Protocol

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Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19 – Preliminary Report

SUPPLEMENTARY APPENDIX
PROTOCOL AND STATISTICAL ANALYSIS PLAN

RECOVERY Collaborative Group

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RECOVERY Trial Protocols

RECOVERY Trial Protocol V1.0

RECOVERY

Randomised Evaluation of COVID-19 Therapy

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, Interferon β, and low-dose corticosteroids. These groups also advised that other treatments will soon emerge that require evaluation. A World Health Organization (WHO) expert group issued broadly similar advice.

Eligibility and randomisation: This protocol describes a randomised trial among adults hospitalised for confirmed COVID-19. Eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital: No additional treatment *vs* Lopinavir-Ritonavir *vs* Interferon β *vs* low-dose corticosteroids. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

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 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 Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Outcomes: The main outcomes will be in-hospital death, discharge, and need for invasive mechanical ventilation (IMV; intubation or tracheostomy). For the main analyses, follow-up will be censored at 28 days after admission. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases such as those managed by NHS Digital and equivalent organisations in the devolved nations.

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. 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, COVID-19 onset date and severity, and any contraindications to the study treatments. The main outcomes will be in-hospital death (with date and probable cause), discharge (with date), and need for ventilation (with number of days recorded). Reminders will be sent if outcome data have not been recorded by 28 days after admission. Suspected Unexpected Serious Adverse

Reactions (SUSARs) to one of the study medication (eg, Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia) will be collected and 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 how large the epidemic becomes. 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, such as those being planned by the WHO.

Add-on studies: Particular countries or groups of hospitals, may well want to collaborate in adding further measurements or observations, such as serial virology, 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 well 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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To RANDOMISE a patient, visit:

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1 BACKGROUND AND RATIONALE

1.1 Setting

In 2019 a novel coronavirus-induced 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 hospitalized 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.

1.2 Treatment Options

There are currently no approved anti-viral or host-directed treatments for COVID-19. This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

Initially randomisation will be between four treatment arms:

No additional treatment: There are currently no approved anti-viral or host-directed treatments for COVID-19.

Lopinavir-Ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. Lopinavir-Ritonavir has shown activity against SARS and MERS CoVs.

Interferon β: Interferons (IFNs) are cytokines with antiviral and immunoregulatory effects. They are licensed for use in multiple sclerosis, leukaemia, lymphoma, and viral hepatitis. IFNs have shown activity against SARS and MERS CoVs.

Low dose corticosteroids: Favourable immune response modulation by low-dose corticosteroids might help treat severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS.

Further details on each of these treatment options is provided in Appendix 1 (see section 8.1)

Modifications to the number of treatment arms: Other arms can be added if evidence emerges that there are suitable candidate therapeutics. Conversely, in some patient populations, not all trial arms are appropriate (e.g. due to contraindications based on co-morbid conditions or concomitant medication) and in some hospitals, not all treatment arms

will be available (e.g. due to manufacturing and supply shortages). In either of these situations, randomisation will be between fewer arms.

1.3 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for confirmed COVID-19 infection in hospitalised adult patients receiving usual standard of care.

There are no known treatments for COVID-19. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched. Under some models of pandemic spread, up to 50% of the adult population may fall sick over a period of 8-12 weeks, of whom around 10% may require hospitalisation. This would involve about 2 million hospital admissions. In this situation, even treatments with only a moderate impact on survival or on hospital resources could be worthwhile. Therefore, the focus of the COVID-19 Core Protocol 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 sub-studies 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 admission, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[5]

2 DESIGN AND PROCEDURES

2.1 Eligibility

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

(i) Aged at least 18 years
(ii) Hospitalised
(iii) Confirmation of SARS-CoV-2 infection by PCR
(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

In addition, if the attending clinician believes that there is a specific contra-indication (see Appendix 2; section 8.2) to one of the active drug treatment arms, then the patient will be excluded from randomisation to that arm.

2.2 Consent

Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation), then consent may be obtained from a relative acting as the patient's legally designated representative. Further consent will then be sought with the patient if they recover sufficiently.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[5]), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

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, NHS number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 symptom onset date
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/extracorporeal membrane oxygenation
- Major cormorbidity (e.g. heart disease, diabetes, chronic lung disease)
- Date of hospitalisation
- Contraindication to the study drug 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.

2.4 Randomisation

Eligible patients will be randomised using a central web-based randomisation service (without stratification or minimization) in a 2:1:1:1 ratio to one of the following treatment arms (in addition to usual care):

Arm 1: No additional treatment

Arm 2: Lopinavir 400mg-Ritonavir 100mg by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge.

Arm 3: Interferon-β-1a . Nebulized solution of IFN-β1a 6MIU (0.5ml of a solution containing 12MIU/ml) once-daily for 10 days or until discharge.

Arm 4: Corticosteroid in the form of dexamethasone administered as an oral liquid or intravenous preparation 6 mg once daily for 10 days or until discharge (Note: It is permitted to switch between the two routes of administration according to clinical circumstances).

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 or 2:1 ratio).

2.5 Administration of allocated treatment

The details of the allocated study treatment will be displayed on the screen and can be printed or downloaded. The hospital clinicians are responsible for administration of the allocated treatment. The patient's own doctors are free to modify or stop study treatment 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 2.8). This study is being conducted within hospitals. Therefore use of medication will be subject to standard pharmacy 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).

2.6 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after 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 (none / previous / ongoing, with days of use and type, if appropriate)
- Use of renal dialysis or haemofiltration (none / previous / ongoing,)

This information will be obtained and entered into the web-based IT system by a member of the hospital clinical or research staff.

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.

2.7 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days post-randomisation (whichever is sooner). It is recognised that in the setting of this trial, there may be some variability in exactly how many days post-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.

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 Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

2.8 Withdrawal of consent

A decision by a participant 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 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).

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 prior to any analyses of aggregate unblinded data being conducted.

3.1 Outcomes

The **primary objective** is to provide reliable estimates of the effect of study treatments on in-hospital death (with subsidiary analyses of cause of death).

The **secondary objectives** are to assess the effects of study treatments on duration of hospital stay and on the need for (and duration of) ventilation; and the need for renal replacement therapy.

Data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital) and from relevant research studies (such as UK Biobank and Genomics England) 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), and longer-term outcomes (e.g. 6 month survival) as well as in particular sub-categories of patient (e.g. by genotype).

3.2 Methods of analysis

Comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

For time-to-event analyses, survival analytic methods will be used to evaluate the time to the first event during the entire study period using the log-rank test, taking discharge without the relevant event as implying safety from it.

The scope for multiple treatment comparisons will be taken into account in multiple pairwise tests. Due allowance will be made in the interpretation of all analyses, taking into account the nature of events and evidence from other studies. Tests of heterogeneity or trend will generally be used to assess disparity in efficacy among different subgroups (e.g. men vs. women; age <50, ≥50<70, ≥70).

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[a] that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction. In making this assessment, there should be consideration of the probability of an alternative cause (for example, COVID-19 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 Suspected Serious Adverse Reactions 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.

The focus of 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; and
(ii) Common events which are the consequence of conditions preceding randomisation.

[a] Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalization or prolongation of existing hospitalization; 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 hospitalization, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

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 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. Other serious or non-serious adverse events will not be recorded. It is anticipated that for some sub-studies, 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 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 Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Unless this happens, the 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).

4.5 Blinding

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

5 QUALITY MANAGEMENT

5.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice 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 infection) and the reliability of the results that would inform the care for future patients.

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. At present, there are no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

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 principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) 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) 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.

In the context of this epidemic, visits to hospital sites is generally not appropriate as they could increase the risks of spreading infection, and in the context of this trial they are generally would not influence the reliability of the trial results or the well-being of the participants. In exceptional circumstances, the CCO may arrange monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data.[6,7] The purpose of 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. No routine source data verification will take place.

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, in the circumstances of this epidemic, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will use 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 unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements.[8] 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 2.7). The sponsor and regulatory agencies will have the right to conduct confidential audits of such records in the CCO and LCCs (but should mindful of the workload facing participating hospitals and the infection control requirements during this epidemic).

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 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 data will be collected, analysed and published independently of the source of funding.

6.2 Funding

This study is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, Health Data Research UK, 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). NHS indemnity operates in respect of the clinical treatment that is provided.

6.4 Local Clinical Centres

The study will conducted at multiple hospitals (Local Clinical Centres) within the UK. 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.

6.5 Supply of study treatments

For licensed treatments (e.g. Lopinavir-Ritonavir, corticosteroids) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription.

For unlicensed treatments (inhaled interferon-β-1a) manufacture, packaging and delivery will be the responsibility of the pharmaceutical company. 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).

Study treatments will not be labelled beyond other than as required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

6.6 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 Digital (anticipated to be 10 years after the last patient is enrolled).

6.7 Publications and reports

The 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 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 Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Steering Committee. The Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. 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.

6.8 Substudies

Proposals for substudies must be approved by the 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 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).

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8 APPENDICES

8.1 Appendix 1: Information about the treatment arms

All patients will receive usual care in the participating hospital.

No additional treatment: There are no proven therapies for COVID-19.

Lopinavir-Ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. It is licensed in adults and children from the age of 14 days (2 years in Scotland). It has been widely used in pregnant women.[1] Lopinavir has in vitro inhibitory activity against SARS coronavirus (SARS-CoV) and MERS-CoV.[2-4 5] In common marmosets infected with MERS-CoV, animals treated with lopinavir/ritonavir had improved clinical, radiological, and pathological outcomes and reduced viral loads compared with untreated animals.[6] In one single-center, open-label study of the addition of lopinavir 400mg/ritonavir 100mg to ribavirin and corticosteroids in SARS patients the risk of adverse clinical outcomes (acute respiratory distress syndrome [ARDS] or death) was significantly lower (2.4% v 28.8%, $p<0.001$) compared to a historical control group.[2]

The most common short-term side effects in adults are diarrhoea, nausea, and vomiting. It must not be used by patients with severe liver disease. It should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see Summary of Product Characteristics). Storage should be as per conditions in the Summary of Product Characteristics.

Interferon β: Interferons are cytokines with antiviral and immunoregulatory effects. Interferons (IFNs) are licensed for use in multiple sclerosis, leukaemia, lymphoma, and viral hepatitis. IFNs have shown activity against SARS and MERS CoVs. IFN-α reduces SAR-CoV replication in mice and monkeys.[7,8] IFN- β may be more effective against SARS-CoV than IFN-α or IFN–γ.[9–11] IFN-α and IFN-β have activity against MERS-CoV in vitro and in monkeys, with IFN-β showing greater activity than IFN-α.[12-14] IFN-β shows greater inhibition of MERS-CoV in vitro than lopinavir-ritonavir and IFN-β activity is not increased by addition of lopinavir-ritonavir.[15]

Parentral IFN-β1a has been licensed for use in multiple sclerosis since 1996 (Avonex™, Rebif™), including in pregnancy if clinically indicated. Commonly reported side effects associated with systemic administration of IFN-β include flu-like symptoms, injection site reaction, decreased white blood cell count, hypertonia, chest pain. Systemic IFN-β should not be administered to people with severe liver disease or severe depression (see Summary of Product Characteristics). Inhaled interferon-β-1a is an investigational product in development to treat or prevent exacerbations of lung diseases caused by respiratory viruses (rhinovirus, influenza, coronavirus, RSV, adenovirus, parainfluenza etc). It has been well tolerated in 230 asthma/COPD patients in the context of viral infections/exacerbations. This IMP should be stored in a refrigerator (5C). These refrigerators will not require temperature monitoring or calibration of any internal thermometers. This IMP will be prescribed by a physician and therefore no trial-specific labelling will be used.

Dexamethasone: 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 coronavirus infections, including COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia (a cytokine 'storm') and development of acute lung injury or adult respiratory distress syndrome (ARDS).[16-19] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[20] A growing volume of clinical trial data from patients with severe community acquired pneumonia, ARDS and septic shock suggest benefit from low-to-moderate dose corticosteroids in relation to mortality and length of stay.[21-23]

In trials of low-to-moderate doses of corticosteroids, the main adverse effect has been hyperglycaemia.[22,24] A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection or neuromuscular weakness; an association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted.[25] Dexamethasone has a) minimal mineralocorticoid activity and does not affect sodium and water balance, thus avoiding potential problems with fluid retention which are not uncommon in severe viral pneumonitis/ARDS, and b) a comparatively long biological half-life of 36 to 54 hours enabling once a day dosing. Storage should be as per conditions in the Summary of Product Characteristics.

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8.2 Appendix 2: Drug specific contraindications

Lopinavir/ritonavir

- Severe hepatic insufficiency*
  Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. This includes alfuzosin, ranolazine, amiodarone, dronaderone, fusidic acid, neratinib, venetoclax, colchicine, astemizole, terfenadine, lurasidone, pimozide, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir, lovastatin, simvastatin, lomitapide, avanafil, sildenafil, vardenafil, midazolam, triazolam (See Summary of Product Characteristics for more detail).

Inhaled interferon-β-1a

- Severe depressive illness*
- Severe hepatic insufficiency*

Dexamethasone

- Known contra-indication to short-term dexamethasone.

* If these conditions are recorded on the baseline case report form, patients will be ineligible for randomisation to that arm of the study.

Note: This study is being conducted within hospitals. Therefore use of medication will be subject to standard pharmacy 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). The doctor may decide whether it is appropriate to stop such medications temporarily to allow the patient to complete the course of their assigned intervention.

8.3 Appendix 3: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

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

Steering Committee
The Steering Committee (see Section 8.4 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.

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 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.

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.

8.4 Appendix 4: Organisational Details

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

Chief Investigator	Peter Horby
Deputy Chief Investigator	Martin Landray
Co-investigator	Wei Shen Lim
Co-investigator (Scotland Lead)	Kenneth Baillie
Clinical Trial Unit Leads	Richard Haynes, Ed Juszczak
Co-investigator	Thomas Jaki

DATA MONITORING COMMITTEE
(Interim analyses and response to specific concerns)

Chair	TBC
Members	TBC
Statistician (non-voting)	TBC

To enquire about the trial, contact the RECOVERY Central Coordinating Office

RECOVERY Central Coordinating Office:
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(copies of this protocol and related forms and information can be downloaded)

To RANDOMISE a patient, visit:

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Website: www.recoverytrial.net

8.5 Appendix 5: Version History

Version number	Date	Brief Description of Changes
1.0	13-Mar-2020	Initial version

RECOVERY Trial Protocol V2.0

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

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, Interferon β, low-dose corticosteroids, and hydroxychloroquine. These groups also advised that other treatments will soon emerge that require evaluation. A World Health Organization (WHO) expert group issued broadly similar advice.

Eligibility and randomisation: This protocol describes a randomised trial among adults hospitalised for confirmed COVID-19. Eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital: No additional treatment *vs* Lopinavir-Ritonavir *vs* Interferon 1β *vs* Low-dose Corticosteroids *vs* Hydroxychloroquine. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

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 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 Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Outcomes: The main outcomes will be in-hospital death, discharge, and need for ventilation. 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 such as those managed by NHS Digital and equivalent organisations in the devolved nations.

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. 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, COVID-19 onset date and severity, and any contraindications to the study treatments. The main outcomes will be in-hospital death (with date and probable cause), discharge (with date), and need for ventilation (with number of days recorded). Reminders will be sent if outcome data have not been recorded by 28 days after randomisation. Suspected Unexpected Serious Adverse Reactions (SUSARs) to one of the study medication (eg, Stevens-Johnson

syndrome, anaphylaxis, aplastic anaemia) will be collected and 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 how large the epidemic becomes. 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, such as those being planned by the WHO.

Add-on studies: Particular countries or groups of hospitals, may well want to collaborate in adding further measurements or observations, such as serial virology, 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 well 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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1 BACKGROUND AND RATIONALE

1.1 Setting

In 2019 a novel coronavirus-induced 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 hospitalized 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.

1.2 Treatment Options

There are currently no approved anti-viral or host-directed treatments for COVID-19. This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

Randomisation may be between the following treatment arms (although not all arms may be available at any one time):

No additional treatment: There are currently no approved anti-viral or host-directed treatments for COVID-19.

Lopinavir-Ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. Lopinavir-Ritonavir has shown activity against SARS and MERS CoVs.

Interferon β: Interferons (IFNs) are cytokines with antiviral and immunoregulatory effects. They are licensed for use in multiple sclerosis, leukaemia, lymphoma, and viral hepatitis. IFNs have shown activity against SARS and MERS CoVs.

Low dose corticosteroids: Favourable immune response modulation by low-dose corticosteroids might help treat severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS.

Hydroxychloroquine: Hydroxychloroquine, a derivative of chloroquine, has been used for many decades to treat malaria and rheumatological diseases. It has antiviral activity against SARS-CoV-2 in cell culture.

Further details on each of these treatment options is provided in Appendix 1 (see section 9.1)

Modifications to the number of treatment arms: Other arms can be added if evidence emerges that there are suitable candidate therapeutics. Conversely, in some patient populations, not all trial arms are appropriate (e.g. due to contraindications based on co-morbid conditions or concomitant medication); in some hospitals, not all treatment arms will be available (e.g. due to manufacturing and supply shortages); and at some times, not all treatment arms will be active (e.g. due to lack of relevant approvals and contractual agreements). In any of these situations, randomisation will be between fewer arms.

1.3 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for confirmed COVID-19 infection in hospitalised adult patients receiving usual standard of care.

There are no known treatments for COVID-19. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched. Under some models of pandemic spread, up to 50% of the adult population may fall sick over a period of 8-12 weeks, of whom around 10% may require hospitalisation. This would involve about 2 million hospital admissions. In this situation, even treatments with only a moderate impact on survival or on hospital resources could be worthwhile. Therefore, the focus of the COVID-19 Core Protocol 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 sub-studies 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 admission, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[5]

2 DESIGN AND PROCEDURES

2.1 Eligibility

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

(i) Aged at least 18 years
(ii) Hospitalised
(iii) SARS-CoV-2 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

In addition, if the attending clinician believes that there is a specific contra-indication (see Appendix 2; section 9.2) to one of the active drug treatment arms, then the patient will be excluded from randomisation to that arm.

2.2 Consent

Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation), then consent may be obtained from a relative acting as the patient's legally designated representative. Further consent will then be sought with the patient if they recover sufficiently.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[5]), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

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, NHS number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 symptom onset date
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/extracorporeal membrane oxygenation
- Major comorbidity (e.g. heart disease, diabetes, chronic lung disease)
- Date of hospitalisation
- Contraindication to the study drug 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.

2.4 Randomisation

Eligible patients will be allocated using a central web-based randomisation service (without stratification or minimization) in to one of the following treatment arms (in addition to usual care):

Arm 1: No additional treatment

Arm 2: Lopinavir 400mg-Ritonavir 100mg by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge.

Arm 3: Interferon-β-1a. Nebulized solution of IFN-β1a 6MIU (0.5ml of a solution containing 12MIU/ml) once-daily for 10 days or until discharge.

Arm 4: Corticosteroid in the form of dexamethasone administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days or until discharge (Note: It is permitted to switch between the two routes of administration according to clinical circumstances).

Arm 5: Hydroxychloroquine by mouth for a total of 10 days as follows:

Timing	Dose
Initial	800 mg
+ 6 hours	800 mg
+ 12 hours	400 mg
+ 24 hours	400 mg
Every 12 hours thereafter for 9 days	400 mg

The randomization programme will allocate patients in a ratio of 2:1 between the no additional care arm and each of the other arms available. Hence if 4 arms are available, then the randomization will be in the ratio 2:1:1:1. 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 or 2:1 ratio).

2.5 Administration of allocated treatment

The details of the allocated study treatment will be displayed on the screen and can be printed or downloaded. The hospital clinicians are responsible for administration of the allocated treatment. The patient's own doctors are free to modify or stop study treatment 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 2.8). This study is being conducted within hospitals. Therefore use of medication will be subject to standard pharmacy 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).

2.6 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after 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 (none / previous / ongoing, with days of use and type, if appropriate)
- Use of renal dialysis or haemofiltration (none / previous / ongoing,)

This information will be obtained and entered into the web-based IT system by a member of the hospital clinical or research staff.

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.

2.7 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.

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 Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

2.8 Withdrawal of consent

A decision by a participant 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 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).

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 prior to any analyses of aggregate unblinded data being conducted.

3.1 Outcomes

The **primary objective** is to provide reliable estimates of the effect of study treatments on in-hospital death (with subsidiary analyses of cause of death and death at various timepoints following discharge).

The **secondary objectives** are to assess the effects of study treatments on duration of hospital stay; the need for (and duration of) ventilation; and the need for renal replacement therapy.

Data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital) and from relevant research studies (such as UK Biobank and Genomics England) 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), and longer-term outcomes (e.g. 6 month survival) as well as in particular sub-categories of patient (e.g. by genotype).

3.2 Methods of analysis

Comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses).

For time-to-event analyses, survival analytic methods will be used to evaluate the time to the first event during the entire study period using the log-rank test, taking discharge without the relevant event as implying safety from it.

The scope for multiple treatment comparisons will be taken into account in multiple pairwise tests. Due allowance will be made in the interpretation of all analyses, taking into account the nature of events and evidence from other studies. Tests of heterogeneity or trend will generally be used to assess disparity in efficacy among different subgroups (e.g. men vs. women; age <50, ≥50<70, ≥70).

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[a] that is believed with a reasonable probability to be due to one of the study treatments will be considered a Suspected Serious Adverse Reaction. In making this assessment, there should be consideration of the probability of an alternative

[a] Serious Adverse Events are defined as those adverse events that result in death; are life-threatening; require in-patient hospitalization or prolongation of existing hospitalization; 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 hospitalization, but may jeopardise the participant or require intervention to prevent one or other of the outcomes listed above).

cause (for example, COVID-19 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 Suspected Serious Adverse Reactions 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.

The focus of 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; 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 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. Other serious or non-serious adverse events will not be recorded. It is anticipated that for some sub-studies, 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 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 Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Unless this happens, the 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).

4.5 Blinding

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

5 QUALITY MANAGEMENT

5.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice 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 infection) and the reliability of the results that would inform the care for future patients.

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. At present, there are no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

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 principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) 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) 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.

In the context of this epidemic, visits to hospital sites is generally not appropriate as they could increase the risks of spreading infection, and in the context of this trial they generally would not influence the reliability of the trial results or the well-being of the participants. In exceptional circumstances, the CCO may arrange monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data.[6,7] The purpose of 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. No routine source data verification will take place.

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, in the circumstances of this epidemic, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will use 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 unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements.[8] 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 2.7). The sponsor and regulatory agencies will have the right to conduct confidential audits of such records in the CCO and LCCs (but should mindful of the workload facing participating hospitals and the infection control requirements during this epidemic).

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 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 data will be collected, analysed and published independently of the source of funding.

6.2 Funding

This study is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, Health Data Research UK, 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). 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 (Local Clinical Centres) within the UK. 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.

6.5 Supply of study treatments

For licensed treatments (e.g. Lopinavir-Ritonavir, corticosteroids) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription.

For unlicensed treatments (inhaled interferon-β-1a) manufacture, packaging and delivery will be the responsibility of the pharmaceutical company. 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).

Study treatments will not be labelled beyond other than as required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

6.6 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 Digital (anticipated to be 10 years after the last patient is enrolled).

6.7 Publications and reports

The 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 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 Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Steering Committee. The Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. 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.

6.8 Substudies

Proposals for substudies must be approved by the 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 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).

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8 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.

9 APPENDICES

9.1 Appendix 1: Information about the treatment arms

All patients will receive usual care in the participating hospital.

No additional treatment: There are no proven therapies for COVID-19.

Lopinavir-Ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. It is licensed in adults and children from the age of 14 days (2 years in Scotland). It has been widely used in pregnant women.[1] Lopinavir has in vitro inhibitory activity against SARS coronavirus (SARS-CoV) and MERS-CoV.[2-4 5] In common marmosets infected with MERS-CoV, animals treated with lopinavir/ritonavir had improved clinical, radiological, and pathological outcomes and reduced viral loads compared with untreated animals.[6] In one single-center, open-label study of the addition of lopinavir 400mg/ritonavir 100mg to ribavirin and corticosteroids in SARS patients the risk of adverse clinical outcomes (acute respiratory distress syndrome [ARDS] or death) was significantly lower (2.4% v 28.8%, $p<0.001$) compared to a historical control group.[2]

The most common short-term side effects in adults are diarrhoea, nausea, and vomiting. It must not be used by patients with severe liver disease. It should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see Summary of Product Characteristics). Storage should be as per conditions in the Summary of Product Characteristics.

Interferon β: Interferons are cytokines with antiviral and immunoregulatory effects. Interferons (IFNs) are licensed for use in multiple sclerosis, leukaemia, lymphoma, and viral hepatitis. IFNs have shown activity against SARS and MERS CoVs. IFN-α reduces SAR-CoV replication in mice and monkeys.[7,8] IFN- β may be more effective against SARS-CoV than IFN-α or IFN–γ.[9–11] IFN-α and IFN-β have activity against MERS-CoV in vitro and in monkeys, with IFN-β showing greater activity than IFN-α.[12-14] IFN-β shows greater inhibition of MERS-CoV in vitro than lopinavir-ritonavir and IFN-β activity is not increased by addition of lopinavir-ritonavir.[15]

Parentral IFN-β1a has been licensed for use in multiple sclerosis since 1996 (Avonex™, Rebif™), including in pregnancy if clinically indicated. Commonly reported side effects associated with systemic administration of IFN-β include flu-like symptoms, injection site reaction, decreased white blood cell count, hypertonia, chest pain. Systemic IFN-β should not be administered to people with severe liver disease or severe depression (see Summary of Product Characteristics). Inhaled interferon-β-1a is an investigational product in development to treat or prevent exacerbations of lung diseases caused by respiratory viruses (rhinovirus, influenza, coronavirus, RSV, adenovirus, parainfluenza etc). It has been well tolerated in 230 asthma/COPD patients in the context of viral infections/exacerbations. This IMP should be stored in a refrigerator (5C). These refrigerators will not require temperature monitoring or calibration of any internal thermometers. This IMP will be prescribed by a physician and therefore no trial-specific labelling will be used.

Dexamethasone: 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 coronavirus infections, including COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia (a cytokine 'storm') and development of acute lung injury or adult respiratory distress syndrome (ARDS).[16-19] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[20] A growing volume of clinical trial data from patients with severe community acquired pneumonia, ARDS and septic shock suggest benefit from low-to-moderate dose corticosteroids in relation to mortality and length of stay.[21-23]

In trials of low-to-moderate doses of corticosteroids, the main adverse effect has been hyperglycaemia.[22,24] A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection or neuromuscular weakness; an association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted.[25] Dexamethasone has a) minimal mineralocorticoid activity and does not affect sodium and water balance, thus avoiding potential problems with fluid retention which are not uncommon in severe viral pneumonitis/ARDS, and b) a comparatively long biological half-life of 36 to 54 hours enabling once a day dosing. Storage should be as per conditions in the Summary of Product Characteristics.

Hydroxycholoroquine: Chloroquine (CQ), an antimalarial drug discovered in 1934 and introduced generally in 1947, is the drug to which humans have been most exposed, with an annual global consumption of hundreds of metric tonnes for over 50 years. It is inexpensive, simple to administer, and, at the appropriate doses, has an excellent safety profile in all age groups and has been the prophylactic drug of choice in pregnancy [26]. In addition to its antimalarial use both chloroquine and the closely related hydroxychloroquine (HCQ) are used in continuous daily dosing for rheumatoid arthritis, systemic and discoid lupus erythematosus and psoriatic arthritis. HCQ is reported to have better safety profile than CQ, better gastrointestinal tolerability, and less retinal toxicity [27].

CQ has significant antiviral activity against SARS-CoV-2 in cell culture (EC_{50} = 1.13 μM; CC_{50} > 100 μM, SI > 88.50), as it does for the related SARS-CoV-1 [28-31]. CQ blocks virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[30] In SARS-CoV-2 infected Vero cells, HCQ (EC_{50}=0.72 μM) has been reported to be more potent than CQ (EC_{50}=5.47 μM) [32], although Liu et al reported that CQ was more potent than HCQ.[33] These are relatively high levels by comparison with therapeutic exposures in the treatment of malaria but could be achieved with daily oral dosing. Chloroquine has complex pharmacokinetic properties and although the relationship between plasma concentrations and concentrations in respiratory epithelium is not known precisely, in rats the concentration in lung is between 124 and 748-fold that in plasma [34]. If active, HCQ concentrations in the human lung would be expected to exceed those required for the EC_{90} after an initial dose. There are preliminary reports emerging from China and France of clinical benefit in the treatment of COVID-19 infections [35,36].

The recommended adult dosing of chloroquine for treatment of non-falciparum malaria (BNF) is: Initially 620 mg, then 310 mg after 6–8 hours, then 310 mg daily for 2 days. This is equivalent to 930mg base in first 24 hours. This is a loading dose to ensure the necessary blood concentrations are achieved rapidly.

Hydroxychloroquine is very similar to chloroquine. It is used mainly to treat rheumatoid arthritis and other related conditions. The adult dose is usually 400-600mg/ day (equivalent to 310 to 465 mg base). Sometimes 800mg/day is given.
The dose in RECOVERY is Hydroyxchloroquine (155mg base per 200 mg tablet):

Initial dose: 4 tablets
6 hours later: 4 tablets
12 hours: 2 tablets
24 hours: 2 tablets
Thereafter: 2 tablets every 12 hours for a total of 10 days

12x155mg = 1860mg base = in first 24 hours

So the loading dose in RECOVERY is twice the normal dose for treating malaria. However, this dose has been selected based on the available data of the IC_{50} for SARS-CoV-2. The objective is to reach plasma concentrations that are inhibitory to the virus as soon as safely possible. The plasma concentrations that will result are at the higher end of those encountered during steady state treatment of rheumatoid arthritis. Given the significant mortality in patients hospitalised with COVID-19, this dose is felt to be justified. This is the schedule that is likely to be adopted by the World Health Organisation.No dose adjustment is required for weight based on the doses defined in this protocol.

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9.2 Appendix 2: Drug specific contraindications and cautions

Lopinavir/ritonavir

- Severe hepatic insufficiency*
- Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. This includes alfuzosin, ranolazine, amiodarone, dronaderone, fusidic acid, neratinib, venetoclax, colchicine, astemizole, terfenadine, lurasidone, pimozide, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir, lovastatin, simvastatin, lomitapide, avanafil, sildenafil, vardenafil, midazolam, triazolam (See Summary of Product Characteristics for more detail). It may be appropriate to temporarily withhold such concomitant medication while the patient is receiving lopinavir/ritonavir.

Inhaled interferon-β-1a

- Severe hepatic insufficiency*

Dexamethasone

- Known contra-indication to short-term dexamethasone.

Hydroxychloroquine

- Known prolonged QTc interval
- Caution: Co-administration with medications that prolong the QT interval (e.g. macrolides, quinolones) is not an absolute contraindication, but it may be appropriate to check the QT interval by performing an ECG.

* If these conditions are recorded on the baseline case report form, patients will be ineligible for randomisation to that arm of the study.

Note: 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). The doctor may decide whether it is appropriate to stop such medications temporarily to allow the patient to complete the course of their assigned intervention.

9.3 Appendix 3: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

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

Steering Committee
The Steering Committee (see Section 9.4 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.

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 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.

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.

9.4 Appendix 4: Organisational Details

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 Leads	Richard Haynes, Ed Juszczak
Co-investigators	Kenneth Baillie (Scotland Lead), Thomas Jaki, Katie Jeffery, Wei Shen Lim, Alan Montgommery, Kathy Rowan

DATA MONITORING COMMITTEE
(Interim analyses and response to specific concerns)

Chair	Peter Sandercock
Members	Janet Darbyshire, David DeMets, Robert Fowler, David Kalloo, Ian Roberts, Janet Wittes
Statistician (non-voting)	Jonathan Emberson, Natalie Staplin

To enquire about the trial, contact the RECOVERY Central Coordinating Office

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

To RANDOMISE a patient, visit:

Website: www.recoverytrial.net

RECOVERY Trial Protocol V6.0

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

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. These groups also advised that other treatments will soon emerge that require evaluation. A World Health Organization (WHO) expert group issued broadly similar advice.

Eligibility and randomisation: This protocol describes a randomised trial among patients hospitalised for COVID-19. All eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital: No additional treatment *vs* lopinavir-ritonavir *vs* low-dose corticosteroids *vs* hydroxychloroquine *vs* azithromycin. In a factorial design, eligible patients are allocated simultaneously to no additional treatment *vs* convalescent plasma. The study allows a subsequent randomisation for patients with progressive COVID-19 (evidence of hyper-inflammatory state): No additional treatment *vs* tocilizumab. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

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 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 Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. 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 such as those managed by NHS Digital and equivalent organisations in the devolved nations.

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. 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, COVID-19 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. Reminders will be sent if outcome data have not been recorded by 28 days after randomisation. Suspected Unexpected Serious Adverse Reactions (SUSARs) to one of the study medications (e.g., Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia) will be collected and 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 how large the epidemic becomes. 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, such as those being planned by the WHO.

Add-on studies: Particular countries or groups of hospitals, may well want to collaborate in adding further measurements or observations, such as serial virology, 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 well 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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1 BACKGROUND AND RATIONALE

1.1 Setting

In 2019 a novel coronavirus-induced 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.

1.2 Treatment Options

1.2.1 Main randomisation

There are currently no approved treatments for COVID-19. This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

From version 6.0 of the protocol, a factorial design will be used such that eligible and consenting participants may be randomised to one of the treatment arms in Randomisation A and, simultaneously, to one of the treatment arms in Randomisation B.

Randomisation part A: Eligible patients will be randomly allocated between the following treatment arms (although not all arms may be available at any one time):

- **No additional treatment:** There are currently no approved anti-viral or host-directed treatments for COVID-19.

- **Lopinavir-ritonavir:** Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. Lopinavir-Ritonavir has shown activity against SARS and MERS CoVs.

- **Low dose corticosteroids:** Favourable immune response modulation by low-dose corticosteroids might help treat severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS.

- **Hydroxychloroquine:** Hydroxychloroquine, a derivative of chloroquine, has been used for many decades to treat malaria and rheumatological diseases. It has antiviral activity against SARS-CoV-2 in cell culture.

- **Azithromycin:** Azithromycin is a macrolide antibiotic with immunomodulatory properties that has shown benefit in inflammatory lung disease.

Randomisation part B: Simultaneously, eligible patients will be randomly allocated between the following treatment arms (provided there are no contraindications and the appropriate consent has been given):

- **No additional treatment:** There are currently no approved anti-viral or host-directed treatments for COVID-19.

- **Convalescent plasma:** Plasma from patients who have recovered from SARS-CoV-2 infection may contain antibodies that can bind to and neutralise the virus. Infusion of convalescent plasma containing high concentrations of neutralising antibody may accelerate clearance of the virus and clinical improvement.

Further details on each of these treatment options is provided in Appendix 1 (see section 8.1).

1.2.2 Second randomisation for patients with progressive COVID-19

Severe COVID-19 is associated with release of pro-inflammatory cytokines, such as IL-1, IL-6 and TNFα, and other markers of systemic inflammation including ferritin and C-reactive protein.[3,5,6] There is a possibility that this response may cause or exacerbate lung injury, leading to life-threatening disease.

Participants with progressive COVID-19 (as evidenced by hypoxia and an inflammatory state) may undergo an optional second randomisation between the following treatment arms:

- **No additional treatment:** There are currently no approved immunomodulatory or other host-directed treatments to prevent the progression of COVID-19.

- **Tocilizumab:** Tocilizumab is an interleukin-6 (IL-6) receptor antibody, which blocks a component of the immune response that may drive progression to ARDS.

Modifications to the number of treatment arms: Other arms can be added to the first or second randomisation if evidence emerges that there are suitable candidate therapeutics. Conversely, in some patient populations, not all trial arms are appropriate (e.g. due to contraindications based on co-morbid conditions or concomitant medication); in some hospitals, not all treatment arms will be available (e.g. due to manufacturing and supply shortages); and at some times, not all treatment arms 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 arms in order to increase trial efficiency during a fluctuating epidemic. In any of these situations, randomisation will be between fewer arms.

1.3 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for suspected or confirmed COVID-19 infection in hospitalised patients receiving usual standard of care.

There are no known treatments for COVID-19. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched. Under some models of pandemic spread, up to 50% of the adult population may fall sick over a period of 8-12 weeks, of whom around 10% may require hospitalisation. This would involve about 2 million hospital admissions. In this situation, 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 sub-studies 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 the main randomisation, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[7]

2 DESIGN AND PROCEDURES

2.1 Eligibility

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

(i) Hospitalised
(ii) SARS-CoV-2 infection (clinically suspected[a] or laboratory confirmed)[b]
(iii) 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

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; section 8.2 and Appendix 3; section 9.3 for children) 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.

2.2 Consent

Informed consent should be obtained from each patient 16 years and over before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation) or prior disease, then consent may be obtained from a relative acting as the patient's legally designated representative or independent doctor. Further consent will then be sought with the patient if they recover sufficiently. 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 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.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[7]), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent

---

[a] In general, SARS-CoV-2 infection should be suspected when a patient presents with (i) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and (ii) compatible chest X-ray findings (consolidation or ground-glass shadowing); and (iii) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). However, the diagnosis remains a clinical one based on the opinion of the managing doctor.

[b] A small number of children (age <18 years old) present with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction. Some do not have significant lung involvement.
(see: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf)

provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

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, NHS number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 symptom onset date
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/extracorporeal membrane oxygenation (ECMO)
- Major comorbidity (e.g. heart disease, diabetes, chronic lung disease) and pregnancy
- Date of hospitalisation
- Contraindication to the study treatment regimens (in the opinion of the attending clinician)
- Willingness to receive a blood product
- 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.

2.4 Main randomisation

In addition to receiving usual care, eligible patients will be allocated using a central web-based randomisation service (without stratification or minimisation). From version 6.0 of the protocol, a factorial design will be used such that eligible patients are randomised to one of the treatment arms in Randomisation A and, simultaneously, to one of the treatment arms in Randomisation B.

2.4.1 Main randomisation part A:

Eligible patients will be randomised to one of the arms listed below. The doses in this section are for adults. Please see Appendix 3 for paediatric dosing. Study treatments do not need to be continued after discharge from hospital.

- **No additional treatment**

- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days.

- **Corticosteroid** in the form of dexamethasone administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days. In pregnancy or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone.

(Note: It is permitted to switch between the two routes of administration according to clinical circumstances.)

- **Hydroxychloroquine** by mouth for a total of 10 days as follows:

Timing	Dose
Initial	800 mg
6 hours after initial dose	800 mg
12 hours after initial dose	400 mg
24 hours after initial dose	400 mg
Every 12 hours thereafter for 9 days	400 mg

- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for 10 days.

For randomisation part A, the randomisation program will allocate patients in a ratio of 2:1 between the no additional treatment arm and each of the other arms available. Hence if 5 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 (i.e. in a 2:1:1:1, 2:1:1 or 2:1 ratio).

2.4.2 Main randomisation part B:

Eligible patients may be randomised to one of the arms listed below. The doses in this section are for adults. Please see Appendix 3 for paediatric dosing.

- **No additional treatment**

- **Convalescent plasma**

  Single unit of ABO compatible convalescent plasma (275mls +/- 75 mls) 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.

For randomisation part B, the randomisation program will allocate patients in a ratio of 1:1 between each of the arms. 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 Randomisation part B.

2.5 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 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).

Note: NHS guidelines require patients to have **two** separate blood samples taken for Group and Screen prior to administration of blood products. Each sample is approximately 5 mL and both need to be taken at any time between admission to hospital and receipt of the first plasma transfusion (as the laboratory will not issue plasma without both samples). The participant's blood group is identified to ensure that blood group-compatible plasma is given and this information would be available to the participant if they wish. Such tests may be required as part of the routine care of the participant if the managing team wish to consider using blood products and samples will be stored, retained and destroyed as per trust standard procedures and protocols.

2.6 Second randomisation for patients with progressive COVID-19

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

(i) Randomised into the RECOVERY trial no more than 21 days ago
(ii) Clinical evidence of progressive COVID-19:
  a. oxygen saturation <92% on room air or requiring oxygen
     (or in children (age <18 years), significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement)[c]; and
  b. C-reactive protein ≥75 mg/L
(iii) 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 this aspect of the RECOVERY trial.
  (Note: Pregnancy and breastfeeding are not specific exclusion criteria.)

Note: Participants may undergo this second randomisation at any point after being first randomised, provided they meet the above criteria, and thus may receive up to three study treatments (one each from Main randomisation parts A and B, plus one from the second randomisation). For some participants the second randomisation may be immediately after the first but for others it may occur a few hours or days later, if and when they deteriorate. Those transferred from the Trust at which they were originally enrolled in the trial will be ineligible for the second randomisation.

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

[c] A small number of children (age <18 years) present with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction. Some do not have significant lung involvement.
(see: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf)

- Patient details (e.g. name, NHS number, date of birth, sex)
- Clinician details (e.g. name)
- COVID-19 severity as assessed by need for supplemental oxygen or ventilation/ECMO
- Markers of progressive COVID-19 (including oxygen saturation, C-reactive protein)
- Contraindication to the study drug treatments (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 own name and e-mail address.

Eligible participants may be randomised between the following treatment arms:

- **No additional treatment:** There are currently no approved anti-viral or host-directed treatments for COVID-19.

- **Tocilizumab** by intravenous infusion with the dose determined by body weight:

Weight*	Dose
>40 and ≤65 kg	400 mg
>65 and ≤90 kg	600 mg
>90 kg	800 mg

* for lower weights, dosing should be 8 mg/kg (see Appendix 3 for paediatric dosing)
(Note: body weight may be estimated if it is impractical to weigh the patient)

Tocilizumab should be given as a single intravenous infusion over 60 minutes in 100ml sodium chloride 0.9%. A second dose may be given ≥12 and <24 hours later if, in the opinion of the attending clinician, the patient's condition has not improved.

The randomisation program will allocate patients in a ratio of 1:1 between the arms being evaluated in the second randomisation. Participants should receive standard management (including blood tests such as liver function tests and full blood count) according to their clinical need.

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)
- Use of any medications included in the RECOVERY trial protocol (including drugs in the same class)

This information will be obtained and entered into the web-based IT system by a member of the hospital clinical or research staff.

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.

2.7.1 Additional assessment of safety of convalescent plasma

For the first 200 participants in Main Randomisation part B (no additional treatment vs. convalescent plasma), the following information will be collected on the following events occurring within the first 72 hours after randomisation:

- Sudden worsening in respiratory status
- Severe allergic reaction
- Temperature >39°C or ≥2°C rise above baseline
- Sudden hypotension, defined as either (i) sudden drop in systolic blood pressure of ≥30 mmHg with systolic blood pressure ≤80 mmHg; or (ii) requiring urgent medical attention
- Clinical haemolysis, defined as fall in haemoglobin plus one or more of the following: rise in lactate dehydrogenase (LDH), rise in bilirubin, positive direct antiglobulin test (DAT), or positive crossmatch.

The Data Monitoring Committee will review unblinded information on these outcomes and advise if, in their view, the collection of such information should be extended to more participants.

In addition, Serious Hazards Of Transfusion (SHOT) reporting will be conducted for all patients receiving convalescent plasma for the full duration of the study (see section 4.1).

2.8 Duration of follow-up

All randomised participants are to be followed up until death, discharge from hospital or 28 days after first 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.

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 Digital, Public Health England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England).

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.

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

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 first 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 duration of hospital stay; the need for (and duration of) ventilation; and, among patients not on ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO.

Other objectives include the assessment of the effects of study treatments on the need for renal replacement therapy and new major cardiac arrhythmias.

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

Data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital) and from relevant research studies (such as UK Biobank and Genomics England) 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), 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 the different treatment arms, 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 also 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 binary outcomes where the timing is unknown, the risk ratio and absolute risk difference will be calculated with confidence intervals and p-value reported. For the primary outcome (death within 28 days of first randomisation), discharge alive before 28 days will assume safety from the event (unless there is additional data confirming otherwise).

Pairwise comparisons within each randomisation will be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation phase A, main randomisation phase B, and second 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. Adjustment for multiple treatment comparisions due to the multi-arm design will be made. All p-values will be 2-sided.

Pre-specified subgroup analysis (e.g., disease severity; time since onset of symptoms; sex; age group) will be conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate),

Further details will be fully described in the Statistical Analysis Plan.

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[d] 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 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.

[d] 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).

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

Suspected serious transfusion reactions in patients who receive convalescent plasma should additionally be reported to Serious Hazards of Transfusions (SHOT) and through the MHRA Serious Adverse Blood Reactions and Events (SABRE) system.[e]

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 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; 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 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. Other serious or non-serious adverse events will not be recorded. It is anticipated that for some sub-studies, 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.

[e] https://www.shotuk.org/reporting/

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 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 Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. Unless this happens, the 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. As described in section 2.7.1, the DMC will advise if collection of information relating to the safety of convalescent plasma should be extended beyond the first 200 patients enrolled to Main Randomisation phase B (no additional treatment *vs.* convalescent plasma).

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 Steering Committee (unless the DMC advises otherwise).

5 QUALITY MANAGEMENT

5.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice 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 suspected or confirmed SARS-CoV-2 infection) and the reliability of the results that would inform the care for future patients.

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. At present, there are no proven treatments for COVID-19, basic hospital care (staffing, beds, ventilatory support) may well be overstretched, and mortality for hospitalised patients may be around 10% (or more in those who are older or have significant co-morbidity).

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 principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) 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) 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.

In the context of this epidemic, visits to hospital sites is generally not appropriate as they could increase the risks of spreading infection, and in the context of this trial they generally would not influence the reliability of the trial results or the well-being of the participants. In exceptional circumstances, the CCO may arrange monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data.[8,9] The purpose of 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. No routine source data verification will take place.

Training of laboratory and transfusion staff and initiation of convalescent plasma delivery will be performed by NHS Blood and Transplant Clinical Trials Unit.

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, in the circumstances of this epidemic, the priority is on the timely entry of data that is sufficient to support reliable analysis and interpretation about treatment effects. CCO staff will use 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 unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements.[10] 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 and LCCs (but should mindful of the workload facing participating hospitals and the infection control requirements during this epidemic).

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 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 data will be collected, analysed and published independently of the source of funding.

6.2 Funding

This study is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, Health Data Research UK, 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). 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 (Local Clinical Centres) within the UK. 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

For licensed treatments (e.g. lopinavir-ritonavir, corticosteroids, tocilizumab) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription.

For unlicensed treatments, manufacture, packaging and delivery will be the responsibility of the pharmaceutical company and Department of Health and Social Care. 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).

For convalescent plasma, manufacture, packaging, and delivery will be the responsibility of the relevant UK Blood Service (NHS Blood and Transplant for England, Welsh Blood Service for Wales, Scottish National Blood Transfusion Service for Scotland, and the Northern Ireland Blood Transfusion Service for Northern Ireland). Convalescent plasma will be labelled in accordance with regulatory requirements and the unit will be issued to the ward for a named patient in a bag marked for clinical trial use only. Treatment issue to randomised participants will be by prescription.

Study treatments will not be labelled beyond other than as required for routine clinical use. They will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

6.6 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 Digital (anticipated to be 10 years after the last patient is enrolled).

6.7 Publications and reports

The 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 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 Steering Committee will also establish a process by which proposals for additional publications (including from independent external researchers) are considered by the Steering Committee. The Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. 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.

6.8 Substudies

Proposals for substudies must be approved by the 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 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 randomization.
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

8 APPENDICES

8.1 Appendix 1: Information about the treatment arms

All patients will receive usual care in the participating hospital.

No additional treatment: There are no proven therapies for COVID-19.

Lopinavir-ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life. It is licensed in adults and children from the age of 14 days (2 years in Scotland). It has been widely used in pregnant women.[11] Lopinavir has in vitro inhibitory activity against SARS coronavirus (SARS-CoV) and MERS-CoV.[12-14 15] In common marmosets infected with MERS-CoV, animals treated with lopinavir/ritonavir had improved clinical, radiological, and pathological outcomes and reduced viral loads compared with untreated animals.[16] In one single-center, open-label study of the addition of lopinavir 400mg/ritonavir 100mg to ribavirin and corticosteroids in SARS patients the risk of adverse clinical outcomes (acute respiratory distress syndrome [ARDS] or death) was significantly lower (2.4% v 28.8%, $p<0.001$) compared to a historical control group.[12]

The most common short-term side effects in adults are diarrhoea, nausea, and vomiting. It must not be used by patients with severe liver disease. It should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (see Summary of Product Characteristics). Storage should be as per conditions in the Summary of Product Characteristics.

Dexamethasone: 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 coronavirus infections, including COVID-19, SARS and MERS. Common to severe cases of these infections is the presence of hypercytokinemia (a cytokine 'storm') and development of acute lung injury or acute respiratory distress syndrome (ARDS).[17-20] Pathologically, diffuse alveolar damage is found in patients who die from these infections.[21] A growing volume of clinical trial data from patients with severe community acquired pneumonia, ARDS and septic shock suggest benefit from low-to-moderate dose corticosteroids in relation to mortality and length of stay.[22-24]

In trials of low-to-moderate doses of corticosteroids, the main adverse effect has been hyperglycaemia.[23,25] A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection or neuromuscular weakness; an association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted.[26] Dexamethasone has a) minimal mineralocorticoid activity and does not affect sodium and water balance, thus avoiding potential problems with fluid retention which are not uncommon in severe viral pneumonitis/ARDS, and b) a comparatively long biological half-life of 36 to 54 hours enabling once a day dosing. In pregnancy, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80

mg twice daily) should be used instead of dexamethasone. Storage should be as per conditions in the Summary of Product Characteristics.

Hydroxycholoroquine: Chloroquine (CQ), an antimalarial drug discovered in 1934 and introduced generally in 1947, is the drug to which humans have been most exposed, with an annual global consumption of hundreds of metric tonnes for over 50 years. It is inexpensive, simple to administer, and, at the appropriate doses, has an excellent safety profile in all age groups and has been the prophylactic drug of choice in pregnancy [27]. In addition to its antimalarial use both chloroquine and the closely related hydroxychloroquine (HCQ) are used in continuous daily dosing for rheumatoid arthritis, systemic and discoid lupus erythematosus and psoriatic arthritis. HCQ is reported to have better safety profile than CQ, better gastrointestinal tolerability, and less retinal toxicity [28].

CQ has significant antiviral activity against SARS-CoV-2 in cell culture (EC_{50} = 1.13 μM; CC_{50} > 100 μM, SI > 88.50), as it does for the related SARS-CoV-1 [29-32]. CQ blocks virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[31] In SARS-CoV-2 infected Vero cells, HCQ (EC_{50}=0.72 μM) has been reported to be more potent than CQ (EC_{50}=5.47 μM) [33], although Liu et al reported that CQ was more potent than HCQ.[34] These are relatively high levels by comparison with therapeutic exposures in the treatment of malaria but could be achieved with daily oral dosing. Chloroquine has complex pharmacokinetic properties and although the relationship between plasma concentrations and concentrations in respiratory epithelium is not known precisely, in rats the concentration in lung is between 124 and 748-fold that in plasma [35]. If active, HCQ concentrations in the human lung would be expected to exceed those required for the EC_{90} after an initial dose. There are preliminary reports emerging from China and France of clinical benefit in the treatment of COVID-19 infections [36,37].

The recommended adult dosing of chloroquine for treatment of non-falciparum malaria (BNF) is: Initially 620 mg, then 310 mg after 6-8 hours, then 310 mg daily for 2 days. This is equivalent to 930mg base in first 24 hours. This is a loading dose to ensure the necessary blood concentrations are achieved rapidly.

Hydroxychloroquine is very similar to chloroquine. It is used mainly to treat rheumatoid arthritis and other related conditions. The adult dose is usually 400-600mg per day (equivalent to 310 to 465 mg base). Sometimes 800mg per day is given.

The dose in RECOVERY is Hydroyxchloroquine (155mg base per 200 mg tablet):

Initial dose:	4 tablets
6 hours after initial dose:	4 tablets
12 hours after initial dose:	2 tablets
24 hours after initial dose:	2 tablets
Thereafter:	2 tablets every 12 hours for a total of 10 days

12x155mg = 1860mg base = in first 24 hours

So the loading dose in RECOVERY is twice the normal dose for treating malaria. However, this dose has been selected based on the available data of the IC_{50} for SARS-

CoV-2. The objective is to reach plasma concentrations that are inhibitory to the virus as soon as safely possible. The plasma concentrations that will result are at the higher end of those encountered during steady state treatment of rheumatoid arthritis. Given the significant mortality in patients hospitalised with COVID-19, this dose is felt to be justified. This is the schedule that has been adopted by the World Health Organisation. No dose adjustment is required for weight based on the doses defined in this protocol.

Azithromycin: Azithromycin is a macrolide antibiotic. In addition to their antimicrobial properties, the macrolide antibiotics are known to have immunomodulatory activity. The mechanism of immunomodulation includes decreased production of pro-inflammatory cytokines and inhibition of neutrophil activation.[38-40] Macrolides are widely used both in infectious pneumonia due to their antimicrobial activity and in chronic inflammatory lung disease due to the immunomodulatory effects.[41] Azithromycin is preferred over other macrolides because data suggest it has stronger immunomodulatory effects than other macrolides.[40]

The use of macrolides in influenza-associated pneumonia has been associated with a faster reduction in inflammatory cytokines and, in combination with naproxen, decreased mortality.[42-44] Observational studies in MERS-CoV have not demonstrated a mortality benefit of macrolide use.[45] Macrolides have not been evaluated in severe betacoronavirus infections in randomised controlled trials. The safety of macrolides is well established.

Tocilizumab is a monoclonal antibody that binds to the receptor for IL-6, blocking IL-6 signalling and reduces inflammation. Tocilizumab is licensed for use in patients with rheumatoid arthritis and for use in people aged at least 2 years with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Severe COVID-19 is associated with a hyper-inflammatory state with elevated ESR, C-reactive protein, D-dimers, lactate dehydrogenase, ferritin, and increased levels of pro-inflammatory cytokines including as IL-1 and IL-6.[4,46,47] _ENREF_3_46There have been published and unpublished (pre-print) case series reports of the successful treatment of COVID-19 patients with IL-6 inhibitors.[46,48] IL-6 inhibitors have not been evaluated for the treatment of COVID-19 in randomised controlled trials.

Convalescent plasma: Convalescent plasma treatment, containing high titres of polyclonal antibody, has been used to treat severe viral pneumonias. Many studies have been small or poorly controlled but have reported beneficial effects in avian influenza[49-51], influenza A (H1N1) infections in 1915-1917[52] and 2009/2010[53,54], and seasonal influenza B[55]. More relevant to SARS-CoV-2, a systematic review of convalescent plasma treatment in SARS-CoV infections in 2003 identified eight observational studies that all reported improved mortality associated with the use of convalescent plasma – infected patients received various amounts of convalescent plasma.[56] Recent studies in seasonal influenza A and in MERS-CoV highlight the importance of high avidity and high titre antibodies respectively.[57,58]

Convalescent plasma therapy had been given to at least 245 COVID-19 patients by the end of February 2020, and, according to a Chinese health official, 91 cases had shown improvement in clinical indicators and symptoms (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). Five small case series (26 patients in total) have been published

that report the use of convalescent plasma in people with COVID-19 infection.[59-63] These studies have reported clinical and radiological improvements after treatment with convalescent plasma. However, these small uncontrolled studies have significant flaws and the reported effects are unreliable. Convalescent plasma is currently being tested in the REMAP-CAP trial among patients on intensive care units.

8.2 Appendix 2: Drug specific contraindications and cautions

Lopinavir/ritonavir

- Severe hepatic insufficiency*
- Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. This includes alfuzosin, ranolazine, amiodarone, dronaderone, fusidic acid, neratinib, venetoclax, colchicine, astemizole, terfenadine, lurasidone, pimozide, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir, lovastatin, simvastatin, lomitapide, avanafil, sildenafil, vardenafil, midazolam, triazolam, ciclosporin, tacrolimus, sirolimus, rivaroxaban and vorapaxar (See Summary of Product Characteristics for more detail). It may be appropriate to temporarily withhold such concomitant medication while the patient is receiving lopinavir/ritonavir. For patients receiving warfarin additional INR monitoring is advised.

Corticosteroid

- Known contra-indication to short-term low-dose corticosteroid.

Hydroxychloroquine

- Known prolonged QTc interval*
- Caution: Co-administration with medications that prolong the QT interval (e.g. macrolides, quinolones) is not an absolute contraindication, but it may be appropriate to check the QT interval by performing an ECG.

Azithromycin

- Known prolonged QTc interval*
- Co-administration with chloroquine or hydroxychloroquine
- Known hypersensitivity to macrolide antibiotic

Tocilizumab

- Known hypersensitivity to tocilizumab.
- Evidence of active TB infection
- Clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)

(Note: Pregnancy and breastfeeding are not exclusion criteria.)

Convalescent plasma

- Known moderate or severe allergy to blood components *
- Not willing to receive a blood product*

* If these conditions are recorded on the baseline case report form, patients will be ineligible for randomisation to that arm of the study.

Note: This study is being conducted within hospitals. Therefore use of medication will be subject to standard medication reviews (typically within 48 hours of enrolment) and clinical assessments (including appropriate blood tests) which will guide modifications to both the study treatment and use of concomitant medication (e.g. in the case of potential drug interactions). The doctor may decide whether it is appropriate to stop such medications temporarily to allow the patient to complete the course of their assigned intervention.

Although all available data on use in pregnancy are reassuring, since the effect of some of the treatments on unborn babies is uncertain, female participants who are not already pregnant will be advised that they should not get pregnant within 3 months of the completion of trial treatment(s).

8.3 Appendix 3: Paediatric dosing information

Arm	Route	Weight #	Dose (Duration for all arms = 10 days or until discharge from hospital)
No additional treatment	-	-	-
Lopinavir-Ritonavir (Kaletra®) - 80/20mg in 1mL oral solution - 100/25mg tablet - 200/50mg tablet Tablets must NOT be crushed	Oral or Nasogastric	Preterm infants with a corrected gestation age of <42 weeks **or** neonates with postnatal age of < 14 days excluded	
		≤ 5 kg	0.2 mL/kg every 12 hours
		6 - 9 kg	1.5 mL every 12 hours
		10 - 13 kg	2 mL every 12 hours
		14 - 19 kg	2.5 mL every 12 hours or 200/50 mg every 12 hours
		20 - 24 kg	3 mL every 12 hours or 200/50 mg every 12 hours
		25 - 34 kg	4 mL every 12 hours or 300/75 mg every 12 hours
		≥ 35 kg	5 mL every 12 hours or 400/100 mg every 12 hours
Corticosteroid - Oral solution* - Tablet* - Soluble tablet* - Solution for injection* *various strengths available	Oral or Nasogastric or Intravenous	All Including pre-term neonates	**Hydrocortisone (IV) – additional option for Preterm infants with a corrected gestation age of <40 weeks:** 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days or **Prednisolone (Oral/NG)**: 1 mg/kg once daily (max: 40 mg; doses can be rounded as per routine clinical practice) or **Methylprednisolone sodium succinate (IV):** 0.8 mg/kg once daily (max: 32 mg) or **Dexamethasone (Oral/NG/IV)**: 150 micrograms/kg (as base) once daily (max: 6 mg)

Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.

Arm	Route	Weight #	Dose (Duration for all arms = 10 days or until discharge from hospital)
Hydroxychloroquine sulfate Dose expressed as hydroxychloroquine sulfate - 200mg tablet (tablets may be crushed and dispersed in water to allow for aliquot dosing – see note below) **A baseline ECG (to check QTc interval) is recommended for paediatric patients randomised to hydroxychloroquine.**	Oral or Nasogastric	Infants with postnatal age of <180 days excluded	
		5 - 10 kg	Initial dose: 100 mg 6 hours after initial dose: 100 mg 12 hours after initial dose: 50 mg 24 hours after initial dose: 50 mg Then 50 mg every 12 hours
		11 - 20 kg	Initial dose: 200 mg 6 hours after initial dose: 200 mg 12 hours after initial dose: 100 mg 24 hours after initial dose: 100 mg Then 100 mg every 12 hours
		21 - 39 kg	Initial dose: 400 mg 6 hours after initial dose: 400 mg 12 hours after initial dose: 200 mg 24 hours after initial dose: 200 mg Then 200 mg every 12 hours
		≥ 40 kg	Initial dose: 800 mg 6 hours after initial dose: 800 mg 12 hours after initial dose: 400 mg 24 hours after initial dose: 400 mg Then 400 mg every 12 hours
Azithromycin - 40mg in 1mL oral suspension - 250mg tablet/capsule - 500mg tablet/capsule - 500mg powder for solution for infusion	Oral or Nasogastric or Intravenous	≤ 16 kg Including preterm neonates	10 mg/kg once daily
		17 - 25 kg	200 mg once daily
		26 - 35 kg	300 mg once daily
		36 - 45 kg	400 mg once daily
		≥ 46 kg	500 mg once daily
Convalescent Plasma	Intravenous		5 mL/kg of ABO compatible convalescent plasma intravenous up to standard adult dose of 275 mLs per day on study days 1 and 2. Minimum of 12 hour interval between 1st and 2nd units. Convalescent plasma for neonates and infants up to one year of age needs to be ordered on a named patient basis from the relevant National Blood Service to ensure the unit meets neonatal requirements. Data transfer storage and retention will be in line with NHSBT standard procedures and protocols.

Weight to be rounded to the nearest kg unless dosage expressed as mg/kg or mL/kg.

Note: Hydroxychloroquine oral solution is not available as authorised medicinal product in the EU. The European Directorate for the Quality of Medicines and the European Paediatric Formulary (PaedF) Working

Party have, in this exceptional situation, complied existing knowledge on paediatric formulations for hydroxychloroquine. As noted in their document, hydroxychloroquine sulfate is a highly soluble drug and it is expected that manipulation of the formulation will have minimal impact on bioavailability. The extemporaneously preparations described in literature is generally prepared by crushing of tablets and mixing with an aqueous base. On these basis and the urgent public health need of this trial, we propose that hydroxychloroquine tablets to be crushed and dispersed in water to allow for aliquot dosing in children if required**.**

Second stage randomisation (Patients < 1 year of age will NOT be eligible)

Arm	Route	Weight	Dose
No additional treatment	-	-	-
Tocilizumab	Intravenous	Infants < 1 year excluded	
		< 30 kg	12 mg/kg A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
		≥ 30 kg	8 mg/kg (max 800 mg) A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.

8.4 Appendix 4: Organisational Structure and Responsibilities

Chief Investigator
The Chief Investigator has overall responsibility for:

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

Steering Committee
The Steering Committee (see Section 8.5 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.

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 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.

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.

8.5 Appendix 5: Organisational Details

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 Leads	Richard Haynes, Edmund Juszczak
Co-investigators	Kenneth Baillie (Scotland Lead), Thomas Jaki, Katie Jeffery, Wei Shen Lim, Alan Montgomery, Kathy Rowan
Other members	Saul Faust, Lucy Chappell, Marion Mafham

DATA MONITORING COMMITTEE

(Interim analyses and response to specific concerns)

Chair	Peter Sandercock
Members	Janet Darbyshire, David DeMets, Robert Fowler, David Lalloo, Ian Roberts, Janet Wittes
Statisticians (non-voting)	Jonathan Emberson, Natalie Staplin

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(copies of this protocol and related forms and information can be downloaded)

To RANDOMISE a patient, visit:

Website: www.recoverytrial.net

Substantial amendments to RECOVERY trial protocol

Protocol version	Date	Randomization	Treatment arms
1.0	13-Mar-2020	Main (part A)	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Nebulised Interferon-ß-1a (never activated)
2.0	23-Mar-2020	Main (part A)	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Hydroxychloroquine
3.0	07-Apr-2020	Main (part A)	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Hydroxychloroquine Azithromycin
4.0	14-Apr-2020	Main (part A) Second[a]	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid Hydroxychloroquine Azithromycin No additional treatment Tocilizumab
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[a]	No additional treatment Lopinavir-ritonavir Low-dose corticosteroid[b] Hydroxychloroquine[c] Azithromycin No additional treatment Convalescent plasma No additional treatment Tocilizumab

[a] 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/dL)
[b] enrolment ceased 8 June 2020 as more than 2,000 patients had been recruited to the active arm
[c] enrolment ceased 5 June 2020 when the Data Monitoring Committee advised that the Chief Investigators review the unblinded data.

Statistical Analysis Plans

Statistical Analysis Plan V1.0

RECOVERY

Randomised Evaluation of COVID-19 Therapy

Statistical Analysis Plan

Version 1.0

Date: 09 June 2020

Protocol version: 6.0, 14 May 2020

IRAS no: 281712
REC ref: EE/20/0101
ISRCTN: 50189673
EudraCT: 2020-001113-21

Nuffield Department of
POPULATION HEALTH

UNIVERSITY OF OXFORD

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Abbreviations

ADaM	Analysis Data Model
AE	adverse event
CDISC	The Clinical Data Interchange Standards Consortium
CI	confidence interval
CoV	Coronavirus
COVID	coronavirus-induced disease
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
CTU	clinical trials unit
CTSU	Clinical Trials Service Unit
DMC	Data Monitoring Committee
ECMO	Extra Corporeal Membrane Oxygenation
eCRF	Electronic case report form
FiO_2	fraction of inspired oxygen
ICD	International Classification of Diseases
IFN	interferon
ICNARC	Intensive Care National Audit and Research Centre
IQR	interquartile range
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
NPEU	National Perinatal Epidemiology Unit
OPCS-4	NHS Classification of Interventions and Procedures
PaO_2	partial pressure of oxygen
RR	risk ratio
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	virus causing COVID-19
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
SD	standard deviation
SC	Steering Committee

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Roles and responsibilities

Trial Statisticians

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Role: To develop the statistical analysis plan and conduct the final comparative analysis. Blinded to trial allocation.

Data Monitoring Committee (DMC) Statisticians

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Role: To conduct regular interim analyses for the DMC. Contribution restricted up until unblinded to trial allocation.

Trial IT systems & Programmers

Andy King, David Murray, Richard Welsh

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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.

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Dr Will Stevens

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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 inpatients for COVID-19 (clinically suspected or laboratory confirmed).

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.[1] Any subsequent analyses of a more exploratory nature will not be bound by this strategy, and will be detailed in a separate analysis plan.

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 to the funder. The analysis will be carried out by an identified, appropriately qualified and experienced statisticians, who will ensure the integrity of the data during their processing e.g. by parallel programming.

This statistical analysis plan is based on the latest version of the protocol. A record of amendments to the protocol can be found in the RECOVERY trial directory: https://www.recoverytrial.net/for-site-staff/site-set-up-1.

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 is 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.

2.2 Objectives of the trial

2.2.1 *Primary objective*

To provide reliable estimates of the effect of study treatments on all-cause mortality within 28 days of randomisation.

2.2.2 *Secondary objectives*

To investigate the effect of study treatments on the duration of hospital stay, the need for (and duration of) ventilation, and the need for renal replacement therapy.

2.3 Trial design

This is a multi-centre, multi-arm, adaptive, open-label, randomised controlled trial with three possible stages of randomisation. In the main randomisation patients are allocated to no additional treatment or one of 4 anti-viral or host-directed treatments. In addition, in a

factorial design, eligible patients can also be allocated simultaneously to no additional treatment or convalescent plasma. Patients who deteriorate according to predefined criteria can be further randomised to no additional treatment or an immunomodulatory treatment. 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
- SARS-Cov-2 infection (clinically suspected or laboratory confirmed)
- 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 (or indicated) arms.

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.

2.5.1 *Main randomisation part A:*

- **No additional treatment**
- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days.
- **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.
- **Hydroxychloroquine** by mouth for 10 days (4 doses in first 24 hours and 1 dose every 12 hours for 9 days).
- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for a total of 10 days.

2.5.2 *Main randomisation part B:*

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 (275mls +/- 75 mls) 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.

2.5.3 *Second randomisation for patients with progressive COVID-19*

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 (or in children, significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement); 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.

2.6 Definitions of primary and secondary outcomes

Outcomes will be assessed at 28 days and then 6 months after randomisation. Analysis of longer-term outcomes collected beyond this will be described in a separate Statistical Analysis Plan.

2.6.1 *Primary outcome*

Mortality (all-cause)

2.6.2 *Secondary clinical outcomes*

- Time to discharge from hospital
- Use of mechanical ventilation/Extra Corporal Membrane Oxygenation (ECMO) or death (among patients not on ventilation or ECMO at baseline)

2.6.3 *Subsidiary clinical outcomes*

- Cause-specific mortality (COVID-19; cardiovascular; non-vascular; other)
- Use of renal dialysis or haemofiltration
- Serious cardiac arrhythmia (recorded in a subset)

- Use of ventilation (overall and by type)
- Duration of ventilation (overall and by type)

2.6.4 *Detailed derivation of outcomes*

The detailed derivation of outcomes included in statistical analysis will be 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. Sample size and recruitment will be monitored by the Steering Committee (SC) throughout the trial.

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. In the event that 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 SC notified if an error in the randomisation process is identified.

2.9.1 *Main randomisation part A*

Simple randomisation will be used with a 2:1:1:1:1 allocation ratio to one of the following treatment arms (in addition to usual care), which is subject to change:

- No additional treatment
- Lopinavir-Ritonavir
- Corticosteroid
- Hydroxychloroquine
- Azithromycin

The randomisation programme will allocate 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 available. 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).

2.9.2 *Main randomisation part B*

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
- Convalescent plasma

2.9.3 *Second randomisation for patients with progressive COVID-19*

Eligible participants may be randomised using simple randomisation with an allocation ratio 1:1 between the following arms:

- No additional treatment
- Tocilizumab

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 SC (unless the DMC advises otherwise). The DMC and DMC statisticians will be unblinded.

2.11 Data collection schedule

Baseline and 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 or not 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 Digital 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 will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, 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. Hence, multiple reviews by the Data Monitoring Committee have no material impact on the final analysis. In such a circumstance, the DMC will inform the SC who will make the results available to the public and amend the trial arms accordingly.

2.13 Trial reporting

The trial will be reported according to the principles of the CONSORT statements.[2, 3, 4] The exact composition of the trial publication(s) depends on the size of the epidemic, the availability of drugs, and the findings from the various pairwise comparative analyses (with the no additional treatment arm) in the main trial.

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, for the main and second randomisation separately. The flow diagram for the nested factorial design (main randomisation part B to convalescent plasma) will be stratified by the 5 arms included in the main randomisation part A. 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.

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.

4.2.1 Main randomisation (part A and B)

- Age at randomisation
- Sex
- Ethnicity
- Time since COVID-19 symptoms onset
- Time since hospitalisation
- Current respiratory support requirement
- Currently requiring renal dialysis or haemofiltration
- Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment)
- If female, known to be pregnant

4.2.2 Second randomisation

In addition to the above:

- Type of ventilation support currently required (none, CPAP alone, non-invasive ventilation, high-flow nasal oxygen, mechanical ventilation, ECMO)
- Latest oxygen saturation measurement (%)
- Latest CRP measurement (mg/L)
- Latest ferritin measurement (ng/mL)
- Latest creatinine measurement (µmol/L)
- Allocation in first randomisation
- 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, or the range if appropriate. There will be no tests of statistical significance performed nor confidence intervals calculated for differences between randomised groups on any baseline variable.

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 Digital, ICNARC, and similar organisations in the devolved nations.

The number and percentage of participants with follow-up information at day 28 and at 6 months after the main 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

For all outcomes, the primary analysis will be performed on the intention to treat (ITT) population at 28 days after the main randomisation. An ITT analysis of all outcomes at 6 months post-randomisation will also be conducted.

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, and second randomisation). 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 part A

5.1.1 *Primary outcome*

Mortality (all-cause) will be summarised with counts and percentages by randomised comparison group. A time-to-event analysis will be conducted using the log-rank test, with the p-value reported. 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 confidence interval for each treatment group versus the no additional treatment group.[5] For the primary outcome, discharge alive before the relevant time period (28 days) will be assumed as absence of the event (unless there is additional data confirming otherwise).

5.1.2 *Secondary outcomes*

5.1.2.1 Time to discharge from hospital

A time-to-event analysis will be used to compare each treatment group with the no additional treatment group using Kaplan-Meier and the log-rank test, as described above. Patients who die in hospital will be censored after 28 days. 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).[6]

5.1.2.2 Use of mechanical ventilation/ECMO or death (among those not on ventilation or ECMO at randomisation)

Counts and percentages will be presented by randomised group and the risk ratio will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Patients who were already on ventilation at randomisation will be excluded from the denominator.

5.1.3 *Subsidiary clinical outcomes*

5.1.3.1 Cause-specific mortality

Cause-specific mortality will be analysed in a similar manner to the primary outcome. Deaths from other causes will be censored at the date of death and a separate survival curve will be presented for each cause of death (COVID-19, other infection, cardiovascular and other).

5.1.3.2 Use of renal dialysis or haemofiltration

Counts and percentages will be presented by randomised group and the risk ratio will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Patients who were already on renal dialysis or haemofiltration at randomisation will be excluded from the denominator.

5.1.3.3 Major cardiac arrhythmia

Counts and percentages will be presented by randomised group and the risk ratio for any major cardiac arrhythmia will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. 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).

5.1.3.4 Use of ventilation (overall and by type)

Counts and percentages will be presented by randomised group for patients who received any assisted ventilation. Patients who were already on assisted ventilation at randomisation will be excluded from the denominator. The number of patients receiving the different types of ventilation will also be reported: (i) CPAP; (ii) other non-invasive; (iii) high-flow nasal oxygen; (iv) mechanical; (v) ECMO, with subtotals for (i)-(iii) (non-invasive) and (iv)-(v) (invasive).

5.1.3.5 Duration of ventilation (overall and by type)

The mean (SD) duration of ventilation will be calculated in days from the main randomisation for each randomised group in those who received ventilation, separately for survivors and non-survivors. This will be reported overall for any assisted ventilation and separately for mechanical ventilation or ECMO. The mean difference and confidence intervals will be presented for each pairwise comparison with the no additional treatment arm.

5.2 Main randomisation part B

For the evaluation of treatment effect in the factorial design, the main effect of convalescent plasma across all arms in main randomisation part A combined, will be presented and tested, as described in 5.1. Data stratified by allocation in part A will also be reported to aid interpretation, but no tests for statistical interaction will be performed.

Additional safety data will be collected in a subset of patients randomised to part B. These will be tabulated separately by allocation (convalescent plasma versus no additional treatment): (i) sudden worsening in respiratory status; (ii) severe allergic reaction; (iii) temperature >39°C or ≥2°C rise since randomisation; (iv) sudden hypotension, clinical haemolysis and thrombotic event.

5.3 Second randomisation

Evaluation of treatment effects in the main randomisation and the second randomisation will be conducted independently, as described in 5.1. In addition to the overall comparison for Tocilizumab vs no additional treatment, results will be stratified according to allocation in the main randomisation (part A and part B), however no interaction tests will be performed between the allocations in the two stages.

5.4 Pre-specified subgroup analyses

Pre-specified subgroup analyses will be conducted for the main randomisation (part A and part B) and the second randomisation, for the following outcomes:

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

The analyses will be conducted using a test for heterogeneity (or test for trend for 3 or more ordered groups). Results will be presented on forest plots as event rate ratios (or risk ratios) with confidence intervals. The following subgroups will be examined:

- Risk group (three risk groups with approximately equal number of deaths based on factors recorded at randomisation)
- Requirement for respiratory support at randomisation (None; Oxygen only; Ventilation or ECMO)
- Time since illness onset (≤7 days; >7 days)
- Age (<70; 70-79; 80+ years)
- Sex (Male; Female)
- Ethnicity (White; Black, Asian or Minority Ethnic; Unknown)

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

5.5 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. 95% confidence intervals will be presented for estimates of between-group effects throughout.

5.6 Statistical software employed

The statistical software SAS version 9.4, R Studio 3.6.2 and Stata/SE version 15 (or later) for Windows will be used for the interim and final analyses.

5.7 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.

7 ADDITIONAL 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 V6.0

Use and duration of ventilation are described as secondary objectives in the protocol, and listed as subsidiary outcomes in the statistical analysis plan. 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 known in advance. While methods for these situations exist it was felt that the resulting change in level of significance was not appropriate.

9 REFERENCES

9.1 Trial documents

Dummy tables and the data derivation document can be found in the RECOVERY trial directory and will be published with this SAP on the trial website.

9.2 Other references

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6. Betensky RA and Schoenfeld DA. Nonparametric Estimation in a Cure Model with Random Cure Times. Biometrics 2001;57:282-286.

10 APPROVAL

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11 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 SC members prior to interim analysis on 28/05/20.	After	Prior
1.0	09/06/20	LL	Revised following the stopping of the hydrochloroquine arm, and prior to the trial statisticians receiving unblinded data for this arm.	After	Prior

Statistical Analysis Plan V1.1 (including summary of changes)

RECOVERY

Randomised Evaluation of COVID-19 Therapy

Statistical Analysis Plan

Version 1.1

Date: 21 June 2020

Protocol version: 6.0, 14 May 2020

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

UNIVERSITY OF OXFORD

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Abbreviations

ADaM	Analysis Data Model
AE	adverse event
CDISC	The Clinical Data Interchange Standards Consortium
CI	confidence interval
CoV	Coronavirus
COVID	coronavirus-induced disease
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
CTU	clinical trials unit
CTSU	Clinical Trials Service Unit
DMC	Data Monitoring Committee
ECMO	Extra Corporeal Membrane Oxygenation
eCRF	Electronic case report form
FiO_2	fraction of inspired oxygen
ICD	International Classification of Diseases
IFN	interferon
ICNARC	Intensive Care National Audit and Research Centre
IQR	interquartile range
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
NPEU	National Perinatal Epidemiology Unit
OPCS-4	NHS Classification of Interventions and Procedures
PaO_2	partial pressure of oxygen
RR	risk ratio
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SARS-CoV-2	virus causing COVID-19
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
SD	standard deviation
SC	Steering Committee

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Roles and responsibilities

Trial Statisticians

Dr Louise Linsell and Jennifer Bell

NDPH, University of Oxford

Role: To develop the statistical analysis plan and conduct the final comparative analysis. Blinded to trial allocation.

Data Monitoring Committee (DMC) Statisticians

Professor Jonathan Emberson and Dr Natalie Staplin

NDPH, University of Oxford

Role: To conduct regular interim analyses for the DMC. Contribution restricted up until unblinded to trial 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 Wallendszuz

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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 inpatients for COVID-19 (clinically suspected or laboratory confirmed).

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.[1] Any subsequent analyses of a more exploratory nature will not be bound by this strategy, and will be detailed in a separate analysis plan.

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 to the funder. The analysis will be carried out by an identified, appropriately qualified and experienced statisticians, who will ensure the integrity of the data during their processing e.g. by parallel programming.

This statistical analysis plan is based on the latest version of the protocol. A record of amendments to the protocol can be found in the RECOVERY trial directory: https://www.recoverytrial.net/for-site-staff/site-set-up-1.

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 is 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.

2.2 Objectives of the trial

2.2.1 *Primary objective*

To provide reliable estimates of the effect of study treatments on all-cause mortality within 28 days of randomisation.

2.2.2 *Secondary objectives*

To investigate the effect of study treatments on the duration of hospital stay, the need for (and duration of) ventilation, and the need for renal replacement therapy.

2.3 Trial design

This is a multi-centre, multi-arm, adaptive, open-label, randomised controlled trial with three possible stages of randomisation. In the main randomisation patients are allocated to no additional treatment or one of 4 anti-viral or host-directed treatments. In addition, in a

factorial design, eligible patients can also be allocated simultaneously to no additional treatment or convalescent plasma. Patients who deteriorate according to predefined criteria can be further randomised to no additional treatment or an immunomodulatory treatment. 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
- SARS-Cov-2 infection (clinically suspected or laboratory confirmed)
- 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 (or indicated) arms.

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.

2.5.1 *Main randomisation part A:*

- **No additional treatment**
- **Lopinavir 400mg-Ritonavir 100mg** by mouth (or nasogastric tube) every 12 hours for 10 days.
- **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.
- **Hydroxychloroquine** by mouth for 10 days (4 doses in first 24 hours and 1 dose every 12 hours for 9 days).
- **Azithromycin 500mg** by mouth (or nasogastric tube) or intravenously once daily for a total of 10 days.

2.5.2 *Main randomisation part B:*

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 (275mls +/- 75 mls) 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.

2.5.3 *Second randomisation for patients with progressive COVID-19*

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 (or in children, significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement); 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.

2.6 Definitions of primary and secondary outcomes

Outcomes will be assessed at 28 days and then 6 months after randomisation. Analysis of longer-term outcomes collected beyond this will be described in a separate Statistical Analysis Plan.

2.6.1 *Primary outcome*

Mortality (all-cause)

2.6.2 *Secondary clinical outcomes*

- Time to discharge from hospital
- Use of mechanical ventilation/Extra Corporal Membrane Oxygenation (ECMO) or death (among patients not on ventilation or ECMO at baseline)

2.6.3 *Subsidiary clinical outcomes*

- Cause-specific mortality (COVID-19; cardiovascular; non-vascular; other)
- Use of renal dialysis or haemofiltration
- Serious cardiac arrhythmia (recorded in a subset)

- Use of ventilation (overall and by type)
- Duration of ventilation (overall and by type)

2.6.4 *Detailed derivation of outcomes*

The detailed derivation of outcomes included in statistical analysis will be 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. Sample size and recruitment will be monitored by the Steering Committee (SC) throughout the trial.

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. In the event that 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 SC notified if an error in the randomisation process is identified.

2.9.1 *Main randomisation part A*

Simple randomisation will be used with a 2:1:1:1:1 allocation ratio to one of the following treatment arms (in addition to usual care), which is subject to change:

- No additional treatment
- Lopinavir-Ritonavir
- Corticosteroid
- Hydroxychloroquine
- Azithromycin

The randomisation programme will allocate 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 available. 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).

2.9.2 *Main randomisation part B*

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
- Convalescent plasma

2.9.3 *Second randomisation for patients with progressive COVID-19*

Eligible participants may be randomised using simple randomisation with an allocation ratio 1:1 between the following arms:

- No additional treatment
- Tocilizumab

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 SC (unless the DMC advises otherwise). The DMC and DMC statisticians will be unblinded.

2.11 Data collection schedule

Baseline and 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 or not 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 Digital 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 will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, 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. Hence, multiple reviews by the Data Monitoring Committee have no material impact on the final analysis. In such a circumstance, the DMC will inform the SC who will make the results available to the public and amend the trial arms accordingly.

2.13 Trial reporting

The trial will be reported according to the principles of the CONSORT statements.[2, 3, 4] The exact composition of the trial publication(s) depends on the size of the epidemic, the availability of drugs, and the findings from the various pairwise comparative analyses (with the no additional treatment arm) in the main trial.

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, for the main and second randomisation separately. The flow diagram for the nested factorial design (main randomisation part B to convalescent plasma) will be stratified by the 5 arms included in the main randomisation part A. 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.

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.

4.2.1 Main randomisation (part A and B)

- Age at randomisation
- Sex
- Ethnicity
- Time since COVID-19 symptoms onset
- Time since hospitalisation
- Current respiratory support requirement
- Currently requiring renal dialysis or haemofiltration
- Comorbidities (diabetes, heart disease, chronic lung disease, tuberculosis, human immunodeficiency virus, severe liver disease, severe kidney impairment)
- If female, known to be pregnant

4.2.2 Second randomisation

In addition to the above:

- Type of ventilation support currently required (none, CPAP alone, non-invasive ventilation, high-flow nasal oxygen, mechanical ventilation, ECMO)
- Latest oxygen saturation measurement (%)
- Latest CRP measurement (mg/L)
- Latest ferritin measurement (ng/mL)
- Latest creatinine measurement (µmol/L)
- Allocation in first randomisation
- 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, or the range if appropriate.

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 Digital, ICNARC, and similar organisations in the devolved nations.

The number and percentage of participants with follow-up information at day 28 and at 6 months after the main 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

For all outcomes, the primary analysis will be performed on the intention to treat (ITT) population at 28 days after the main randomisation. An ITT analysis of all outcomes at 6 months post-randomisation will also be conducted.

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, and second randomisation). 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 part A

5.1.1 *Primary outcome*

Mortality (all-cause) will be summarised with counts and percentages by randomised comparison group. A time-to-event analysis will be conducted using the log-rank test, with the p-value reported. 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 confidence interval for each treatment group versus the no additional treatment group.[5] For the primary outcome, discharge alive before the relevant time period (28 days) will be assumed as absence of the event (unless there is additional data confirming otherwise).

5.1.2 *Secondary outcomes*

5.1.2.1 Time to discharge from hospital

A time-to-event analysis will be used to compare each treatment group with the no additional treatment group using Kaplan-Meier and the log-rank test, as described above. Patients who die in hospital will be censored after 28 days. 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).[6]

5.1.2.2 Use of mechanical ventilation/ECMO or death (among those not on ventilation or ECMO at randomisation)

Counts and percentages will be presented by randomised group and the risk ratio will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Each component of this composite outcome will also be

summarised. Patients who were already on ventilation or ECMO at randomisation will be excluded from the denominator.

5.1.3 *Subsidiary clinical outcomes*

5.1.3.1 Cause-specific mortality

Cause-specific mortality will be analysed in a similar manner to the primary outcome. Deaths from other causes will be censored at the date of death and a separate survival curve will be presented for each cause of death (COVID-19, other infection, cardiovascular, and other).

5.1.3.2 Use of renal dialysis or haemofiltration

Counts and percentages will be presented by randomised group and the risk ratio will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. Patients who were already on renal dialysis or haemofiltration at randomisation will be excluded from the denominator.

5.1.3.3 Major cardiac arrhythmia

Counts and percentages will be presented by randomised group and the risk ratio for any major cardiac arrhythmia will be calculated for each pairwise comparison with the no additional treatment arm, with confidence intervals and p-values reported. The absolute risk difference will also be presented with confidence intervals. 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).

5.1.3.4 Use of ventilation (overall and by type)

Counts and percentages will be presented by randomised group for patients who received any assisted ventilation. Patients who were already on assisted ventilation or required oxygen (as this includes people on CPAP, other non-invasive ventilation and high-flow nasal oxygen) at randomisation will be excluded from the denominator. The number of patients receiving the different types of ventilation will also be reported: non-invasive ventilation (i.e. CPAP, other non-invasive ventilation or high-flow nasal oxygen), and invasive mechanical ventilation (i.e. invasive mechanical ventilation or ECMO).

5.1.3.5 Duration of ventilation (overall and by type)

The mean (SD) duration of ventilation will be calculated in days from the main randomisation for each randomised group in those who received ventilation, separately for survivors and non-survivors. This will be reported overall for any assisted ventilation and separately for mechanical ventilation or ECMO. The mean difference and confidence intervals will be presented for each pairwise comparison with the no additional treatment arm.

5.2 Main randomisation part B

For the evaluation of treatment effect in the factorial design, the main effect of convalescent plasma across all arms in main randomisation part A combined, will be presented and tested,

as described in 5.1. Data stratified by allocation in part A will also be reported to aid interpretation, but no tests for statistical interaction will be performed.

Additional safety data will be collected in a subset of patients randomised to part B. These will be tabulated separately by allocation (convalescent plasma versus no additional treatment): (i) sudden worsening in respiratory status; (ii) severe allergic reaction; (iii) temperature >39°C or ≥2°C rise since randomisation; (iv) sudden hypotension, clinical haemolysis and thrombotic event.

5.3 Second randomisation

Evaluation of treatment effects in the main randomisation and the second randomisation will be conducted independently, as described in 5.1. In addition to the overall comparison for Tocilizumab vs no additional treatment, results will be stratified according to allocation in the main randomisation (part A and part B), however no interaction tests will be performed between the allocations in the two stages.

5.4 Pre-specified subgroup analyses

Pre-specified subgroup analyses will be conducted for the main randomisation (part A and part B) and the second randomisation, for the following outcomes:

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

The analyses will be conducted using a test for heterogeneity (or test for trend for 3 or more ordered groups). Results will be presented on forest plots as event rate ratios, or risk ratios with confidence intervals. The following subgroups will be examined:

- Risk group (three risk groups with approximately equal number of deaths based on factors recorded at randomisation)
- Requirement for respiratory support at randomisation (None; Oxygen only; Ventilation or ECMO)
- Time since illness onset (≤7 days; >7 days)
- Age (<70; 70-79; 80+ years)
- Sex (Male; Female)
- Ethnicity (White; Black, Asian or Minority Ethnic)

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

5.5 Adjustment for baseline characteristics

The main analyses described above will be unadjusted for baseline characteristics. However, in the event that there are any important imbalances between the randomised groups in key baseline subgroups (see section 5.4), emphasis will be placed on analyses that are adjusted for the relevant baseline characteristic(s). This will be done through the use of Cox regression for the estimation of adjusted hazard ratios and a log-binomial regression model for the estimation of adjusted risk ratios.

5.6 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. 95% confidence intervals will be presented for the main comparisons.

5.7 Statistical software employed

The statistical software SAS version 9.4, R Studio 3.6.2 and Stata/SE version 15 (or later) for Windows will be used for the interim and final analyses.

5.8 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.

7 ADDITIONAL 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 V6.0

Use and duration of ventilation are described as secondary objectives in the protocol, and listed as subsidiary outcomes in the statistical analysis plan. 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 known in advance. While methods for these situations exist it was felt that the resulting change in level of significance was not appropriate.

9 REFERENCES

9.1 Trial documents

Dummy tables and the data derivation document can be found in the RECOVERY trial directory and will be published with this SAP on the trial website.

9.2 Other references

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2. Schulz KF, Altman DG, Moher D for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:698-702.

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4. Dimairo M, Coates E, Pallmann P, Todd S, Julious SA, Jaki T, Wason J, Mander AP, Weir CJ, Koenig F, Walton MK. Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design. BMC medicine 2018;16(1):210.

5. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II: analysis and examples. Br J Cancer 1977;35:1-39.

6. Betensky RA and Schoenfeld DA. Nonparametric Estimation in a Cure Model with Random Cure Times. Biometrics 2001;57:282-286.

10 APPROVAL

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11 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 SC members prior to interim analysis on 28/05/20.	After	Prior
1.0	09/06/20	LL	Revised following the stopping of the hydrochloroquine 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.