bleeding ie, intra-cranial bleeding or bleeding that required intervention (eg, surgery, endoscopy or vasoactive drugs) or a blood transfusion? *

- ◯ Yes
- ◯ No

◯ Unknown

8.1 Please indicate the site(s) of bleeding *

Select all that apply

- ☐ Intra-cranial
- ☐ Gastrointestinal
- ☐ Other

8.2 Please indicate which interventions were required to manage the bleed *

Select all that apply

- ☐ Blood transfusion
- ☐ Surgery
- ☐ Endoscopy
- ☐ Vasoactive drugs (e.g. inotropes on ICU)
- ☐ None of the above

» Other infections

9. During the first 28 days after randomisation (or until discharge if sooner), did the participant develop another infection? *

- ◯ Yes
- ◯ No
- ◯ Unknown

9.1 Please indicate the type of infection

Select all that apply

- ☐ Pneumonia
- ☐ Urinary tract
- ☐ Biliary
- ☐ Other intra-abdominal
- ☐ Blood stream
- ☐ Skin
- ☐ Other

Pneumonia - please indicate the putative organism

◯ Bacterial ◯ Fungal ◯ Viral ◯ Other ◯ Unknown

Please indicate the virus

NB do not record the virus leading to study entry

☐ SARS-CoV-2 ☐ Influenza ☐ Other/unknown

Urinary tract - please indicate the putative organism

◯ Bacterial ◯ Fungal ◯ Other ◯ Unknown

Biliary - please indicate the putative organism

Bacterial Fungal Other Unknown

Intra-abdominal - please indicate the putative organism

Bacterial Fungal Other Unknown

Blood stream - please indicate the putative organism

Please only select this if positive blood culture but no known anatomical site found

Bacterial Fungal Other Unknown

Skin - please indicate the putative organism

Bacterial Fungal Viral Other Unknown

Other - please indicate the putative organism

Bacterial Fungal Other Unknown

Please describe the anatomical site

» Metabolic complications

10. During the first 28 days after randomisation (or until discharge if sooner), did the participant have any of the following?

	Yes	No	Unknown
Ketoacidosis * *Ketoacidosis is defined as (i) ketosis (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) AND (ii) metabolic acidosis (eg, bicarbonate <15 mmol/L) AND (iii) no obvious alternative cause of acidosis*	◯	◯	◯
Hyperglycaemic hyperosmolar state *	◯	◯	◯
Other hyperglycaemia requiring new use of insulin *	◯	◯	◯
Severe hypoglycaemia * *Hypoglycaemia causing reduced conscious level requiring another person to help recover.*	◯	◯	◯

» Other safety outcomes

11. Did the participant experience a seizure after randomisation? *

◯ Yes

◯ No

◯ Unknown

11.1 Does the patient have a history of seizures or epilepsy?

Yes

No

Unknown

11.2 Please enter the highest ALT (or AST) level recorded after randomisation until 28 days later. If below the limit of detection, enter 0

Date *	Result *	Upper limit of normal *	Units

yyyy-mm-dd			◉ IU/L or U/L ○ µmol/L ○ µkat/L

11.3 Please enter the highest bilirubin level recorded after randomisation until 28 days later. If below the limit of detection, enter 0

Date *	Result *	Upper limit of normal *	Units
yyyy-mm-dd			◉ µmol/L ○ mg/dL

» Other trials

12. Please indicate if the participant participated in any other COVID-19 or influenza trials

Select all that apply

- ☐ PRINCIPLE
- ☐ REMAP-CAP
- ☐ Other treatment trial(s)
- ☐ COVID-19 vaccine trial(s)

Please give name of other treatment trial(s)

Please give name of COVID-19 vaccine trial(s)

» Pregnancy

13. If this woman was pregnant at randomisation (or had recently delivered), please enter UKOSS ID here.

Enter the full UKOSS case ID eg, COR_123

Interim analyses: role of the Data Monitoring Committee

The independent Data Monitoring Committee reviewed unblinded analyses of the study data and any other information considered relevant at intervals of around 2-3 months. The committee was charged with determining if, in their view, the randomised comparisons in the study provide evidence on mortality that is strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies. In such a circumstance, the Committee would inform the Steering Committee who would make the results available to the public and amend the trial arms accordingly. Unless that happened, the Steering Committee, investigators, and all others involved in the trial would remain blind to the interim results until 28 days after the last patient had been randomised to a particular intervention arm. Further details about the role and membership of the independent Data Monitoring Committee are provided in the protocol.

The Data Monitoring Committee determined that to consider recommending stopping a treatment early for benefit would require at least a 3 to 3·5 standard error reduction in mortality. The Committee concluded that examinations of the data at every 10% (or even 5%) of the total data would lead to only a marginal increase in the overall type I error rate.

Between 4 January 2022 and 31 March 2024 the DMC reviewed data on sotrovimab 9 times (https://www.recoverytrial.net/uk/for-site-staff/site-set-up-1/data-monitoring-committee-correspondence).

Supplementary Tables

Webtable 1: Baseline characteristics of patients considered unsuitable for randomisation to sotrovimab compared with those randomised to sotrovimab versus usual care

	Randomised (n=1723)	Unsuitable (n=65)
Age, years	70.7 (14.8)	69.3 (13.8)
<70	711 (41%)	33 (51%)
≥70 to <80	523 (30%)	14 (22%)
≥80	489 (28%)	18 (28%)
Sex		
Male	1033 (60%)	36 (55%)
Female	690 (40%)	29 (45%)
Ethnicity		
White	1485 (86%)	55 (85%)
Black, Asian, and minority ethnic	129 (7%)	4 (6%)
Unknown	109 (6%)	6 (9%)
Number of days since symptom onset	6 (3-11)	6 (3-11)
Number of days since admission to hospital	2 (1-5)	2 (1-6)
Respiratory support received		
None	256 (15%)	13 (20%)
Simple oxygen	1069 (62%)	43 (66%)
Non-invasive ventilation	337 (20%)	8 (12%)
Invasive mechanical ventilation	61 (4%)	1 (2%)
Previous diseases		
Diabetes	468 (27%)	17 (26%)
Heart disease	531 (31%)	22 (34%)
Chronic lung disease	652 (38%)	24 (37%)
Tuberculosis	6 (<0.5%)	0 (0%)
HIV	11 (1%)	1 (2%)
Severe liver disease *	35 (2%)	0 (0%)
Severe kidney impairment †	158 (9%)	5 (8%)
Any of the above	1180 (68%)	45 (69%)
Severely immunocompromised ‡	414 (24%)	15 (23%)
Received a COVID-19 vaccine	1389 (81%)	49 (75%)
Use of other treatments		
Corticosteroids §	1556 (90%)	56 (86%)
Remdesivir	628 (36%)	20 (31%)
Tocilizumab	281 (16%)	6 (9%)
Plan to use tocilizumab within the next 24 hours	115 (7%)	4 (6%)

Data are mean (SD), n (%), or median (IQR). * Defined as requiring ongoing specialist care. † Defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2. ‡ In the opinion of the managing clinician. § Including all those randomised into the comparison of high vs low dose steroids.

Webtable 2: Baseline characteristics by patient baseline antigen status and randomised allocation

	High antigen patients		Low antigen patients		Antigen status unknown	
	Sotrovimab (n=355)	Usual care (n=365)	Sotrovimab (n=339)	Usual care (n=378)	Sotrovimab (n=134)	Usual care (n=152)
Age, years	72.5 (13.3)	72.1 (13.7)	70.5 (14.6)	71.1 (15.6)	68.0 (15.0)	64.4 (17.2)
<70	123 (35%)	141 (39%)	153 (45%)	143 (38%)	66 (49%)	85 (56%)
≥70 to <80	123 (35%)	121 (33%)	85 (25%)	107 (28%)	43 (32%)	44 (29%)
≥80	109 (31%)	103 (28%)	101 (30%)	128 (34%)	25 (19%)	23 (15%)
Sex						
Male	218 (61%)	226 (62%)	197 (58%)	222 (59%)	75 (56%)	95 (63%)
Female	137 (39%)	139 (38%)	142 (42%)	156 (41%)	59 (44%)	57 (38%)
Ethnicity						
White	301 (85%)	333 (91%)	302 (89%)	330 (87%)	103 (77%)	116 (76%)
Black, Asian, and minority ethnic	32 (9%)	16 (4%)	17 (5%)	25 (7%)	15 (11%)	24 (16%)
Unknown	22 (6%)	16 (4%)	20 (6%)	23 (6%)	16 (12%)	12 (8%)
Number of days since symptom onset	6 (3-11)	6 (3-12)	4 (3-9)	5 (2-8)	8 (5-13)	7 (4-12)
Number of days since admission to hospital	2 (1-5)	2 (1-5)	2 (1-6)	2 (1-5)	2 (1-4)	2 (1-4)
Respiratory support received						
None	43 (12%)	54 (15%)	57 (17%)	66 (17%)	19 (14%)	17 (11%)
Simple oxygen	226 (64%)	213 (58%)	219 (65%)	253 (67%)	67 (50%)	91 (60%)
Non-invasive ventilation	71 (20%)	87 (24%)	57 (17%)	49 (13%)	40 (30%)	33 (22%)
Invasive mechanical ventilation	15 (4%)	11 (3%)	6 (2%)	10 (3%)	8 (6%)	11 (7%)
Previous diseases						
Diabetes	107 (30%)	84 (23%)	98 (29%)	97 (26%)	44 (33%)	38 (25%)
Heart disease	119 (34%)	113 (31%)	103 (30%)	115 (30%)	37 (28%)	44 (29%)
Chronic lung disease	123 (35%)	128 (35%)	156 (46%)	149 (39%)	48 (36%)	48 (32%)
Tuberculosis	0 (0%)	1 (<0.5%)	2 (1%)	3 (1%)	0 (0%)	0 (0%)
HIV	3 (1%)	1 (<0.5%)	1 (<0.5%)	2 (1%)	2 (1%)	2 (1%)
Severe liver disease *	6 (2%)	3 (1%)	8 (2%)	8 (2%)	5 (4%)	5 (3%)
Severe kidney impairment †	45 (13%)	41 (11%)	22 (6%)	25 (7%)	17 (13%)	8 (5%)
Any of the above	242 (68%)	237 (65%)	240 (71%)	273 (72%)	96 (72%)	92 (61%)
Severely immunocompromised ‡	112 (32%)	112 (31%)	56 (17%)	61 (16%)	38 (28%)	35 (23%)
Received a COVID-19 vaccine	296 (83%)	292 (80%)	280 (83%)	317 (84%)	99 (74%)	105 (69%)
Use of other treatments						
Corticosteroids §	329 (93%)	334 (92%)	301 (89%)	333 (88%)	125 (93%)	134 (88%)
Remdesivir	144 (41%)	128 (35%)	135 (40%)	136 (36%)	36 (27%)	49 (32%)
Tocilizumab	66 (19%)	60 (16%)	43 (13%)	44 (12%)	35 (26%)	33 (22%)
Plan to use tocilizumab within the next 24 hours	28 (8%)	33 (9%)	15 (4%)	19 (5%)	5 (4%)	15 (10%)
Viral load in baseline nose swab						
Median level (log viral copies per ml)	6.1 (4.6-7.0)	6.1 (5.0-7.2)	4.7 (2.5-6.4)	4.9 (2.8-6.2)	5.7 (3.9-6.5)	5.0 (2.9-6.1)
Serostatus (anti N)						
Positive	62 (17%)	76 (21%)	152 (45%)	163 (43%)	0 (0%)	1 (1%)
Negative	293 (83%)	289 (79%)	187 (55%)	215 (57%)	1 (1%)	0 (0%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	133 (99%)	151 (99%)
Serostatus (anti S)						
Positive	252 (71%)	262 (72%)	316 (93%)	348 (92%)	1 (1%)	0 (0%)
Negative	103 (29%)	103 (28%)	23 (7%)	30 (8%)	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	133 (99%)	152 (100%)

Data are mean (SD), n (%), or median (IQR). * Defined as requiring ongoing specialist care. † Defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2. ‡ In the opinion of the managing clinician. § Including all those randomised into the comparison of high vs low dose steroids.

Webtable 3: Treatments given by randomised allocation

	High antigen patients		All patients	
	Sotrovimab (n=355)	Usual care (n=365)	Sotrovimab (n=828)	Usual care (n=895)
Compliance data available	353	363	820	890
Sotrovimab	335 (95%)	8 (2%)	767 (94%)	14 (2%)
Other treatments received				
Corticosteroid	296 (84%)	307 (85%)	687 (84%)	748 (84%)
Azithromycin or other macrolide	57 (16%)	57 (16%)	112 (14%)	126 (14%)
Tocilizumab or sarilumab	68 (19%)	60 (17%)	114 (14%)	126 (14%)
Remdesivir	133 (38%)	131 (36%)	282 (34%)	302 (34%)
Aspirin	31 (9%)	34 (9%)	83 (10%)	77 (9%)
Baricitinib	17 (5%)	23 (6%)	31 (4%)	49 (6%)
Empagliflozin	68 (19%)	73 (20%)	170 (21%)	195 (22%)
Molnupiravir	95 (27%)	93 (26%)	187 (23%)	198 (22%)
Paxlovid	20 (6%)	25 (7%)	40 (5%)	48 (5%)

Percentages are of those with a completed follow-up form.

Webtable 4: Effect of allocation to sotrovimab on key study outcomes in all patients

	Sotrovimab (n=828)	Usual care (n=895)	RR (95% CI) or mean difference	p-value
Primary outcome				
28-day mortality	177 (21%)	201 (22%)	0.95 (0.77-1.16)	0.60
Secondary outcomes				
Median (IQR) time to being discharged alive, days	11 (6 to >28)	11 (6 to >28)		
Discharged from hospital within 28 days	563 (68%)	609 (68%)	0.96 (0.85-1.08)	
Receipt of invasive mechanical ventilation or death*	184/799 (23%)	201/863 (23%)	0.98 (0.84-1.16)	
Invasive mechanical ventilation	39/799 (5%)	36/863 (4%)	1.16 (0.76-1.77)	
Death	164/799 (21%)	186/863 (22%)	0.95 (0.79-1.13)	
Subsidiary clinical outcomes				
Use of ventilation†	70/631 (11%)	83/694 (12%)	0.92 (0.68-1.23)	
Non-invasive ventilation	67/631 (11%)	77/694 (11%)	0.95 (0.70-1.28)	
Invasive mechanical ventilation	15/631 (2%)	16/694 (2%)	1.00 (0.50-1.99)	
Successful cessation of invasive mechanical ventilation ‡	11/29 (38%)	13/32 (41%)	0.82 (0.37-1.83)	
Use of haemodialysis or haemofiltration §	31/814 (4%)	22/879 (3%)	1.51 (0.89-2.56)	
Virological outcomes				
Baseline-adjusted viral load (log copies/ml) on day 3	4.34 (0.06)	4.38 (0.07)	-0.04 (-0.22, 0.14)	
Baseline-adjusted viral load (log copies/ml) on day 5	3.72 (0.09)	3.85 (0.08)	-0.13 (-0.36, 0.10)	

Data are n (%) or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality and hospital discharge, risk ratio for other clinical outcomes, and mean difference for virological outcomes. CI=confidence interval. Estimates of the RR or mean difference and their 95% CIs are adjusted for age in three categories (<70 years, 70-79 years, and 80 years or older) and ventilation status at randomisation in four categories (none, simple oxygen, non-invasive ventilation, and invasive mechanical ventilation). For the outcome of use of haemodialysis or haemofiltration, however, adjustment is for age in three categories (<70 years, 70-79 years, and 80 years or older) and ventilation status at randomisation in three categories (none, simple oxygen, non-invasive ventilation or invasive mechanical ventilation) due to model convergence issues. * Excluding patients receiving invasive mechanical ventilation at randomisation. † Excluding patients receiving invasive or non-invasive ventilation at randomisation. ‡ Excluding patients not receiving invasive mechanical ventilation at randomisation. § Excluding patients receiving renal replacement therapy at randomisation.

Webtable 5: Effect on cause-specific 28-day mortality

	High antigen patients		All patients	
Cause of death	**Sotrovimab (n=355)**	**Usual care (n=365)**	**Sotrovimab (n=828)**	**Usual care (n=895)**
COVID	68 (19.2%)	80 (21.9%)	134 (16.2%)	146 (16.3%)
Other infection	3 (0.8%)	2 (0.5%)	4 (0.5%)	3 (0.3%)
Cardiac	1 (0.3%)	4 (1.1%)	5 (0.6%)	8 (0.9%)
Stroke	0 (0.0%)	2 (0.5%)	1 (0.1%)	6 (0.7%)
Other vascular	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Cancer	3 (0.8%)	6 (1.6%)	7 (0.8%)	13 (1.5%)
Other medical	6 (1.7%)	9 (2.5%)	22 (2.7%)	19 (2.1%)
External	1 (0.3%)	3 (0.8%)	3 (0.4%)	5 (0.6%)
Unknown cause	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total: 28-day mortality	82 (23.1%)	106 (29.0%)	177 (21.4%)	201 (22.5%)

Webtable 6: Effect on non-coronavirus infection, new cardiac arrhythmia, thrombotic events, clinically significant bleeds, metabolic complications and other outcomes

	High antigen patients		All patients	
	Sotrovimab (n=355)	Usual care (n=365)	Sotrovimab (n=828)	Usual care (n=895)
Non-coronavirus infection				
Pneumonia	34 (9.6%)	53 (14.5%)	85 (10.3%)	111 (12.4%)
Urinary tract	11 (3.1%)	5 (1.4%)	22 (2.7%)	14 (1.6%)
Biliary	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other intra-abdominal	4 (1.1%)	1 (0.3%)	8 (1.0%)	1 (0.1%)
Blood stream	7 (2.0%)	1 (0.3%)	10 (1.2%)	7 (0.8%)
Skin	3 (0.8%)	3 (0.8%)	4 (0.5%)	5 (0.6%)
Other	13 (3.7%)	9 (2.5%)	29 (3.5%)	31 (3.5%)
Subtotal: Any non-coronavirus infection	66 (18.6%)	66 (18.1%)	145 (17.5%)	151 (16.9%)
New cardiac arrhythmia				
Atrial flutter or atrial fibrillation	11 (3.1%)	10 (2.7%)	19 (2.3%)	22 (2.5%)
Other supraventricular tachycardia	1 (0.3%)	1 (0.3%)	6 (0.7%)	2 (0.2%)
Subtotal: Supraventricular tachycardia	12 (3.4%)	11 (3.0%)	23 (2.8%)	24 (2.7%)
Ventricular tachycardia	1 (0.3%)	4 (1.1%)	1 (0.1%)	6 (0.7%)
Ventricular fibrillation	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Subtotal: Ventricular tachycardia or fibrillation	1 (0.3%)	4 (1.1%)	2 (0.2%)	6 (0.7%)
Atrioventricular block requiring intervention	1 (0.3%)	0 (0%)	2 (0.2%)	0 (0%)
Unknown / not recorded	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Subtotal: Any major cardiac arrhythmia	14 (3.9%)	15 (4.1%)	28 (3.4%)	30 (3.4%)
Thrombotic events				
Pulmonary embolism	6 (1.7%)	4 (1.1%)	13 (1.6%)	15 (1.7%)
Deep-vein thrombosis	0 (0%)	0 (0%)	2 (0.2%)	3 (0.3%)
Ischaemic stroke	2 (0.6%)	0 (0%)	4 (0.5%)	2 (0.2%)
Myocardial infarction	0 (0%)	2 (0.5%)	2 (0.2%)	4 (0.4%)
Systemic arterial embolism	0 (0%)	1 (0.3%)	0 (0%)	1 (0.1%)
Subtotal: Any thrombotic event	8 (2.3%)	6 (1.6%)	21 (2.5%)	23 (2.6%)
Clinically significant bleeds				
Intra-cranial	0 (0%)	1 (0.3%)	0 (0%)	3 (0.3%)
Gastrointestinal	3 (0.8%)	3 (0.8%)	10 (1.2%)	10 (1.1%)
Other/unrecorded site	4 (1.1%)	3 (0.8%)	7 (0.8%)	7 (0.8%)
Requiring blood transfusion	4 (1.1%)	5 (1.4%)	13 (1.6%)	15 (1.7%)
Requiring surgery	2 (0.6%)	0 (0%)	2 (0.2%)	1 (0.1%)
Requiring endoscopy	1 (0.3%)	1 (0.3%)	3 (0.4%)	4 (0.4%)
Requiring vasoactive drugs	1 (0.3%)	1 (0.3%)	3 (0.4%)	3 (0.3%)
Subtotal: Any clinically significant bleeding	7 (2.0%)	7 (1.9%)	17 (2.1%)	20 (2.2%)
Metabolic complications				
Ketoacidosis	1 (0.3%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Hyperglycaemic hyperosmolar state	6 (1.7%)	3 (0.8%)	9 (1.1%)	8 (0.9%)
Other hyperglycaemia requiring new use of insulin	22 (6.2%)	25 (6.8%)	49 (5.9%)	50 (5.6%)
Subtotal: Any clinically significant hyperglycaemia	27 (7.6%)	26 (7.1%)	55 (6.6%)	54 (6.0%)
Severe hypoglycaemia	2 (0.6%)	1 (0.3%)	5 (0.6%)	2 (0.2%)
Acute kidney injury*				
Stage 1	13/347 (3.7%)	14/356 (3.9%)	32/814 (3.9%)	37/879 (4.2%)
Stage 2	3/347 (0.9%)	8/356 (2.2%)	8/814 (1.0%)	21/879 (2.4%)
Stage 3	23/347 (6.6%)	14/356 (3.9%)	51/814 (6.3%)	38/879 (4.3%)
Subtotal: Any acute kidney injury	39/347 (11.2%)	36/356 (10.1%)	91/814 (11.2%)	96/879 (10.9%)
Other outcomes				
Seizures	1 (0.3%)	2 (0.5%)	5 (0.6%)	5 (0.6%)
ALT >3x ULN	24 (6.8%)	18 (4.9%)	42 (5.1%)	38 (4.2%)
ALT >3x ULN and bilirubin >2x ULN	2 (0.6%)	2 (0.5%)	3 (0.4%)	4 (0.4%)

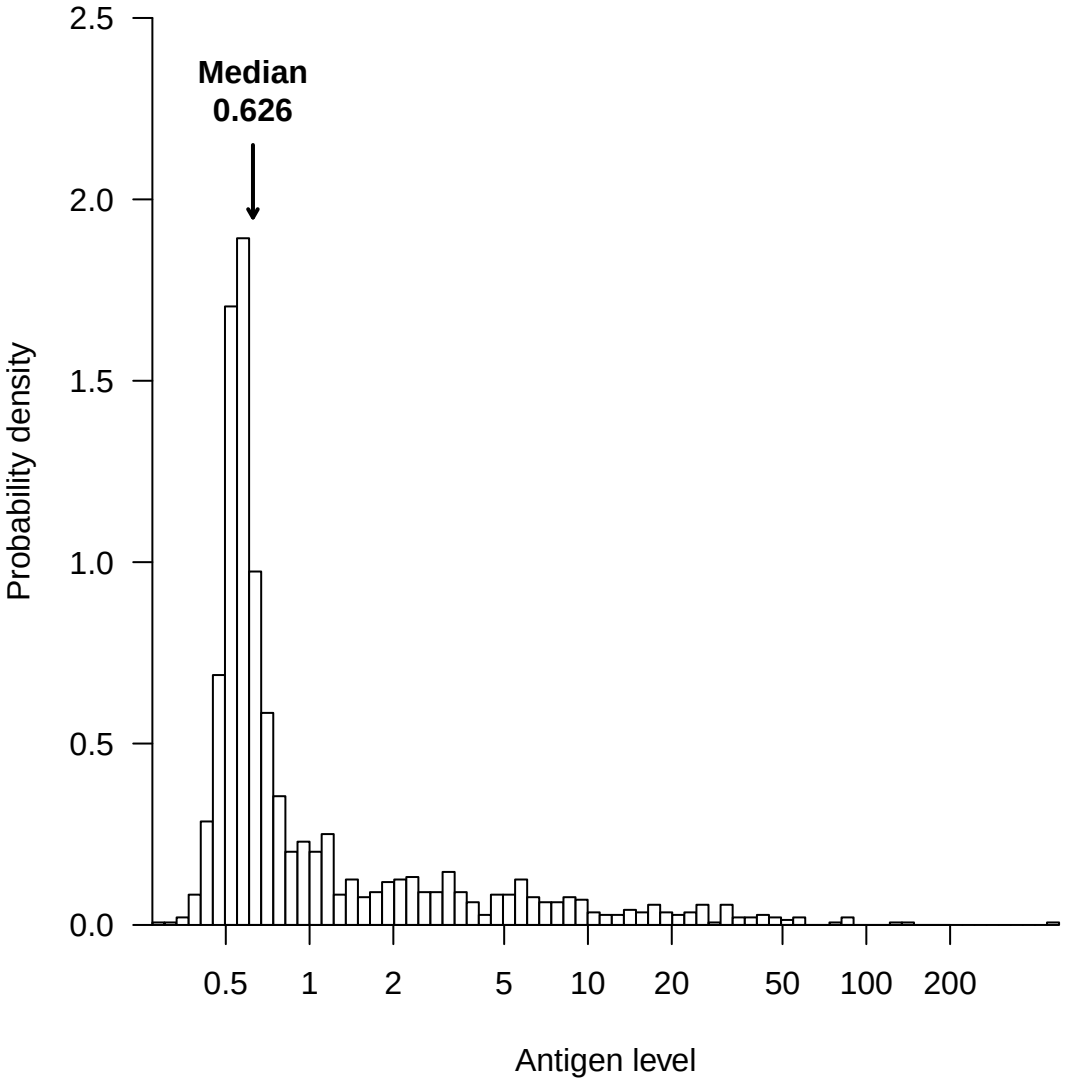
* Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Webtable 7: Details of participants developing new sotrovimab resistance mutations on treament

Age	Sex	Immunosuppressed according to managing clinician?	Other comorbidities	Allocated sotrovimab	Received sotrovimab	New spike mutation	Status at day 28
56	F	Yes	Chronic kidney disease	No	No	E340D	Alive, discharged
66	F	Yes	Chronic lung disease	Yes	Yes	K356M	Alive, discharged
59	F	Yes	None	Yes	Yes	E340K	Alive, in hospital

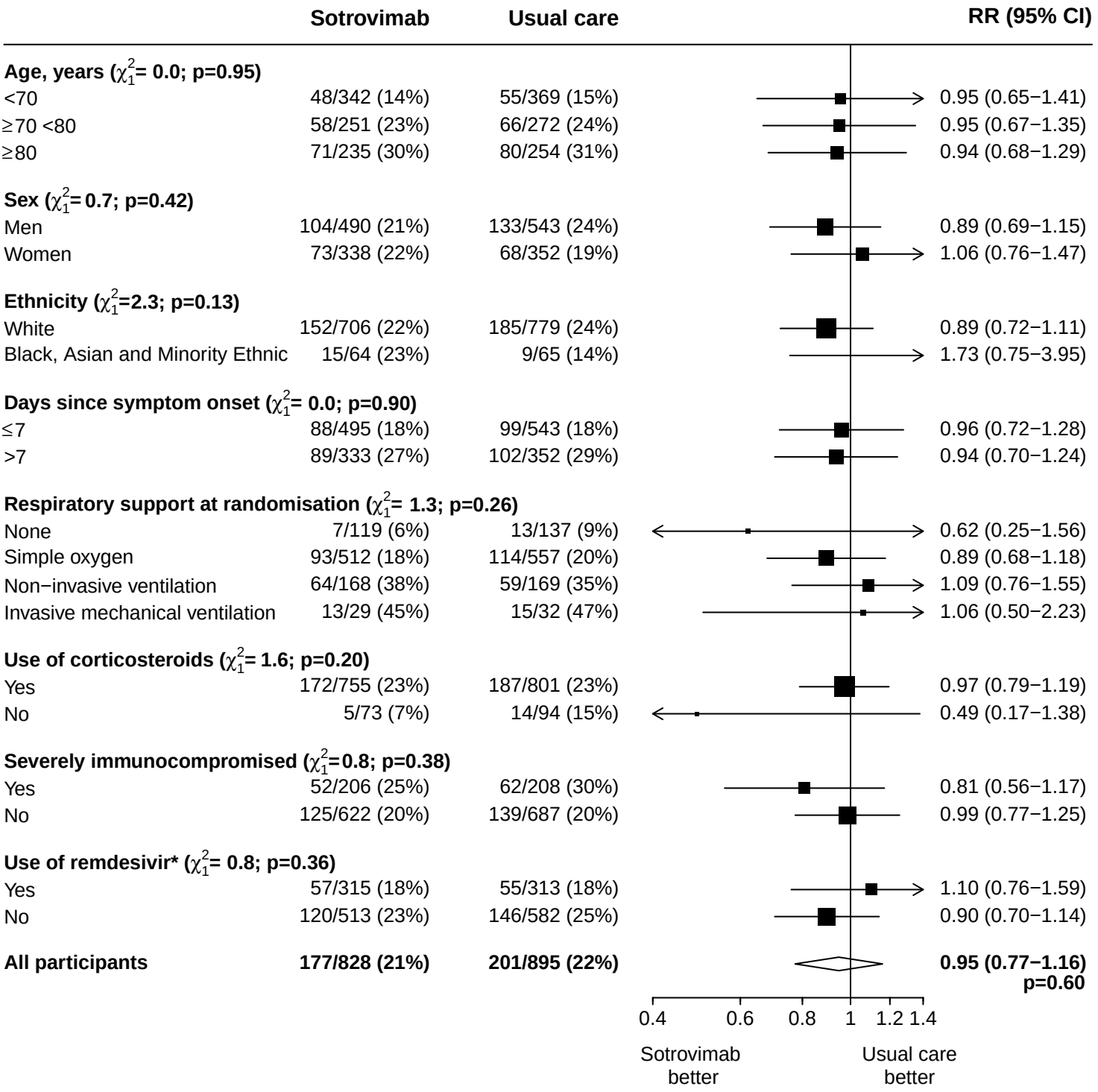
Supplementary Figures

Webfigure 1: Distribution of serum antigen levels at randomisation



Distribution shown on the logarithmic scale

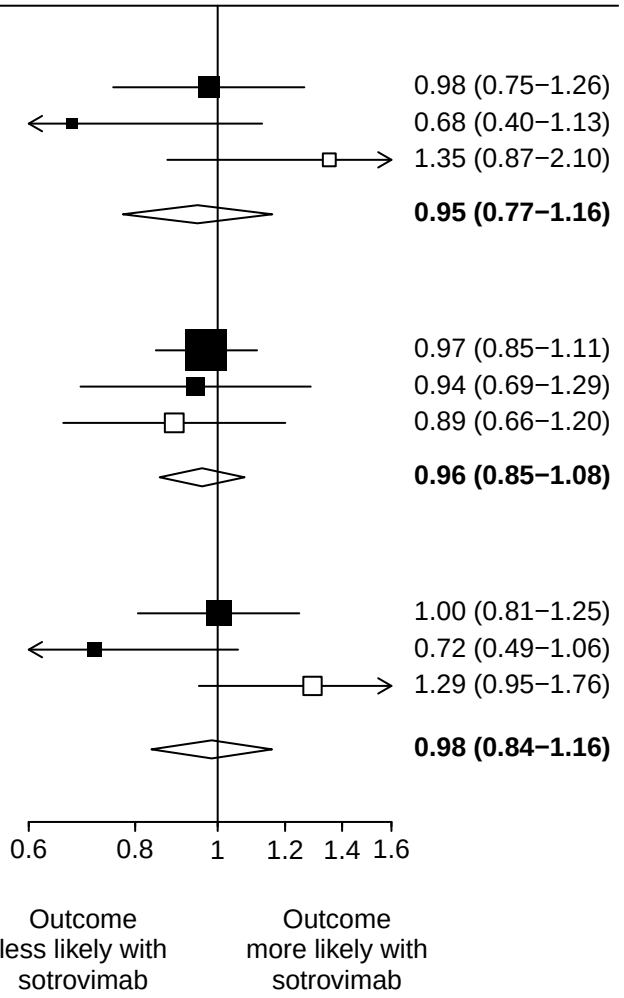
Webfigure 2: Effect of allocation to sotrovimab on 28−day mortality in all participants, by baseline characteristics



Subgroup−specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. The ethnicity subgroup excludes patients with missing data, but these patients are included in the overall summary diamond. RR=Rate ratio adjusted for age and respiratory support status at randomisation. * Post−hoc subgroup analysis requested during peer review.

Webfigure 3: Primary and secondary outcomes, overall and by Roche anti−S status

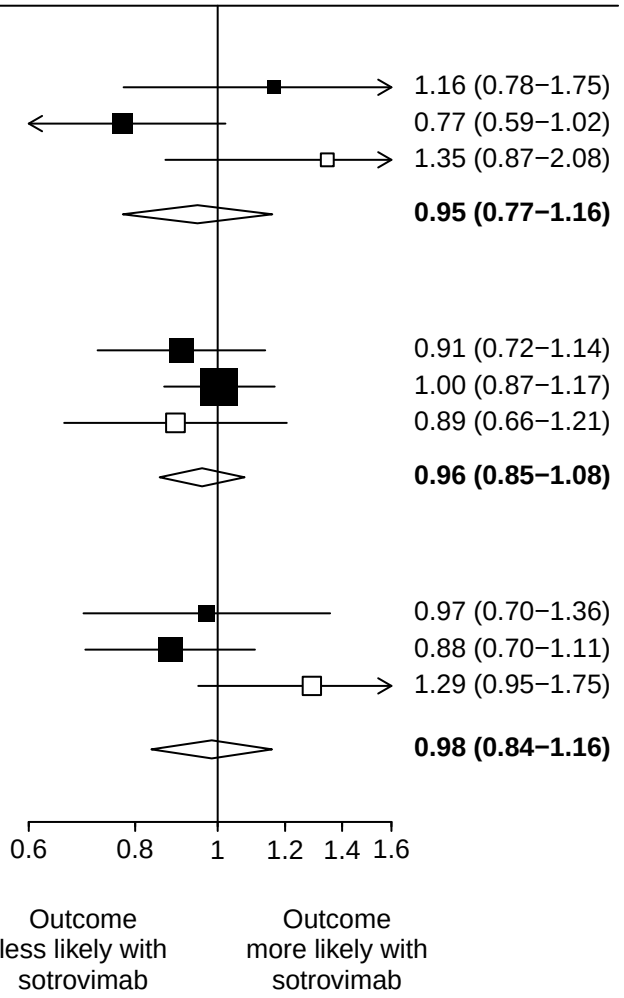
Outcome, subgroup	Sotrovimab	Usual care	RR (95% CI)
Death within 28 days (χ^2_1= 1.6; p=0.21)			
Positive	111/569 (20%)	120/610 (20%)	0.98 (0.75−1.26)
Negative	24/126 (19%)	42/133 (32%)	0.68 (0.40−1.13)
Unknown status	42/133 (32%)	39/152 (26%)	1.35 (0.87−2.10)
All participants	**177/828 (21%)**	**201/895 (22%)**	**0.95 (0.77−1.16)**
Discharge alive from hospital (χ^2_1=0.0; p=0.87)			
Positive	400/569 (70%)	427/610 (70%)	0.97 (0.85−1.11)
Negative	84/126 (67%)	82/133 (62%)	0.94 (0.69−1.29)
Unknown status	79/133 (59%)	100/152 (66%)	0.89 (0.66−1.20)
All participants	**563/828 (68%)**	**609/895 (68%)**	**0.96 (0.85−1.08)**
Invasive mechanical ventilation or death (χ^2_1=2.2; p=0.14)			
Positive	112/550 (20%)	120/594 (20%)	1.00 (0.81−1.25)
Negative	26/124 (21%)	43/128 (34%)	0.72 (0.49−1.06)
Unknown status	46/125 (37%)	38/141 (27%)	1.29 (0.95−1.76)
All not on invasive mechanical ventilation at randomisation	**184/799 (23%)**	**201/863 (23%)**	**0.98 (0.84−1.16)**



Subgroup−specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. Open squares represent participants with unknown status. The tests for heterogeneity compare the log RRs in seropositive vs seronegative patients (i.e. excluding those with unknown serostatus). RR=risk ratio for the composite outcome of invasive mechanical ventilation or death, and rate ratio for the other outcomes.

Webfigure 4: Primary and secondary outcomes, overall and by Roche anti−N status

Outcome, subgroup	Sotrovimab	Usual care	RR (95% CI)
Death within 28 days (χ^2_1= 2.6; p=0.10)			
Positive	47/214 (22%)	46/240 (19%)	1.16 (0.78−1.75)
Negative	88/481 (18%)	116/504 (23%)	0.77 (0.59−1.02)
Unknown status	42/133 (32%)	39/151 (26%)	1.35 (0.87−2.08)
All participants	**177/828 (21%)**	**201/895 (22%)**	**0.95 (0.77−1.16)**
Discharge alive from hospital (χ^2_1=0.6; p=0.46)			
Positive	141/214 (66%)	162/240 (68%)	0.91 (0.72−1.14)
Negative	343/481 (71%)	348/504 (69%)	1.00 (0.87−1.17)
Unknown status	79/133 (59%)	99/151 (66%)	0.89 (0.66−1.21)
All participants	**563/828 (68%)**	**609/895 (68%)**	**0.96 (0.85−1.08)**
Invasive mechanical ventilation or death (χ^2_1=0.2; p=0.63)			
Positive	44/203 (22%)	50/230 (22%)	0.97 (0.70−1.36)
Negative	94/471 (20%)	113/493 (23%)	0.88 (0.70−1.11)
Unknown status	46/125 (37%)	38/140 (27%)	1.29 (0.95−1.75)
All not on invasive mechanical ventilation at randomisation	**184/799 (23%)**	**201/863 (23%)**	**0.98 (0.84−1.16)**



Subgroup−specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. Open squares represent participants with unknown status. The tests for heterogeneity compare the log RRs in seropositive vs seronegative patients (i.e. excluding those with unknown serostatus). RR=risk ratio for the composite outcome of invasive mechanical ventilation or death, and rate ratio for the other outcomes.

Appendices

Appendix 1: RECOVERY Trial Protocol V26.0

RECOVERY TRIAL PROTOCOL

This protocol describes the RECOVERY Trial, a randomised trial among patients hospitalised for COVID-19 and/or influenza (its full title, Randomised Evaluation of COVID-19 ThERapY, reflects its initial focus on COVID-19 alone when it opened in March 2020).

Background: In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, low-dose corticosteroids, and Hydroxychloroquine (which has now been done). A World Health Organization (WHO) expert group issued broadly similar advice. These groups also advised that other treatments would soon emerge that require evaluation. Since then, progress in COVID-19 treatment has highlighted the need for better evidence for the treatment of pneumonia caused by other pathogens, such as influenza, for which therapies are widely used without good evidence of benefit or safety.

Eligibility and randomisation: Eligible patients are randomly allocated between one or more treatment arms, each to be given in addition to the usual standard of care in the participating hospital. The study is dynamic, and treatments are added and removed as results and suitable treatments become available. The randomised treatment comparisons in this version of the protocol (which should be checked and confirmed as the current version) are shown in Table 1. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer comparisons.

Table 1: Current comparisons

Condition	**Randomised comparisons, each vs. usual care alone**	**Eligibility criteria specific to comparison**
COVID-19	High-dose corticosteroids	requiring ventilatory support[a]; without suspected or confirmed influenza infection
	Sotrovimab	
Influenza	Baloxavir	
	Oseltamivir	
	Low-dose corticosteroids	hypoxia; without suspected or confirmed SARS-CoV-2 infection

[a] non-invasive ventilation (including high-flow nasal oxygen), invasive mechanical ventilation or extra-corporeal membranous oxygenation (ECMO)

See Appendix 6 for details of the active comparisons in each participating country, and for region-specific information including age, pregnancy and breastfeeding restrictions. Information on completed comparisons is in Section 7.

In a partial factorial design, participants may be entered into one or more randomised comparisons of active treatment plus usual care vs. usual care alone, simultaneously. This allows the effects of one treatment to be assessed in the presence or absence of another which generates useful information for clinicians and health policy-makers. In particular, this

allows antiviral therapies to be assessed as monotherapy and in combination, which will provide important information on efficacy, safety and the development of resistance. This protocol indicates clearly where specific combinations are not desirable.

Adaptive design: The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The most important task for the DMC will be to assess whether the randomised comparisons in the study have provided evidence that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Regardless, follow-up will continue for all randomised participants, including those previously assigned to trial arms that are modified or ceased. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Outcomes: The main outcomes will be death, discharge, need for ventilation and need for renal replacement therapy. For the main analyses, follow-up will be censored at 28 days after randomisation. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases where available (such as those managed by NHS England and equivalent local, regional or national organisations).

Simplicity of procedures: To facilitate collaboration, even in hospitals that suddenly become overloaded, patient enrolment (via the internet) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal. Randomisation via the internet is simple and quick, at the end of which the allocated treatment is displayed on the screen and can be printed or downloaded. Key follow-up information is recorded at a single timepoint and may be ascertained by contacting participants in person, by phone or electronically, or by review of medical records and databases.

Data to be recorded: At randomisation, information will be collected on the identity of the randomising clinician and of the patient, age, sex, major co-morbidity, pregnancy, illness onset date and severity, and any contraindications to the study treatments. The main outcomes will be death (with date and probable cause), discharge (with date), need for ventilation (with number of days recorded) and need for renal replacement therapy. Other information to be recorded relevant to safety will include acute kidney or liver injury, cardiac arrhythmia, infection, thrombosis, bleeding, metabolic disturbances, and seizures.

Reminders will be sent if outcome data have not been recorded by 28 days after randomisation. Suspected Serious Adverse Reactions (SSARs) to one of the study medications (e.g., Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia) will be collected, and unexpected SSARs (SUSARs) will be reported in an expedited fashion. Other adverse events will not be recorded but may be available through linkage to medical databases.

Numbers to be randomised: The larger the number randomised the more accurate the results will be but the numbers that can be randomised will depend critically on the epidemiology of the relevant infections over the next few years. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial.

Heterogeneity between populations: If sufficient numbers are studied, it may be possible to generate reliable evidence in certain patient groups (e.g. those with major co-morbidity or who are older). To this end, data from this study may be combined with data from other trials of treatments for COVID-19 or influenza.

Add-on studies: Particular countries or groups of hospitals, may want to collaborate in adding further measurements or observations, such as serial blood gases or chemistry, serial lung imaging, or serial documentation of other aspects of disease status. While well-organised additional research studies of the natural history of the disease or of the effects of the trial treatments could be valuable (although the lack of placebo control may bias the assessment of subjective side-effects, such as gastro-intestinal problems), they are not core requirements.

To enquire about the trial, contact the RECOVERY Central Coordinating Office
Nuffield Department of Population Health, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom
Tel: 0800 1385451 | E-mail: recoverytrial@ndph.ox.ac.uk | Website: www.recoverytrial.net
To enquire about the trial outside of the UK, contact the relevant Clinical Trial Units
To RANDOMISE a patient, visit: www.recoverytrial.net

1 BACKGROUND AND RATIONALE

1.1 Setting

In 2019 a novel coronavirus-disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent.[1] The clinical manifestations of COVID-19 range from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure. As many patients do not progress to severe disease the overall case fatality rate per infected individual is low, but hospitals in areas with significant community transmission have experienced a major increase in the number of hospitalised pneumonia patients, and the frequency of severe disease in hospitalised patients can be as high as 30%.[2-4] The progression from prodrome (usually fever, fatigue and cough) to severe pneumonia requiring oxygen support or mechanical ventilation often takes one to two weeks after the onset of symptoms.[2] The kinetics of viral replication in the respiratory tract are not well characterized, but this relatively slow progression provides a potential time window in which antiviral therapies could influence the course of disease.

Since the RECOVERY trial began in 2020, it has identified several life-saving treatments for COVID-19, and shown that other widely used treatments were ineffective.[5-14] In contrast, the treatment of hospitalised patients with pneumonia caused by influenza has progressed little in the last 20 years and there is substantial uncertainty and disagreement about optimal treatment of these patients. Corticosteroids reduce the risk of death in patients with severe COVID-19, but there is insufficient evidence to know if they produce a similar benefit in influenza.[15] Anti-SARS-CoV-2 antivirals can improve outcomes in hospitalised COVID-19 patients, but there is no similar evidence for anti-influenza antivirals.[16]

1.2 Treatment Options

The protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19 and influenza. All patients will receive usual care for the participating hospital. The current treatments under evaluation are summarised in Table 1 above with further details provided in sections 2.4-2.6 and in Appendices 1-4 (sections 8.1-8.4).

1.3 Modifications to the number of treatment comparisons

Other treatment comparisons can be added if evidence emerges that there are suitable candidate therapeutics. Conversely, in some patient populations, not all trial comparisons are appropriate (e.g. due to contraindications based on co-morbid conditions or concomitant medication); in some hospitals or countries, not all treatments will be available (e.g. due to manufacturing and supply issues); and at some times, not all treatments will be active (e.g. due to lack of relevant approvals and contractual agreements). The Trial Steering Committee may elect to pause one or more of the comparisons in order to increase trial efficiency during a fluctuating epidemic. In any of these situations, randomisation will be between fewer arms. Depending on the availability and suitability of treatments, it may be allowed for participants to be randomised in only one or two parts of the main randomisations.

1.4 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for confirmed COVID-19 and/or influenza infection in hospitalised patients receiving usual standard of care. COVID-19 and influenza are common causes of hospital admission, particularly during seasonal respiratory virus epidemics, and carry a substantial risk of death, so even treatments with only a moderate impact on survival or on hospital resources could be worthwhile. Therefore, the focus of RECOVERY is the impact of candidate treatments on mortality and on the need for hospitalisation or ventilation.

Critically, the trial is designed to minimise the burden on front-line hospital staff working within an overstretched care system during a major epidemic. Eligibility criteria are therefore simple and trial processes (including paperwork) are minimised.

The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing:

- a broad range of patients to be enrolled in large numbers;
- randomisation between only those treatment arms that are *both* available at the hospital *and* not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications);
- treatment arms to be added or removed according to the emerging evidence; and
- additional substudies may be added to provide more detailed information on side effects or sub-categorisation of patient types but these are not the primary objective and are not required for participation.

In a cohort of 191 hospitalised COVID-19 patients with a completed outcome, the median time from illness onset to discharge was 22.0 days (IQR 18.0-25.0) and the median time to death was 18.5 days (15.0-22.0). Thirty-two patients (17%) required invasive mechanical ventilation and the median time from onset to mechanical ventilation was 14.5 days. Therefore, early endpoint assessment, such as 28 days after randomisation, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[17] For influenza, the average length of hospital stay in the UK is around 9 days, so assessment at 28 days will capture most outcomes.[18]

1.5 Potential for effective treatments to become available

In early 2020, when the trial first started, there were no known treatments for COVID-19. However, over time, effective treatments have become available, typically as the result of reliable information from randomised trials (including from this study). For example, in June 2020, results from the RECOVERY trial showed that dexamethasone 6mg once daily reduces the mortality in COVID-19 patients requiring mechanical ventilation or oxygen.[14] In response, many clinical guidelines now recommend the use of dexamethasone 6mg once daily as standard of care for these types of patients.

The RECOVERY trial randomises eligible participants to usual standard of care for the local hospital alone vs usual standard of care plus one or more additional study treatments. Over time, usual standard of care has evolved (e.g. as a consequence of results from trials such as RECOVERY) and it is anticipated that it will evolve further in the future. Thus randomisation will always be relevant to the current clinical situation and the incremental effects of the study treatments will be appropriately assessed.

2 DESIGN AND PROCEDURES

2.1 Eligibility

Patients are eligible for the study if all of the following are true:

(i) Hospitalised

(ii) Viral pneumonia syndrome

In general, viral pneumonia should be suspected when a patient presents with:

a) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
b) compatible chest imaging (consolidation or ground-glass shadowing on X-ray or CT); and
c) alternative causes have been considered unlikely or excluded (e.g. heart failure, bacterial pneumonia).

However, the diagnosis remains a clinical one based on the opinion of the managing doctor.

(iii) Confirmed SARS-CoV-2 infection and/or influenza A or B infection

(iv) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

Patients with SARS-CoV-2 and influenza co-infection are eligible, but would be excluded from certain comparisons (as described in the table on page 1). In addition, if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see Appendix 2, Appendix 3 for children, and Appendix 4 for pregnant and breastfeeding women) or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient. For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial.

Patients who have been previously recruited into RECOVERY are eligible to be recruited again as long as their previous randomisation was >6 months ago. Patients will not be recruited into the same randomised comparison (e.g. sotrovimab vs. usual care) on more than one occasion, regardless of how far apart they occur.

In some locations, children (aged <18 years) will not be recruited, to comply with local and national regulatory approvals (see Appendix 6).

2.2 Consent

Informed consent should be obtained from each patient 16 years and over before enrolment into the study. Due to the poor outcomes in patients who require ventilation (>90% mortality in one cohort[17]), patients who lack capacity to consent due to severe disease (e.g. needs ventilation) or a prior condition, and for whom a relative to act as the legally designated representative is not available (in person), randomisation and consequent treatment will

proceed with consent provided by a clinician (independent of the trial[a]) who will act as the legally designated representative (if allowed by local regulations).

If they regain capacity, such participants should be provided with information about the trial (ideally prior to discharge, but otherwise as soon as possible thereafter), what their rights are and how to exercise them, but it is not necessary to obtain their written consent[b]. Provision of such information (i.e. the current participant information sheet) will be documented in the medical record.

For children aged <16 years old consent will be sought from their parents or legal guardian. Where possible, children aged between 10-15 years old will also be asked for assent. Children aged ≥16 years old will asked for consent as for adults. Witnessed[c] consent may be obtained over the telephone or web video link if hospital visiting rules or parental infection mean a parent/guardian cannot be physically present.

Information about participants' involvement will be included in routine clinical communications (e.g. discharge summaries) provided to participants (and, in the UK their GPs). If any other relevant information arises during the trial, this may also be sent to GPs.

2.3 Baseline information

The following information will be recorded on the web-based form by the attending clinician or delegate:

- Patient details (e.g. name or initials [depending on privacy requirements], NHS/CHI number [UK only] or medical records number, date of birth, sex)
- Clinician details (e.g. name)
- Symptom onset date
- Disease severity as assessed by need for supplemental oxygen, non-invasive ventilation or invasive mechanical ventilation/extracorporeal membrane oxygenation (ECMO)
- Oxygen saturations on air, oxygen delivery device, and oxygen flow rate (if available),
- Latest routine measurement of respiratory rate and blood pressure
- Presence of new or worsened confusion
- Presence of lung consolidation on chest X-ray or CT (if available)
- Latest routine measurement of creatinine, urea, and C-reactive protein (if available)
- SARS-CoV-2 and influenza test results (if available)
- Major co-morbidity (e.g. heart disease, diabetes, chronic lung disease) and pregnancy (including pregnancy test result in all women of child-bearing potential[d])
- Use of relevant medications (e.g. corticosteroids, anti-virals) and prior vaccination
- Date of hospitalisation

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[a] Independent clinicians may complete study training, but have no other involvement in the trial, e.g. eligibility assessment, or randomisation

[b] Unless required by local regulations. (This is not required in the UK.)

[c] The witness should be impartial i.e. not a member of the research team, but they do not require specific training or knowledge of the trial.

[d] A woman of childbearing potential is defined as a post-menarchal pre-menopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose male partners have been vasectomized or whose male partners have received or are utilizing mechanical contraceptive devices. The potential inclusion of any pregnant women should be discussed with a consultant obstetrician (or obstetric physician).

- Contraindication to the study treatment regimens (in the opinion of the attending clinician)
- Name of person completing the form

The person completing the form will then be asked to confirm that they wish to randomise the patient and will then be required to enter their name and e-mail address.

2.3.1 Baseline sample collection[e]

2.3.1.1 Participants with COVID-19

Participants in the UK with COVID-19 entering the sotrovimab comparison should have a serum sample collected **after obtaining consent and prior to randomisation** in which the presence of SARS-CoV-2 and immune responses against it may be tested (including anti-SARS-CoV-2 antibodies or cytokines). In addition, a nasal swab should be collected in which the level of SARS-CoV-2 viral RNA (and genotyping for resistance markers) will be measured. Participants outside the UK do not require any baseline sample collection.

2.3.1.2 Participants with influenza pneumonia

Participants in the UK with influenza pneumonia should have a nasal swab collected in which the presence of influenza virus will be measured. Participants outside the UK do not require baseline sample collection, although if the influenza diagnosis was based on a rapid antigen test alone then a nose or throat swab will be collected for influenza PCR at a clinical laboratory (if this testing is locally available). This swab will be collected after obtaining consent and prior to randomisation, and patients with a positive antigen test may proceed to randomisation before results of influenza PCR are available.

2.4 Randomised allocation of treatment for COVID-19

In addition to receiving usual care, eligible patients with confirmed SARS-CoV-2 infection will be allocated treatment(s) using a central web-based randomisation service (without stratification or minimisation). A factorial design is used such that eligible patients may be randomised simultaneously to one or more of the study treatment arms (depending on location and infection). The doses in this section are for adults (see Appendix 3 for paediatric dosing). Region-specific exclusions, including those related to age, pregnancy or breastfeeding, are given in Appendix 6.

2.4.1 Randomisation part E

Eligible patients (adult patients ≥18 years old without suspected or confirmed influenza co-infection) and requiring ventilatory support (i.e. non-invasive ventilation [high-flow nasal oxygen[f], continuous positive airways pressure, bilevel positive airways pressure], invasive mechanical ventilation, or ECMO) may be randomised in a ratio of 1:1 to one of the arms listed below.

- **No additional treatment[g]**

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[e] Collection of these samples will continue until the Steering Committee determine (on the basis of data blinded to treatment allocation) that sufficient information is available to assess the effect of treatment on viral load and/or resistance markers.

[f] high-flow nasal oxygen: humidified high flow oxygen through a special device, normally used in a critical care area, with a flow rate >20l/min

[g] Usual care in patients requiring ventilatory support is expected to include low dose (6mg daily) dexamethasone

- **High-dose corticosteroids: dexamethasone 20 mg (base) once daily** by mouth, nasogastric tube or intravenous infusion for 5 days follow by **dexamethasone 10 mg (base) once daily** by mouth, nasogastric tube or intravenous infusion for 5 days. [h,i]

2.4.2 Randomisation part J (UK only):

Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.

- **No additional treatment**

- **Sotrovimab 1000 mg in 100 mL 0.9% sodium chloride or 5% dextrose** by intravenous infusion over 1 hour as soon as possible after randomisation.

2.5 Randomised allocation of treatment for influenza

In addition to receiving usual care, eligible patients with confirmed influenza A or B infection will be allocated treatment(s) using a central web-based randomisation service (without stratification or minimisation). A factorial design is used such that eligible patients may be randomised simultaneously to one or more of the study treatment arms (depending on location and infection). The doses in this section are for adults (see Appendix 3 for paediatric dosing). Region-specific exclusions, including those related to age, pregnancy or breastfeeding, are given in Appendix 6.

2.5.1 Randomisation part G

Eligible patients (with or without SARS-CoV-2 co-infection) may be randomised in a ratio of 1:1 to one of the arms listed below.

- **No additional treatment**

- **Baloxavir marboxil 40mg (or 80mg if weight ≥80kg) once daily** by mouth or nasogastric tube to be given on day 1 and day 4[j].

2.5.2 Randomisation part H

Eligible patients (with or without SARS-CoV-2 co-infection) may be randomised in a ratio of 1:1 to one of the arms listed below.

- **No additional treatment**

- **Oseltamivir 75mg twice daily** by mouth or nasogastric tube for five days[j,k].

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[h] Treatment should be discontinued at 10 days or on discharge from hospital if sooner. Participants can be given a short 'weaning' course when they complete their study allocation if considered clinically necessary.

[i] Pregnant women should receive either prednisolone (130 mg) orally or hydrocortisone (540 mg in divided doses) intravenously or methylprednisolone (100 mg) intravenously for five days, followed by either prednisolone (65 mg) orally or hydrocortisone (270 mg in divided doses) intravenously or methylprednisolone (50 mg) intravenously for five days.

[j] If participant is discharged before course is complete, the participant should be provided with medication to complete the course at home.

[k] Course can be extended to 10 days for immunosuppressed patients at the managing clinician's discretion.

2.5.3 Randomisation part I

Eligible patients (without suspected or confirmed SARS-CoV-2 infection) and with clinical evidence of hypoxia (i.e. receiving oxygen or with oxygen saturations <92% on room air) may be randomised in a ratio of 1:1 to one of the arms listed below.

- **No additional treatment**

- **Low-dose corticosteroids: Dexamethasone 6mg once daily given** orally or intravenously for ten days or until discharge (whichever happens earliest)[l]

2.6 Administration of allocated treatment

The details of the allocated study treatments will be displayed on the screen and can be printed or downloaded. The hospital clinicians are responsible for prescription and administration of the allocated treatments. The patient's own doctors are free to modify or stop study treatments if they feel it is in the best interests of the patient without the need for the patient to withdraw from the study (see section 2.9). This study is being conducted within hospitals. Therefore use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) which will guide modifications to both the study treatment and use of concomitant medication (e.g. in the case of potential drug interactions).

2.7 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after first randomisation (whichever is sooner):

- Vital status (alive / dead, with date and presumed cause of death, if appropriate)
- Hospitalisation status (inpatient / discharged, with date of discharge, if appropriate)
- Use of ventilation (with days of use and type, if appropriate)
- Use of renal dialysis or haemofiltration
- Documented new major cardiac arrhythmia (including atrial and ventricular arrhythmias)
- Major bleeding (defined as intracranial bleeding or bleeding requiring transfusion, endoscopy, surgery, or vasoactive drugs)
- Thrombotic event, defined as either (i) acute pulmonary embolism; (ii) deep vein thrombosis; (iii) ischaemic stroke; (iv) myocardial infarction; or (v) systemic arterial embolism.
- Non-coronavirus/non-influenza infection, categorised by site and putative organism (virus, bacteria, fungus, other)
- Use of any medications included in the RECOVERY trial protocol (including drugs in the same class) or other purported COVID-19 and influenza treatments (e.g. remdesivir, neuraminidase inhibitors)
- Participation in other randomised trials of interventions (vaccines or treatments) for COVID-19 or influenza.
- Metabolic complications: Ketoacidosis; hyperglycaemic hyperosmolar state; hyperglycaemia requiring new use of insulin; severe hypoglycaemia (defined as

[l] In pregnancy or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone. For dosing in children see Appendix 3.

hypoglycaemia causing reduced conscious level requiring another person to help recover)
- Seizures
- Laboratory results: highest creatinine, alanine (or aspartate) transaminase and bilirubin recorded during admission
- Infusion reactions to Sotrovimab
- For pregnant women in UK, ID number in UK Obstetric Surveillance System

Follow-up information is to be collected on all study participants, irrespective of whether or not they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means including medical staff, reviewing information from medical notes, routine healthcare systems, and registries.

For all randomised participants, vital status (alive / dead, with date and presumed cause of death, if appropriate), and readmission to hospital is to be ascertained at 28 days after first randomisation. This may be achieved through linkage to routine death registration data (e.g. in the UK) or through direct contact with the participant, their relatives, or medical staff and completion of an additional follow-up form. Where available, data from routine healthcare records (including linkage to medical databases held by organisations such as NHS England and equivalent local, regional or national organisations) will be used to supplement data collected by trial sites. Further details are described in the Definition and Derivation of Baseline Characteristics and Outcomes standard operating procedure.[m]

2.7.1 Follow-up swab samples (UK only)[n]

2.7.1.1 Participants with COVID-19

Participants with COVID-19 in the sotrovimab comparison should have a nasal swab collected on days 3 and 5 in which the level of SARS-CoV-2 viral RNA (and genotyping for resistance makers) will be measured. Participants outside the UK do not require any sample collection.

2.7.1.2 Participants with influenza pneumonia

Participants with influenza pneumonia should have a nasal swab collected on day 5 in which the presence of influenza virus (and genotyping for baloxavir or oseltamivir resistance markers) will be measured. Participants outside the UK do not require any sample collection.

2.8 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner). It is recognised that in the setting of this trial, there may be some variability in exactly how many days after randomisation, information on disease status is collected. This is acceptable and will be taken account of in the analyses and interpretation of results, the principle being that some information about post-randomisation disease status is better than none.

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[m] Available at www.recoverytrial.net/results

[n] Collection of these samples will continue until the Steering Committee determine (on the basis of data blinded to treatment allocation) that sufficient information is available to assess the effect of treatment on viral load and/or resistance markers. Participants discharged before day 5 will be asked to take this sample at home and will be provided with instructions and materials to do so.

In the UK, longer term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS England, UK Health Security Agency and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England). Outside the UK, due to the absence of electronic health data linkage, additional follow-up will be conducted at 6 months after first randomisation by telephone or in person (at a clinic) in order to collect information on mortality (including date and cause) and re-admission to hospital (including date[s] and primary reason[s]). This information will be captured on a web-based case report form.

2.9 Withdrawal of consent

A decision by a participant (or their parent/guardian) that they no longer wish to continue receiving study treatment should **not** be considered to be a withdrawal of consent for follow-up. However, participants (or their parent/guardian) are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed).

For participants who lack capacity, if their legal representative withdraws consent for treatment or methods of follow-up then these activities would cease. If such participants regain capacity and no longer wish to participate then they can withdraw the consent given on their behalf as above.

3 STATISTICAL ANALYSIS

All analyses for reports, presentations and publications will be prepared by the coordinating centre at the Nuffield Department of Population Health, University of Oxford. A more detailed statistical analysis plan will be developed by the investigators and published on the study website whilst still blind to any analyses of aggregated data on study outcomes by treatment allocation.

3.1 Outcomes

3.1.1 Primary and secondary outcomes for evaluation of potential treatments for COVID-19

For each pairwise comparison with the ‘no additional treatment’ arm, the **primary objective** is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

The **secondary objectives** are to assess the effects of study treatments on (a) duration of hospital stay (time to discharge alive within the first 28 days); and, (b) among patients not on invasive mechanical ventilation at baseline, the composite endpoint of death or need for invasive mechanical ventilation or ECMO.

3.1.2 Primary and secondary outcomes for evaluation of potential treatments for influenza

For each pairwise comparison with the 'no additional treatment' arm, the **co-primary objectives** are to provide reliable estimates of the effect of study treatments on (a) all-cause mortality at 28 days after randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge) and (b) time to discharge alive from hospital. Holm's procedure will be used to control the family-wise error rate across these two co-primary outcomes at 5%.[19] ENREF 14

The **secondary objective** is to assess the effects of study treatments on the composite endpoint of death or need for invasive mechanical ventilation or ECMO among patients not on invasive mechanical ventilation at baseline.

3.1.3 Safety and other outcomes for evaluation of all treatments

Objectives include the assessment of the effects of study treatments on the need for any ventilation (and duration of invasive mechanical ventilation), acute kidney injury and renal replacement therapy, thrombosis, bleeding, new major cardiac arrhythmias, infections, acute liver injury, seizures, and metabolic complications (ketoacidosis, hyperglycaemic hyperosmolar state, hyperglycaemia requiring new use of insulin, severe hypoglycaemia). Virological outcomes include viral RNA levels in the nasopharynx and the frequency of detection of resistance markers.

Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after randomisation.

Where available, data from routine healthcare records (including linkage to medical databases held by organisations such as NHS England in the UK) and from relevant research studies (such as UK Biobank, Genomics England, ISARIC-4C, the UK Obstetric Surveillance System and PHOSP-COVID) will allow subsidiary analyses of the effect of the study treatments on particular non-fatal events (e.g. ascertained through linkage to Hospital Episode Statistics), the influence of pre-existing major co-morbidity (e.g. diabetes, heart disease, lung disease, hepatic insufficiency, severe depression, severe kidney impairment, immunosuppression), the maternal and infant outcomes in women pregnant at randomisation, and longer-term outcomes as well as in particular sub-categories of patient (e.g. by genotype, pregnancy).

3.2 Methods of analysis

For all outcomes, comparisons will be made between all participants randomised to each treatment and its control, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

For time-to-event analyses, each treatment group will be compared with the no additional treatment group using the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). The log-rank 'observed minus expected' statistic (and its variance) will be used to estimate the average event rate ratio (and its confidence interval) for those allocated to each treatment group versus the no additional treatment group. For the primary outcome, participants discharged before 28 days will, in the absence of information to the contrary, be assumed to have survived for 28 days. For

binary outcomes where the timing of the event is unknown, the risk ratio and its 95% confidence interval (and associated p-value) will be reported.

Pairwise comparisons within each randomisation will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation. However, since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest. All p-values will be 2-sided.

Pre-specified subgroup analysis (e.g., level of respiratory support, time since onset of symptoms; sex; age group; ethnicity; use of corticosteroids) will be conducted, with tests for heterogeneity (or trend) performed to assess if the effect in any particular subgroup varies materially from the overall effect. The effect of each treatment (versus its control) will be assessed in the presence or absence of other relevant treatments the patients may receive either (a) as part of their usual care; or (b) as part of the trial (i.e., other factorial randomisations). Further details are fully described in the Statistical Analysis Plan.[o]

4 DATA AND SAFETY MONITORING

4.1 Recording Suspected Serious Adverse Reactions

The focus is on those events that, based on a single case, are highly likely to be related to the study medication. Examples include anaphylaxis, Stevens-Johnson Syndrome, or bone marrow failure, where there is no other plausible explanation.

Any Serious Adverse Event[p] that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction (SSAR). In making this assessment, there should be consideration of the probability of an alternative cause (for example, COVID-19 or influenza itself or some other condition preceding randomisation), the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

All SSARs should be reported by telephone to the Central Coordinating Office and recorded on the study IT system immediately.

4.2 Central assessment and onward reporting of SUSARs

Clinicians at the Central Coordinating Office are responsible for expedited review of reports of SSARs received. Additional information (including the reason for considering it both serious and related, and relevant medical and medication history) will be sought.

[o] Available at www.recoverytrial.net/results

[p] Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalisation or prolongation of existing hospitalisation; result in persistent or significant disability or incapacity; result in congenital anomaly or birth defect; or are important medical events in the opinion of the responsible investigator (that is, not life-threatening or resulting in hospitalisation, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

The focus of Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting will be on those events that, based on a single case, are highly likely to be related to the study medication. To this end, anticipated events that are either efficacy endpoints, consequences of the underlying disease, or common in the study population will be exempted from expedited reporting. Thus the following events will be exempted from expedited reporting:

(i) Events which are the consequence of COVID-19 or influenza; and
(ii) Common events which are the consequence of conditions preceding randomisation.

Any SSARs that are not exempt will be reviewed by a Central Coordinating Office clinician and an assessment made of whether the event is “expected” or not (assessed against the relevant Summary of Product Characteristics or Investigator Brochure). Any SSARs that are not expected would be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

All confirmed SUSARs will be reported to the Chair of the DMC and to relevant regulatory authorities, ethics committees, and investigators in an expedited manner in accordance with regulatory requirements.

4.3 Recording safety information and other Adverse Events

In addition to recording Suspected Serious Adverse Reactions (see section 4.1), information will be collected on all deaths and efforts will be made to ascertain the underlying cause. The occurrence of a range of safety outcomes will be collected on the follow-up form (see sections 2.7 and 3.1.3). These include information on need for any ventilation (and duration of invasive mechanical ventilation), acute kidney injury and renal replacement therapy, thrombosis, bleeding, new major cardiac arrhythmias, secondary infections, acute liver injury, seizures, and metabolic complications (ketoacidosis, hyperglycaemic hyperosmolar state, hyperglycaemia requiring new use of insulin, severe hypoglycaemia).

Other serious or non-serious adverse events will not be recorded unless specified in section 2.7. [q] It is anticipated that for some substudies, more detailed information on adverse events (e.g. through linkage to medical databases) or on other effects of the treatment (e.g. laboratory or radiological features) will be recorded and analysed but this is not a requirement of the core protocol.

4.4 Role of the Data Monitoring Committee (DMC)

During the study, interim analyses of all study data will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will determine if, in their view, the randomised comparisons in the study have provided evidence that is strong enough (with a range of uncertainty around the results

[q] Outside the UK, additional serious adverse event information (event description, date of onset, outcome, relatedness to study treatment) will be collected if required by national regulations. This will be collected on a web-based case report form and any forms required by local regulations.

that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Unless this happens, the Trial Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the interim results until 28 days after the last patient has been randomised for a particular intervention arm (at which point analyses may be conducted comparing that arm with the no additional treatment arm).

The DMC will review the safety and efficacy analyses among children (age <18 years) both separately and combined with the adult data.

4.5 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results of study outcomes by allocated treatment allocation will not be available to the research team, patients, or members of the Trial Steering Committee (unless the DMC advises otherwise).

5 QUALITY MANAGEMENT

5.1 Quality By Design Principles

In accordance with the International Conference on Harmonisation (ICH) Principles for Good Clinical Practice, the Good Clinical Trials Collaborative (GCTC) Guidance for Good Randomized Clinical Trials, and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (hospitalised patients with confirmed SARS-CoV-2 or influenza infection) and the reliability of the results that would inform the care for future patients.[20]

The critical factors that influence the ability to deliver these quality objectives are:

- to minimise the burden on busy clinicians working in an overstretched hospital during a major epidemic
- to ensure that suitable patients have access to the trial medication without impacting or delaying other aspects of their emergency care
- to provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care
- to allow individual clinicians to use their judgement about whether any of the treatment arms are not suitable for the patient
- to collect comprehensive information on the mortality and disease status

In assessing any risks to patient safety and well-being, a key principle is that of proportionality. Risks associated with participation in the trial must be considered in the context of usual care.

5.2 Training and monitoring

The focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results). Remedial actions would focus on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

The study will be conducted in accordance with the ICH Principles for Good Clinical Practice, GCTC Guidance for Good Randomized Clinical Trials, and relevant local, national and international regulations. Any serious breach of GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Prior to initiation of the study at each Local Clinical Centre (LCC), the Central Coordinating Office (CCO) or relevant Regional Coordinating Centre (RCC) will confirm that the LCC has adequate facilities and resources to carry out the study. LCC lead investigators and study staff will be provided with training materials.

On-site monitoring will focus on critical to quality data items (e.g. participants' admitted status at the time of randomisation, consent, and primary and secondary outcomes). Where practical, many of these checks can be done remotely or using external data sources (e.g. routine healthcare records from NHS England and other organisations). Therefore source data verification will only be done if required after a country-specific risk assessment. In some circumstances, the CCO or RCC may arrange additional monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data.[21,22] The purpose of all such visits will be to ensure that the study is being conducted in accordance with the protocol, to help LCC staff to resolve any local problems, and to provide extra training focussed on specific needs.

5.3 Data management

LCC clinic staff will use the bespoke study web-based applications for study management and to record participant data (including case report forms) in accordance with the protocol. Data will be held in central databases located at the CCO or on secure cloud servers. In some circumstances (e.g. where there is difficulty accessing the internet or necessary IT equipment), paper case report forms may be required with subsequent data entry by either LCC or CCO staff. Although data entry should be mindful of the desire to maintain integrity and audit trails, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will be responsible for provision of the relevant web-based applications and for generation of data extracts for analyses.

All data access will be controlled by usernames and passwords, and any changes to data will require the user to enter their username and password._ENREF_13 Staff will have access restricted to the functionality and data that are appropriate for their role in the study.

5.4 Source documents and archiving

Source documents for the study constitute the records held in the study main database. These will be retained for at least 25 years from the completion of the study. Identifiable data will be retained only for so long as it is required to maintain linkage with routine data sources (see section 2.8), with the exception of children for whom such data must be stored until they reach 21 years old (due to the statute of limitations). The sponsor and regulatory

agencies will have the right to conduct confidential audits of such records in the CCO, RCCs and LCCs (but should mindful of the workload facing participating hospitals and any relevant infection control requirements).

6 OPERATIONAL AND ADMINISTRATIVE DETAILS

6.1 Sponsor and coordination

The University of Oxford will act as the trial Sponsor. The trial will be coordinated by a Central Coordinating Office (CCO) within the Nuffield Department of Population Health staffed by members of the two registered clinical trials units – the Clinical Trial Service Unit and the National Perinatal Epidemiology Unit Clinical Trials Unit. The CCO will oversee Regional Coordinating Centres which will assist with selection of Local Clinical Centres (LCCs) within their region and for the administrative support and monitoring of those LCCs. The data will be collected, analysed and published independently of the source of funding.

6.2 Funding

This study is supported by grants to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR), the Wellcome Trust, and Flu Lab, and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, UK Foreign, Commonwealth and Development Office, Health Data Research UK, NIHR Health Protection Unit in Emerging and Zoonotic Infections and the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding.

6.3 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). In the UK, NHS indemnity operates in respect of the clinical treatment that is provided.

6.4 Local Clinical Centres

The study will be conducted at multiple hospitals (LCCs) within each region. At each LCC, a lead investigator will be responsible for trial activities but much of the work will be carried out by medical staff attending patients with COVID-19 within the hospital and by hospital research nurses, medical students and other staff with appropriate education, training, and experience. Where LCCs plan to recruit children the principal investigator will co-opt support from a local paediatrician and/or neonatologists to oversee the management of children and infants in the trial.

6.5 Supply of study treatments

6.5.1 Licensed treatments

For licensed treatments (e.g. corticosteroids, oseltamivir) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatments issued to randomised participants will be by prescription. Such study treatments may be labelled either as required for routine clinical use, or according to the requirements for an unlicensed treatment (if this facilitates IMP supply). They will be stored alongside other routine medications with no additional

monitoring. No accountability records will be kept beyond those used for routine prescriptions.

6.5.2 Unlicensed treatments

For unlicensed treatments, manufacture, packaging, labelling and delivery will be the responsibility of the pharmaceutical company and, in the UK, the Department of Health and Social Care. Each LCC will maintain an accountability log and will be responsible for the storage and issue of study treatment. If treatments require storage at a specific temperature, LCCs can use existing temperature-controlled facilities and associated monitoring. Treatment issue to randomised participants will be in accordance with local practice (and may be in line with the processes required for routine prescriptions or compassionate use). Treatment will be issued to randomised participants by prescription.

6.6 End of trial

The end of the scheduled treatment phase is defined as the date of the last follow-up visit of the last participant. In the UK, it is intended to extend follow-up for a year or more beyond the final study visit through linkage to routine medical records and central medical databases. The end of the study is the date of the final data extraction from NHS England (anticipated to be 10 years after the last patient is enrolled).

6.7 Publications and reports

The Trial Steering Committee will be responsible for drafting the main reports from the study and for review of any other reports. In general, papers initiated by the Trial Steering Committee (including the primary manuscript) will be written in the name of the RECOVERY Collaborative Group, with individual investigators named personally at the end of the report (or, to comply with journal requirements, in web-based material posted with the report).

The Trial Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Trial Steering Committee. The Trial Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. However, the Trial Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Trial Steering Committee will have the right to review and comment on any draft manuscripts prior to publication.

6.8 Substudies

Proposals for substudies must be approved by the Trial Steering Committee and by the relevant ethics committee and competent authorities (where required) as a substantial amendment or separate study before they begin. In considering such proposals, the Trial Steering Committee will need to be satisfied that the proposed substudy is worthwhile and will not compromise the main study in any way (e.g. by impairing recruitment or the ability of the participating hospitals to provide care to all patients under their care).

7 VERSION HISTORY

Version number	Date	Brief Description of Changes
1.0	13-Mar-2020	Initial version
2.0	21-Mar-2020	Addition of hydroxychloroquine. Administrative changes and other clarifications.
3.0	07-Apr-2020	Extension of eligibility to those with suspected COVID-19 Addition of azithromycin arm. Addition of inclusion of adults who lack permanently lack capacity. Change to primary outcome from in-hospital death to death within 28 days of randomisation.
4.0	14-Apr-2020	Addition of second randomisation to tocilizumab vs. standard of care among patients with progressive COVID-19.
5.0	24-Apr-2020	Addition of children to study population.
6.0	14-May-2020	Addition of convalescent plasma
7.0	18-Jun-2020	Allowance of randomisation in part B of main randomisation without part A. Removal of hydroxychloroquine and dexamethasone treatment arms.
8.0	03-Jul-2020	Removal of lopinavir-ritonavir Addition of intravenous immunoglobulin arm for children Changes to corticosteroid dosing for children. Addition of baseline serum sample in convalescent plasma randomisation
9.0	10-Sep-2020	Addition of synthetic neutralizing antibodies Additional baseline data collection Addition of countries outside UK
9.1	18-Sep-2020	Addition of information about vaccination of children of pregnant mothers receiving REGN10933+REGN10987
9.2 [not submitted in UK]	15-Oct-2020	Additional information for countries outside UK
10.0	26-Oct-2020	Addition of main randomisation part C General updates to avoid duplication and improve clarity
10.1	01-Nov-2020	Additional information for pregnant women
11.0	19-Nov-2020	Addition of colchicine to main randomisation part A Removal of azithromycin from main randomisation part A Change in randomisation ratio in main randomisation part A from 2:1 to 1:1
11.1	21-Nov-2020	Clarification of colchicine age thresholds
11.2 [not submitted in UK]	01-Dec-2020	Addition of modified aspirin dose if 150mg not available
12.0	10-Dec-2020	Allow second randomisation of children without first randomisation
12.1	16-Dec-2020	Clarification of change in V12.0
13.0	26-Jan-2021	Addition of baricitinib and anakinra (and change to allocation ratio in second randomisation for children); addition of pregnancy test for women of child-bearing potential (and change to colchicine eligibility); removal of tocilizumab for adults; removal of convalescent plasma and additional assessment of antibody-based therapy; addition of dexamethasone as substitute if methylprednisolone unavailable
14.0	15-Feb-2021	Addition of Early Phase Assessments; the inclusion of dimethyl fumarate for initial early phase assessment; restriction of main randomisation part B to children with COVID-19 pneumonia; modification of baricitinib and tocilizumab co-administration guidance
15.0	12-Apr-2021	Removal of aspirin and colchicine; addition of infliximab and high-dose corticosteroids (ex-UK only)
15.1 [not submitted in UK]	18-May-2021	Addition of South Africa

Version number	Date	Brief Description of Changes
16.0	05-Jul-2021	Removal of REGN-COV2 and main randomisation part B Removal of infliximab from main randomisation part E (and associated endemic infection monitoring section) Addition of empagliflozin as main randomisation part F and metabolic outcomes Addition of India, Sri Lanka and Pakistan
V16.1	08-Jul-2021	Clarification of design in introduction
V17.0	06-Aug-2021	Addition of additional exclusion criteria and safety monitoring for empagliflozin arm Removal of corticosteroids and intravenous immunoglobulin in main randomisation part A (for children)
V17.1	10-Aug-2021	Clarification of design for children
V18.0	13-Oct-2021	Update to consent section Change in primary outcome and sample size for DMF comparison Clarification of eligibility for PIMS-TS randomisation Removal of 3 month follow-up form for non-UK countries
V18.1	24-Oct-2021	Clarification of witnesses for consent of children
V19.0	12-Nov-2021	Addition of baloxavir marboxil, oseltamivir, and low-dose corticosteroids as randomised comparisons each vs. usual care alone for patients with influenza (in UK only). Removal of early phase assessment of dimethyl fumarate. Updated statistical analysis section to align with statistical analysis plan and include influenza analyses.
V19.1	16-Nov-21	Clarification of baloxavir and weight eligibility
V20.0	29-Nov-21	Removal of baricitinib. Extension of COVID-19 high-dose corticosteroid and empagliflozin comparisons to other countries.
V21.0	17-Dec-21	Addition of sotrovimab and molnupiravir. Addition of baseline and follow-up samples. Re-randomisation of patients recruited >6 months ago.
V21.1	19-Dec-21	Clarifications post-REC review.
V22.0	19-Jan-22	Addition of Paxlovid. (Not implemented.)
V23.0	08-Mar-22	Clarifications following MHRA review. UKOSS added to section 3.1.3. Extension of molnupiravir to other countries. Removal of tocilizumab/anakinra for PIMS-TS.
23.1	15-Mar-22	Correction of footnotes
24.0 [not implemented]	13-May-22	Change to high-dose dexamethasone eligibility criteria following urgent safety measure (instituted 13 May 2022)
25.0	23-May-22	Addition guidance around corticosteroids to be used with nirmatrelvir/ritonavir following urgent safety measure.
25.1 [not submitted in UK]	07-Jun-22	Addition of The Gambia
26.0	22-Jun-23	Removal of empagliflozin, Paxlovid, and molnupiravir. Extension of influenza comparisons to non-UK countries. Removal of The Gambia, Sri Lanka and Pakistan Updated text to reflect post-pandemic setting & addition of Appendix 6 Collection of additional baseline data Updated monitoring plan to allow on-site monitoring Sampling plan updated to allow cytokine measurement

Completed comparisons

The last version of the protocol to include the IMP is shown in the table above.

IMP	Citation
Hydroxychloroquine	New Engl J Med 2020; 383: 2030-40
Dexamethasone (COVID-19)	New Engl J Med 2021; 384: 693-704
Lopinavir-ritonavir	Lancet 2020; 396: 1345-1352
Azithromycin	Lancet 2021; 397: 605-12
Convalescent plasma	Lancet 2021; 397: 2049-59
Tocilizumab	Lancet 2021; 397: 1637-1645
Aspirin	Lancet 2022; 397: 143-151
Colchicine	Lancet Resp Med 2021; 9: 1419-26
REGN-COV2	Lancet 2022; 399: 665-76
Methylprednisolone (PIMS-TS)	Analysis ongoing
Intravenous immunoglobulin (PIMS-TS)	Analysis ongoing
Tocilizumab (PIMS-TS)	Analysis ongoing
Anakinra (PIMS-TS)-	Analysis ongoing
Dimethyl fumarate	Medrxiv: 10.1101/2022.09.23.22280285v1
Baricitinib	Lancet 2022; 400: 359-68
Empagliflozin	Medrxiv: 10.1101/2023.04.13.23288469v1
Higher dose corticosteroids in hypoxic patients not requiring ventilatory support (this comparison remains open in patients requiring ventilatory support)	Lancet 2023 epub ahead of print. PMID: 37060915
Paxlovid	Analysis ongoing
Molnupiravir	Analysis ongoing

8 APPENDICES

8.1 Appendix 1: Information about the treatment arms

All patients will receive usual care in the participating hospital.

Corticosteroids: RECOVERY is assessing the effects of corticosteroids in two different contexts: higher dose *vs* usual care in adults with COVID-19 and hypoxia who require ventilatory support; and lower dose dexamethasone in adults and children with influenza and hypoxia.

Favourable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial in the treatment of severe acute respiratory infections, including influenza, COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia and the development of acute lung injury or acute respiratory distress syndrome (ARDS).[23-26] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[27]

Corticosteroids in influenza

RECOVERY and other randomised trials have now demonstrated the benefit of corticosteroids in hypoxic COVID-19 patients.[14,28] However, the potential role of corticosteroids in severe influenza remains uncertain, with differing practices and controversy. Whilst observational studies report higher mortality associated with the use of corticosteroids in severe influenza, these studies are prone to biases, with a major concern being confounding by indication (the propensity to use corticosteroids only in the more severe patients as a rescue therapy).[29] In practice, use of corticosteroids in severe influenza is variable and widespread.[15] This therapeutic dilemma will only be resolved through an adequately powered randomised trial.

Corticosteroids in COVID-19

RECOVERY showed that dexamethasone at a dose of 6mg once daily for ten days or until discharge (whichever happens earliest) provided a significant reduction in mortality. Combining the IL-6 inhibitor tocilizumab with low dose dexamethasone resulted in a further reduction in mortality. This raises the question whether simply increasing the dose of corticosteroid could confer a similar clinical benefit to that of adding tocilizumab, but at substantially lower cost. Of note, even with dexamethasone 6mg and tocilizumab, mortality remained high at 29%. Although other randomised clinical trials in critically ill COVID-19 patients have used higher doses of dexamethasone (20mg once daily for five days followed by 10mg once daily for a further five days) and reported clinical benefit, these doses have not been compared with the lower dose used in RECOVERY. There is, therefore, uncertainty regarding the optimal dose of corticosteroids in moderate to severe COVID-19.Uncertainty remains about whether higher doses of corticosteroids may provide additional benefit in adults with hypoxia hospitalised with COVID-19. On 11 May 2022 the Data Monitoring Committee recommended stopping recruitment of patients who require no oxygen or simple oxygen only at the time of randomisation due to safety concerns. The DMC encouraged continuing recruitment of patients who, at randomisation, require either non-invasive ventilation, invasive mechanical ventilation or ECMO. The eligibility criteria for this comparison were amended in line with this advice as an urgent safety measure (implemented on 13 May 2022).

Unlike lower doses, higher doses (>15mg dexamethasone) would completely saturate cytosolic glucocorticoid receptors and have enhanced non-genomic effects. _ENREF_18 In

conditions where rapid control of inflammatory processes are required, short-term, high to very high doses of corticosteroids are used e.g.

- Sepsis dexamethasone 7.5 - 15mg equivalent daily[30]
- ARDS: dexamethasone 20mg for five days followed by 10mg for five days[31]
- Bacterial meningitis: dexamethasone 40mg daily for four days[32]
- Tuberculous Meningitis dexamethasone 0.4mg/kg/day for 7 days then reducing over 8 weeks.[33]
- Rheumatoid arthritis flare: dexamethasone 120mg pulse therapy.[34]
- Community acquired pneumonia: dexamethasone 0.6mg/day for 2 days and methyl prednisolone 200mg /day then 80mg /day for 10 days.[35]

Sotrovimab: Sotrovimab (VIR-7831) is a neutralising monoclonal antibody targeting the SARS-CoV-2 spike glycoprotein receptor binding domain. It was identified by screening antibodies from a patient who had been infected during the 2003 SARS-CoV-1 outbreak, and its ability to also neutralise SARS-CoV-2 implies that its binding site is highly conserved, maybe meaning mutational escape will be difficult.[36] The Fc portion of the parent antibody has been modified to extend sotrovimab's half-life to around 49 days. It is given as a single intravenous dose and been well tolerated in clinical studies, although occasional serious hypersensitivity reactions have occurred.

It is licenced in the UK for the treatment of COVID-19 in patients who do not require oxygen and are at high risk of developing severe disease (at a 500 mg dose). The COMET-ICE trial, conducted in 583 such patients, showed that when given within five days of symptom onset it reduced the risk of hospitalisation by 85%, from 7% in the control group to 1% in the sotrovimab group.[37] Evidence in hospitalised patients is limited, and the sotrovimab arm of ACTIV-3 was stopped due to futility after recruiting 344 participants, although no safety concerns were raised.[38] However, by recruiting around 10,000 patients, RECOVERY subsequently showed that another neutralising monoclonal antibody treatment (casirivimab+imdevimab) reduced mortality by 20% in hospitalised patients who were anti-spike antibody negative at baseline.

The Omicron SARS-CoV-2 variant that emerged in late 2021 has multiple spike protein mutations, which have led to its rapid expansion in immune populations. These also appear to cause near complete loss of neutralising activity by the monoclonal antibodies in casirivimab+imdevimab,[39] and reduce the neutralising activity of Sotrovimab about 10-fold.[40,41] Data comparing the peak and day 29 concentrations following 2.4 g casirivimab+imdevimab and 500 mg Sotrovimab demonstrate much lower concentrations of Sotrovimab.[42] These pharmacodynamics and pharmacokinetic considerations underlie the selection of a 1000 mg dose in this trial. The published safety of Sotrovimab and higher doses of other anti-spike human monoclonal antibodies (including the 8g dose of casirivimab+imdevimab used in RECOVERY) do not suggest a safety concern with this increased dose.

Baloxavir marboxil: Baloxavir marboxil is a cap-dependent endonuclease (CEN) inhibitor. CEN is an influenza virus-specific enzyme in the polymerase acidic subunit of the viral RNA polymerase complex. Through its action on CEN, baloxavir inhibits the transcription of influenza virus genomes resulting in inhibition of influenza A and B virus replication. It is approved in the USA, Japan, Australia, Europe, and the United Kingdom for the treatment of uncomplicated influenza and for post-exposure prophylaxis in individuals aged 12 years

and older. Baloxavir is given in 2 oral doses (on day 1 and day 4) and is well tolerated, with allergic reactions being the only reported adverse reactions.

Baloxavir is not approved for the treatment of complicated influenza. A phase III placebo-controlled trial of baloxavir in adults hospitalised with severe influenza (Flagstone NCT03684044) did not find a significant reduction in the primary endpoint of time to clinical improvement (personal communication, Roche). However, time to clinical improvement, time to clinical response, influenza related complications, mortality, and time to cessation of viral shedding were all in favour of baloxavir. Fewer adverse events were observed in the baloxavir arm than in the standard of care arm. The Flagstone trial was small, comparing 214 subjects who received baloxavir with 125 who received usual care alone, and a larger study is need to determine whether baloxavir has modest but clinically relevant benefit in patients hospitalised with influenza.

Oseltamivir: The neuraminidase inhibitors (oseltamivir and zanamivir) are influenza specific antivirals that have been shown in randomised controlled trials to improve outcomes in uncomplicated influenza and to be effective as post-exposure prophylaxis. They have not, however, been shown to be effective in patients hospitalised with severe influenza. Although observational studies have reported clinical benefit in patients hospitalised with severe influenza, there are no randomised controlled trial data. Consequently, the use of neuraminidase inhibitors in this patient population is variable. A randomised controlled trial of neuraminidase inhibitors in patients hospitalised with severe influenza has been recommended by an expert group convened by the Academy of Medical Sciences and the Wellcome Trust, and most clinicians would welcome such a trial.[16,43] The duration of treatment (5 days, or 10 days if the patient is immunosuppressed in the opinion of the managing clinician) is the same as that used in clinical practice and in the Summary of Product Characteristics.

8.2 Appendix 2: Drug specific contraindications and cautions

Corticosteroid

Contraindications:

- Known contra-indication to short-term corticosteroid.
- Patients with suspected or confirmed influenza co-infection are not eligible for the high-dose dexamethasone comparison for COVID-19 (Randomisation part E).
- Patients with suspected or confirmed SARS-CoV-2 co-infection are not eligible for the low-dose dexamethasone comparison for influenza infection because of the proven benefits of dexamethasone in COVID-19 (Randomisation part I).
- Current use of Paxlovid, ritonavir or other potent CYP3A inhibitors.

Cautions:

- Endemic infections may be screened for as required by local practice.
- Other immunomodulatory therapies are not contraindicated, but investigators should consider the total burden of therapy (eg, combining IL-6 receptor antagonist therapy with high-dose dexamethasone).

Sotrovimab

Contraindications:

- Weight <40kg (if <18 years old; no weight restriction for adults)
- Known hypersensitivity to sotrovimab or the drug product excipients

Cautions: no dose adjustment for kidney or liver function is required.

Baloxavir Marboxil

Contraindications:

- Weight <40kg (regardless of age)
- Known hypersensitivity to baloxavir marboxil or the drug product excipients
- Participants who have received baloxavir marboxil for the current influenza infection

Oseltamivir

Contraindications:

- Known hypersensitivity to oseltamivir or the drug product excipients
- Participants who have received oseltamivir for the current influenza infection

Cautions:

- Dose should be reduced in presence of renal impairment
    - eGFR ≥30 mL/min/1.73m^2: dose as in normal renal function (75 mg twice daily)
    - eGFR ≥10 <30 mL/min/1.73m^2: 75 mg once daily
    - eGFR <10 mL/min/1.73m^2: 75 mg as a single dose on day 1
- Dose should be reduced for adult patients weighing <40 kg to 60 mg twice daily

8.3 Appendix 3: Paediatric dosing information

Children (aged <18 years old) will be recruited in the UK only.

Randomisation of children with COVID-19 Pneumonia (Patients <12 years of age will NOT be eligible)

Arm	Route	Weight	Dose
No additional treatment	-	-	-
Sotrovimab	Intravenous	Children <12 years old excluded	
		<40 kg	Excluded regardless of age
		≥40 kg	1000 mg intravenous in 100 mL of 0.9% NaCl or 5% dextrose over 1 hour

Influenza Randomisations

<table>
<tr><th>Arm</th><th>Route</th><th>Weight/Age</th><th>Dose</th></tr>
<tr><td rowspan="3">Oseltamivir

- 30, 45 and 75 mg capsules

- Oral suspension [a]</td><td rowspan="3">Oral
<u>or</u>
Other enteral routes</td><td>Less than 36 weeks corrected gestational age</td><td>1 mg/kg twice daily for 5 days [b]</td></tr>
<tr><td>0 - 12 months (≥36 weeks corrected gestational age)</td><td><table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td><10</td><td>3 mg/kg twice daily for 5 days [b]</td></tr><tr><td>≥ 10</td><td>30 mg twice daily for 5 days [b]</td></tr></table></td></tr>
<tr><td>≥ 1 year</td><td><table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td><10</td><td>3 mg/kg twice daily for 5 days [b]</td></tr><tr><td>≥ 10 to 15</td><td>30 mg twice daily for 5 days [b]</td></tr><tr><td>> 15 to 23</td><td>45 mg twice daily for 5 days [b]</td></tr><tr><td>> 23 to 40</td><td>60 mg twice daily for 5 days [b]</td></tr><tr><td>> 40</td><td>75 mg twice daily for 5 days [b]</td></tr></table>
Those within significant renal impairment (CrCl 10 - 30 mL/min) should receive once daily dosing. Those with CrCl <10 ml/min should receive only a single dose on day 1.</td></tr>
<tr><td>Baloxavir marboxil

- 20 and 40 mg tablets</td><td>Oral
<u>or</u>
Other enteral routes</td><td>≥ 12 years old</td><td><table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td><40</td><td>Not eligible</td></tr><tr><td>≥40 < 80</td><td>40 mg on day 1 and day 4</td></tr><tr><td>≥ 80</td><td>80 mg on day 1 and day 4</td></tr></table></td></tr>
<tr><td rowspan="2">Low dose corticosteroids</td><td rowspan="2">Oral
<u>or</u>
Other enteral routes
<u>or</u>
Intravenous</td><td>Less than 36 weeks corrected gestational age</td><td>Hydrocortisone (IV)
0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days</td></tr>
<tr><td>≥0 month (≥36 weeks corrected gestational age)</td><td>Dexamethasone:
150 micrograms/kg (as base) once daily (max: 6 mg once daily) for 10 days (or until discharge if sooner)</td></tr>
</table>

[a] Public Health England advises that oseltamivir oral suspension should be reserved for children under the age of 1 year. Children over 1 year of age, those with swallowing difficulties, and those receiving nasogastric oseltamivir, should use capsules which can be opened and mixed into an appropriate sugary liquid.
[b] 10 days if immunocompromised

8.4 Appendix 4: Use of IMPs in pregnant and breastfeeding women

All trial drugs (except sotrovimab and baloxavir) have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The existing data related to each drug is summarised below. The potential inclusion of any pregnant women should be discussed with a consultant obstetrician (or obstetric physician) and all consent discussions should be documented in the medical records. Region-specific exclusions relating to pregnancy and breastfeeding are given in Appendix 6.

Corticosteroids

Prednisolone or, in women unable to take oral medicine, hydrocortisone or methylprednisolone are recommended instead of dexamethasone treatment in light of accumulating evidence that repeated doses of dexamethasone have deleterious effects on long-term neurodevelopment of the fetus.[44-46] While 90% dexamethasone is transferred transplacentally to the fetus, both hydrocortisone and prednisolone are converted by 11β-hydroxysteroid dehydrogenase to inactive glucocorticoids and considerably less drug is transferred to the fetus. Glucocorticoids can worsen maternal glycaemic control, so blood glucose should be checked and managed appropriately. Otherwise there is no convincing evidence that prednisolone use is associated with increased rates of adverse pregnancy outcomes when taken in the first trimester or later pregnancy.[47] Very low concentrations of prednisolone enter breastmilk. There is a paucity of data about pharmacological use of hydrocortisone, but it is likely that this is also safe when breastfeeding,[47] as also reviewed in the Lactmed database (www.ncbi.nlm.nih.gov/books/NBK501076/). Prednisolone (or hydrocortisone) should be used in breastfeeding women, in preference to dexamethasone.

Sotrovimab

There are no data from the use of sotrovimab in pregnant women. Since sotrovimab is a human immunoglobulin G animal studies have not been evaluated with respect to reproductive toxicity. No off-target binding was detected in a cross-reactive binding assay using a protein array enriched for human embryofetal proteins. Since sotrovimab is a human immunoglobulin G, it has the potential for placental transfer from the mother to the developing foetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing foetus is not known. Sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.

There are no data on the excretion of sotrovimab in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known. Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Baloxavir marboxil

There are no data from the use of baloxavir marboxil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Baloxavir treatment may be of particular benefit to pregnant women with influenza, as they are at increased risk of developing severe disease. Preclinical animal models of exposure in pregnancy do not provide evidence of adverse embryo-fetal effects at doses up to five and seven times the human therapeutic dose respectively. The risk of harm from baloxavir in pregnancy is likely to be low given the animal model data, together with the therapeutic target for baloxavir being a virus specific enzyme. It is unknown whether baloxavir marboxil or baloxavir are excreted in human milk, and baloxavir may be considered.

Oseltamivir

There are observational data on the use of oseltamivir in pregnant women including >1000 women exposed during the first trimester. These studies found no evidence of adverse embryo-fetal effects. Oseltamivir is currently used in pregnant women. Its use may also be considered in breastfeeding women: it is excreted in breast milk but at low concentrations that would be subtherapeutic dose to the infant.

8.5 Appendix 5: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

(i) Design and conduct of the Study in collaboration with the Trial Steering Committee;
(ii) Preparation of the Protocol and subsequent revisions.

Trial Steering Committee
The Trial Steering Committee (see below for list of members) is responsible for:

(i) Agreement of the final Protocol and the Data Analysis Plans;
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes;
(iii) Review and approval of study publications and substudy proposals;
(iv) Reviewing new studies that may be of relevance.

International Steering Committee
The International Steering Committee (see below for list of members) is responsible for:

(i) Reviewing progress of the study in sites outside the UK;
(ii) Review of study publications and substudy proposals;
(iii) Considering potential new therapies to be included in sites outside the UK;
(iv) Assisting RCC in selection of LCCs;
(v) Reviewing new studies that may be of relevance.

Data Monitoring Committee
The independent Data Monitoring Committee is responsible for:

(i) Reviewing unblinded interim analyses according to the Protocol;
(ii) Advising the Steering Committee if, in their view, the randomised data provide evidence that may warrant a change in the Protocol (e.g. modification or cessation of one or more of the treatment arms).

Central Coordinating Office (CCO)
The CCO is responsible for the overall coordination of the Study, including:

(i) Study planning and organisation of Steering Committee meetings;
(ii) Ensuring necessary regulatory and ethics committee approvals;
(iii) Development of Standard Operating Procedures and computer systems
(iv) Monitoring overall progress of the study;
(v) Provision of study materials to RCCs/LCCs;
(vi) Monitoring and reporting safety information in line with the Protocol and regulatory requirements;
(vii) Dealing with technical, medical and administrative queries from LCCs.

Regional Coordinating Centre (RCC)
The RCCs are responsible for:

(i) Ensuring necessary regulatory and ethics committee approvals;
(ii) Provision of study materials to LCCs;
(iii) Dealing with technical, medical and administrative queries from LCCs.

Local Clinical Centres (LCC)
The LCC lead investigator and LCC clinic staff are responsible for:

(i) Obtaining all relevant local permissions (assisted by the CCO);
(ii) All trial activities at the LCC, including appropriate training and supervision for clinical staff;
(iii) Conducting trial procedures at the LCC in line with all relevant local policies and procedures;
(iv) Dealing with enquiries from participants and others.

STEERING COMMITTEE

(Major organisational and policy decisions, and scientific advice; blinded to treatment allocation)

Chief Investigator	Peter Horby
Deputy Chief Investigator	Martin Landray
Clinical Trial Unit Lead	Richard Haynes
Co-investigators	Kenneth Baillie (Scotland Lead), Maya Buch, Saul Faust, Thomas Jaki, Katie Jeffery, Edmund Juszczak, Marian Knight, Wei Shen Lim, Marion Mafham, Alan Montgomery, Aparna Mukherjee, Andrew Mumford, Kathy Rowan, Guy Thwaites

International Committees

Asia	
Chair	Do Van Dung
Regional Lead Investigators	Guy Thwaites, Jeremy Day
Independent members:	Vietnam : Nguyen Ngo Quang, Prof. Binh Indonesia: Erlina Burhan, Bachti Alisjahbana Nepal: Janak Koirala, Sudha Basnet
Other members:	Evelyne Kestelyn, Buddha Basnyat, Pradip Gyanwali, Raph Hamers, Peter Horby
Africa	
Chair	TBC
Independent members:	Ghana: TBD South Africa: TBD
Other members:	John Amuasi, Peter Horby, Jeremy Nel

DATA MONITORING COMMITTEE

(Interim analyses and response to specific concerns)

Chair	Peter Sandercock
Members	Janet Darbyshire, David DeMets, Robert Fowler, David Lalloo, Mohammed Munavvar, Adilia Warris, Janet Wittes
Statisticians (non-voting)	Jonathan Emberson, Natalie Staplin

8.6 Appendix 6: Eligibility by Trial Region, Age, and Pregnancy/Breastfeeding Status

Condition	Comparison‡	UK	Nepal	India	Vietnam	Indonesia	South Africa	Ghana
COVID-19	Higher dose corticosteroids	✓ ≥18 years	✓ ≥18 years	X	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years*
	Sotrovimab	✓ ≥12 years	X	X	X	X	X	X
Influenza	Oseltamivir	✓ any age	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years
	Baloxavir	✓ ≥12 years	✓ ≥18 years*	✓ ≥18 years*	✓ ≥18 years*	✓ ≥18 Years*	✓ ≥18 years*	✓ ≥18 years*
	Low-dose corticosteroids	✓ any age	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years

‡ Each comparison is versus usual care alone without the relevant treatment
* Pregnant and breastfeeding women are excluded

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10 CONTACT DETAILS

Website: www.recoverytrial.net
(copies of this protocol and related forms and information can be downloaded)

RECOVERY Central Coordinating Office:
Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF
United Kingdom

Tel: +44 (0)800 1385451
E-mail: recoverytrial@ndph.ox.ac.uk

RECOVERY Vietnam:
Oxford University Clinical Research Unit, Centre for Tropical Medicine, 764 Vo Van Kiet, District 5, Ho Chi Minh City, Vietnam
Tel: +84 8 39241983
E-mail: recoverytrial@oucru.org

RECOVERY Indonesia:
Eijkman Oxford Clinical Research Unit (EOCRU), Eijkman Institute for Molecular Biology
Jl. P. Diponegoro No. 69, Jakarta-Indonesia 10430
Tel: +62 21 31900971

RECOVERY Nepal:
Clinical Trial Unit, Oxford University Clinical Research Unit-Nepal, Patan Academy of Health Sciences, Kathmandu, Nepal
Tel : +977 01 5522295

RECOVERY Ghana:
Kumasi Center for Collaborative Research in Tropical Medicine
KNUST, Southend Asuogya Road, GPS: AK-312-1059, Kumasi, Ghana
Tel: +233 278 364 389

RECOVERY South Africa:
Wits Health Consortium, 31 Princess of Wales Terrace, Parktown, Johannesburg, South Africa
Tel: +27 11 274 9200

RECOVERY India:
Indian Council of Medical Research, Division of Epidemiology and Communicable Diseases, Ramalingaswami Bhavan, Ansari Nagar, ICMR-110029
Tel: +91 996 840 8999

To RANDOMISE a patient, visit: www.recoverytrial.net

Appendix 2: RECOVERY Trial Statistical Analysis Plan V5

RECOVERY

Statistical Analysis Plan

Version 5.0

Date: 25 June 2024

Aligned with protocol version: 27.0, 13 September 2023

IRAS no: 281712
REC ref: EE/20/0101
ISRCTN: 50189673
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Nuffield Department of
POPULATION HEALTH

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Abbreviations

ADaM	Analysis Data Model
AE	Adverse event
CAP	Community-acquired pneumonia
CDISC	The Clinical Data Interchange Standards Consortium
CI	Confidence interval
COVID	Coronavirus-induced disease
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
DMC	Data Monitoring Committee
ECMO	Extra Corporeal Membrane Oxygenation
eCRF	Electronic case report form
ICD	International Classification of Diseases
ICNARC	Intensive Care National Audit and Research Centre
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
OPCS-4	National Health Service OPCS Classification of Interventions and Procedures version 4
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S/F_{94} ratio	Ratio of peripheral oxygen saturation to fractional inspired oxygen concentration when peripheral oxygen saturation at or below 94%
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TSC	Trial Steering Committee

List of authors and reviewers (up to and including SAP version 1.1)

Authors

Dr Louise Linsell, Lead Trial Statistician, Nuffield Department of Population Health (NDPH), University of Oxford

Jennifer Bell, Trial Statistician, NDPH, University of Oxford

Reviewers

Professor Jonathan Emberson, Data Monitoring Committee (DMC) Statistician, NDPH, University of Oxford (prior to unblinded interim analysis of trial outcomes)

Professor Richard Haynes, Clinical Coordinator, NDPH, University of Oxford

Professor Peter Horby, Chief Investigator (CI), Nuffield Department of Medicine, University of Oxford

Professor Thomas Jaki, TSC Member, Department of Mathematics and Statistics, Lancaster University

Associate Professor Edmund Juszczak, TSC Member, NDPH, University of Oxford (until 6 July 2020)

Professor Martin Landray, Deputy CI, NDPH, University of Oxford

Professor Alan Montgomery, TSC Member, Nottingham Clinical Trials Unit, University of Nottingham

Dr Natalie Staplin, DMC Statistician, NDPH, University of Oxford (prior to unblinded interim analysis of trial outcomes)

List of authors and reviewers (version 2.0 onwards)

Professor Edmund Juszczak, TSC Member (University of Nottingham from 6 July 2020)

Professor Alan Montgomery (University of Nottingham), TSC Member

Professor Thomas Jaki (University of Cambridge) co-investigator and TSC Member

Enti Spata, Trial Statistician, NDPH, University of Oxford (until 4 March 2022)

Professor Richard Haynes, Clinical Coordinator, NDPH, University of Oxford

Professor Martin Landray, Deputy CI, NDPH, University of Oxford

Professor Peter Horby, CI, Nuffield Department of Medicine, University of Oxford

Leon Peto, Clinical Coordinator, NDPH, University of Oxford

Roles and responsibilities

Trial Statisticians

Until 30 September 2020: Dr Louise Linsell and Jennifer Bell (NDPH, University of Oxford)

Role: To develop the statistical analysis plan (blinded to trial allocation) and conduct the final comparative analyses for Lopinavir-Ritonavir¸ Corticosteroid (dexamethasone) and Hydroxychloroquine (main randomisation part A).

From 1 October 2020 until 4 March 2022: Enti Spata (NDPH, University of Oxford)

Role: To develop the statistical analysis plan (blinded to trial allocation) and conduct the final comparative analyses for all other treatment arms in this period.

From 1 April 2022: Professor Jonathan Emberson and Dr Natalie Staplin (NDPH, University of Oxford)

Role: To develop the statistical analysis plan (only for those aspects to which they are currently blinded) and to conduct the final comparative analyses on completion.

Data Monitoring Committee (DMC) Statistician (non-voting)

Professor Jonathan Emberson (NDPH, University of Oxford)

Until 13 March 2024: Natalie Staplin (NDPH, University of Oxford)

Role: To conduct regular interim analyses for the DMC. Other contributions are restricted until completion of each comparison.

Statisticians on the Trial Steering Committee (TSC)

Professor Thomas Jaki (University of Cambridge)

From 13 March 2024: Natalie Staplin (NDPH, University of Oxford)

Until 25 June 2024: Professor Alan Montgomery (University of Nottingham) and Professor Edmund Juszczak (University of Nottingham)

Role: Major organisational and policy decisions, and scientific advice; blinded to treatment allocation.

Trial IT systems & Programmers

Andy King, David Murray, Richard Welsh (NDPH, University of Oxford)

Role: To generate and prepare reports monitoring the randomisation schedule. To supply data snapshots for interim and final analysis. Responsibility for randomisation system, clinical databases and related activities.

Bob Goodenough (NDPH, University of Oxford)

Role: Validation of IT systems

Dr Will Stevens, Karl Wallendszus (NDPH, University of Oxford)

Role: To produce analysis-ready datasets according to CDISC standards.

1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the multicentre randomised controlled trial RECOVERY (ISRCTN50189673) to investigate multiple treatments on major outcomes in patients hospitalised with COVID-19, influenza, or community-acquired pneumonia related to other pathogens.

The results reported in these papers will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan (SAP).[1] Any subsequent analyses of a more exploratory nature will not be bound by this strategy.

Suggestions for subsequent analyses by oversight committees, journal editors or referees, will be considered carefully in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and justified in the final report. The analysis will be carried out by identified, appropriately qualified and experienced statisticians, who will ensure the integrity of the data during their processing.

This SAP is based on multiple versions of the protocol. All regulatory documents can be found in the RECOVERY trial directory: https://www.recoverytrial.net/for-site-staff/site-set-up-1/regulatory-documents.

SAP versions 1.0 & 1.1 applied to the first three principal comparisons (hydroxychloroquine, dexamethasone, and lopinavir-ritonavir versus no additional treatment respectively), for which data matured in the first UK wave of the pandemic. However, due to its later introduction, enrolment of patients in the azithromycin arm was much slower. Over time, factorial randomisations and a second randomisation have been added, introducing new treatment arms including convalescent plasma, tocilizumab, synthetic neutralizing antibodies, and aspirin. Version 2.0 of the SAP was produced in response to these changes, combined with the fact that use of corticosteroids (one of the original treatment arms) is now the usual standard of care for many patients. SAP version 3.0 included revisions for REGEN-COV2 (casirivimab+imdevimab), early phase assessments, and 6 month follow-up. SAP version 4.0 included additional COVID-19 comparisons (sotrovimab, molnupiravir, and Paxlovid), introduced influenza comparisons (baloxavir, oseltamivir, and corticosteroids), added virology outcomes, and modified 6 month follow-up analyses.

SAP version 5.0 introduces a new corticosteroid comparison for patients with community-acquired pneumonia (CAP) not related to SARS-CoV-2 or influenza, updates the recruitment status of existing comparisons, and finalises the analysis plan for SARS-CoV-2 antivirals (including monoclonal antibodies).

2 BACKGROUND INFORMATION

2.1 Rationale

In early 2020, as the protocol was being developed, there were no approved treatments for COVID-19. The aim of the trial was to provide reliable evidence on the efficacy of candidate therapies (including re-purposed and novel drugs) for suspected or confirmed COVID-19 infection on major outcomes in hospitalised adult patients receiving standard care.

In late 2021, the protocol was extended to include evaluation of potential treatments for influenza occurring in isolation or in combination with COVID-19 (protocol version 19 onwards) and this was approved by MHRA and the ethics committee. However, at the request of the RECOVERY funder, introduction of the influenza comparisons was delayed. These opened at a small number of sites in early 2023, and more widely during winter 2023/24. The CAP comparison was approved in November 2023 and introduced in January 2024. At the time of finalising the current version of the SAP (version 5.0), the enrolment of patients with COVID-19 has closed (on 31 March 2024) but the trial remains open to patients with either pneumonia due to influenza or CAP

2.2 Objectives of the trial

2.2.1 *Primary and secondary objectives for COVID-19 and CAP comparisons*

The primary objective is to provide reliable estimates of the effect of study treatments on all-cause mortality within 28 days of the relevant randomisation. The secondary objectives are to investigate the effect of study treatments on the duration of hospital stay and on the combined endpoint of use of invasive mechanical ventilation (including Extra Corporal Membrane Oxygenation [ECMO]) or death.

2.2.2 *Primary and secondary objectives for influenza comparisons*

The co-primary objectives are to provide reliable estimates of the effect of study treatments on (a) all-cause mortality within 28 days of the relevant randomisation and (b) the duration of hospital stay. The secondary objective is to investigate the effect of study treatments on the combined endpoint of use of invasive mechanical ventilation (including Extra Corporal Membrane Oxygenation [ECMO]) or death.

2.3 Trial design

This is a multi-centre, multi-arm, adaptive, open label, randomised controlled trial with three possible stages of randomisation, as described below. The trial is designed with streamlined processes in order to facilitate rapid large-scale recruitment with minimal data collection.

2.4 Eligibility

2.4.1 *Inclusion criteria*

Patients are eligible for the trial if all of the following are true:

- Hospitalised
- Pneumonia syndrome
- One of the following diagnoses:
    - Confirmed SARS-CoV-2 infection (closed on 31 March 2024)
    - Confirmed influenza A or B infection
    - Community-acquired pneumonia with planned antibiotic treatment (without suspected or confirmed SARS-COV-2, influenza, pulmonary tuberculosis or *Pneumocystis jirovecii* infection)
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial.

2.4.2 *Exclusion criteria*

If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining arms. Details of specific contraindications and cautions for each treatment are listed in Appendix 2 of the protocol.

2.4.3 *Randomisation on more than one occasion*

From protocol version 21.1, patients who have been previously recruited into RECOVERY are eligible to be recruited again as long as their previous randomisation was >6 months ago. Patients will not be recruited into the same randomised comparison on more than one occasion, regardless of the time interval.

2.5 Treatments

All patients will receive standard management for the participating hospital. The main randomisation will be between the following treatment arms (although not all arms may be available at any one time). The doses listed are for adults; paediatric dosing is described in the protocol.

COVID-19 Comparisons

2.5.1 *Main randomisation part A (enrolment closed):*

- **No additional treatment**
- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days. [Introduced in protocol version 1.0; **enrolment closed** 29 June 2020]
- **Corticosteroid** in the form of dexamethasone**,** administered as an oral liquid or intravenous preparation 6 mg once daily for 10 days. In pregnancy, prednisolone 40

mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead. [Introduced in protocol version 1.0; **enrolment closed to adults** 8 June 2020]

- **Hydroxychloroquine** by mouth for 10 days (4 doses in first 24 hours and 1 dose every 12 hours for 9 days). [Introduced in protocol version 2.0; **enrolment closed** 5 June 2020]
- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for a total of 10 days. [Introduced in protocol version 3.0; **enrolment closed** 27 November 2020]
- **Colchicine** by mouth for 10 days (1.5 mg in first 12 hours then 0.5 mg twice daily). [Introduced in protocol version 12.0; **enrolment closed** 5 March 2021.]
- **Dimethyl fumarate** 120 mg every 12 hours for 4 doses followed by 240 mg every 12 hours by mouth for 8 days (10 days in total). [Introduced in protocol version 14.0 as Early Phase Assessment; **enrolment closed** 19 November 2021.]

2.5.2 *Main randomisation part B (enrolment closed):*

In a factorial design, eligible patients may be randomised to the arms below. The doses listed are for adults; paediatric dosing is described in the protocol.

- **No additional treatment**
- **Convalescent plasma** Single unit of ABO compatible convalescent plasma (275ml ± 75ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-hour interval between 1st and 2nd units). ABO identical plasma is preferred if available. The second transfusion should not be given if patient has a suspected serious adverse reaction during or after the first transfusion. [Introduced in protocol version 6.0; **enrolment closed** 15 January 2021]
- **Synthetic neutralising antibodies** (REGEN-COV2; adults and children aged ≥12 years only - children who weigh <40kg will also not be eligible for this treatment). A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250ml 0.9% saline infused intravenously over 60 minutes ± 15 minutes as soon as possible after randomisation. [Introduced in protocol version 9.1; **enrolment closed** 22 May 2021]

2.5.3 *Main randomisation part C (enrolment closed):*

In a factorial design, eligible patients may be randomised to the arms below. The dose listed is for adults; children are excluded from this comparison.

- **No additional treatment**
- **Aspirin** 150 mg by mouth (or nasogastric tube) or per rectum once daily until discharge. [Introduced in protocol version 10.1; **enrolment closed** 21 March 2021]

2.5.4 *Main randomisation part D (enrolment closed):*

In a factorial design, eligible patients may be randomised to the arms below. The dose listed is for adults; children <2 years old or with PIMS-TS are excluded from this comparison.

- **No additional treatment**
- **Baricitinib** 4 mg by mouth (or nasogastric tube) once daily for 10 days. [Introduced in protocol version 13.0; **enrolment closed** 29 December 2021]

2.5.5 *Main randomisation part E (enrolment closed):*

In a factorial design, eligible patients may be randomised to the arms below. The dose listed is for adults; children <18 years old are excluded from this comparison.

- **No additional treatment**
- **High-dose corticosteroids** dexamethasone 20 mg once daily for 5 days, followed by dexamethasone 10 mg once daily for 5 days. [Introduced outside UK in protocol version 13.0 and within UK in protocol version 20.0; eligibility criteria modified in protocol version 25.0; **enrolment closed** on 31 March 2024]

On 11 May 2022, the RECOVERY DMC 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.*" Consequently, on 13 May 2022, recruitment to this comparison was closed for patients on no oxygen or simple oxygen only. The protocol (version 25.0) was updated accordingly. The comparison closed for all patients on 31 March 2024.

2.5.6 *Main randomisation part F (enrolment closed):*

In a factorial design, eligible patients (with or without influenza infection) may be randomised to the arms below. The dose listed is for adults; children <18 years old are excluded from this comparison.

- **No additional treatment**
- **Empagliflozin** 10 mg once daily for 28 days. [Introduced in protocol version 16.1; **enrolment closed** 7 March 2023]

2.5.7 *Main randomisation part J (enrolment closed):*

In a factorial design, eligible patients (with or without influenza infection) may be randomised to the arms below. The dose listed is for adults; children <12 years old are excluded from this comparison.

- **No additional treatment**

- **Sotrovimab 1000 mg once** as soon as possible after randomisation. [Introduced in protocol version 21.1; **enrolment closed** 31 March 2024]

2.5.8 *Main randomisation part K (enrolment closed):*

In a factorial design, eligible patients (with or without influenza infection) may be randomised to the arms below. The dose listed is for adults; children <18 years old are excluded from this comparison.

- **No additional treatment**
- **Molnupiravir 800 mg twice daily** for 5 days by mouth. [Introduced in protocol version 21.1; **enrolment closed** 24 May 2023]

2.5.9 *Main randomisation part L (enrolment closed):*

In a factorial design, eligible patients (with or without influenza infection) may be randomised to the arms below. The dose listed is for adults; children <18 years old are excluded from this comparison.

- **No additional treatment**
- **Paxlovid (nirmatrelvir/ritonavir) 300/100 mg twice daily** for 5 days by mouth. [Introduced in protocol version 23.1; **enrolment closed** 24 May 2023]

2.5.10 *Second randomisation for adults with progressive COVID-19 (enrolment closed)*

Patients enrolled in the main RECOVERY trial and with clinical evidence of a hyper-inflammatory state may be considered for a second randomisation if they meet the following criteria:

- Randomised into the main RECOVERY trial no more than 21 days ago
- Clinical evidence of progressive COVID-19:
  - oxygen saturation <92% on room air or requiring oxygen; and
  - C-reactive protein (CRP) ≥75 mg/L
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in this aspect of the RECOVERY trial

Eligible participants may be randomised between the following treatment arms:

- **No additional treatment**
- **Tocilizumab** by intravenous infusion with the dose determined by body weight. [Introduced in protocol version 4.0; **enrolment closed** 24 January 2021]

Influenza Comparisons

2.5.11 *Main randomisation part G:*

In a factorial design, eligible patients (with or without SARS-CoV-2 co-infection) may be randomised to the arms below. The dose listed is for adults; children <12 years old are excluded from this comparison.

- **No additional treatment**
- **Baloxavir marboxil 40mg (or 80mg if weight ≥80kg) once daily** by mouth or nasogastic tube to be given on day 1 and day 4. [Introduced in protocol version 19.1; **enrolment ongoing**]

2.5.12 *Main randomisation part H:*

In a factorial design, eligible patients (with or without SARS-CoV-2 co-infection) may be randomised to the arms below.

- **No additional treatment**
- **Oseltamivir 75mg twice daily** by mouth or nasogastric tube for five days (If participant is discharged before course is complete, the participant should be provided with medication to complete the course at home. Course can be extended to 10 days for immunosuppressed patients at the managing clinician's discretion). [Introduced in protocol version 19.1; **enrolment ongoing**]

2.5.13 *Main randomisation part I:*

In a factorial design, eligible patients (without suspected or confirmed SARS-CoV-2 infection and with clinical evidence of hypoxia) may be randomised to the arms below.

- **No additional treatment**
- Corticosteroids: **Dexamethasone 6mg once daily given** orally or intravenously for ten days or until discharge (whichever happens earliest). [Introduced in protocol version 19.1; **enrolment ongoing**]

Community-Acquired Pneumonia (CAP) Comparison

2.5.14 *Main randomisation part M:*

In a factorial design, eligible patients (with planned antibiotic treatment, and without suspected or confirmed SARS-CoV-2, influenza, pulmonary tuberculosis, or *Pneumocystis jirovecii* infection) may be randomised to the arms below.

- **No additional treatment**
- Corticosteroids: **Dexamethasone 6mg once daily given** orally or intravenously for ten days or until discharge (whichever happens earliest). [Introduced in protocol version 27.0; **enrolment ongoing**]

2.6 Definitions of outcomes

Outcomes will be assessed at 28 days after the relevant randomisation. (Analyses of 6 month are described in section 10.)

2.6.1 *Primary outcome*

For COVID-19 and CAP comparisons: Mortality (all-cause)
For influenza comparisons: Co-primary outcomes of Mortality (all-cause) and Time to discharge alive from hospital

2.6.2 *Secondary clinical outcomes*

- Time to discharge alive from hospital (for COVID-19 and CAP comparisons)
- Use of invasive mechanical ventilation (including Extra Corporal Membrane Oxygenation [ECMO]) or death (among patients not on invasive mechanical ventilation or ECMO at time of randomisation)

2.6.3 *Subsidiary clinical outcomes*

- Use of ventilation (overall and by type) among patients not on ventilation (of any type) at time of randomisation
- Duration of invasive mechanical ventilation among patients on invasive mechanical ventilation at time of randomisation (defined as time to successful cessation of invasive mechanical ventilation: see section 5.1.2.2)
- Use of renal dialysis or haemofiltration (among patients not on renal dialysis or haemofiltration at time of randomisation)
- Thrombotic events (overall and by type; introduced in Protocol version 10.1)

2.6.4 *Virological outcomes*

- SARS-CoV-2 and influenza RNA levels in the nasopharynx (parts G, H, I, J, K and L only)
- SARS-CoV-2 and influenza viral resistance markers (parts J, K and L, and parts G and H, respectively)

2.6.5 *Safety outcomes*

- Cause-specific mortality (COVID-19, influenza, CAP, other infection, cardiac, stroke, other vascular, cancer, other medical, external, unknown cause)
- Major cardiac arrhythmia (recorded on follow-up forms completed from 12 May 2020 onwards)
- Major bleeding (overall and by type; introduced in Protocol version 10.1)
- Early safety of antibody-based therapy (sudden worsening in respiratory status; severe allergic reaction; temperature >39°C or ≥2°C rise since randomisation; sudden hypotension; clinical haemolysis; and thrombotic events within the first 72 hours; (Main randomisation part B only)
- Non-coronavirus infection (overall and by site and putative organism [virus, bacteria, fungus, other]; introduced in Protocol version 14.0)
- Metabolic, kidney and liver complications:
    - severe hyperglycaemia: overall and by type (ketoacidosis, hyperosmolar hyperglycaemic state, hyperglycaemia requiring new use of insulin)
    - severe hypoglycaemia

- acute kidney injury (ratio of post-randomisation peak creatinine to baseline value >1.5 or new use of renal dialysis/haemofiltration; introduced in protocol V16.1)
- liver dysfunction: peak alanine (or aspartate) transaminase and possible liver injury (defined as ALT >3x ULN plus bilirubin >2x ULN; introduced in protocol V23.1).

- Seizures (introduced in protocol V23.1)
- Infusion reactions to sotrovimab (Main randomisation part J only; introduced in protocol V21.1)

2.6.6 *Detailed derivation of outcomes*

The detailed derivation of outcomes included in statistical analysis is described separately in a data derivation document and included in the Study Data Reviewer's Guide.

2.7 Hypothesis framework

For each of the primary, secondary and subsidiary outcomes, the null hypothesis will be that there is no true difference in effect between any of the treatment arms.

2.8 Sample size

The larger the number randomised, the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with moderate disease and a few thousand with severe disease. Some indicative sample sizes and projected recruitment will be estimated using emerging data for several different scenarios.

The TSC will monitor recruitment and primary event rate (in active and control arms combined, i.e. blind to knowledge of the unblinded results) for ongoing comparisons. In general, the TSC will continue recruitment until such time as there are sufficient patients enrolled in the comparison to provide at least 90% power at 2P=0.01 to detect a clinically relevant proportional reduction (typically one-fifth) in the primary outcome.

2.9 Randomisation

Eligible patients will be randomised using a 24/7 secure central web-based randomisation system, developed and hosted within NDPH, University of Oxford. Users of the system will have no insight into the next allocation, given that simple randomisation is being used. If a patient is randomised inadvertently more than once during the same hospital admission, the first allocation will be used.

The implementation of the randomisation procedure will be monitored by the Senior Trials Programmer, and the TSC notified if an error in the randomisation process is identified.

COVID-19 treatment comparisons

2.9.1 *Main randomisation part A (enrolment closed)*

Simple randomisation will be used to allocate participants to one of the following treatment arms (in addition to usual care), which is subject to change:

- No additional treatment
- Lopinavir-Ritonavir [Introduced in protocol version 1.0; **enrolment closed** 29 June 2020]
- Corticosteroid [Introduced in protocol version 1.0; **enrolment closed to adults** 8 June 2020]
- Hydroxychloroquine [Introduced in protocol version 2.0; **enrolment closed** 5 June 2020]
- Azithromycin [Introduced in protocol version 3.0; **enrolment closed** 27 November 2020]
- Colchicine [Introduced in protocol version 11.1; **enrolment closed** 5 March 2021]
- Dimethyl fumarate [Introduced in protocol version 14.0; **enrolment closed** 19 November 2021]

The randomisation programme will allocated patients in a ratio of 2:1 between the no additional treatment arm and each of the other arms that are not contra-indicated and are available when multiple arms were included in the protocol. Hence if all 4 active treatment arms are available, then the randomisation will be in the ratio 2:1:1:1:1. If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining arms (in a 2:1:1:1, 2:1:1 or 2:1 ratio). Since the closure of the azithromycin comparison, all comparisons in part A have used a 1:1 ratio.

2.9.2 *Main randomisation part B (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Convalescent plasma [Introduced in protocol version 6.0; **enrolment closed** 15 January 2021]
- Synthetic neutralising antibodies [Introduced in protocol version 9.1; **enrolment closed** 22 May 2021]

If the active treatment is not available at the hospital, the patient does not consent to receive convalescent plasma, or is believed, by the attending clinician, to be contraindicated for the specific patient, then this fact will be recorded via the web-based form and the patient will be excluded from the relevant arm in Randomisation part B.

2.9.3 *Main randomisation part C (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment

- Aspirin [Introduced in protocol version 10.1; **enrolment closed** 21 March 2021]

2.9.4 *Main randomisation part D (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Baricitinib [Introduced in protocol version 13.0; **enrolment closed** 29 December 2021]

2.9.5 *Main randomisation part E (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- High-dose corticosteroids [Introduced outside UK in protocol version 13.0 and within UK in protocol version 20.0; eligibility criteria modified in protocol version 25.0; **enrolment closed** 31 March 2024]

2.9.6 *Main randomisation part F (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Empagliflozin [Introduced in protocol version 16.1; **enrolment closed** 7 March 2023]

Note: From protocol version 7.0 onwards, randomisation is permitted in part B of main randomisation without randomisation in part A. From protocol version 10.1 onwards, randomisation is permitted in any combination of parts (A, B, C, etc).

2.9.7 *Main randomisation part J (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms:

- No additional treatment
- Sotrovimab [Introduced in protocol version 21.1; **enrolment closed** 31 March 2024]

2.9.8 *Main randomisation part K (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Molnupiravir [Introduced in protocol version 21.1; **enrolment closed** 24 May 2023]

2.9.9 *Main randomisation part L (enrolment closed)*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Paxlovid [Introduced in protocol version 23.1; **enrolment closed** 24 May 2023]

2.9.10 *Second randomisation for adults with progressive COVID-19 (enrolment closed)*

Eligible participants will be randomised using simple randomisation with an allocation ratio 1:1 between the following arms, which is subject to change:

- No additional treatment
- Tocilizumab [Introduced in protocol version 4.0; **enrolment closed** 24 January 2021]

Influenza treatment comparisons

2.9.11 *Main randomisation part G*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms:

- No additional treatment
- Baloxavir [Introduced in protocol version 19.1; **enrolment ongoing**]

2.9.12 *Main randomisation part H*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Oseltamivir [Introduced in protocol version 19.1; **enrolment ongoing**]

2.9.13 *Main randomisation part I*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment
- Corticosteroids [Introduced in protocol version 19.1; **enrolment ongoing**]

CAP treatment comparisons

2.9.14 *Main randomisation part M*

In a factorial design, eligible patients will be randomised simultaneously using simple randomisation with allocation ratio 1:1 to one of the following arms, which is subject to change:

- No additional treatment

- Corticosteroids [Introduced in protocol version 27.0; **enrolment ongoing**]

2.10 Blinding

This is an open-label study. However, while the study is in progress, access to tabular results of study outcomes by treatment allocation will not be available to the research team, CIs, trial statisticians, clinical teams, or members of the TSC (unless the DMC advises otherwise). The DMC and DMC statisticians will be unblinded.

2.11 Data collection schedule

Baseline and 28-day outcome information will be collected on trial-specific electronic case report forms (eCRFs) and entered into a web-based IT system by a member of the hospital or research staff. Follow-up information will be collected on all study participants, irrespective of whether they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means, including routine healthcare systems and registries.

All randomised participants will be followed up until death or 6 months post-randomisation to the main trial (whichever is sooner). NHS England and equivalent organisations in the devolved nations will supply data fields relevant to trial baseline and outcome measures to NDPH, University of Oxford on a regular basis, for participants enrolled into the trial. This will be combined with the trial-specific data collected via the web-based IT system and adjudicated internally.

Longer term (up to 10 years) follow-up of UK participants only will be sought through linkage to electronic healthcare records and medical databases including those held by NHS England, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

2.12 Data monitoring

During the study all study data will be supplied in strict confidence to the independent DMC for independent assessment and evaluation. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

The DMC has been requested to determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the TSC who will make the results available to the public and amend the trial arms accordingly.

The Data Monitoring Committee has determined that, in general, to consider recommending stopping a treatment early for benefit would require at least a 3 to 3·5 standard error reduction in mortality. Examinations of the data at every 10% (or even 5%) of the total data would lead to only a marginal increase in the overall type I error rate. Hence, multiple reviews by the Data Monitoring Committee have no material impact on the final analysis.

Further details about the role and membership of the independent Data Monitoring Committee are provided in the protocol.

2.13 Trial reporting

The trial will be reported according to the principles of the CONSORT statements.[2, 3, 4]

3 ANALYSIS POPULATIONS

3.1 Population definitions

The intention to treat (ITT) population will be all participants randomised, irrespective of treatment received. This ITT population will be used for analysis of efficacy and safety data. For interim analyses, baseline data will be reported for all participants with data available and outcome data will be reported for all participants who have died, been discharged from hospital, or reached day 28 after the first randomisation.

4 DESCRIPTIVE ANALYSES

4.1 Participant throughput

The flow of participants through the trial will be summarised for each separate pairwise comparison using a CONSORT diagram. The flow diagram will show the contribution of participants from each of the paths (from each of the parts of the main randomisation and from the second randomisation), where applicable. The flow diagrams will describe the numbers of participants randomly allocated, who received allocation, withdrew consent, and included in the ITT analysis population. The flow diagrams for arms in the main randomisation will also report the number of participants who underwent the second randomisation (where applicable).

4.2 Baseline comparability of randomised groups

The following characteristics will be described separately for patients randomised to each main comparison (for each separate pairwise comparison of active treatment with the no additional treatment arm), and separately for the first and second randomisation.

COVID-19 treatment comparisons

4.2.1 Main randomisation – COVID-19 comparisons (parts A, B, C, D, E, F, J, K, L)

- Age at randomisation
- Sex
- Ethnicity
- Region (UK, non-UK)
- Time since symptom onset
- Time since hospitalisation
- Current respiratory support (none, oxygen only, non-invasive ventilation, invasive mechanical ventilation [including ECMO])

- Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment)
- SARS-CoV-2 test result
- If female, known to be pregnant
- Use of systemic corticosteroid (including those allocated to corticosteroid in parts A or I)
- Use of other relevant treatments (e.g. remdesivir, interleukin-6 antagonist, monoclonal anti-SARS-CoV-2 neutralising antibody, baricitinib, molnupiravir, paxlovid)
- Prior SARS-CoV-2 vaccination
- For parts B, J, K and L only, serum anti-SARS-CoV-2 antibody status (anti-S and anti-N)
- For parts J, K and L only, serum SARS-CoV-2 antigen concentration
- For parts J, K and L only, nasal/oropharyngeal SARS-CoV-2 RNA level
- Laboratory markers (introduced in protocol v9.1):
  - C-reactive protein
  - Estimated glomerular filtration rate (calculated using the CKD-EPI formula)
  - D-dimer

4.2.2 Second randomisation

In addition to the above:

- Current respiratory support
- Latest oxygen saturation measurement
- Latest C-reactive protein
- Latest ferritin
- Latest estimated glomerular filtration rate (calculated using the CKD-EPI formula)
- Allocation in main randomisation parts A, B, C, D and E
- Interval between first and second randomisation

The number and percentage will be presented for binary and categorical variables. The mean and standard deviation or the median and the interquartile range will be presented for continuous variables.

Influenza treatment comparisons

4.2.3 Main randomisation – influenza comparisons (parts G, H, I)

- Age at randomisation
- Sex
- Ethnicity
- Region (UK, EU, Asia, Africa)
- Time since symptoms onset
- Time since hospitalisation
- Current respiratory support (none, oxygen only, non-invasive ventilation, invasive mechanical ventilation [including ECMO])

- Pneumonia severity (CURB-65 score)[a]
- Presence of unilateral/bilateral lung consolidation on imaging
- Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment)
- Influenza test result
- If female, known to be pregnant
- Use of systemic corticosteroid (including those allocated to corticosteroid in part I)
- Use of other relevant treatments (e.g. oseltamivir, baloxavir)
- Prior influenza vaccination (within the past 12 months)
- Laboratory markers:
  - C-reactive protein
  - Procalcitonin
  - Estimated glomerular filtration rate (calculated using the CKD-EPI formula)

CAP treatment comparisons

4.2.4 Main randomisation – CAP comparisons (part M)

- Age at randomisation
- Sex
- Ethnicity
- Region (UK, EU, Asia, Africa)
- Time since symptoms onset
- Time since hospitalisation
- Current respiratory support (none, oxygen only, non-invasive ventilation, invasive mechanical ventilation [including ECMO])
- Pneumonia severity (CURB-65 score)[a]
- Presence of unilateral/bilateral lung consolidation on imaging
- Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment)
- Influenza test result
- If female, known to be pregnant
- Use of systemic corticosteroid (including those allocated to corticosteroid in part I)
- Use of other relevant treatments (e.g. oseltamivir, baloxavir)
- Laboratory markers:
  - C-reactive protein
  - Procalcitonin

[a] The CURB-65 Score (Lim WS et al. Thorax 2003:58:377–82) has been validated for predicting mortality in community-acquired pneumonia and is recommended by the British Thoracic Society. Each risk factor scores one point, for a maximum score of 5:

- Confusion of new onset (defined for this study as presence of new or worsened confusion)
- Blood Urea nitrogen >7 mmol/L (19 mg/dL)
- Respiratory rate of ≥30 breaths per minute
- Blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg
- Age ≥65 years

- Estimated glomerular filtration rate (calculated using the CKD-EPI formula)

4.3 Completeness of follow-up

All reasonable efforts will be taken to minimise loss to follow-up, which is expected to be minimal as data collection for primary and secondary outcomes using trial-specific eCRFs is combined with linkage to routine clinical data on study outcomes from NHS England, ICNARC, and similar organisations in the devolved nations.

The number and percentage of participants with follow-up information at day 28 after the relevant randomisation will be reported. Data will be shown for each of the following: all-cause mortality, hospital discharge status, ventilation status, and will be shown for each randomised group for the main and second randomisation separately.

4.4 Adherence to treatment

The number and proportion of patients who did not receive the treatment they were allocated to will be reported. If any other trial treatment options were known to be received, instead of or in addition to, the allocated treatment during the 28-day follow-up period after the first randomisation, these will be collected and reported. Details on the number of days (or doses) of treatment received will be reported for all trial treatments received where available.

5 COMPARATIVE ANALYSES AT 28 DAYS

For all outcomes, the primary analysis will be performed on the intention to treat (ITT) population at 28 days after randomisation. (Additional details specific to the comparison of REGEN-COV2 vs. usual care [part B] are provided in Appendix I and for the comparison of sotrovimab vs. usual care [part J], molnupiravir vs. usual care [part K], and Paxlovid vs. usual care [part L] are provided in Appendix II.)

Pairwise comparisons will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation part A, main randomisation part B, main randomisation part C, etc.). Since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a given comparison if, at the point of their randomisation, they *could* alternatively have been randomised to the active treatment of interest (i.e. the active treatment was available at the time and it was not contra-indicated). The same applies to treatment arms added at a later stage; they will only be compared to those patients recruited concurrently.

5.1 Main randomisation (all parts)

In each component of the factorial design, the main effects of treatments evaluated in a particular part will be presented and tested across all arms in the other main randomisation parts combined, as described in this section. (Assessments of whether the effects of treatments in the part in question vary depending on other randomised treatments are described in section 5.6).

5.1.1 *Primary and secondary outcome*

5.1.1.1 Mortality

Mortality (all-cause) will be summarised with counts and percentages by randomised comparison group. A time-to-event analysis will be conducted using Cox proportional hazards regression, adjusted for baseline characteristics as described in Section 5.4, to estimate the hazard ratio, 95% confidence interval and corresponding p-value for each treatment group versus the no additional treatment group. Kaplan-Meier estimates for the time to event will also be plotted. For the primary outcome, discharge alive before the relevant time period (28 days after randomisation) will be assumed as absence of the event (unless there is additional data confirming otherwise).

5.1.1.2 Time to discharge alive from hospital

A time-to-event analysis will be used to compare each treatment group with the no additional treatment group. As described for the primary outcome, the adjusted hazard ratio and its confidence interval will be estimated using Cox proportional hazards regression, adjusted for baseline characteristics as described in Section 5.4, to estimate the hazard ratio, 95% confidence interval and corresponding p-value for each treatment group versus the no additional treatment group. Kaplan-Meier curves will be drawn. Patients who die in hospital will be censored after 28 days after randomisation. This gives an unbiased estimate of the recovery rate and comparable estimates to the competing risks approach in the absence of other censoring (which is expected to be very minimal).[5]

5.1.1.3 Use of invasive mechanical ventilation (including ECMO) or death

Counts and percentages will be presented by randomised group and a log-binomial regression model, adjusted for baseline characteristics as described in Section 5.4, will be used to estimate the risk ratio, confidence interval and p-value for each pairwise comparison with the no additional treatment arm. Each component of this composite outcome will also be summarised. Patients who were already on invasive mechanical ventilation or ECMO at randomisation will be excluded from these analyses.

5.1.2 *Subsidiary clinical outcomes*

5.1.2.1 Use of ventilation (overall and by type)

Counts and percentages will be presented by randomised group for patients who received any assisted ventilation, together with adjusted risk ratios and confidence intervals for each pairwise comparison with the no additional treatment arm estimated using log-binomial regression, as described above. The number of patients receiving the two main types of ventilation will also be reported: non-invasive ventilation (including CPAP, other non-invasive ventilation or high-flow nasal oxygen), and invasive mechanical ventilation (including ECMO). Patients who were already receiving ventilation[b] at randomisation will be excluded from these analyses.

[b] Participants recruited to the main randomisation prior to protocol version 9.1 who were already receiving oxygen at randomisation will also be excluded from these analyses (since it is not possible to distinguish those who were already receiving non-invasive ventilation).

5.1.2.2 Duration of invasive mechanical ventilation (time to successful cessation of invasive mechanical ventilation)

Successful cessation of invasive mechanical ventilation will be defined as removal of invasive mechanical ventilation within (and survival to) 28 days after randomisation. A time-to-event analysis will be used to compare each treatment group with the no additional treatment group using Cox proportional hazards regression to estimate the hazard ratio and its confidence interval, as described above. Kaplan-Meier curves will be drawn. Patients who die within 28 days of randomisation will be censored *after* 28 days after randomisation. Patients who were not already on invasive mechanical ventilation or ECMO at randomisation will be excluded from these analyses.

5.1.2.3 Use of renal dialysis or haemofiltration

Counts and percentages will be presented by randomised group and the adjusted risk ratio will be calculated for each pairwise comparison with the no additional treatment arm using log-binomial regression, with confidence intervals and p-values reported. Patients who were already on renal dialysis or haemofiltration at randomisation will be excluded from these analyses.

5.1.2.4 Thrombotic event

Counts and percentages will be presented by randomised group. The absolute risk differences (and associated confidence intervals) will also be estimated by applying the adjusted risk ratio (or its 95% upper and lower limits) to the risk in the no additional treatment arm and then calculating the absolute difference between these values and the risk seen in the no additional treatment arm. Type of thrombotic event will also be described: (i) acute pulmonary embolism; (ii) deep vein thrombosis; (iii) ischaemic stroke, (iv) myocardial infarction; (v) systemic arterial embolism; and (vi) all sites combined.

5.1.3 *Virological outcomes*

5.1.3.1 SARS-CoV-2 RNA levels in the nasopharynx

For parts J, K and L only: Geometric mean and standard error SARS-CoV-2 RNA levels will be presented at days 3 and 5. Comparisons will be made between treatment groups. Estimates will be obtained from analysis of covariance (ANCOVA) using the log transformed values after adjustment for each participant's baseline value and the baseline characteristics as described in section 5.4. Missing values will be imputed using the same procedures set out for continuous early phase outcomes described in section 9.3.2.5.

5.1.3.2 Influenza RNA levels in the nasopharynx

For parts G, H and I only: Geometric mean and standard error influenza RNA levels will be presented at day 5. Comparisons will be made between treatment groups. Estimates will be obtained from analysis of covariance (ANCOVA) using the log transformed values after adjustment for each participant's baseline value and the baseline characteristics as described in section 5.4. Missing values will be imputed using the same procedures set out for continuous early phase outcomes described in section 9.3.2.5.

5.1.3.3 SARS-CoV-2 and influenza viral resistance markers

Counts and percentages of SARS-CoV-2 (for parts J, K and L) and influenza (for parts G, H and I) viral resistance markers will be presented by randomised group.

5.2 Second randomisation

Evaluation of treatment effects in the main randomisation and the second randomisation will be conducted independently, as described in 5.1.

5.3 Pre-specified subgroup analyses

Pre-specified subgroup analyses will be conducted for each part of the main randomisation and for the second randomisation, for the following outcomes:

- Mortality (all-cause)
- Time to discharge from hospital
- Use of invasive mechanical ventilation (including ECMO) or death

Tests for heterogeneity (or tests for trend for 3 or more ordered groups) will be conducted to assess whether there is any good evidence that the effects in particular subgroups differ materially from the overall effect seen in all patients combined. Results will be presented on forest plots as hazard ratios, or risk ratios, with confidence intervals. The following subgroups will be examined based on information at randomisation:

- Age (<70; 70-79; 80+ years)
- Sex (Male; Female)
- Ethnicity (White; Black, Asian or Minority Ethnic)
- Region (UK, non-UK)
- Time since illness onset (≤7 days; >7 days)
- Requirement for respiratory support
    - For main randomisation: None; Oxygen only; Non-invasive ventilation; Invasive mechanical ventilation (including ECMO)[c]
    - For second randomisation: No ventilator support (including no or low-flow oxygen); Non-invasive ventilation (including CPAP, other non-invasive ventilation, or high-flow nasal oxygen), Invasive mechanical ventilation (including ECMO)
- CURB-65 score (<3; ≥3)
- Use of systemic corticosteroid (including dexamethasone)
- Concomitant viral infection:
    - For parts J, K and L: presence or absence of confirmed influenza infection
    - For parts G and H: presence or absence of confirmed SARS-CoV-2 infection
- For part B only: Recipient anti-SARS-CoV-2 anti-S antibody status at randomisation (negative, positive as defined by the assay manufacturer, Roche). (This is the key subgroup for the REGEN-COV2 comparison; see Appendix I.)

[c] Participants recruited before protocol V9.1 who were receiving oxygen would be presented in a fifth subgroup but not included in the test for trend

- For parts J, K and L only: Recipient anti-SARS-CoV-2 anti-N antibody concentration at randomisation (negative; positive) as defined by the assay manufacturer, Roche). See Appendix II.
- For parts J, K and L only: Serum SARS-CoV-2 antigen level (< and ≥ median) at randomization. See Appendix II.
- For parts G, H, I and M only; presence of lung consolidation on imaging
- Immunosuppression in the opinion of the managing doctor

5.4 Adjustment for baseline characteristics

The main analyses described above will be adjusted for age and requirement for respiratory support at baseline (using categories defined in section 4.2). Adjustment for these two major predictors of mortality is desirable because it provides a safeguard against the impact that any chance imbalances in their frequencies between randomised groups may have on the randomised comparisons, whilst also leading to a small expected increase in statistical power. Analyses with *further* adjustment for other pre-specified subgroups (see section 4.2) will also be done and presented as sensitivity analyses.

5.5 Sensitivity analyses

For parts A to F only, sensitivity analyses of the primary and secondary outcomes will be conducted among those patients with a positive test for SARS-COV-2 (i.e. confirmed cases).

Sensitivity analyses of the primary and secondary outcomes will be conducted (a) without adjustment for characteristics at randomisation and (b) with adjustment for all key baseline pre-specified subgroups (see section 5.4).

5.6 Other exploratory analyses

In addition, for each randomised assessment, exploratory analyses will be conducted to test for interactions with other treatments allocated in each of the different randomisations, provided that doing so does not lead to premature unblinding of results for ongoing comparators.

Non-randomised exploratory analyses will be used to explore the likely influence of different levels of convalescent plasma antibody concentrations on the efficacy of convalescent plasma.

Additional analyses will set the results for children (<18 years) and pregnant women in the context of the overall results.

5.7 Significance levels and adjustment of p-values for multiplicity

Evaluation of the primary trial (main randomisation) and secondary randomisation will be conducted independently, and no adjustment be made for these. Formal adjustment will not be made for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses (with one exception; see Appendix I). However, due

allowance for multiple testing will be made in the interpretation of the results: the larger the number of events on which a comparison is based and the more extreme the P-value after any allowance has been made for the nature of the particular comparison (i.e. primary or secondary; pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered. 95% confidence intervals will be presented for the main comparisons.

For each of the influenza comparisons (parts G, H, and I), Holm's procedure will be used to control the family-wise error rate across the two co-primary outcomes at 5%.[7]

5.8 Statistical software employed

The statistical software SAS version 9.4 and R Studio 4.2.3 (or later) for Windows will be used for the interim and final analyses.

5.9 Data standards and coding terminology

Datasets for analysis will be prepared using CDISC standards for SDTM and ADaM. Wherever possible, clinical outcomes (which may be obtained in a variety of standards, including ICD10 and OPCS-4) will be coded using MedDRA version 20.1.

6 SAFETY DATA

Suspected serious adverse reactions (SSARs) and suspected unexpected serious adverse reactions (SUSARs) will be listed by trial allocation.

For each of the following, counts and percentages will be presented by randomised group. Where possible, the absolute risk differences will also be presented with confidence intervals (estimated using the methods described in section 5.1.2.4).

6.1 Cause-specific mortality

Cause-specific mortality (COVID-19, other infection, cardiac, stroke, other vascular, cancer, other medical, external, unknown cause) will be analysed in a similar manner to the primary outcome.

6.2 Major cardiac arrhythmia

Type of arrhythmia will also be described: (i) atrial flutter or fibrillation; (ii) supraventricular tachycardia; (iii) ventricular tachycardia; (iv) ventricular fibrillation; (v) atrioventricular block requiring intervention, with subtotals for (i)-(ii) and (iii)-(iv).

6.3 Major bleeding

Type of bleeding will also be described: (i) intracranial bleeding; (ii) gastro-intestinal bleeding; (iii) other bleeding site, and (iv) all sites combined.

6.4 Early safety of anti-coronavirus antibody-based therapy

Additional safety data will be collected in a subset of patients randomised to part B: (i) sudden worsening in respiratory status; (ii) severe allergic reaction; (iii) temperature >39°C or ≥2°C

rise since randomisation; (iv) sudden hypotension; (v) clinical haemolysis; and (vi) thrombotic event.

6.5 Other infections

Other infections occurring after randomisation will be described. These will be classified primarily by site (pneumonia, urinary tract, biliary, other intra-abdominal, blood stream, skin, other). Information on putative organism (other virus, bacterial, fungal, other and unknown) is also collected.

6.6 Metabolic, kidney and liver complications

Incidence of the following metabolic and biochemical complications after randomisation will be described:

- Severe hyperglycaemia (separately and overall; introduced 28 Jul 2021):
  - Ketoacidosis (defined as combination of ketosis [blood ketones ≥1.5 mmol/L or urine ketones ≥2+] and acidosis [venous bicarbonate <15 mmol/L])
  - Hyperglycaemic hyperosmolar state (defined as glucose >33 mmol/L and calculated osmolality >320 mOsm/L)
  - Other hyperglycaemia requiring new use of insulin
- Severe hypoglycaemia (causing reduced conscious level requiring another person to help recover; introduced 28 Jul 2021)
- Acute kidney injury (defined as ratio of post-randomisation peak creatinine to baseline value >1.5x or new use of renal dialysis/haemofiltration; introduced 28 Jul 2021):
- Liver dysfunction (for parts K and L and part G; introduced 28 Mar 2022):
  - Peak alanine (or aspartate) transaminase in the following categories (<3 x upper limit of normal [ULN]; ≥3 <5x ULN; ≥5x ULN)
  - Peak bilirubin (≤2x ULN; >2x ULN)
  - Possible liver injury (defined as ALT >3x ULN plus bilirubin >2x ULN)

6.7 Seizures

The incidence of seizures (introduced on 28 Mar 2022)

6.8 Infusion reactions to sotrovimab

For part J, the frequency and percentage of infusion reactions to sotrovimab will described (overall and by severity)

7 ADDITIONAL POST-HOC EXPLORATORY ANALYSIS

Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan.

8 DIFFERENCES FROM PROTOCOL

The testing of multiple treatment arms will not formally be adjusted for, but given the number of comparisons, due allowance will be made in their interpretation. Formal methods of adjustment for multiplicity were not adopted because of treatment arms being added over time (including the factorial convalescent plasma comparison), unequal recruitment into each arm, and the ultimate number of treatments under evaluation not being known in advance.

9 EARLY PHASE ASSESSMENTS

The following approach is required for the evaluation of treatments indicated as undergoing Early Phase Assessment in the protocol (introduced in Protocol version 14.0):

9.1 Definitions of clinical outcomes

9.1.1 *Primary outcome*

- WHO ordinal scale on day 5

9.1.2 *Secondary clinical outcomes*

- Time to sustained improvement (i.e., value better than baseline value persisting for >1 day) by at least one category on the WHO ordinal scale from baseline
- S/F_{94} ratio at day 5
- Time to discharge from hospital
- Improvement in clinical status at day 10
- Blood C-reactive protein at day 5

9.1.3 *Subsidiary clinical outcomes*

- All other subsidiary outcomes as described above (section 2.6.3)

9.1.4 *Safety outcomes*

- Flushing (incidence, severity)
- Gastrointestinal symptoms (incidence, severity)
- Reasons for stopping study treatment
- Transaminitis (ALT >3x upper limit of normal)
- Acute kidney injury (creatinine >1.5x value entered at randomisation)
- All other subsidiary outcomes as described above (section 2.6.5)

9.2 Baseline comparability of randomised groups

Unless otherwise specified, analyses will follow the plan described above (section 4). In addition, the following characteristics will be described:

- Oxygen saturation measurement on air (if available)
- S/F_{94} ratio
- WHO Ordinal Scale
- All other characteristics as described above (section 4.2)

9.3 Comparative analysis

Unless otherwise specified, comparative analyses will follow the plan described above (section 5). In addition,

9.3.1 *Primary outcome*

The primary comparison will involve an "intention to treat" analysis among all participants randomised between the active arm and its control of the effect of the active treatment on WHO scale at day 5, adjusted for baseline score. A proportional odds model will be used to assess the common odds ratio of better outcome for each pairwise comparison with the no additional treatment arm.[8] In addition, a sensitivity analysis to the proportional odds model using Howard's method will be performed if the proportional odds assumption is not satisfied.[9]

9.3.2 *Secondary outcomes*

9.3.2.1 Time to sustained improvement by at least one category on the WHO ordinal scale from baseline

A time-to-event analysis will be used to compare each treatment group with the no additional treatment group using the log-rank test (restricted to the first 10 days of the trial as the WHO score is not collected after this). The rate ratio and its confidence interval will be estimated from the log-rank observed minus expected statistic and its variance, and Kaplan-Meier curves will be drawn.

9.3.2.2 Improvement in clinical status at day 10

Counts and percentages will be presented by randomised group for patients with an improvement of at least one category on the WHO ordinal scale from baseline, together with odds ratios and confidence intervals for each pairwise comparison with the no additional treatment arm.

9.3.2.3 Blood C-reactive protein at day 5

Geometric mean C-reactive protein at day 5 will be compared between treatment arms. Estimates will be obtained from analysis of covariance (ANCOVA) for the log transformed CRP values after adjustment for each participant's baseline value. Approximate standard errors for the geometric means will be calculated from the confidence intervals. Missing CRP values will be handled as described in section 9.3.2.5.

9.3.2.4 S/F_{94} ratio at day 5

Mean S/F_{94} ratio at day 5 will be compared between treatment arms. Estimates will be obtained from analysis of covariance (ANCOVA) after adjustment for each participant's baseline S/F_{94} ratio. Missing S/F_{94} ratio values will be handled as described in section 9.3.2.5

9.3.2.5 Imputation of missing data

All analyses will be done according to the intention-to-treat principle and, hence, missing secondary outcome data will be imputed. For each of the continuous outcomes (e.g., CRP, S/F_{94} ratio) missing post-randomisation results will be imputed using multiple imputation, using 20 imputed data sets, with results across imputations being combined using the methods of Rubin.[10] The imputation procedure will take into consideration each participant's key baseline characteristics (listed in section 5.8), treatment allocation and any intermediate follow-up values of the biomarker, where available. For S/F_{94} ratio, WHO ordinal scale values on days 3 and 5 will also be used in the imputation procedure. For patients who are discharged from hospital and for whom it is not possible to measure S/F_{94} ratio at day 5, a value of 4.76[d]

[d] 4.76 = 1.0/0.21 (ie, the value of healthy lungs which provide 100% saturations when breathing 21% oxygen)

will be imputed. The results from these analyses will be compared with those from equivalent "complete-case" analyses, but primary emphasis will be placed on the results after multiple imputation. All multiple imputation analyses will be implemented using the multiple imputation procedure in SAS version 9.4 (SAS Institute, Cary NC), using the expectation-maximization algorithm (which assumes a multivariate normal distribution) to impute values. For any continuous variables with missing baseline values, the mean among those with observed values will be imputed.

9.3.3 *Safety outcomes*

Counts and percentages will be presented by randomised group. The absolute risk differences will also be presented with confidence intervals for each of the following:

- Flushing (incidence, severity)
- Gastrointestinal symptoms (incidence, severity)
- Reasons for stopping study treatment
- Transaminitis (ALT >3x upper limit of normal)
- Acute kidney injury (creatinine >1.5x value entered at randomisation)

10 6-MONTH AND LONGER-TERM ASSESSMENTS

This section details the proposed analysis of the clinical outcomes 6 months after initial randomisation in the RECOVERY trial (for all participants). A similar approach will be used for analyses of longer-term outcomes for UK participants only.

10.1 Objectives

The **primary objective** of these analyses is to provide reliable estimates of study treatments on all-cause mortality within 6 months of the relevant randomisation.

The **key safety objectives** are to provide reliable estimates of these on non-COVID infections and non-COVID causes of death.

10.2 Comparative analyses at 6 months

The primary analyses will be performed on the ITT population at 6 months. Pairwise comparisons will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation using the same approach described for the 28 day analyses (see section 5).

10.2.1 *Primary outcome*

The primary outcome is **6-month mortality** (all-cause). This will be summarised with counts and percentages by randomised comparison group. A time-to-event analysis will be conducted using the approach described for the 28-day analyses (see section 5.1.1.1). Results will be interpreted in the context of the results of analyses at 28 days.

For the analysis of REGEN-COV2, the primary outcome will first be assessed among those participants who are known to be seronegative (anti-S SARS-CoV-2 antibody negative) at randomisation (see Appendix I).

For the analysis of sotrovimab, the primary outcome will first be assessed among participants with a blood SARS-CoV-2 antigen concentration above the median value (see Appendix II).

10.2.2 *Pre-specified subgroup analyses*

Subgroup analyses will be conducted for 6-month mortality (all-cause) using methods described in section 5.3. The following subgroups will be examined based on information at randomisation:

- For dexamethasone comparisons: Requirement for respiratory support (with test for trend)
- For tocilizumab comparison: Use of systemic corticosteroid (including dexamethasone) (with test for heterogeneity)
- For REGEN-COV2 comparison: Recipient anti-SARS-CoV-2 anti-S antibody concentration (positive, negative, unknown; with test for heterogeneity between seronegative and seropositive participants)
- For baricitinib comparison: use of systemic corticosteroid (including dexamethasone) and, separately, use of interleukin-6 antagonist (e.g. tocilizumab, sarilumab) (each with test for heterogeneity)
- For sotrovimab comparison: Recipient anti-SARS-CoV-2 anti-N antibody concentration (positive, negative, unknown; with test for heterogeneity between seronegative and seropositive participants) and SARS-CoV-2 antigen level (< or ≥ median)
- For high-dose dexamethasone comparison: Requirement for respiratory support (with test for trend)

Other subgroup analyses (see section 5.3) may be conducted but will be considered exploratory in nature.

10.2.3 *Adjustment for baseline characteristics*

The main analyses will be adjusted for age and level of respiratory support at baseline (and potentially for other important imbalances) using the approach described in section 5.1.1.1.

10.2.4 *Sensitivity analyses*

Sensitivity analyses of the primary outcome will be conducted with adjustment for all key baseline pre-specified subgroups (see section 5.4).

10.2.5 *Significance levels and adjustment of p-values for multiplicity*

This will take the same approach as described for 28-day analyses (see section 5.7)

10.3 Safety data

The key safety outcome is **major non-COVID infection** (associated with hospitalisation or death). These will be presented overall, and by site (e.g. pneumonia, urinary tract, biliary,

other intra-abdominal, bloodstream, skin, other) and, where possible, by putative organism (e.g. virus, bacteria, fungus, other). Counts and percentages will be presented by randomised group. Where possible, the absolute risk differences will also be presented with confidence intervals.

10.4 Other exploratory analyses

Secondary, subsidiary clinical and other safety outcomes (as specified earlier in this document) may be assessed in exploratory analyses. In addition, hospital recorded diagnoses (see Definition and Derivation of Baseline Characteristics and Outcomes SOP section 8.1.2) may be explored to assess other long-term effects of study treatments.

The selection and interpretation of these additional analyses will be informed by the 28-day results and what is known about the potential longer term impacts of the study treatments (particularly with respect to known hazards of treatment).

10.5 Censoring and analysis

For the 6 month analyses, participants will be censored at the earliest of death, withdrawal of consent, known exit from the NHS,[e] or on study day 184 (where day of randomisation is study day 1). For later analyses, a similar censoring approach will be used (e.g. day 731 for a 2 year analysis).

[e] NHS England (and equivalent organisations in the devolved nations) are notified if patients are no longer receiving NHS care (typically due to emigration).

11 REFERENCES

11.1 Trial documents

Study protocol, case report forms, training materials, and statistical analysis plan are published on the trial website.

11.2 Other references

1. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA 2017;318(23):2337-2343.

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8. McCullagh P. Regression models for ordinal data. J R Statist Soc B. 1980; 42: 109-42

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12 APPENDIX I: ANALYSES OF REGEN-COV2

12.1 Background & rationale

The RECOVERY trial is testing multiple interventions in a broad population of patients hospitalised with COVID-19. The protocol and statistical analysis plan outline the methods that are to be used in the analysis of these interventions and, to date, the same approach has been appropriate for all completed comparisons. However, it is important that the statistical analysis plan be informed by the best available information about the treatment being tested[1] and the pathophysiology of the disease.

Relevant new information about the effects of REGEN-COV2 have emerged since it was added to the trial in September 2020.

REGEN-COV2 is a mixture of two synthetic monoclonal antibodies which bind to the receptor binding domain of the SARS-CoV-2 spike protein and neutralise the virus.[2] Recently-published trials of REGEN-COV2 in ambulatory patients (i.e. those recently diagnosed in the community) have demonstrated that it has larger effects on viral load among people who are "seronegative" at the time of randomisation (i.e. they do not have detectable antibodies of their own against SARS-CoV-2), and seropositive patients derive little or no benefit (in terms of reduction in viral load) from REGEN-COV2, compared to placebo.[3] Participant serostatus therefore is a potentially key modifier of the effect of REGEN-COV2 that may be observed in RECOVERY.

All participants entering the REGEN-COV2 comparison in RECOVERY are asked to provide a serum sample which is sent to a central laboratory at the University of Oxford, where antibodies against SARS-CoV-2 are measured using a validated assay. Previous assessments of this assay alongside commercially available assays shows excellent performance at discriminating prior SARS-CoV-2 infection with sensitivity and specificity above 98%.[4]

Earlier versions of the statistical analysis plan recognised the importance of the seronegative subgroup, but review of the emerging literature and regulatory guidance[5] has led to a change in approach to these analyses. The revised analysis plan for the REGEN-COV2 comparison explicitly tests the hypothesis that any benefit of REGEN-COV2 on the primary outcome may be wholly or largely restricted to patients who are seronegative at the time of randomisation with little or no benefit among those who are seropositive at that point.

For the avoidance of doubt, all decisions about this modification to the analytical plan were made before recruitment was complete and before any members of the trial steering committee (who are responsible for drafting and approving the SAP) or investigators had access to any unblinded analyses of clinical outcome data for the REGEN-COV2 comparison. No members of the independent Data Monitoring Committee (who are the only individuals who can review interim unblinded analyses) were involved in this change.

12.2 Analytical plan

The primary outcome and secondary outcomes remain unchanged. For each outcome, rate ratios and 95% confidence intervals will be calculated separately for participants who are

seronegative, seropositive, or with unknown status as well as for the whole trial population. A test for heterogeneity between seronegative and seropositive participants will be presented. The results will be interpreted based on the totality of the evidence.

For the purposes of any regulatory submission: Because any beneficial effect of REGEN-COV2 is hypothesised to be larger among seronegative participants (and may be negligible in seropositive participants), the primary outcome will first be assessed among participants who are known to be seronegative at randomisation. If the null hypothesis is rejected in the seronegative group at 2-tailed p=0.05, then the primary outcome will be assessed among the whole population (i.e. seronegative, seropositive, and those with unknown status combined). Otherwise, no further hypothesis testing will be performed.

A similar approach will be taken for each of the two pre-specified secondary outcomes (discharge alive within 28 days and, among patients not on invasive mechanical ventilation at baseline, the use of invasive mechanical ventilation or death) if both primary hypotheses are rejected. Hypothesis testing will first be conducted among the participants who are known to be seronegative at randomisation and, if the null hypothesis is rejected at 2-tailed p=0.025, then will be assessed among the whole population (see Table).

Table: Hierarchical Testing Order

Hierarchy Number	Type of Outcome	Outcome	Analysis Population	Significance level, α (2-sided)
1.	Primary	Mortality (all-cause), 28 days after randomisation	Seronegative at randomisation	0.05
2.	Primary	Mortality (all-cause), 28 days after randomisation	All participants randomised	0.05
3.*	Secondary	Time to discharge alive from hospital, within 28 days after randomisation	Seronegative at randomisation	0.025
4.	Secondary	Time to discharge alive from hospital, within 28 days after randomisation	All participants randomised	0.025
3.*	Secondary	Use of invasive mechanical ventilation (including ECMO) or death	Seronegative and not on invasive mechanical ventilation at randomisation	0.025
4.	Secondary	Use of invasive mechanical ventilation (including ECMO) or death	All participants randomised not on invasive mechanical ventilation at randomisation	0.025

* These will be performed simultaneously. Testing will only proceed to the respective overall population if the null hypothesis is rejected in the seronegative group at the specified level of statistical significance.

12.3 References

1. Food and Drug Administration. E9 Statistical Principles for Clinical Trials. 1998.

2. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369:1010-4.
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5. Food and Drug Administration. Enrichment strategies for clinical trials to support determination of effectiveness of human drugs and biological products - guidance for industry. 2019.

13 APPENDIX II: ANALYSES OF SOTROVIMAB AND OTHER ANTI-VIRALS FOR COVID-19

13.1 Background & rationale

The RECOVERY trial is testing multiple interventions in a broad population of patients hospitalised with COVID-19. The protocol and statistical analysis plan outline the methods that are to be used in the analysis of these interventions. With the exception of REGEN-COV2 (see Appendix I), the same approach has been used for all completed comparisons. However, it is important that the statistical analysis plan be informed by the best available information about the treatment being tested[1] and the pathophysiology of the disease.

At the point at which sotrovimab was added to the protocol (protocol version 21.1; approved 20th December 2021), the number of infections with the omicron variant of SARS-CoV-2 was rising exponentially, doubling approximately every 2 days. There was an enormous national effort to maximise vaccination such that by 20th December 2021, around 90% of adults aged >18 years had received a 1st dose of vaccine, 82% had received 2 doses, and 50% had received 3 doses (with around 0.5-1 million vaccine doses being administered each day). However, there were several important unknowns including the propensity for the omicron variant to cause severe disease, hospitalisation and death (either with or without vaccination).

The previous evaluation of REGEN-COV2 in RECOVERY established that the monoclonal neutralising antibody combination was effective in patients who were anti-spike antibody negative, and no meaningful effect was seen among those who were anti-spike antibody positive. However, that evaluation was carried out prior to the emergence of the omicron variant and at a point when <10% participants had any vaccine dose (and almost nobody had had more than one). Hence, seropositive status at that time largely reflected an acute immune response to the active SARS-CoV-2 infection. By December 2021, the situation was more complicated – seropositive status could reflect an acute immune response (as before) or a legacy effect of prior infection (with a different variant) or prior vaccination (against a different variant). Given the immune escape demonstrated by omicron, it is reasonable to expect that at least some seropositive patients may benefit from treatment with a neutralising monoclonal antibody in the form of sotrovimab or an anti-viral treatment such as molnupiravir or paxlovid.

There is some evidence from the ACTIV-3 study programme[2] that serum viral antigen concentration may be a useful predictor of both poor outcome and of response to monoclonal neutralising antibody treatment. Serum samples will be collected and analysed for both anti-SARS-CoV-2 antibody concentration and viral antigen concentrations. The TSC will review data on the distribution of these and their association with primary and secondary outcomes (blinded to information about treatment allocation) before determining the most scientifically and clinically relevant primary analysis population.[3] (For example, the TSC might determine that the primary analysis should be restricted to those patients who are anti-N antibody negative or alternatively who have high viral antigen load, and decide on an analysis approach analogous to that used for patients who were seronegative [anti-S antibody negative] in the REGEN-COV2 analysis.)

For the avoidance of doubt, all decisions about this modification to the analytical plan will be made before before any members of the trial steering committee (who are responsible for

drafting and approving the SAP) or investigators have access to any unblinded analyses of clinical outcome data for the sotrovimab, molnupiravir and paxlovid comparisons. No members of the independent Data Monitoring Committee (who are the only individuals who can review interim unblinded analyses) will be involved in this decision.

Addendum 25 June 2024: Selection of primary analysis population for the sotrovimab, molnupiravir and Paxlovid comparisons

Paxlovid and molnupiravir
A substantial fall in the number of patients admitted to hospital with COVID-19 lung disease from early 2022 meant that recruitment to these comparisons remained low (924 participants in the molnupiravir comparison, and 137 participants in the Paxlovid comparison). Because of low recruitment these comparisons were closed early, in May 2023. Selecting a subgroup as the primary analysis population was considered futile, and so *for these comparisons all analyses based on viral antibody/antigen status are exploratory*.

Sotrovimab
Recruitment to the sotrovimab comparison closed on 31st March 2024 when funding ended. At the time of finalising this SAP (version 5.0) the RECOVERY investigators remain blind to the results of this comparison.

By January 2024, SARS-CoV-2 seropositivity among blood donors was 90% for anti-N antibodies (reflecting previous infection) and 99.9% for anti-S antibodies (reflecting previous infection or vaccination).[4] As a result, the presence of SARS-CoV-2 antibodies in hospitalised patients is now likely to reflect previous infection or vaccination rather than indicate the adequacy of the immune response to their current infection.

A review of participant serostatus and outcomes in the sotrovimab comparison (blinded to treatment allocation) supports this. In September 2023, only 19% of participants were anti-S negative, making this unsuitable as the primary analysis population. 70% were anti-N negative, most of whom were recruited in early 2022 when anti-N seroprevalence in the UK population was low. However, anti-N seronegativity was not associated with increased mortality (20% among those who were seropositive vs 21% among those who were seronegative). This contrasts with RECOVERY participants recruited in 2020/21, in whom mortality was strongly associated with anti-N serostatus (14% among those who were seropositive vs 30% among those who were seronegative in patients not receiving neutralising antibody therapy), and suggests that anti-N serostatus is no longer a good marker of immune response to the acute infection.[5]

Unlike measurement of anti-SARS-COV-2 antibodies, the detection of viral nucleocapsid antigen in the blood must relate to the current infection, and may represent a phase of infection before specific antibodies have developed to clear the virus. In keeping with this, viral nucleocapsid antigen concentration above the median value (cut-off index 0.626) is associated with significantly higher mortality in the sotrovimab comparison (26% vs 16%). Participants with higher blood antigen concentration seem most likely to benefit from antibody therapy, and so ***the primary analysis population for the sotrovimab comparison will be participants who have a blood antigen concentration above the median value*.**

The primary outcome and secondary outcomes remain unchanged. For each outcome, rate ratios and 95% confidence intervals will be calculated separately for participants who have high antigen, low antigen, or with unknown status, as well as for the whole trial population. A test for heterogeneity between participants with high and low antigen will be presented. The results will be interpreted based on the totality of the evidence.

Because any beneficial effect of sotrovimab is hypothesised to be larger among high antigen participants (and may be negligible in low antigen participants), the primary outcome will first be assessed among participants who are known to have high antigen at randomisation. If the null hypothesis is rejected in the high antigen group at 2-tailed p=0.05, then the primary outcome will be assessed among the whole population (i.e. high antigen, low antigen and those with unknown status combined). Otherwise, no further hypothesis testing will be performed.

A similar approach will be taken for each of the two pre-specified secondary outcomes (discharge alive within 28 days and, among patients not on invasive mechanical ventilation at baseline, the use of invasive mechanical ventilation or death) if both primary hypotheses are rejected. Hypothesis testing will first be conducted among the participants who are known to be high antigen at randomisation and, if the null hypothesis is rejected at 2-tailed p=0.025, then will be assessed among the whole population (see Table).

Table: Hierarchical Testing Order

Hierarchy Number	Type of Outcome	Outcome	Analysis Population	Significance level, α (2-sided)
1.	Primary	Mortality (all-cause), 28 days after randomisation	High antigen at randomisation	0.05
2.	Primary	Mortality (all-cause), 28 days after randomisation	All participants randomised	0.05
3.*	Secondary	Time to discharge alive from hospital, within 28 days after randomisation	High antigen at randomisation	0.025
4.	Secondary	Time to discharge alive from hospital, within 28 days after randomisation	All participants randomised	0.025
3.*	Secondary	Use of invasive mechanical ventilation (including ECMO) or death	High antigen and not on invasive mechanical ventilation at randomisation	0.025
4.	Secondary	Use of invasive mechanical ventilation (including ECMO) or death	All participants randomised not on invasive mechanical ventilation at randomisation	0.025

* These will be performed simultaneously. Testing will only proceed to the respective overall population if the null hypothesis is rejected in the high antigen group at the specified level of statistical significance.

13.2 References

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14 APPROVAL

Chief Investigator	Name: Professor Peter Horby	
	Signature:	Date:
Deputy Chief Investigator	Name: Professor Martin Landray	
	Signature:	Date:
Steering Committee Statistician	Name: Professor Thomas Jaki	
	Signature:	Date:

15 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
0.1	20/03/20	LL/JB	First draft.	Prior	Prior
0.2	01/04/20	LL/JB	Comments and amendments from Martin Landray, Jonathan Emberson & Natalie Staplin. Also aligned with updated protocol and CRFs.	Prior	Prior
0.3	01/04/20	EJ/LL	Further edits and comments.	Prior	Prior
0.4	07/04/20	JB/EJ/ LL	Following statistics group meeting on 02/04/20.	Prior	Prior
0.5	22/04/20	JB/LL/ EJ	Following statistics group meeting on 09/04/20 and further protocol update.	After	Prior
0.6	24/04/20	LL	Following statistics group meeting on 23/04/20.	After	Prior
0.7	10/05/20	LL	Protocol update.	After	Prior
0.8	15/05/20	LL	Following statistics group meeting on 15/05/20.	After	Prior
0.9	27/05/20	LL	Further comments from TSC members prior to interim analysis on 28/05/20.	After	Prior
1.0	09/06/20	LL	Revised following the stopping of the hydroxychloroquine arm, and prior to the trial statisticians receiving unblinded data for this arm.	After	Prior
1.1	21/06/20	LL/JB/ RH	Additional clarification of ventilation denominators. Adjustment for any imbalances of subgroup characteristics between treatment arms at randomisation. Clarification of analysis of composite outcome. Removal of 'Unknown' ethnicity subgroup. Addition of section 5.5 Adjustment for baseline characteristics.	After	After unblinding of hydroxychloroquine and dexamethasone arms.

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
2.0	04/11/20	EJ/ES	Revised to reflect changes in protocol, including introduction of factorial randomisations and new arms, including convalescent plasma, tocilizumab, synthetic neutralizing antibodies (REGEN-COV2, and aspirin.	Prior to interim analysis of aspirin arm After interim analyses of all other arms	After unblinding of 28-day results for hydroxychloroquine, lopinavir-ritonavir, and dexamethasone arms. Prior to unblinding of any other arms
2.1	02/12/20	ES	Addition of colchicine. Modification of definition of recipient antibody concentration subgroup.	Prior to interim analyses including antibody results or of colchicine arm.	After unblinding of 28-day results for hydroxychloroquine, lopinavir-ritonavir, and dexamethasone arms. Prior to unblinding of any other arms
2.2	27/01/21	ES	Clarification of non-invasive ventilation-related subgroups. Addition of baricitinib.	Prior to interim analyses of baricitinib arm.	After unblinding of 28-day results for hydroxychloroquine, lopinavir-ritonavir, azithromycin and dexamethasone arms (and primary outcome in overall population in convalescent plasma arm). Prior to unblinding of any other arms

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
3.0	15/05/21	ES	Specification of method for REGEN-COV2 comparison (appendix A). Addition of early phase assessment of dimethyl fumarate. Addition of infliximab and high-dose corticosteroids.	Prior to interim analyses of infliximab or high-dose steroids.	After unblinding of 28-day results for hydroxychloroquine, lopinavir-ritonavir, azithromycin, dexamethasone, colchicine and convalescent plasma arms. Prior to unblinding of any other arms.
3.1	29/10/21	RH	Modification of early phase assessments to align with protocol V18.1 Modification of 6 months analysis section.	Prior to early phase assessments or 6 month analyses.	Prior to unblinding of dimethyl fumarate or 6 month outcome data.
3.2	17/12/21	RH	Update to early phase assessments	Prior to 6 month analyses	Prior to unblinding of dimethyl fumarate
4.0	20/09/22	MJL	Revised to reflect changes in protocol versions 19-25. Now includes information on comparisons for influenza and for sotrovimab, molnupiravir and paxlovid. Update to 6 month and long-term assessments.	Prior to interim analyses of these arms.	Prior to commencement of enrolment to influenza comparisons. Prior to unblinding of sotrovimab, molnupiravir, paxlovid, empagliflozin, and high dose corticosteroid comparisons for participants on non-invasive ventilation or invasive mechanical ventilation.

Version	Date	Edited by	Comments/Justification	Timing in relation to unblinded interim monitoring	Timing in relation to unblinding of Trial Statisticians
5.0	25/06/24	LP	Addition of CAP comparison. Update to reflect opening of flu comparisons & closing of empagliflozin, molnupiravir, Paxlovid, high dose corticosteroid, and sotrovimab comparisons. Finalisation of analysis plan for SARS-CoV-2 antivirals in Appendix II.	After interim analyses of all comparisons.	Prior to unblinding of sotrovimab, flu & CAP comparisons (parts G, H, I, J & M). After unblinding of molnupiravir & Paxlovid comparisons (parts K & L)

Appendix 3: Definition and Derivation of Baseline Characteristics and Outcomes

Definition and Derivation of Baseline Characteristics and Outcomes

Contents

1 Version

Date	Version	Comments
06-Jun-2020	0.1	Initial version
08-Jun-2020	0.2	Minor updates
09-Jun-2020	1.0	First released version
11-Dec-2020	2.0	Update to sections 6.4 (use of assisted ventilation) and 6.6 (use of renal replacement therapy)
06-Jan-2020	3.0	Update to clarify the derivation of outcomes and baseline data for the second randomisation and define complete follow-up
14-April-2022	4.0	Updates to frequency of dataset transfers and additional datasets. Addition of section 8relating to 6-month outcomes. Addition of appendix 4 to provide detail on discharge outcome

2 Scope

This document describes the definition and derivation of the primary, secondary and other outcomes of the RECOVERY trial for the published trial analyses. It should be read alongside the study protocol which defines the study outcomes briefly, and the Statistical Analysis Plan (SAP) which describes the statistical methods used to analyse these outcomes. The SAP

refers to this document (see Section 2.6.4 Detailed derivation of outcomes) which provides detail on how the outcomes are defined, captured and derived.

Most outcomes have more than one potential source which improves completeness of capture but also will inevitably identify discrepancies between different sources. This document describes the principles for how such discrepancies are resolved; the rules for this were developed blind to results. Further details of the methods are described in the RECOVERY trial internal operating procedure for identifying data discrepancies.

3 Abbreviations

ADDE	Annual District Death Extract
CCDS	Critical Care Dataset
CHESS	COVID-19 Hospitalisation in England Surveillance System
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
ECMO	Extra-corporeal membrane oxygenation
eCRF	Electronic Case Report Form
FCE	Finished Consultant Episode
FU	Follow-up
HESAPC	Hospital Episode Statistics Admitted Patient Care
HFNO	High-flow nasal oxygen
ICD-10	International Classification of Diseases 10th edition
ICNARC	Intensive Care National Audit and Research Centre
IMV	Invasive mechanical ventilation
NHSCR	NHS Central Register (Scotland)
NIV	Non-invasive ventilation
NRS	National Records of Scotland
ONS	Office for National Statistics (ONS)
OPCS-4	Office of Population Censuses Surveys Classification of Surgical Operations and Procedures 4th revision
PDS	Patient Demographic Service
PEDW	Patient Episode Database for Wales
RRT	Renal replacement therapy
PHE	Public Health England
SAP	Statistical Analysis Plan
SICSAG	Scottish Intensive Care Society Audit Group
SMR	Scottish Morbidity Record
SUSAPC	Secondary Use Service Admitted Patient Care
UKRR	UK Renal Registry
WDSD	Welsh Demographic Service
WRRS	Welsh Results Reporting Service

4 Data sources

4.1 Electronic case report forms

4.1.1 Main randomisation

The Randomisation eCRF is completed by hospital staff after patients (or a legal representative) have given consent to participate in the trial. It collects the following participant information:

- Identifiers
    - First name, family name

  - NHS number
  - Date of birth
  - Sex (male/female/unknown)
- Inclusion criteria
  - COVID-19 symptom onset date
  - Date of hospitalisation
- Details of acute illness
  - Requirement for oxygen[1]
  - Requirement for ventilatory support (none, continuous positive airway pressure, non-invasive ventilation, high-flow nasal oxygen, invasive mechanical ventilation (IMV) or extra-corporeal membrane oxygenation) (ECMO)
  - Latest oxygen saturation
  - Latest C-reactive protein, creatinine and D-dimer measurement (if available)
- Comorbidities
  - Diabetes
  - Heart disease
  - Chronic lung disease
  - Tuberculosis
  - HIV
  - Severe chronic liver disease
  - Severe kidney impairment (eGFR <30 mL/min/1.73m^2 or on dialysis)
  - Long QT syndrome
  - Pregnancy
- Current treatment
  - Macrolide antibiotics
  - Aspirin or other antiplatelet therapy
  - Warfarin or direct oral anticoagulant
  - Venous thromboembolism prophylaxis (standard or increased dose due to COVID-19)
  - Remdesivir
  - Systemic corticosteroids
- Other
  - Weight (children only)

4.1.2 Second randomisation

The Second Randomisation eCRF is completed by hospital staff when they wish to randomise participants between tocilizumab or standard care alone if they fulfil the protocol-defined oxygenation and inflammation criteria. It collects the following participant information:

[1] NHS England advice published on 9 April 2020 stated that the usual oxygen target saturation for prescribed oxygen should change from 94-98% to 92-96% in the first instance. Hospitals may further reduce this to 90-94% if clinically appropriate according to prevailing oxygen demands. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0256-specialty-guide-oxygen-therapy-and-coronavirus-9-april-2020.pdf. Guidance on admission to hospital was similar in Scotland. https://www.nhsggc.org.uk/media/259232/covid-19_gps_national_supporting_guidance_for_scottish_general_practice.pdf although hospital guidelines in Scotland did not specify a target oxygen saturation.

- Inclusion criteria
    - Requirement for oxygen
    - Current level of ventilation support (none/CPAP/NIV/HFNO/IMV/ECMO)
    - Latest CRP
- Other information
    - Latest ferritin and creatinine

4.1.3 Convalescent plasma safety eCRF

This eCRF is completed by hospital staff as soon as possible after 72 hours post-main randomisation for participants who entered the convalescent plasma comparison. It collects the following information:

- Adherence to convalescent plasma allocation (number of units received, whether any were stopped early)
- Adverse events
    - Sudden worsening of respiratory status
    - Severe allergic reaction
    - Temperature ≥39C (or rise ≥2C above baseline)
    - Sudden hypotension
    - Clinical haemolysis
    - Thrombotic event

4.1.4 Follow-up

The FU eCRF is completed by hospital staff at the earliest of (i) discharge from acute care (see Section 6.3 below), (ii) death, or (iii) 28 days after the main randomisation. It collects the following information from date of randomisation onwards:

- Adherence to randomised allocation, and receipt of other study treatments or relevant therapies (and number of days of treatment)
- Vital status and underlying cause of death (COVID, other infection, cardiovascular, other; if other, a free text description is collected)
- Date of discharge
- Requirement for assisted ventilation (CPAP, NIV, HFNO, IMV, ECMO) and number of days of assisted ventilation and IMV/ECMO separately
- Occurrence of major cardiac arrhythmia (atrial flutter/fibrillation, supraventricular tachycardia, ventricular tachycardia [including torsades de pointes], ventricular fibrillation or bradycardia requiring intervention) (from 12 May 2020)
- Occurrence of thrombotic event (pulmonary embolism; deep-vein thrombosis; ischaemic stroke; myocardial infarction; systemic arterial embolism; other) (from 6 November 2020)
- Occurrence of clinically-significant bleeding i.e. intracranial or requiring intervention (blood transfusion; surgery; endoscopy; vasoactive drug or blood transfusion), by site (intra-cranial; gastrointestinal; other) (from 6 November 2020)
- Requirement for renal replacement therapy and peak creatinine after randomisation
- Other infections after randomisation (by site and by organism type)
- Metabolic complications (ketoacidosis, hyperglycaemia, hypoglycaemia)

4.1.5 Non-UK sites

Whereas in the UK participants will be followed by linkage with routinely collected data (see Section 4.2) for up to 10 years after randomisation, in other countries this is not possible. Sites will be asked to complete an additional case report form for participants discharged

alive from hospital at 28 days after randomisation to confirm vital status (and date and cause of death if relevant).

4.2 Registries and NHS datasets

4.2.1 Hospital admissions datasets

4.2.1.1 Secondary Use Service Admitted Patient Care

The SUSAPC dataset is a repository of data hosted by NHS Digital that relates to in-patient care provided in England, which aims to enable reporting and analyses to support the NHS in the delivery of healthcare services. These data are submitted on a regular basis by NHS hospital trusts and at pre-arranged dates during the year. Submissions are consolidated, validated and cleaned and then incorporated into the HESAPC dataset. Data may be incomplete in places and is not quality assured to the same extent as HES, but is available more rapidly.

In the SUSAPC dataset, each record contains data relating to a continuous period of care under one consultant known as a Finished Consultant Episode (FCE). FCEs can be grouped together to form 'Spells'. Each spell is a continuous periods of inpatient care within one hospital. Each FCE contains data about the patient (e.g. sex, ethnicity), the specialty providing the care (e.g. cardiology), ICD-10 diagnostic and OPCS-4 procedure codes, along with dates for each procedure and details about the admission and discharge and other data.

For the main RECOVERY analyses the following data are used;

- Admission method (which indicates whether the admission was emergency or elective and whether it involved a transfer from another healthcare provider)
- Admission source (used to identify transfers between hospitals)
- Ethnicity
- Sex
- Date of admission and discharge
- Start and end date of the FCE
- Discharge method and destination (which may indicate death of participant)
- Diagnoses recorded during FCE (ICD-10 coded)
- Procedures performed during FCE (OPCS-4 coded) and corresponding dates

Linked SUSAPC data are imported to the RECOVERY trial database approximately monthly.

4.2.1.2 Hospital Episode Statistics Admitted Patient Care

HESAPC contains data relating to admissions to NHS hospitals in England and is produced from the SUSAPC following a number of cleaning and validation steps. For participants in England, HESAPC is available for the 5 year period prior to enrolment in the study. For the main RECOVERY analyses these data are used to identify prior medical conditions on the basis of recorded ICD-10 and OPCS-4 codes (excluding the admission during which the patient was randomised). For the analysis of 6-month outcomes, these data are used to identify the Hospital Recorded Diagnoses (see section 8). Linked HESAPC data are imported to the RECOVERY trial database quarterly.

4.2.1.3 NHS Central Register Scottish Morbidity Record One

The NHSCR SMR01 data set holds episode level data on hospital inpatient and day case discharges from acute specialities from hospitals in Scotland. The data fields used in the RECOVERY trial are equivalent to those used in SUSAPC and HESAPC. Linked NHSCR-SMR01 data are imported approximately monthly.

4.2.1.4 Patient Episode Data Wales

4.2.2 PEDW contains data relating to admissions to NHS hospitals in Wales. The data fields used in the RECOVERY trial are equivalent to those used in SUSAPC and HESAPC Mortality datasets

4.2.2.1 Patient Demographic Service

The PDS is the electronic database of NHS patient details such as name, address, date of birth and NHS Number for patients in England. For RECOVERY it is used to provide information on fact and date of death. It provides both 'informal' notifications of death (which occur when a health care provider is informed of their patients death and records the reported date of death in their electronic data systems) and 'formal' notifications of death (which are provided by the Office for National Statistics).

4.2.2.2 Office for National Statistics Mortality data

The ONS mortality data contains information related to a person's death taken from the death certificate for all deaths registered in England and Wales. The following data are provided

- The underlying cause of death
- Contributory causes of death
- Other conditions recorded on the death certificate but not contributing to death
- Whether a post-mortem took place

Clinical data are recorded using ICD-10 codes. Linked ONS mortality data are imported into the RECOVERY trial via a quarterly extract from NHS Digital.

4.2.2.3 Welsh Demographic Service

WDS data are the electronic database of NHS patient details for patients in Wales and are similar to PDS (4.2.2), providing fact and date of death (including formal or informal notifications). Linked data for RECOVERY participants recruited via sites in Wales will be available for future analysis.

4.2.2.4 National Records of Scotland Mortality Data

The NRS mortality data contain information related to a person's death taken from the death certificate for all deaths registered in Scotland. The data provided includes the date of death and the underlying and contributory causes of death coded in ICD-10. Linked data are imported into the RECOVERY trial database approximately monthly.

4.2.3 COVID specific datasets

4.2.3.1 Public Health England Second Generation Surveillance data

The SGSS is an application that captures, stores and manages routine laboratory surveillance data on infectious diseases and antimicrobial resistance from laboratories across England. Once the reports have been loaded into SGSS, each record is subject to a number of validation processes, and local LIMS codes are translated to SGSS codes to standardise the data for analysis. The data is stored in a central database within PHE and details of tests indicating SAR-CoV-2 have been made available to NHS Digital for dissemination for a limited time period. For each test, the following data are available

- Date the sample was collected
- Date the result was reported
- Organism identified (only SARS-CoV-2)

Linked PHE SGSS data are imported into the RECOVERY trial approximately monthly.

4.2.3.2 Public Health Scotland COVID-19 laboratory antigen test positive list

The Electronic Communication of Surveillance in Scotland (ECOSS) collects routine laboratory surveillance data on infectious diseases from laboratories in Scotland. The data provided to RECOVERY is limited to SARS-CoV-2 results along with the date of the sample and result.

4.2.3.3 Welsh Results Reporting Service Pathology Data

The WRRS contains all Pathology Test Results for Wales in a single database. Tests indicating a positive SAR-CoV-2 antigen linked to the trial participants are obtained.

4.2.3.4 COVID-19 Hospitalisation in England Surveillance System

PHE has established the COVID-19 Hospitalisation in England Surveillance System (CHESS), which collects epidemiological data (demographics, risk factors, clinical information on severity, and outcome) on COVID-19 infection in patients requiring hospitalisation and ICU/HDU level care. This dataset has been made available to NHS Digital for dissemination for a limited time period. For RECOVERY the following information is used;

- Date of ICU/HDU admission and discharge
- Use of respiratory support during the admission (including oxygen via cannulae or mask, high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation and ECMO)
- Complications during the admission (including viral pneumonia, secondary bacterial pneumonia, ARDS, unknown, and other co-infections)

The CHESS dataset is imported into the RECOVERY trial approximately monthly.

4.2.3.5 GPES Data for Pandemic Planning and Research (COVID-19) (GDPPR)

GDPPR data is available for RECOVERY participants in England. Data includes patient demographic information and coded medical information (mainly in SNOMED codes).

4.2.4 Intensive Care Datasets

4.2.4.1 Intensive Care National Audit and Research Centre

The ICNARC Case Mix Programme is the national clinical audit covering all NHS adult, general intensive care and combined intensive care/high dependency units in England, Wales and Northern Ireland, plus some additional specialist and non-NHS critical care units. Data are collected about the first 24 hours in ICU/HDU and at discharge from the ICU/HDU with a further data collection point after discharge from hospital. For RECOVERY, the following data recorded at discharge from ICU/HDU are used:

- Date of admission to and discharge from ICU/HDU
- Use of Advanced Respiratory Support (ARS), Basic Respiratory Support (BRS) or Renal Support during the admission
- The number of days of ARS, BRS or Renal Support during the admission
- Date of death (if relevant)

Linked ICNARC data is requested for hospitals recruiting to RECOVRY and are imported approximately monthly.

4.2.4.2 Scottish Intensive Care Society Audit Group

SICSAG collects data from all general adult Intensive Care Units, Combined Units and the majority of High Dependency Units in Scotland using the WardWatcher system. The following data are used in the RECOVERY trial:

- Date of admission and discharge from ICU/HDU

- Used of mechanical ventilation via endotracheal tube or tracheostomy and use of haemofiltration for each day of during admission

Linked SICSAG data are imported into the RECOVERY trial approximately monthly.

4.2.4.3 Critical Care dataset

In England and Wales much of the key data collected by ICNARC is also available in the CCDS from NHS Digital or the SAIL datalink Wales. However, both the ICNARC and CCDS data can be subject to different delays during collection, consolidation and dissemination and therefore either source may be incomplete at any one time-point. Both sources are therefore combined to provide information about ICU/HDU care for participants in England and Wales.

4.2.5 Disease specific registries

4.2.5.1 UK Renal Registry

The UK Renal Registry collates data from renal units and hospital laboratories in all four nations in the UK. Linked data relating to laboratory tests for patients who trigger a hospital laboratory "acute kidney injury alert" are available for a subset of patients. Data relating to the provision of care for end stage kidney disease discuss is provided to RECOVERY on an annual basis.

5 Baseline characteristics

Baseline characteristics for the trial cohort are obtained from the first randomisation eCRF for the main randomisation comparisons. For the second randomisation comparisons, the baseline data are obtained either from the second randomisation form directly (e.g. baseline use of respiratory support) or from a calculation based on the first randomisation form data and the number of days between the first and second randomisation forms (e.g. days since symptom onset).

Where fields are missing, they may be supplemented by data from the linked health care data. Generally corrections to the randomisation eCRF data are not made. Exceptions to this would include key participant identifiers (Date of birth, NHS or CHI number) or cases where information is missing. For example, if a site later report that the date of birth was entered incorrectly, this would be confirmed with the site (recorded in the trial data query system) and updated (with appropriate audit trail).

5.1.1 Baseline corticosteroid use

Baseline steroid use is determined as follows:

- Baseline steroid use = yes if allocated dexamethasone in main randomisation OR responded 'yes' to baseline steroid question on main randomisation form (OR [for tocilizumab comparison only] responded 'yes' to baseline steroid question on second randomisation form
- Otherwise, Baseline steroid use = no if answered 'no' to steroid question on main OR [for tocilizumab comparison only] second randomisation forms
- Otherwise, Baseline steroid use = not asked if recruited prior to June 18th[2]
- Otherwise, Baseline steroid use = unknown

[2] From 18th June onwards a question on baseline systemic corticosteroid use was added to the main randomisation form following the release of the dexamethasone comparison results.

For the purposes of analysis, baseline steroid use = no and not asked will be combined for subgroup analyses. Participants with baseline steroid use = unknown will be exluded from subgroup analysis, but the number in this subgroup provided in a footnote.

5.2 Additional baseline characteristics

Some baseline characteristics that are not collected on the randomisation eCRF may be extracted from registry data or other sources. These include:

- Ethnicity by Office for National Statistics 2001 census categories (White, BAME [Mixed, Asian or Asian British, Black or Black British, Other Ethnic Groups], Unknown) from linked health care records. Ethnic groups characterised using SNOMED codes within the GDPPR data are mapped to these categories. Where ethnicity records are discrepant between individual episodes in HES/SMR01/PEDW, the most frequently recorded code is used. Within the GDPPR dataset ethnicity is recorded in two places, the ethnic field in the patient table and the presence of a relevant SNOMED code in the journals table. The most recent code in the journals table is used, where available, otherwise the code from the patient table is used. Where there is discrepancy between the best estimate from GDPPR and HES/SMR01/PEDW existsthe GDPPR code is used. Where neither are available the most frequent fode in the SUS data is used. Individual SNOMED codes are categorised as defined with the SNOMED hierarchy and ethnicity categoriese according to the UK department of health categories.[3]
- Confirmed SARS-CoV-2 diagnostic test from linked health care records. A positive SARS-CoV-2 with a test date within 28 days of the date of first randomisation is considered as confirmed SARS-CoV-2. In the absence of such data for a participant, the data from the randomisation eCRF may be used.
- Comorbidity score: It is possible to calculate comorbidity and frailty scores (e.g. Charlston Comorbidity Score) from prior linked hospital admissions data and this will be done for future exploratory analyses (not specified in the trial SAP).
- Prior End Stage Kidney Disease (see section 6.6)
- Risk: The risk of death by 28 days can be modelled using available baseline characteristics (in the overall trial population) and a risk score derived. Participants will be divided into thirds based on this score (such that each third has approximately the same number of deaths), with the tertiles rounded to clinically-relevant values. For the main trial analyses the groups will defined as risk of death by 28 days of <30%; ≥30 ≤45%; and >45%.

6 Outcomes

6.1 All-cause mortality

The primary outcome is all-cause mortality at 28 days after randomisation. All-cause mortality will also be assessed at 6 months and other later time points.

6.1.1 Sources

Information on death may come from the following sources:

- FU eCRF (for deaths within first 28 days after randomisation)
- PDS (for participants in England)
- PDS Wales ((or participants in Wales)
- SUSAPC (for participants in England)

[3] https://www.ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups

- SMR01 (for participants in Scotland)
- PEDW (for participants in Wales)
- ONS mortality data (for participants in England and Wales)
- NRS mortality data (for participants in Scotland)

In general, the primary source will be considered ONS (which includes formal death notification within PDS) and NRS mortality data as these are the official national death registries.

6.1.2 Discrepancies

6.1.2.1 Fact of death

The ONS and NRS mortality data will be considered the defining source for fact of death. In order to allow rapid analysis of results, other sources (e.g. informal death notification via PDS, report of death on the FU eCRF, report of death from SUSAPC) are used for DMC and interim analyses. Cases where these reports are not later substantiated by ONS or NRS are individually reviewed and are not considered as deaths, unless a suitable explanation exists.

6.1.2.2 Date of death

The ONS and NRS data will be considered the defining source for date of death. In order to allow rapid analysis of data, other sources may be used. Where data sources are discrepant the following hierarchy is applied;

- ONS/NRS (most reliable for date of death), then
- Linked hospital admissions data, then
- FU eCRF , then
- PDS informal death notification (least reliable for date of death)

6.2 Cause-specific mortality

The cause of death for the 28 day analysis will be the underlying cause of death as provided by ONS. The causes of death will be categorised as follows:

- Non-vascular death
    - Death from infection
        - Death from COVID-19
        - Death from other infection
    - Death from cancer
    - Death from other medical causes
    - External deaths
- Vascular death
    - Cardiac death
    - Stroke death
    - Other vascular death
- Unknown death

The ICD-10 codes contributing to these categories are available to download from the RECOVERY website.

6.3 Time to discharge

Time to discharge (which is a more accurate term for duration of admission because only the period from randomisation onwards is relevant) is defined as the number of days a participant remained in hospital for acute care after randomisation. Discharge excludes transfer to

another acute hospital, but might include transfer to community hospital for rehabilitation or a hospice for end-of-life care.

6.3.1 Sources

Information on date of discharge may come from the following sources:

- FU eCRF
- SUSAPC (for participants in England)
- PEDW (for participants in Wales)
- SMR01 (for participants in Scotland)

The participant is considered to have been discharged from hospital if there is a discharge date recorded with a discharge method and destination which do not indicate that the participant died or was transferred (see appendix 4). In addition there must be no other admission with an admission date up to 4 days before or 1 day after the discharge date where either the method or source of the admission recorded suggest transfer from another hospital (see appendix 4). The first date of discharge which fulfils these criteria after first or second randomisation is used to determine time to discharge.

6.3.2 Discrepancies

Linked hospital admissions data will be used if date of discharge is discrepant with FU eCRF data. If no linked hospital admissions data are available and the FU eCRF indicates discharge without a date, the date of completion for the FU eCRF will be used.

6.4 Use and duration of ventilation

Assisted ventilation can be broadly divided into

i. Invasive mechanical ventilation (IMV) which includes ECMO (a secondary outcome in combination with all-cause mortality)
ii. Non-invasive ventilation which includes CPAP, NIV and HFNO (which are included in the subsidiary outcomes)

Information on non-invasive ventilation was collected because at the time the trial was designed there were concerns that the availability of mechanical ventilators would be insufficient to meet demand, so some patients would be treated with non-invasive ventilation when in other circumstances they would have received invasive mechanical ventilation. In reality this situation did not occur, so the emphasis of the analyses (and efforts to resolve discrepancies) is on invasive mechanical ventilation.

6.4.1 Sources

Information on ventilation may come from the following sources:

- FU eCRF
- SUSAPC/SMR01/PEDW
- ICNARC
- SICSAG
- CHESS
- CCDS

However, the coding of ventilation is different in each source.

6.4.2 Fact of assisted ventilation

A participant is considered to have received IMV/ECMO if use of these treatments was recorded on the FU eCRF; if a relevant procedure code was recorded in

SUSAPC/SMR01/PEDW within 28 days of randomisation (Appendix 1); if days of advanced respiratory support (ARS) in the ICNARC/CCDS data were considered to fall between randomisation and 28 days (see section 6.4.3) or if the daily SICSAG record indicated that the participant was receiving respiratory support via an endotracheal tube or tracheostomy.

A participant is considered to have received non-invasive ventilation if the site recorded 'yes' to the question 'did the participant receive assisted ventilation' or 'yes' to any of the individual types of non-invasive ventilation (CPAP, BIPAP, HFNO) on the FU eCRF; if a relevant procedure code was recorded in SUSAPC/SMR01/PEDW within 28 days of randomisation (Appendix 2) or if use of HFNO or NIV was recorded in CHESS when the admission and discharge date were both between randomisation and 28 days.

6.4.3 Duration of invasive mechanical ventilation

The data from the critical care datasets (ICNARC, CCDS and SICSAG) are considered the primary source of the duration of IMV. Within ICNARC/CCDS, ARS is considered to be equivalent to IMV, however only the dates of admission and discharge from ICU/HDU and the number of days of ARS are provided. The days of ARS within each critical care episode are assumed to be continuous. The days of ARS were assumed to include randomisation if the participant was recorded as receiving IMV at baseline on the first or second randomisation eCRF as appropriate. Otherwise, the days of ARS are assumed to start from admission to critical care, occur at the mid-point of the critical care admission or end on discharge from critical care depending on the level of care recorded on admission and discharge and, in some cases, the destination on discharge (Appendix 2). Using these assumptions, the information from both ICNARC and the CCDS were used to identify whether IMV was received on each of the 28 days following randomisation. The SICSAG daily record indicated use of IMV on each day.

If no relevant information on IMV is received from ICNARC/CCDS/SICSAG, then the duration of IMV was obtained from the FU eCRF. Cessation of mechanical ventilation is deemed successful if it occurs within (and the participant survives until) 28 days after randomisation.

6.5 Major cardiac arrhythmia

Major cardiac arrhythmias are defined as either:

i. Atrial flutter or fibrillation
ii. Supraventricular tachycardia
iii. Ventricular tachycardia (including torsades de pointes)
iv. Ventricular fibrillation
v. Significant bradycardia (requiring intervention)

6.5.1 Sources

Information on cardiac arrhythmias is collected on the FU eCRF (but only for those eCRFs completed from 12 May 2020 onwards when these outcomes were added).

6.6 Renal replacement therapy

Renal replacement therapy (RRT) includes haemodialysis, haemofiltration (and their combination) and peritoneal dialysis. (Kidney transplantation is not relevant in this case.) Individuals receiving RRT at baseline are identified as follows;

- Patients already receiving renal replacement for End Stage Kidney Disease at baseline are identified using linked hospitalisation data (appendix 3).

- From the ICNARC/CCDS data, the combination of the number of Renal Support Days and the start and end date of a critical episode may imply that they must have been receiving renal support at randomisation.
- The SICSAG daily record indicates that Renal Support was received on the day of, or on the day before randomisation.
- A procedure code in SUS/SMR01/PEDW indicating dialysis or haemofiltration with a date within the 3 days prior to first or second randomisation as appropriate (appendix 1).
- (When available) A record of prior RRT (without documented recovery) from the UK Renal Registry

6.6.1 Sources

- FU eCRF
- Linked hospitalisation data (SUSAPC, HES, PEDW, SMR01)
- ICNARC
- SICSAG
- UKRR

6.6.2 Discrepancies

Use of RRT is collected on the FU eCRF. Use of RRT is also identified within the linked hospitalisation data from relevant OPCS-4 codes (Appendix 1). Use of RRT in the ICNARC/CCDS is identified from the recording of Renal Support days where the both the date of admission to and discharge from critical care fall between randomisation and 28 days. The SICSAG daily record indicates RRT if Renal Support is recorded on any day between randomisation and 28 days.

Further information on renal outcomes may become available from the UK Renal Registry data.

7 Competeness of Follow-up

For the 28 day analysis, follow-up information is considered to be complete if a FU eCRF has been completed, or data has been received from a hospital admissions dataset (SUSAPC, PEDW or SMR01) which includes data from the admission during which the participant was randomised.

8 Analysis of outcomes at 6-months

8.1 Collection of outcomes at 6-months in the UK

In the UK, outcome collection after the initial 28-day follow-up is undertaken by linkage to the routine healthcare datasets, with no further eCRF completion by the site staff. Unless indicated below, the outcomes analysed at 6-months are derived in the same way as for the main trial analyses described in section 6.

8.1.1 Use of ventilation

For the analysis of outcomes at 6-months, use of ventilation is defined in the same way as described in section 6.4. However, periods of ventilation during an elective (i.e. planned) admission following the index admission are excluded, since such procedures are likely to be related to elective surgery rather than complications of COVID-19. Dates of subsequent admissions are obtained from HESAPC and categorised into elective admission or non-

elective admission (including emergency admissions and transfers) on the basis of recorded the admission method (see Appendix 4).

8.1.2 Hospital recorded diagnosis

Diagnoses recorded as the primary reason for a period of in-hospital care are extracted from HESAPC, SMR01 and PEDW. Diagnostic codes are restricted to the first diagnostic position and ICD-10 codes in other positions are not considered. ICD-10 codes within the same block (e.g. I25.1 and I25.2) are considered to relate to the same hospital recorded diagnosis. For each hospital spell the first ICD-10 code recorded within the relevant block is extracted along with a start and end date. The start date is defined as the start of the first episode in which an ICD-10 code in the relevant block is recorded within that spell. The end date is defined as the end of the episode in which an ICD-10 code in the relevant block is recorded within that spell. Examples showing how the dates are extracted are shown in Appendix 5.

Diagnoses for which the first record in that spell is in an episode which started after randomisation are considered to be post-randomisation. Only post-randomisation diagnoses are to be used for the analyses.

Caution should be applied when considering absolute event rates derived from the hospital recorded diagnosis. As can be seen from example 1 and 3 in Appendix 5, more than one hospital recorded diagnoses could be derived from one clinical event, where ICD-10 codes from different blocks are used to record the same clinical event in subsequent episodes. While this is unlikely to result in bias when assessing the proportional effects of treatment, the absolute number of hospital recorded diagnoses should not be interpreted as the absolute number of serious adverse events.

8.1.3 Total duration of critical and hospital in-patient care

Total duration of hospital in-patient care during the 6-months after randomisation is derived from HESAPC based on admission and discharge dates. This is categorised separately by elective vs non-elective (including transfers) as defined in Appendix 4. The total duration of critical care during the 6-months after randomisation is derived from the dates of admission to and discharge from critical care in ICNARC, SUSCCDS, PEDWCCDS and SICSAG. If a period of critical care exists in any of these datasets it will contribute days to this outcome.

8.2 Collection of 6-month outcomes outside the UK

Sites will complete a case report form at 6 months after randomisation to capture information on vital status, use of ventilation and any admissions to hospital.

9 Appendix 1: OPCS-4 and ICD-10 codes used to identify assisted ventilation and other outcomes in the linked hospitalisation data

Outcome	code	Code type	Description
Use of CPAP	E85.6	OPCS	Continuous positive airway pressure
Use of NIV	E85.2	OPCS	Non-invasive ventilation NEC
Use IMV	E85.1	OPCS	Invasive ventilation
Use of ECMO	X58.1	OPCS	Extracorporeal membrane oxygenation
Use of RRT	X40.1	OPCS	Renal dialysis
	X40.3	OPCS	Haemodialysis NEC
	X40.4	OPCS	Haemofiltration

(OPCS and ICD-10 codes used to identify serious arrhythmia and other non-fatal outcomes to be added at a later date.)

10 Appendix: 2: Rules for determining start/end of advanced respiratory support days in the critical care datasets

Information is available in ICNARC/CCDS on

- The start and end date of the critical care episode
- The level of care at admission to the unit
- The level of care at discharge from the unit
- The reason for discharge from the unit
- The number of days of Advance Respiratory Support (ARS) received during the episode

The table below defines the rules for deciding whether the days on ARS in an ICNARC/CCDS episode should count from admission onwards (A), before discharge (D) or at the midpoint between admission and discharge (M)

		Level of care at admission to the unit				
		0	1	2	3	blank
Level of care at discharge from the unit	0	M	M	M	A	A
	1	M	M	M	A	A
	2	M	M	M	A	A
	3	D	D	D	A	D
	blank	*	*	*	A	A

* If the reason for discharge from the unit is ‘comparable critical care’ or ‘more-specialist critical care’ then D, otherwise M.

The following definitions are taken from the ICNARC data collection manual Version 3.1 (29 June 2009).

Level 3 – indicated by one or more of the following:

- admissions receiving advanced respiratory monitoring and support due to an acute illness
- admissions receiving monitoring and support for two or more organ system dysfunctions (excluding gastrointestinal support) due to an acute illness
- admissions solely receiving basic respiratory monitoring and support and basic cardiovascular monitoring and support due to an acute illness only meet Level 2

Level 2 – indicated by one or more of the following:

- admissions receiving monitoring and support for one organ system dysfunction (excluding gastrointestinal support) due to an acute illness
- admissions solely receiving advanced respiratory monitoring and support due to an acute illness meet Level 3
- admissions solely receiving basic respiratory and basic cardiovascular monitoring and support due to an acute illness meet Level 2
- admissions receiving pre-surgical optimisation including invasive monitoring and treatment to improve organ system function
- admissions receiving extended post-surgical care either because of the procedure and/or the condition of the admission
- admissions stepping down to Level 2 from Level 3 care

Level 1 – indicated by one or more of the following:

- admission recently discharged from a higher level of care
- admissions receiving a greater degree of observation, monitoring, intervention(s), clinical input or advice than Level 0 care
- admissions receiving critical care outreach service support fulfilling the medium-score group, or higher, as defined by NICE Guidelines 50

Level 0 – indicated by the following:

- admissions in hospital and receiving normal ward care

11 Appendix 3: Definition of prior RRT for End Stage Renal Disease

A previously validated algorithm was adapted to identify people requiring dialysis for ESRD from the prior HES/SMR01/PEDW.

Individuals who met the criteria for Rules 2-4 during a hospital admission prior to the admission during which they were randomised were considered to have prior ESRD provided they did not meet the criteria for Rule 1 after meeting the other criteria.

Rule 1: Kidney Transplantation

Occurrence of any incident kidney transplant code (with no removal within 90 days), or a prevalent kidney transplant code with no removal having occurred prior to the record.

Rule 2: Peritoneal maintenance dialysis

Occurrence of any admission with a peritoneal dialysis code (without diagnosis of acute kidney injury).

Rule 3: Definite maintenance dialysis

Occurrence of a dialysis code in a patient who has had:

(a) a diagnostic code for ESRD any time prior to, or within 365 days; or

(b) the insertion of an AV fistula or graft any time prior to, or within 365 days.

Rule 4: Probable maintenance dialysis

The occurrence of at least two episodes containing a dialysis code, with at least 90 days between the start of the first recorded dialysis, and the start of any subsequent dialysis (without agnosis of acute kidney injury).

Relevant ICD-10 and OPCS-4 codes for Rules 1-4 above

Group	Category	ICD-10	OPCS-4	Description
Diagnosis	Acute kidney injury	N17		Acute renal failure
Diagnosis	End-stage renal disease	N18.0		End-stage renal disease
Diagnosis	End-stage renal disease	N18.5		Chronic kidney disease, stage 5
Diagnosis	End-stage renal disease	Q60.1		Renal agenesis, bilateral
Dialysis	Dialysis	E85.3		Secondary systemic amyloidosis (dialysis related)
Dialysis	Dialysis	Y60.2		Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care; during kidney dialysis…..
Dialysis	Dialysis	Y61.2		Foreign object accidentally left in body during surgical and medical care; during kidney dialysis or other perfusion
Dialysis	Dialysis	Y62.2		Failure of sterile precautions during surgical and medical care; during kidney dialysis or other perfusion
Dialysis	Dialysis	Y84.1		Other medical procedures as the cause of abnormal reaction of the patient, or of later complication; kidney dialysis
Dialysis	Dialysis	Z99.2		Dependence on enabling machines and devices, not elsewhere classified; dependence on renal dialysis
Dialysis	Dialysis		X40.1	Renal dialysis
Dialysis	Haemodialysis	T82.4		Mechanical complication of vascular dialysis catheter
Dialysis	Haemodialysis	Z49.1		Care involving dialysis; extracorporeal dialysis
Dialysis	Haemodialysis		X40.3	Haemodialysis NEC
Dialysis	Haemodialysis		X40.4	Haemofiltration
Dialysis	Insertion of AVF or graft		L74.1	Insertion of arteriovenous prosthesis
Dialysis	Insertion of AVF or graft		L74.2	Creation of arteriovenous fistula NEC
Dialysis	Insertion of AVF or graft		L74.6	Creation of graft fistula for dialysis
Dialysis	Insertion of AVF or graft		L74.8	Other specified arteriovenous shunt
Dialysis	Insertion of AVF or graft		L74.9	Unspecified arteriovenous shunt
Dialysis	Insertion of PD catheter		X41.1	Insertion of ambulatory peritoneal dialysis catheter
Dialysis	Peritoneal dialysis	Z49.2		Care involving dialysis; other dialysis
Dialysis	Peritoneal dialysis		X40.2	Peritoneal dialysis NEC
Dialysis	Peritoneal dialysis		X40.5	Automated peritoneal dialysis
Dialysis	Peritoneal dialysis		X40.6	Continuous ambulatory peritoneal dialysis
Dialysis	Tunnelled line insertion		L91.5	Insertion of tunnelled venous catheter
Transplantation	Incident kidney transplant		M01.2	Allotransplantation of kidney from live donor
Transplantation	Incident kidney transplant		M01.3	Allotransplantation of kidney from cadaver NEC
Transplantation	Incident kidney transplant		M01.4	Allotransplantation of kidney from cadaver heart beating
Transplantation	Incident kidney transplant		M01.5	Allotransplantation of kidney from cadaver heart non-beating
Transplantation	Incident kidney transplant		M01.8	Other specified transplantation of kidne
Transplantation	Incident kidney transplant		M01.9	Unspecified transplantation of kidney
Transplantation	Prevalent kidney transplant	N16.5		Renal tubulo-interstitial disorders in transplant rejection
Transplantation	Prevalent kidney transplant	T86.1		Kidney transplant failure and rejection
Transplantation	Prevalent kidney transplant	Z94.0		Kidney transplant status
Transplantation	Prevalent kidney transplant		M08.4	Exploration of transplanted kidney
Transplantation	Prevalent kidney transplant		M17.4	Post-transplantation of kidney examination - recipient
Transplantation	Prevalent kidney transplant		M17.8	Other specified interventions associated with transplantation of kidney
Transplantation	Prevalent kidney transplant		M17.9	Unspecified interventions associated with transplantation of kidney
Transplantation	Removal of kidney transplant		M02.6	Excision of rejected transplanted kidney

12 Appendix 4: Definitions of discharge and of elective/planned admissions

Definition of discharge used for the time to discharge outcome (see section 6.3)

Dataset	Criteria	Definition
PEDW	Discharge method not died or tranfer	Discharge method not 4 or 8, and Discharge destination not 49, 51, 52, 53, 55, 56, 57, 79, 87, 98
	No other admission up to 4 days before or 1 day after discharge which suggests transfer	Admission source 51 or 87, or Admission method 2B, 81 or 28
HES/SUS	Discharge not died or tranfer	Discharge method not 4 or 8, and Discharge destination not 49, 50, 51, 52, 53, 79, 87 or 98
	No other admission up to 4 days before or 1 day after discharge which suggests transfer	Admission source 51 or 87, or Admission method 2B, 81 or 28
SMR01	Discharge not died or tranfer	Discharge type not 40-43, and Discharge type is 10, 11, 18, 19, 70, 20-23, 28, 29
	No other admission up to 4 days before or 1 day after discharge which suggests transfer	Admission type 18, 30, 36, 38, 39, 40

Definition of planned / elective admissions used for the 6-months outcomes (see section 8.1.1)

Dataset	Admission type	Definitions
PEDW	Planned	If admission method NOT (21 or 22 or 23 or 24 or 25 or 27 or 28 or 81)
HES/SUS	Planned	IF admission method NOT (21 or 22 or 23 or 24 or 25 or 28 or 81 or 2A or 2B or 2C or 2D)
SMR01	Planned	IF admission type NOT (18 or 20 or 21 or 22 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 38 or 39)

13 Appendix 5: Example hospital recorded diagnoses showing extraction of start and end dates

Table: Four example HESAPC spells each containing three episodes

	Example 1	**Example 2**	**Example 3**	**Example 4**
Episode 1 Episode start date 01/02/2021 Episode end date 02/02/2021	R07.4 Chest pain unspecified	I219 Acute myocardial infarction, unspecified	J18.0 Bronchopneumonia unspecified	N17.9 Acute renal failure unspecified
Episode 2 Episode start date 02/02/2021 Episode end date 05/02/2021	I21.4 Acute subendocardial myocardial infarction	I210 Acute transmural myocardial infarction of anterior wall	J15.9 Bacterial pneumonia unspecified	I26.0 Pulmonary embolism with mention of acute cor pulmonale
Episode 3 Episode start date 05/02/2021 Episode end date 08/02/2021	A04.7 Enterocolitis due to Clostridium difficile	I210 Acute transmural myocardial infarction of anterior wall	J15.2 Pneumonia due to staphylococcus	N17.9 Acute renal failure unspecified

The hospital recorded diagnoses and relevant dates which would be extracted from these examples are as follows:

Example 1:

- R07.4 Start date 01/02/2021 End date 02/02/2021
- I21.4 Start date 02/02/2021 End date 05/02/2021
- A04.7 Start date 05/02/2021 End date 08/02/2021

Example 2:

- I219 Start date 01/02/2021 End date 08/02/2021

Example 3:

- J18.0 Start date 01/02/2021 End date 02/02/2021
- J15.9 Start date 02/02/2021 End date 08/02/2021

Example 4:

- N17.9 Start date 01/02/2021 End date 08/02/2021
- I26.0 Start date 02/02/2021 End date 05/02/2021

Appendix 4: Validation of serum nucleocapsid antigen assay

UK Health Security Agency

Assessment of antigen assays for the detection of SARS-CoV-2 antigen in serum and plasma samples

Emerging Pathogen Serology Group, Vaccine Development Evaluation and Preparedness Centre (VDEP), UK Health Security Agency, Porton Down

Contents

1. Contributors

Name	Role
Dr Ash Otter	Group Leader
Cathy Rowe	General Project Manager
Tom Coleman	Research Scientist
Bethany Hicks	Research Scientist

2. Introduction

The assays described in this validation report were used solely for research purposes and were not intended for diagnostic use, as part of supporting the RECOVERY trial. No financial incentives or sponsorship were provided by manufacturers, and the manufacturers or operators had no role in the analysis or interpretation of the final data. All testing was conducted under blinded conditions to ensure impartiality in the testing procedures, and all operators involved in running the assay were fully trained and qualified in its application.

Roche Elecsys Antigen assay

The Elecsys SARS-CoV-2 antigen assay is an *in vitro* qualitative electrochemiluminescence immunoassay (ECLIA) specifically targeting the nucleocapsid protein of SARS-CoV-2, one of the most abundant structural proteins of SARS-CoV-2[1].

Diagnostic confirmation of SARS-CoV-2 infection can be achieved through the amplification of unique viral RNA sequences through the use of PCR or through the detection of unique viral proteins, such as the Elecsys SARS-CoV-2 antigen assay, these rapid diagnostic methods can be utilised to help slow the spread of transmission as viral antigens are only expressed when the virus is replicating[2,3,4].

The manufacturer states this assay can be used on a variety of sample types including viral transport media swabs and dry swabs (either oropharyngeal or nasopharyngeal), using the automated and closed Roche e801 and e402 platforms. However, serum samples are currently not a validated sample recommended by the manufacturer. Samples are considered positive (e.g. the presence of nucleocapsid antigen) if the cut off index (COI) is ≥1.0, whilst samples with a COI of <1.0 are considered negative.

In brief, the Roche antigen assay employs a double-antibody sandwich principle, with a total duration of 18 minutes. The mechanism of the assay is as follows: a sandwich complex is formed with patient samples (those that are likely to contain SARS-CoV-2 antigen, e.g. VTM or dry swab) and incubated with biotinylated monoclonal anti-SARS-CoV-2-Ab antibodies, and ruthenium complex-labelled monoclonal anti-SARS-CoV-2-Ab antibodies. Steptavadin-coated

[1] Ke Z, Oton J, Qu K et al., Structures and distributions of SARS-CoV-2 spike proteins or intact virions. Nature. Aug 17 2020

[2] World Health Organisation. Diagnostic testing for SARS-CoV-2. Interim guidance. Website: https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2. Accessed: 06/05/2022

[3] World Health Organisation. Advice on the use of point-of-care immunodiagnostic tests for COVID-19. Website: https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19. Accessed: 06/05/2022

[4] Centers for Disease Control and Prevention. Interim guidance for rapid antigen testing for SARS-CoV-2. Website: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html. Accessed: 06/05/2022

microparticles are introduced into the complex causing it to become bound to the solid-phase, ProCell II M removes any unbound particles and chemiluminescence is induced through the application of a voltage to the electrode[5]. Photomultipliers within the Roche platforms then measure this chemiluminescence and provide a COI.

MSD

The MesoScale Discovery (MSD) SARS-CoV-2 antigen assay is similarly an ultra-sensitive electrochemiluminescence immunoassay targeting the nucleocapsid protein of SARS-CoV-2 in human serum, EDTA plasma, saliva, and nasopharyngeal swabs[6].

The S-PLEX assay can have up to a 1000-fold lower limit of detection compared to other assays, enabling the use of lower volumes of sample and key reagents alike. This assay works similarly to the Roche antigen ECLIA but is performed on an MSD S-PLEX plate. In brief, the assay requires coating with biotin-conjugated capture antibody and turbo-boost detection antibody, followed by the addition of samples. Enhance and detection solution are added to each well prior to the addition of the final detection antibody. Plates are then read by the MSD instrument for luminescence[5].

Comparisons

Assays were compared in their capability for throughput, detection limits and cross-reactions to determine their feasibility as a research-grade assay for detecting antigen within serum samples.

[5] Roche Diagnostics, Elecsys® SARS-CoV-2 Antigen assay. Website: https://diagnostics.roche.com/global/en/products/params/elecsys-sars-cov-2-antigen-test.html. Accessed: 06/06/2022.

[6] MesoScaleDiscovery – SARS-CoV-2 antigen assay, S-PLEX SARS-CoV-2 N kit. Website: https://www.mesoscale.com/en/products/S-PLEX-SARS-CoV-2-n-kit-sector-1-pl-k150adhs/. Accessed: 06/05/2022

3. Methods and platforms

All Roche testing was performed on the Roche e801 automated platform as recommended by the manufacturer using Roche Elecsys SARS-CoV-2 Antigen kits (COV2AG, product number: 09345299190; kit lot: 60899000). Similarly, samples tested on the MSD S-PLEX Antigen assay (Product number: K150ADHS-2; lot: Z0050018) were performed as recommended by the manufacturer, with plates washed using the Biotek 405-TS plate washer (using settings recommended by MSD) before reading on the MSD QuickPlex SQ 120.

4. Linearity and Limit of Detection

Initial stock concentrations of recombinant protein (2.5 mg/ml, ThermoFisher Life Sciences Ltd, # **RP-87665**) were diluted into PBS (Gibco, #10010023) to generate a stock concentration. Further dilutions of 1 in 2, 1 in 4, 1 in 10, and 3 in 4 were done to provide a range of dilutions (Figure 1) and each of these dilutions were subsequently serially diluted 10-fold, up to eight times in human negative serum (Merck, #H4522-100ML). This dilution series panel was run in triplicate on the Roche Antigen ECLIA and the MSD antigen assay. Additionally, SRS-CoV-2 Omicron recombinant N protein (1.33 mg/ml, The Native Antigen Company, #REC32014-100) and SARS-CoV-1 recombinant N protein (100 µg/ml, abcam, #AB49042) were similarly serially diluted in human negative serum.

The Roche assay was found to have a limit of detection between 2.5 and 6.25 pg/ml (Figure 1). However, the hook-effect was observed with the Roche antigen assay. A similar limit of detection was seen for recombinant Omicron nucleocapsid protein, with a detection limit between 2.5 and 6.25 pg/ml, suggesting minimal loss of assay sensitivity when detecting the Omicron recombinant protein. SARS-CoV-1 showed strong cross-reactivity, comparable to SARS-CoV-2.

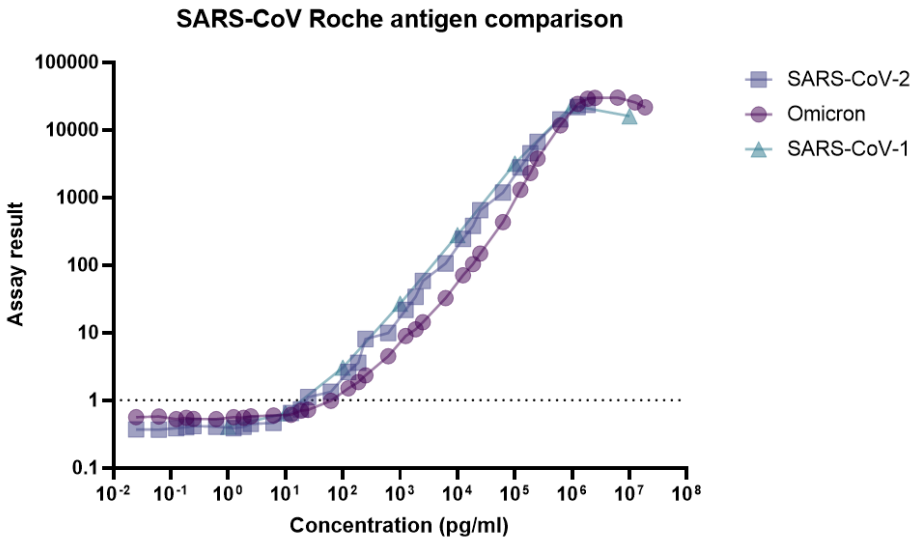

Figure 1: Serial dilution of recombinant protein of SAR-CoV-2, SARS-CoV-2 Omicron (B.1.1.529) and SARS-CoV-1.

5. Comparing Roche and MSD limits of detection

To compare limits of detection between the Roche and MSD antigen assays, the same dilution series were plotted according to their protein concentration (pg/ml) and the assay results (Roche; COI and MSD; U/ml).

The Roche assay showed a wide dynamic range, from ~0.3 up to 29,000 COI (corresponding to 6.25 to 6,250,000 pg/ml), however the MSD showed a saturation at lower protein concentration but detection at a lower concentration, with an assay range of 0.039 up to 4,300 U/ml (corresponding to 0.000625 to 250,000 pg/ml). This is likely explained by the nature of the MSD assay, requiring samples be diluted up to 1 in 10,000 to within the detection range of the assay, whereas the Roche platform requires no additional dilutions.

The Roche assay had an estimated limit of detection between 2.5 and 6.25 pg/ml whilst the MSD assay was found to have an estimated limit of detection between 0.000625 and 0.025 pg/ml.

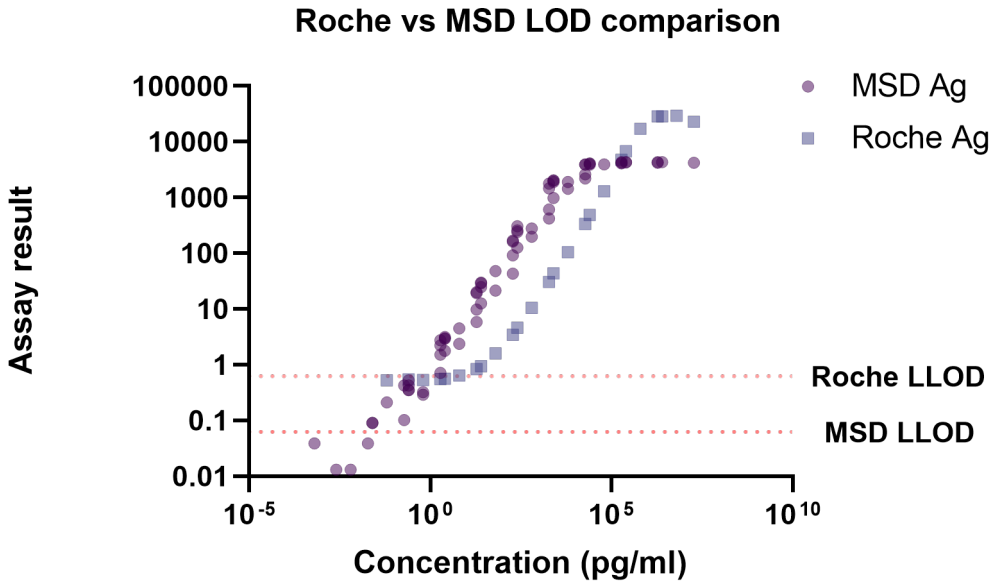

Figure 2: Comparison of sensitivity between Roche SARS-CoV-2 antigen assay and MSD S-PLEX antigen plate

6. Cross-reactivity

Three sample sets were used to determine cross-reactivity of the Roche antigen assay: a serial dilution of SARS-CoV-1 recombinant N protein (shown in Figure 1), 50 pre-pandemic negatives (sourced from a study during 2017), and four seasonal human coronaviruses recombinant proteins/viral lysates: HKU1, NL63, 229E, and OC43 (Product codes are listed within the Appendix).

Pre-pandemic serum samples

50 pre-pandemic samples were tested, and all were below the manufacturers recommended assay cut off (<1.0 COI) (Figure 3), with an average COI of 0.3965 (95% CI, 0.3913 – 0.4018). However, due to slight variations between lots numbers, this number may vary slightly.

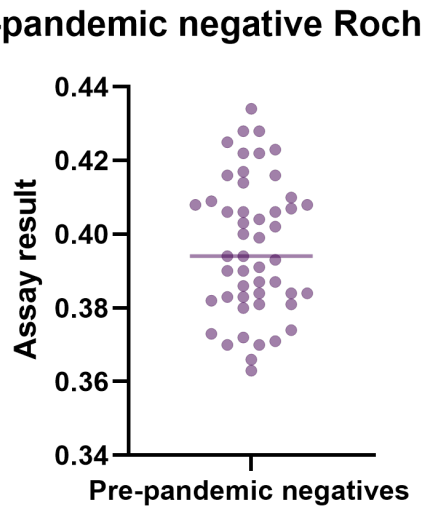

Figure 3: Pre-pandemic negative samples, tested on Roche SARS-CoV-2 antigen assay. (Mean: 0.397; Standard Deviation: 0.019)

Human seasonal coronavirus dilutions

Four purified human coronavirus lysates containing potentially cross-reacting nucleocapsid proteins were serially diluted 10-fold in PBS. No cross-reactivity was observed (Figure 4), with all samples below 0.431 COI.

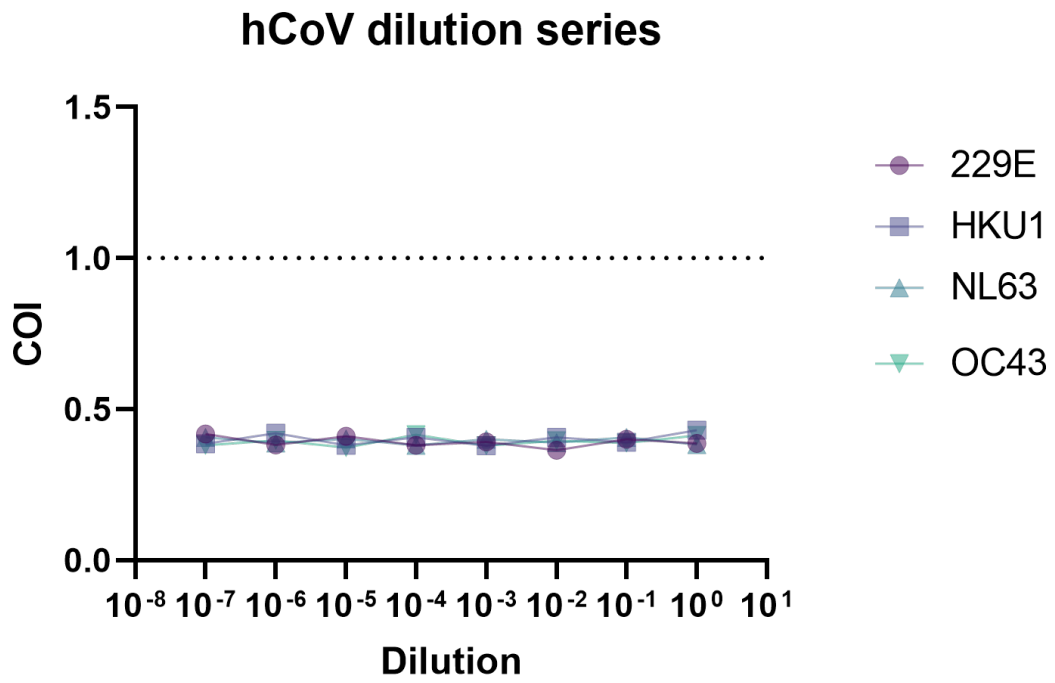

Figure 4: Seasonal human coronaviruses (229E, HKU1, NL63 and OC43) serially diluted and tested using the Roche SARS-CoV-2 antigen assay.

7. Repeatability

To determine the repeatability of the assay, recombinant protein dilutions were run consecutively across 20 days, whilst antigen containing serum or plasma samples (sourced as part of the RECOVERY testing) were tested repeatedly across 5-8 days, with storage at 4°C in between testing.

Internal quality controls

Recombinant SARS-CoV-2 nucleocapsid protein was diluted in human negative serum to a COI of ~15 for the positive IQC. Negative IQCs were comprised of human negative serum only. All IQCs were aliquoted and stored at -20°C until use. IQCs were run for 20 consecutive days and the data tracked using Levy-Jennings plot to generate a mean with three +/- standard deviations.

The results can be found in the attached Excel spreadsheet under the “IQC range” tab within the attached spreadsheet.

Repeated sample testing

Additionally, 19 SARS-CoV-2 (10 serum and 9 plasma samples) were run 5-8 consecutive days. The covariance ranged between 1.749-4.591%, thereby indicating high repeatability of the Elecsys SARS-CoV-2 Antigen assay (Table 1). Data can be found within the attached spreadsheet under the “Sample repeatability” tabs, data is split by positive and negative/borderline samples.

Table 1: RECOVERY serum and plasma samples tested on Elecsys SARS-CoV-2 Antigen assay over consecutive days, stored at 4°C

Sample Repeatability													
Sample Type	**Sample ID**	**Original Result**	**Repeat 1**	**Repeat 2**	**Repeat 3**	**Repeat 4**	**Repeat 5**	**Repeat 6**	**Repeat 7**	**Repeat 8**	**Mean**	**StDev**	**%CV**
Plasma	1	57.2	57.2	60.9	64.6	64.2	65.5	66	64.5	63.2	63.263	2.904	4.591
	2	1.58	1.58	1.68	1.65	1.67	1.65	1.62	1.53	1.63	1.626	0.050	3.065
	3	2.24	2.24	2.33	2.39	2.37	2.42	2.45	2.37	2.39	2.370	0.063	2.678
	4	0.53	0.539	0.541	0.525	0.53	0.519	N/A	N/A	N/A	0.531	0.009	1.749
	5	1.43	1.55	1.54	1.48	1.43	1.5	N/A	N/A	N/A	1.500	0.048	3.232
	6	0.557	0.562	0.584	0.559	0.557	0.562	N/A	N/A	N/A	0.565	0.011	1.937
	7	0.908	0.966	0.967	0.937	0.908	0.971	N/A	N/A	N/A	0.950	0.027	2.844
	8	6.05	6.05	6.37	6.39	6.39	6.38	6.31	6.15	6.1	6.268	0.144	2.290
	9	22.3	22.3	24.5	23.9	23.9	24.5	24.3	22.7	22.2	23.538	0.980	4.162
Serum	1	8.53	8.53	8.88	8.65	8.52	8.52	8.62	8.14	7.84	8.463	0.324	3.834
	2	139	139	151	148	150	150	149	144	142	146.625	4.406	3.005
	3	5.41	4.97	5.2	5.41	5.21	5.19	5.17	4.97	5.05	5.146	0.147	2.848
	4	5.71	5.71	6.22	5.98	6.11	5.89	6.04	5.66	5.66	5.909	0.215	3.637
	5	1.8	1.8	1.89	1.87	1.85	1.86	1.92	1.84	1.8	1.854	0.041	2.232
	6	8.92	8.92	9.77	9.61	9.51	9.11	9.33	8.8	8.75	9.225	0.387	4.198
	7	5.34	5.34	5.59	5.54	5.6	5.54	5.63	5.36	5.24	5.480	0.145	2.652
	8	0.597	0.631	0.61	0.611	0.596	0.598	N/A	N/A	N/A	0.609	0.014	2.290
	9	0.649	0.699	0.697	0.679	0.677	0.729	N/A	N/A	N/A	0.696	0.021	3.003
	10	0.683	0.739	0.721	0.694	0.69	0.743	N/A	N/A	N/A	0.717	0.025	3.438

8. Freeze Thawing

Eleven SARS-CoV-2 (4 plasma and 7 serum) samples were tested on 8 consecutive days, whereas, 11 (7 plasma and 4 serum) were tested on 5 consecutive days. Thereby, completing 8 and 5 freeze thaw cycles, respectively (Figure 5). Overall, freeze thaws did not have a detrimental effect on detecting SARS-CoV-2 antigen and the samples remained consistent through 8 freeze-thaw cycles, indicating repeated freeze-thawing does not degrade SARS-CoV-2 antigen in serum or plasma. Data can be found within the “Sample Freeze Thaw” tab on the attached spreadsheet.

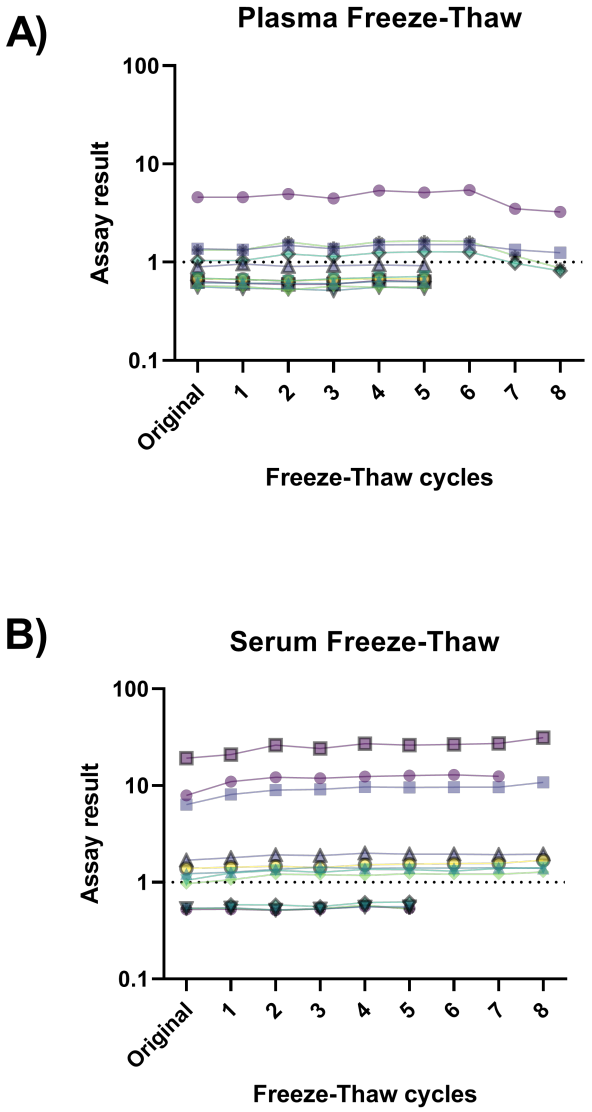

Figure 5: Variation in antigen results across a number of freeze-thaw cycles using the Roche antigen assay. Each line represents a single sample.

9. Summary of Results

In conclusion, both the Roche Elecsys® SARS-CoV-2 Antigen assay and the MSD S-PLEX SARS-CoV-2 Nucleocapsid antigen assay offer a reliable way to measure antigen within serum and plasma samples.

Both assays performed well using a dilution series of recombinant nucleocapsid protein, with the MSD outperforming the Roche with a lower limit of detection, however, due to the nature of the MSD assay, samples were required to be diluted up to 1 in 1,000 to get within the detection range of the assay. Conversely, the Roche antigen assay did not require this sample dilution step but did suffer from the 'hook effect' at high concentrations of recombinant SARS-CoV-2 protein.

Due to the throughput required, the Roche antigen assay was used for further characterisation for use on serum samples. No cross-reactivity to seasonal human coronaviruses was observed and no loss in assay sensitivity was found when using a recombinant SARS-CoV-2 Omicron nucleocapsid protein (the most prevalent VOC at the time of the trial). However, SARS-CoV-1 recombinant protein did cross-react. Repeated measurement of samples across 5 to 8 days showed minimal variation, with a %CV of <5%. Freeze-thawing was found to have a minimal impact on detecting SARS-CoV-2 nucleocapsid in serum or plasma, however, was observed when detecting recombinant protein likely due to protein degradation in serum.

10. Appendix

Appendix 1: Human Coronavirus product details:

- Purified Lysate viral - OC43, Product code: NAT41606-100
- Purified Lysate viral - 229E, Product code: NAT41608-100
- Purified Lysate viral - NL63, Product code: NAT41607-100
- Recombinant nucleoprotein – HKU1, Product code: REC31856-100

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation health secure.

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Version 1

Prepared by Ashley Otter, Bethany Hicks, Tom Coleman, and Cathy Rowe.
For queries relating to this document, please contact Ashley Otter, +44 (0) 1980 619723, ashley.otter@ukhsa.gov.uk