RECOVERY TRIAL PROTOCOL

This protocol describes the RECOVERY Trial, a randomised platform trial among patients hospitalised for pneumonia caused by influenza and other pathogens (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 the RECOVERY trial was being set up, 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. Opening in March 2020, RECOVERY evaluated twenty SARS-CoV-2 therapies, providing reliable evidence about their efficacy and safety that has informed the treatment of patients worldwide. Since then, the progress in COVID-19 treatment has highlighted the need for better evidence for the treatment of pneumonia caused by other pathogens, such as influenza and bacteria, for which therapies are widely used without good evidence of benefit or safety.

Eligibility and randomisation: This protocol (version 28.0) includes treatment comparisons for influenza and community-acquired pneumonia. No COVID-19 comparisons are currently open in the trial. 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, or as new infectious respiratory threats emerge. 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
Influenza	Baloxavir marboxil	No baloxavir marboxil use for current infection
	Oseltamivir	No neuraminidase inhibitor use for current infection
	Corticosteroids	hypoxia; without suspected or confirmed SARS-CoV-2 infection; no corticosteroid use for current infection
Community-acquired pneumonia	Corticosteroids	without suspected or confirmed SARS-CoV-2, influenza, TB[a] or PJP[b]; no corticosteroid use for current infection

[a]active pulmonary tuberculosis; [b]*Pneumocystis jirovecii* pneumonia (also known as PCP)

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 viral or bacterial pneumonia.

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
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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 ranged from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure. Many countries experienced a major increase in the number of hospitalised pneumonia patients, and mortality in hospitalised patients was as high as 30%.[2–4] The RECOVERY platform trial was initially set up to evaluate treatments for this new 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 or bacterial infection 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 and bacterial infection.[15,16] Anti-SARS-CoV-2 antivirals can improve outcomes in hospitalised COVID-19 patients, but there is no similar evidence for anti-influenza antivirals.[17,18]

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 pneumonia. 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 2.4-2.5 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 patients hospitalised with pneumonia receiving usual standard of care. Pneumonia is a common cause of hospital admission, particularly during seasonal respiratory virus epidemics, and carries 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.

For influenza and community-acquired pneumonia, the average length of hospital stay is around 7-9 days, and most mortality occurs within 28 days of admission, so assessment at 28 days will capture most outcomes.[19,20]

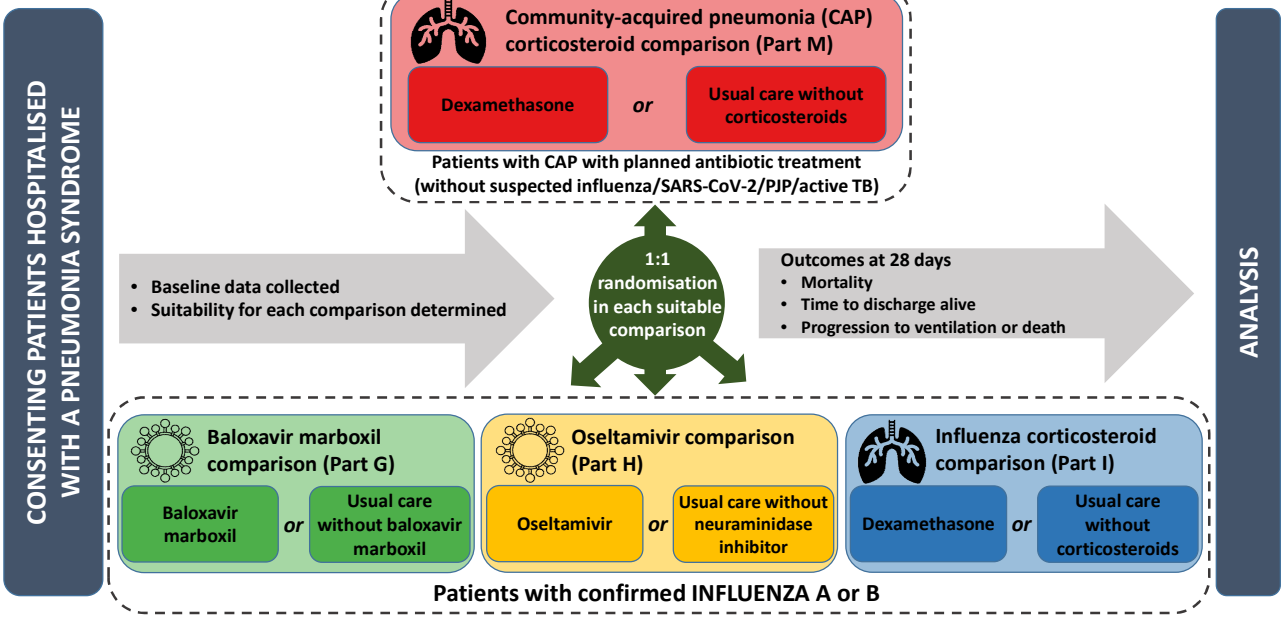
1.5 Potential for effective treatments to become available

In early 2020, when the trial first started, there were no known treatments for COVID-19. However, over time, effective treatments became 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.[6] 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

Figure 1: RECOVERY trial design



A summary of trial procedures is provided in Appendix 7 (schedule of assessments).

2.1 Eligibility

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

(i) Hospitalised

(ii) Pneumonia syndrome

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

a) typical symptoms of a new respiratory tract infection (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
b) objective evidence of acute lung disease (e.g. consolidation or ground-glass shadowing on X-ray or CT, hypoxia, or compatible clinical examination); and
c) alternative causes have been considered unlikely or excluded (e.g. heart failure).

However, the diagnosis remains a clinical one based on the opinion of the managing doctor (the above criteria are just a guide).

(iii) One of the following diagnoses:

a) Confirmed influenza A or B infection (including patients with SARS-CoV-2 co-infection)
b) Community-acquired pneumonia (CAP) with planned antibiotic treatment (excluding patients with suspected or confirmed SARS-CoV-2, influenza, active pulmonary tuberculosis or *Pneumocystis jirovecii* pneumonia)

(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 suspected or confirmed active pulmonary tuberculosis or *Pneumocystis jirovecii* pneumonia (also known as PCP or PJP) are excluded from the CAP comparison, as these infections are caused by specific organisms with distinct pathologies, and so are not usually categorised as CAP. Eligibility for the CAP comparison also requires planned antibiotic treatment, so patients being treated solely for fungal or viral pneumonia are not eligible.

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. If a patient does not have capacity to consent due to severe disease (e.g. needing ventilation) or a prior condition, then legal representative consent is required for the patient to participate in the trial. Due to the poor outcomes in patients hospitalised with pneumonia (5-10% mortality, rising to over 40% in those with severe disease[21,22]), patients who lack capacity to consent and for whom a relative to act as the legally designated representative is not available (in person), randomisation and consequent treatment can proceed with consent provided by a clinician (independent of the trial[a]) who can 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.

[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.)

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 (depending on local privacy requirements, this may include name or initials, 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, C-reactive protein, and procalcitonin (if available)
- Influenza test results (if available, and note confirmation of influenza infection is required for entry into influenza comparisons)
- 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, antivirals) and prior vaccination
- Date of hospitalisation
- 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.

[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).

2.3.1 Baseline sample collection[e]

2.3.1.1 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 (not at sites in the EU, and only 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.

2.3.1.2 Participants with community-acquired pneumonia

These participants do not require any samples to be collected.

2.4 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.

2.4.1 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[f].

2.4.2 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[f,g].

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

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

2.4.3 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**
- **Corticosteroids: Dexamethasone 6mg once daily given** orally or intravenously for ten days or until discharge (whichever happens earliest)[h]

2.5 Randomised allocation of treatment for community-acquired pneumonia

In addition to receiving usual care, eligible patients with a diagnosis of community-acquired pneumonia (without suspected or confirmed COVID-19, influenza, tuberculosis, or *Pneumocystis jirovecii* infection) will be allocated treatment using a central web-based randomisation service (without stratification or minimisation). Region-specific exclusions, including those related to age, pregnancy and breastfeeding, are given in Appendix 6.

2.5.1 Randomisation part M

Eligible patients (≥18 years old) may be randomised in a ratio of 1:1 to one of the arms listed below.

- **No additional treatment**
- **Corticosteroids: Dexamethasone 6mg once daily given** orally or intravenously for ten days or until discharge (whichever happens earliest)[h]

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 (for example, if the condition of a participant who had been allocated to usual care changed to the extent that their doctor considered that an active and routinely available treatment was now clearly indicated, then such a treatment may be given, but the participant should not be withdrawn from the study). 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)

[h] 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 with influenza see Appendix 3.

- 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.
- 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 pneumonia treatments
- Participation in other randomised trials of interventions (vaccines or treatments) for pneumonia.
- Metabolic complications: ketoacidosis; hyperglycaemic hyperosmolar state; hyperglycaemia requiring new use of insulin; severe hypoglycaemia (defined as 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
- 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.[i]

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

2.7.1.1 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.

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

[j] 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.

2.7.1.2 Participants with community-acquired pneumonia

No follow-up samples are required from participants with community-acquired pneumonia.

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.

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, coded data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data in the study database 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 is available on the study website.[k]

3.1 Outcomes

3.1.1 Primary and secondary outcomes for evaluation of potential treatments for community-acquired pneumonia

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

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

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%.[23]

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) 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.[k]

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[l] 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, pneumonia 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.

[l] 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).

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.

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 influenza or community-acquired pneumonia; 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.[m] 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.

[m] 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.

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 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 pneumonia) and the reliability of the results that would inform the care for future patients.[24]

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,[24] 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.[25,26] 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. 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 be 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 the 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 RCCs which will assist with selection of 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 has been supported by grants to the University of Oxford from UK Research and Innovation/National Institute for Health and Care 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 pneumonia 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).

Proposals for additional analyses and publications using trial data (including from independent external researchers) are considered by the Trial Steering Committee or, when the data have been transferred to them, the Data Access Committee of the Infectious Diseases Data Observatory (an organisation that hosts a dedicated data-sharing platform; www.iddo.org). The relevant committee will facilitate the use of the study data and approval will not be unreasonably withheld. However, the 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 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
27.0	13-Sep-2023	Addition of low dose dexamethasone vs usual care comparison for patients with community-acquired pneumonia Addition of EU collaborators
28.0	30-Jun-2025	Removal of closed comparisons (sotrovimab and high dose dexamethasone for COVID-19). Addition of clarifications requested in regulatory feedback on V27.0 (including removal of the term ‘low dose’ dexamethasone and clarification of data sharing plans) Update to table 1 to clarify comparison-specific eligibility criteria.

Version number	Date	Brief Description of Changes
		Update to background information and information about treatment arms. Addition of trial design figure Update to appendix 2 (exclusion of patients who have received corticosteroids from corticosteroid comparisons). Updates to appendix 5 (committee membership) Update to appendix 6 (removal of India, pregnant women in Indonesia now ineligible, new EU countries, baloxavir marboxil comparison open in EU) Addition of appendix 7 (schedule of assessments) Addition of appendix 8 (abbreviations)

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)	Lancet Child Adolesc Health 2024; 8: 190-200
Intravenous immunoglobulin (PIMS-TS)	Lancet Child Adolesc Health 2024; 8: 190-200
Tocilizumab (PIMS-TS)	Lancet Child Adolesc Health 2024; 8: 190-200
Anakinra (PIMS-TS)	Lancet Child Adolesc Health 2024; 8: 190-200
Dimethyl fumarate	Nat Commun 2024; 15: 924
Baricitinib	Lancet 2022; 400: 359-68
Empagliflozin	Lancet Diabetes Endocrinol 2023; 11: 905-914
Higher dose corticosteroids	Lancet 2023; 401: 1499-1507 EClinicalMedicine 2025; 81: 103080
Paxlovid	Lancet Infect Dis 2025; S1473-3099
Molnupiravir	Lancet Infect Dis 2025; S1473-3099
Sotrovimab	Medrxiv: 10.1101/2024.05.23.24307731v1

Links to trial news items, preprints and publications are at www.recoverytrial.net/results

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: dexamethasone in adults and children with influenza and hypoxia; and dexamethasone in adults with community-acquired pneumonia (without suspected COVID-19 or influenza).

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 and community-acquired pneumonia. 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).[27–30] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[31]

Corticosteroids in community-acquired pneumonia

RECOVERY and other randomised trials have demonstrated the benefit of corticosteroids in patients with COVID-19 pneumonia.[6,32] However, the potential role of corticosteroids in CAP of other aetiology remains uncertain. Several randomised trials have demonstrated that corticosteroids improve time to clinical stability and discharge in patients hospitalised with CAP, but this may simply relate to suppression of fever and inflammatory markers rather than a true improvement in disease outcomes.[33,34] Previous trials have produced conflicting results on mortality, but have mostly been underpowered for this outcome. In aggregate they do not demonstrate any definite effect on mortality, but they also do not rule out a substantial benefit (e.g. a reduction of around a third).[16] The recent CAPE COD trial reported a significant reduction in mortality associated with corticosteroid use in ICU patients, but no effect was observed in the similar ESCAPe or REMAP-CAP trials.[35–37] The role of corticosteroids in CAP remains unclear, use in clinical practice is variable, and corticosteroid treatment is not recommended in current US or UK CAP treatment guidelines.[38,39] An adequately powered randomised trial is needed to resolve this uncertainty.

Corticosteroids in influenza

RECOVERY and other randomised trials have now demonstrated the benefit of corticosteroids in hypoxic COVID-19 patients.[6,32] 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).[40] 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.

Baloxavir marboxil: Baloxavir marboxil ('baloxavir') 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, the EU, and the United Kingdom for the treatment of uncomplicated influenza and for post-exposure prophylaxis. Baloxavir is not approved for the treatment of complicated influenza, although it has been used in clinical

practice in hospitalised patients. A multicentre retrospective observational study of hospitalised influenza patients in the US compared 359 who received baloxavir with 431 who received oseltamivir, and found that baloxavir use was associated with significantly faster time to hypoxia resolution.[41]

The only reported randomised trial in hospitalised patients is a phase III placebo-controlled trial of baloxavir in adults with severe influenza (Flagstone NCT03684044). This multinational trial was conducted in 25 countries, including 10 in the EU, and did not find a significant reduction in the primary endpoint of time to clinical improvement.[42] However, it was underpowered to rule out important benefits in clinical outcomes, for example 95% confidence intervals included a possible reduction in time to clinical stability of up to 50 hours, or a halving of in-hospital mortality. Time to cessation of viral shedding was in favour of baloxavir (median 24h vs 64h, p<0.0001). In Flagstone, baloxavir was given as 2 oral doses (on day 1 and day 4), rather than the single dose given for uncomplicated influenza. This repeated dose was well tolerated, with no safety signal identified, and drug exposures similar to those observed in outpatient studies (as measured by pharmacokinetic analyses). Fewer adverse events were observed in the baloxavir arm than in the standard of care arm. The Flagstone trial was small, comparing 241 subjects assigned to baloxavir with 125 assigned to 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, randomised controlled trial data are lacking, and published studies have been inconclusive.[18] 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.[17,43] 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 SARS-CoV-2 co-infection are not eligible for the dexamethasone comparison for influenza infection because of the proven benefits of dexamethasone in COVID-19 (Randomisation part I).
- Patients who have received systemic corticosteroids for >24h during the current illness at a glucocorticoid equivalent of ≥10mg prednisolone/day (equivalent to ≥1.5mg dexamethasone/day or ≥40mg hydrocortisone/day)

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 dexamethasone).
- Use of potent CYP3A4 inhibitors (including clarithromycin and erythromycin) is not contraindicated with corticosteroids, but investigators should consider the possible risk of increased corticosteroid side-effects with co-administration. Note that azithromycin, an alternative macrolide antibiotic used in the treatment of CAP, is not a potent CYP3A4 inhibitor.

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.

Influenza Randomisations

<table>
<tr><th>Arm</th><th>Route</th><th>Weight/Age</th><th>Dose</th></tr>
<tr><td rowspan="4">Oseltamivir

- 30, 45 and 75 mg capsules

- Oral suspension [a]</td><td rowspan="4">Oral
or
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

- 20mg tablets</td><td>Oral
or
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">Corticosteroids</td><td rowspan="2">Oral
or
Other enteral routes
or
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] The UK Health Security Agency 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 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.

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. Baloxavir may be considered in pregnant and breastfeeding women recruited in the UK, where existing surveillance systems can be used to monitor obstetric and infant outcomes. Pregnant and breastfeeding women outside the UK are excluded from this comparison.

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 Europe;
(ii) Review of study publications and substudy proposals;
(iii) Considering potential new therapies to be included in sites outside Europe;
(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), Marc Bonten, 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
Statistician	Natalie Staplin

International Committee

Chair	Do Van Dung
Regional Lead Investigator	Guy Thwaites
Independent members:	Vietnam : Nguyen Ngo Quang, Prof. Binh Indonesia: Erlina Burhan, Rianto Setiabudy Nepal: Janak Koirala, Sudha Basnet
Other members:	Evelyne Kestelyn, Buddha Basnyat, Pradip Gyanwali, Raph Hamers, Peter Horby, John Amuasi, 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
Statistician (non-voting)	Jonathan Emberson

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

Condition	Comparison‡	UK	EU†	Nepal	Vietnam	Indonesia	South Africa	Ghana
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*
	Corticosteroids	✓ any age	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years*	✓ ≥18 years	✓ ≥18 years
Community-acquired pneumonia	Corticosteroids	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 years	✓ ≥18 Years*	✓ ≥18 years	✓ ≥18 years

‡ Each comparison is versus usual care alone without the relevant treatment

† France, Italy, the Netherlands, Belgium, Spain, Portugal, Sweden, Estonia, and Romania. See the EU region-specific appendix for further details of trial procedures in the EU (the EU appendix may be appended to the end of this protocol, or can be downloaded as a separate document at www.recoverytrial.net/eu)

* Pregnant and breastfeeding women are excluded

8.7 Appendix 7: Schedule of assessments

Procedure	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D28†	D180
Eligibility assessment	X											
Consent	X											
Baseline data collection & randomisation	X											
Concomitant medication assessment	X										X	
Study treatment* (baloxavir marboxil)	X			X								
Study treatment* (oseltamivir)	X	X	X	X	X							
Study treatment* (corticosteroids)	X	X	X	X	X	X	X	X	X	X		
Initial follow-up† (medical records +/- call to participant)											X	
6-month follow-up‡ (medical records +/- call to participant)												X
Adverse event monitoring§	X	X	X	X	X	X	X	X	X	X		

* Only administered to patients allocated treatment in the relevant comparison. Baloxavir marboxil and oseltamivir continue after discharge if needed to complete the course. Corticosteroids stop on discharge.

† Initial follow-up to be completed at discharge, death or on day 28, whichever is earliest. At non-UK/non-EU sites, discharged patients or their relatives are also contacted on day 28 to confirm vital status.

‡ 6-month follow-up form is not completed in the UK, as this information is obtained via linkage to national healthcare records. At non-UK sites, 6-month follow-up should be completed from local medical records plus contact with the patient/relative (unless all necessary information can be obtained from local medical records).

§ Participants are monitored for serious adverse reactions to study treatment by their clinical team.

8.8 Appendix 8: Abbreviations

CAP	Community-acquired pneumonia
CCO	Central Coordinating Office
DMC	Data Monitoring Committee
ECMO	Extracorporeal membrane oxygenation
GCP	Good Clinical Practice
LCC	Local Clinical Centre (i.e. a trial site)
RCC	Regional Coordinating Centre
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

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