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A randomised trial of treatments to prevent death in patients hospitalised with pneumonia

Submission date
30/03/2020

Recruitment status
Recruiting

Registration date
02/04/2020

Overall study status
Ongoing

Last Edited
01/09/2025

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
In early 2020, as this study was being developed, there were no approved treatments for COVID-19, a disease caused by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including lopinavir + ritonavir, low-dose corticosteroids and hydroxychloroquine (which has now been done). A World Health Organization (WHO) expert group issued broadly similar advice. These groups also advised that other treatments will soon emerge that require evaluation. Since then, progress in COVID-19 treatment has highlighted the need for better evidence for the treatment of pneumonia caused by other pathogens, such as influenza and bacteria, for which therapies are widely used without good evidence of benefit or safety.
This study is comparing several different treatments that may be useful for patients hospitalised with pneumonia caused by COVID-19, influenza or other organisms. RECOVERY is a platform trial which is able to compare multiple treatments at the same time using a single protocol. This type of trial allows new treatments to be added, and treatments that are ineffective to be dropped, throughout the course of the trial.

Who can participate?
Patients may be included in this study if they have one of the following diagnoses and are in hospital:
a) Confirmed SARS-CoV-2 infection
b) Confirmed influenza A or B infection
c) Community-acquired pneumonia with planned antibiotic treatment (excluding patients with suspected or confirmed SARS-CoV-2, influenza, active pulmonary tuberculosis or Pneumocystis jirovecii pneumonia)
Patients will not be included if the attending doctor thinks there is a particular reason why none of the study treatments are suitable.

What does the study involve?
If a patient decides to join, they will be asked to sign the consent form (for children, their parent /guardian will sign the consent form). Next, brief details identifying them and answering a few questions about their health and medical conditions will be entered into a computer. The

computer will then allocate them at random (like rolling a dice) to one of the possible treatment options. Neither patients nor their doctors can choose which of these options will be allocated. In all cases, treatment will include the usual standard of care for the hospital.
Please see the trial website https://www.recoverytrial.net/ for details of the current study treatments.

What are the possible benefits and risks of participating?
The study treatment may or may not help patients personally, but this study should help future patients.
Some of the treatments being investigated may cause side effects from mild issues such as an upset tummy to more unlikely severe allergic reactions. All participants will be given information about possible risks in the Participant Information Sheet. This information is also available on our website at https://www.recoverytrial.net/study-faq.
Patients should ask their hospital doctor if they would like more information.
Once included in the study, patients and their doctors will know which treatment the computer has allocated for them. Doctors will be aware of whether there are any particular side effects that they should look out for.
Women who are pregnant may be included, however, the effect of some of the treatments on unborn babies is not known. Pregnant women will not be eligible to receive some of the available treatments as they may be harmful in pregnancy or when breast-feeding. Nearly all the available treatments have previously been used in pregnancy for other medical conditions without safety concerns being raised. Where a treatment has not been given to a pregnant woman before, as a precaution we advise that women who are not pregnant, should not get pregnant within 3 months of the completion of the trial treatment(s).

Where is the study run from?
The study is being conducted by researchers at the University of Oxford (UK), working with doctors at many hospitals across the UK and other countries.

When is the study starting and how long is it expected to run for?
The study started in March 2020. Funding is in place for recruitment to continue until June 2026 (although funding for some comparisons may end earlier).

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

Who is the main contact?
Prof. Peter Horby (Chief Investigator)
recoverytrial@ndph.ox.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Peter Horby

ORCID ID
https://orcid.org/0000-0002-9822-1586

Contact details
University of Oxford
New Richards Building
Old Road Campus
Headington
Oxford
United Kingdom
OX3 7LG
-
recoverytrial@ndph.ox.ac.uk

Type(s)
Public

Contact name
Ms Michelle Nunn

ORCID ID
https://orcid.org/0000-0003-3195-2613

Contact details
CTSU, Nuffield Department of Population Health
University of Oxford
Richard Doll Building
Old Road Campus
Oxford
United Kingdom
OX3 7LF
-
recoverytrial@ndph.ox.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2020-001113-21

Integrated Research Application System (IRAS)
281712

ClinicalTrials.gov (NCT)
NCT04381936

Protocol serial number
NDPHRECOVERY, CPMS 45388, IRAS 281712

Study information

Scientific Title
Randomized evaluation of COVID-19 therapy

Acronym
RECOVERY

Study objectives
Current study hypothesis as of 04/12/2023:
To determine which treatments prevent death in hospitalised patients with pneumonia.

Previous study hypothesis as of 25/02/2021:
To determine which treatments prevent death in hospitalised patients with COVID-19.

Previous study hypothesis as of 03/02/2021:
Does treatment with lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, intravenous immunoglobulin (children only), colchicine, convalescent plasma, synthetic neutralising antibodies, tocilizumab (children only), aspirin, baricitinib, or anakinra (children only), prevent death in hospitalised patients with COVID-19?

Previous study hypothesis as of 27/11/2020:
Does treatment with lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, intravenous immunoglobulin (children only), colchicine, convalescent plasma, synthetic neutralising antibodies, tocilizumab or aspirin prevent death in hospitalised patients with COVID-19?

Previous study hypothesis as of 09/11/2020:
Does treatment with lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, intravenous immunoglobulin (children only), convalescent plasma, synthetic neutralising antibodies, tocilizumab or aspirin prevent death in hospitalised patients with COVID-19?

Previous study hypothesis as of 25/09/2020:
Does treatment with lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, intravenous immunoglobulin (children only), convalescent plasma, synthetic neutralising antibodies or tocilizumab prevent death in hospitalised patients with COVID-19?

Previous study hypothesis as of 21/08/2020:
Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, intravenous immunoglobulin (children only), convalescent plasma or tocilizumab prevent death in hospitalised patients with COVID-19?

Previous study hypothesis as of 27/05/2020:
Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab prevent death in hospitalised patients with COVID-19?

Previous study hypothesis as of 07/05/2020:
Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin or tocilizumab prevent death in hospitalised patients with COVID-19?

Original study hypothesis:
Does treatment with either lopinavir + ritonavir, inhaled interferon β1a, hydroxychloroquine or low-dose corticosteroids prevent death in hospitalised patients with COVID-19?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/03/2020, East of England - Cambridge East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 972 2503; CambridgeEast.REC@hra.nhs.uk), REC ref: 20/EE/0101

Study design
Randomized adaptive trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Severe Acute Respiratory Syndrome, COVID-19 (SARS coronavirus 2 [SARS-CoV-2] infection), Influenza A, Influenza B, Viral pneumonia syndrome, Community-acquired pneumonia, Bacterial pneumonia syndrome

Interventions
Current interventions as of 04/12/2023:

RECOVERY is a randomised trial among people hospitalised for pneumonia. 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. 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.

RECOVERY has an adaptive trial design. The interim trial results are monitored by an independent Data Monitoring Committee (DMC). The DMC will assess whether the randomised comparisons in the study have provided evidence that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accordingly. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

Drug dosage and duration - COVID-19 arms:

COVID-19 Main randomisation part A (recruitment to Part A is now finished)
One of the following treatments will be allocated simultaneously with randomisation part D, E or F (if appropriate, not all treatments are available in all countries)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)

2. 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 (treatment arm closed, results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration; treatment arm closed)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose; treatment arm closed)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days (10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced (treatment arm closed, results reported).
8. No additional treatment

COVID-19 Main randomisation part B (recruitment to Part B is now finished)
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed, results reported)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of casirivimab+imdevimab8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation (treatment arm closed, results reported)
3. No additional treatment

COVID-19 Main Randomisation Part C (recruitment to Part C is now finished)
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years (treatment arm closed, results reported)
2. No additional treatment

COVID-19 Main Randomisation Part D (recruitment to Part D is now finished)
One of the following treatments will be allocated simultaneously with randomisation part A, E or F (if appropriate, not all treatments are available in all countries). [The infliximab arm previously included in randomisation D never started recruitment.]
1. Baricitinib ((UK [age ≥2 years with COVID pneumonia] and India [age ≥18 years with COVID-19 pneumonia]): 4 mg once daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
2. No additional treatment

COVID-19 Main Randomisation Part E (some results reported, arm still open to recruitment)
Eligible patients (adults ≥18 years without suspected or confirmed influenza co-infection, and requiring ventilatory support) may be randomised in a 1:1 ratio to one of the arms listed below.
1. High dose corticosteroids: dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days followed by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days.
2. No additional treatment

COVID-19 Main Randomisation Part F (recruitment to Part F is now finished)
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. Empagliflozin (adults ≥18 years): 10 mg once daily by mouth for 28 days (or until discharge, if earlier). (treatment arm closed, results reported)
2. No additional treatment

COVID-19 Main Randomisation Part J
Eligible patients (patients ≥12 years old) may be randomised in a 1:1 ratio to one of the arms listed below.
1. Sotrovimab : 1000 mg in 100 ml 0.9% sodium chloride or 5% dextrose by intravenous infusion over 1 hour as soon as possible after randomisation.
2. No additional treatment

COVID-19 Main Randomisation Part K (recruitment to Part K is now finished)
Eligible patients (patients aged ≥18 years) may be randomised in a 1:1 ratio to one of the arms listed below.
1. No additional treatment
2. Molnupiravir 800 mg twice daily for 5 days by mouth. (treatment arm closed)

COVID-19 Main Randomisation Part L (UK only) (recruitment to Part L is now finished):
Eligible patients (patients aged ≥18 years) may be randomised in a 1:1 ratio to one of the arms listed below.
1. No additional treatment
2. Paxlovid (nirmatrelvir/ritonavir) 300/100 mg twice daily for 5 days by mouth. (treatment arm closed)
COVID-19 Randomisation for children with PIMS-TS (hyper-inflammatory state associated with COVID-19) (recruitment to these arms has finished)
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9% (treatment arm closed).
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight (treatment arm closed).
3. No additional treatment

Dose and Duration – Influenza arms:

Influenza Randomised comparison Part G:
Eligible patients (≥12 years old with or without SARS-CoV-2 co-infection) may be randomised in a ratio of 1:1 to one of the arms listed below.
1. Baloxavir marboxil 40mg (or 80mg if weight ≥80kg) once daily by mouth or nasogastic tube to be given on day 1 and day 4.
2. No additional treatment

Influenza Randomised comparison Part H:
Eligible patients (any age, with or without SARS-CoV-2 co-infection) may be randomised in a ratio of 1:1 to one of the arms listed below:
1. Oseltamivir 75mg twice daily by mouth or nasogastric tube for five days.
2. No additional treatment

Influenza Randomised comparison Part I:
Eligible patients (any age without suspected or confirmed SARS-CoV-2 infection) and with clinical evidence of hypoxia (i.e. receiving oxygen or with oxygen saturations <92% on room air) may be randomised in a ratio of 1:1 to one of the arms listed below:
1. Low-dose corticosteroids: Dexamethasone 6mg once daily given orally or intravenously for ten days or until discharge (whichever happens earliest)
2. No additional treatment

Community-acquired pneumonia arm:
Community-acquired pneumonia Main Randomisation part M:
Eligible patients (≥18 years old) with a diagnosis of community-acquired pneumonia (without suspected or confirmed COVID-19, influenza, tuberculosis, or Pneumocystis jirovecii infection), may be randomised in a ratio of 1:1 to one of the arms listed below.
1. Low-dose corticosteroids: Dexamethasone 6mg once daily given orally or intravenously for ten days or until discharge (whichever happens earliest)
2. No additional treatment

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

In the UK, longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS England and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C, the UK Obstetric Surveillance and PHOSP-COVID).

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Previous intervention as of 28/03/2022:

RECOVERY is a randomised trial among people hospitalised for 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. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A (recruitment to Part A is now finished):
One of the following treatments will be allocated simultaneously with randomisation part D, E or F (if appropriate, not all treatments are available in all countries)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)
2. 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 (treatment arm closed, results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration; treatment arm closed)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose; treatment arm closed)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days (10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced (treatment arm closed, results reported).
8. No additional treatment

Main randomisation part B (recruitment to Part B is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed, results reported)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of casirivimab+imdevimab8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation (treatment arm closed, results reported)
3. No additional treatment

Main Randomisation Part C (recruitment to Part C is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years (treatment arm closed, results reported)
2. No additional treatment

Main Randomisation Part D (recruitment to Part D is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, E or F (if appropriate, not all treatments are available in all countries). [The infliximab arm previously

included in randomisation D never started recruitment.]
1. Baricitinib ((UK [age ≥2 years with COVID pneumonia] and India [age ≥18 years with COVID-19 pneumonia]): 4 mg once daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
2. No additional treatment

Main Randomisation Part E (results reported)
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. High dose corticosteroids (adults ≥18 years with hypoxia only): dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days followed by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days.
2. No additional treatment

Main Randomisation Part F
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. Empagliflozin (adults ≥18 years): 10 mg once daily by mouth for 28 days (or until discharge, if earlier).
2. No additional treatment

Main Randomisation Part J:
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. Sotrovimab (patients ≥12 years old): 1000 mg in 100 ml 0.9% sodium chloride or 5% dextrose by intravenous infusion over 1 hour as soon as possible after randomisation.
2. No additional treatment

Main Randomisation Part K:
Eligible patients (patients aged ≥18 years) may be randomised in a 1:1 ratio to one of the arms listed below.
1. No additional treatment
2. Molnupiravir 800 mg twice daily for 5 days by mouth.

Main Randomisation Part L (UK only):
Eligible patients (patients aged ≥18 years) may be randomised in a 1:1 ratio to one of the arms listed below.
1. No additional treatment
2. Paxlovid (nirmatrelvir/ritonavir) 300/100 mg twice daily for 5 days by mouth.

Randomisation for children with PIMS-TS (hyper-inflammatory state associated with COVID-19) (recruitment to these arms has finished)
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9% (treatment arm closed).
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight (treatment arm closed).
3. No additional treatment

Note: Children with COVID-19 pneumonia are not eligible for this comparison.

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

In the UK, longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C, the UK Obstetric Surveillance and PHOSP-COVID).

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Previous intervention as of 30/12/2021:

RECOVERY is a randomised trial among people hospitalised for 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. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A (recruitment to Part A is now finished):
One of the following treatments will be allocated simultaneously with randomisation part D, E or F (if appropriate, not all treatments are available in all countries)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)
2. 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 (treatment arm closed, results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration; treatment arm closed)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose; treatment arm closed)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days

(10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced (treatment arm closed).
8. No additional treatment

Main randomisation part B (recruitment to Part B is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed, results reported)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of casirivimab+imdevimab8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation (treatment arm closed, results reported)
3. No additional treatment

Main Randomisation Part C (recruitment to Part C is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years (treatment arm closed, results reported)
2. No additional treatment

Main Randomisation Part D (recruitment to Part D is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, E or F (if appropriate, not all treatments are available in all countries). [The infliximab arm previously included in randomisation D never started recruitment.]
1. Baricitinib ((UK [age ≥2 years with COVID pneumonia] and India [age ≥18 years with COVID-19 pneumonia]): 4 mg once daily by mouth or nasogastric tube for 10 days in total (treatment arm closed)
2. No additional treatment

Main Randomisation Part E
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. High dose corticosteroids (adults ≥18 years with hypoxia only): dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days followed by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days.
2. No additional treatment

Main Randomisation Part F
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. Empagliflozin (adults ≥18 years): 10 mg once daily by mouth for 28 days (or until discharge, if earlier).
2. No additional treatment
Main Randomisation Part J:
Eligible patients may be randomised in a 1:1 ratio to one of the arms listed below.
1. Sotrovimab (patients ≥12 years old): 1000 mg in 100 ml 0.9% sodium chloride or 5% dextrose by intravenous infusion over 1 h as soon as possible after randomisation.
2. No additional treatment

Randomisation for children with PIMS-TS (hyper-inflammatory state associated with COVID-19)
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9%.
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight.
3. No additional treatment

Note: Children with COVID-19 pneumonia are not eligible for this comparison.

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

In the UK, longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 21/10/2021:

RECOVERY is a randomised trial among people hospitalised for 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. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
One of the following treatments will be allocated simultaneously with randomisation part D, E or F (if appropriate, not all treatments are available in all countries)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)
2. 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 (treatment arm closed to adults, results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for

dose and duration; treatment arm closed)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose; treatment arm closed)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days (10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced.
8. No additional treatment

Main randomisation part B (recruitment to Part B is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed, results reported)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation (treatment arm closed, results reported)
3. No additional treatment

Main Randomisation Part C (recruitment to Part C is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years (treatment arm closed, results reported)
2. No additional treatment

Main Randomisation Part D:
One of the following treatments will be allocated simultaneously with randomisation part A, E or F (if appropriate, not all treatments are available in all countries). [The infliximab arm previously included in randomisation D never started recruitment.]
1. Baricitinib ((UK [age ≥2 years with COVID pneumonia] and India [age ≥18 years with COVID-19 pneumonia]): 4 mg once daily by mouth or nasogastric tube for 10 days in total
2. No additional treatment

Main Randomisation Part E
One of the following treatments will be allocated simultaneously with randomisation part A, D or F (if appropriate, not all treatments are available in all countries)
1. High dose corticosteroids (Ex-UK, adults with hypoxia only): dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days follow by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days.
2. No additional treatment

Main Randomisation Part F
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)
1. Empagliflozin (adults ≥18 years): 10 mg once daily by mouth for 28 days (or until discharge, if earlier).
2. No additional treatment

Randomisation for children with PIMS-TS (hyper-inflammatory state associated with COVID-19)
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9%.
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight.
3. No additional treatment

Note: Children with COVID-19 pneumonia are not eligible for this comparison.

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

In the UK, longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 23/07/2021:

RECOVERY is a randomised trial among people hospitalised for 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. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
One of the following treatments will be allocated simultaneously with randomisation part D, E or F (if appropriate, not all treatments are available in all countries)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)
2. 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 (treatment arm closed to adults, results reported) Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration; treatment arm closed)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose; treatment arm closed)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total (treatment arm closed, results reported)
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days (10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced.
8. No additional treatment

Main randomisation part B (recruitment to Part B is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed, results reported)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation (treatment arm closed, results reported)
3. No additional treatment

Main Randomisation Part C (recruitment to Part C is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years (treatment arm closed, results reported)
2. No additional treatment

Main Randomisation Part D:
One of the following treatments will be allocated simultaneously with randomisation part A, E or F (if appropriate, not all treatments are available in all countries). [The infliximab arm previously included in randomisation D never started recruitment.]
1. Baricitinib (UK only, adults and children ≥2 years old with COVID-19 pneumonia): 4 mg once daily by mouth or nasogastric tube for 10 days in total
2. No additional treatment

Main Randomisation Part E
One of the following treatments will be allocated simultaneously with randomisation part A, D or F (if appropriate, not all treatments are available in all countries)
1. High dose corticosteroids (Ex-UK, adults with hypoxia only): dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days follow by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days.
2. No additional treatment

Main Randomisation Part F
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)
1. Empagliflozin 10 mg once daily by mouth for 28 days (or until discharge, if earlier).
2. No additional treatment

One of the following treatments will be allocated for the second randomisation for children with PIMS-TS:
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9%.
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight.
3. No additional treatment

[Note: the tocilizumab second randomisation treatment arm for adults is closed and results have been reported]

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

In the UK, longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 28/04/2021:

RECOVERY is a randomised trial among people hospitalised for 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. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
One of the following treatments will be allocated simultaneously with randomisation part B, D or E (if appropriate, not all treatments are available in all countries)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)
2. 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 (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total (treatment arm closed)
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days (10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced.
8. No additional treatment

Main randomisation part B:
One of the following treatments will be allocated simultaneously with randomisation part A, D or E (if appropriate, not all treatments are available in all countries)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation
3. No additional treatment

Main Randomisation Part C (recruitment to Part C is now finished):
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years (treatment arm closed)
2. No additional treatment

Main Randomisation Part D:
One of the following treatments will be allocated simultaneously with randomisation part A, B or E (if appropriate, not all treatments are available in all countries)
1. Baricitinib (UK only, adults and children ≥2 years old with COVID-19 pneumonia): 4 mg once daily by mouth or nasogastric tube for 10 days in total
2. Infliximab (Ex-UK, adults only): 5 mg/kg in 250 mL 0.9% sodium chloride by intravenous infusion over 2 hours given once as soon as possible after randomisation
3. No additional treatment

Main Randomisation Part E
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate, not all treatments are available in all countries)
1. High dose corticosteroids (Ex-UK, adults with hypoxia only): dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days follow by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days.
2. No additional treatment

One of the following treatments will be allocated for the second randomisation for children with PIMS-TS:
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9%.
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight.
3. No additional treatment

[Note: the tocilizumab second randomisation treatment arm for adults is closed and preliminary results have been reported]

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

In the UK, longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 25/02/2021:

RECOVERY is a randomised trial among people hospitalised for 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. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
One of the following treatments will be allocated simultaneously with randomisation part B, C or D (if appropriate)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, results reported)
2. 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 (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total
7. Dimethyl fumarate (UK adults ≥18 years only, excluding those on ECMO; early phase assessment): 120 mg every 12 h for 4 doses followed by 240 mg every 12 h by mouth for 8 days (10 days in total). If 240 mg every 12 h cannot be tolerated, the dose may be reduced.
8. No additional treatment

Main randomisation part B:
One of the following treatments will be allocated simultaneously with randomisation part A, C or D (if appropriate)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed)
2. Synthetic neutralising antibodies for participants aged ≥12 years only with COVID-19 pneumonia: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation
3. No additional treatment

Main Randomisation Part C:
One of the following treatments will be allocated simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or rectum once daily until discharge, for adults aged ≥18 years
2. No additional treatment

Main Randomisation Part D:
One of the following treatments will be allocated simultaneously with randomisation part A, B or C (if appropriate)
1. Baricitinib: 4 mg once daily by mouth or nasogastric tube for 10 days in total
2. No additional treatment

One of the following treatments will be allocated for the second randomisation for children with PIMS-TS:
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in 100 ml sodium chloride 0.9%.
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight.
3. No additional treatment

[Note: the tocilizumab second randomisation treatment arm for adults is closed and preliminary results have been reported]

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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 and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 03/02/2021:

RECOVERY is a randomised trial among people hospitalised for 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: (Part A) no additional treatment vs corticosteroids (children only) vs colchicine vs intravenous immunoglobulin (children only). In a factorial design (Part B), eligible patients are allocated simultaneously to no additional treatment vs synthetic neutralising antibodies. Separately (Part C), all participants aged 18 years or older will be allocated to no additional treatment vs aspirin, and in a further factorial, baricitinib vs no additional treatment (Part D). The study allows a subsequent randomisation for children with PIMS-TS (hyper-inflammatory state associated with COVID-19): No additional treatment vs tocilizumab vs anakinra. 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
Simultaneously with randomisation part B, C or D (if appropriate)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, preliminary results reported)
2. 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 (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, preliminary results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed, preliminary results reported)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)
6. Colchicine for men aged ≥18 years and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 h later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total

Main randomisation part B:
Simultaneously with randomisation part A, C or D (if appropriate)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units) (treatment arm closed)
2. Synthetic neutralising antibodies for participants aged ≥12 years only: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation

Main Randomisation Part C:
Simultaneously with randomisation part A, B or D (if appropriate)
1. Aspirin: 150 mg by mouth (or nasogastric tube) or per rectum once daily until discharge, for adults aged ≥18 years

Main Randomisation Part D:
Simultaneously with randomisation part A, B or C (if appropriate)
1. Baricitinib: 4 mg once daily by mouth or nasogastric tube for 10 days in total

Second randomisation for children with PIMS-TS:
1. Tocilizumab (children aged ≥1 and <18 years only): a single intravenous infusion over 60 min in

100ml sodium chloride 0.9%.
2. Anakinra (children aged ≥1 and <18 years only): subcutaneously or intravenously once daily for 7 days or discharge (if sooner). NB Anakinra will be excluded from the randomisation of children <10 kg in weight.

Full dosing information for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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 and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 27/11/2020:

RECOVERY is a randomised trial among people hospitalised for 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 corticosteroids (for children only) vs colchicine vs intravenous immunoglobulin (children only). In a factorial design, eligible patients are allocated simultaneously to no additional treatment vs convalescent plasma vs synthetic neutralising antibodies. Separately, all participants aged 18 years or older will be allocated to no additional treatment vs aspirin. The study allows a subsequent randomisation for patients with progressive COVID-19 (evidence of hypoxia [or in children a hyper-inflammatory state] and raised inflammatory markers): 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
Simultaneously with randomisation part B or C (if appropriate)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, preliminary results reported)
2. 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) (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-

TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, preliminary results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days (treatment arm closed)
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)
6. Colchicine for men aged ≥18 years old and women aged ≥55 years only. 1 mg after randomisation followed by 500 µg 12 hours later and then 500 µg twice daily by mouth or nasogastric tube for 10 days in total

Main randomisation part B:
Simultaneously with randomisation part A or C (if appropriate)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units).
2. Synthetic neutralising antibodies for participants aged ≥12 years only: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation

Main Randomisation Part C:
Simultaneously with randomisation part A or B (if appropriate)
Aspirin: 150 mg by mouth (or nasogastric tube) or per rectum once daily until discharge, for adults ≥18 years old.

Second randomisation for patients with progressive COVID-19:

Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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 and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 09/11/2020:

RECOVERY is a randomised trial among people hospitalised for 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 corticosteroids (for children only) vs azithromycin vs intravenous immunoglobulin (children only). In a factorial design, eligible patients are allocated simultaneously to no additional treatment vs convalescent plasma vs synthetic neutralising antibodies. Separately, all participants aged 18 years or older will be allocated to no additional treatment vs aspirin. The study allows a subsequent

randomisation for patients with progressive COVID-19 (evidence of hypoxia [or in children a hyper-inflammatory state] and raised inflammatory markers): 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration

Main randomisation part A:
Simultaneously with randomisation part B or C (if appropriate)

1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, preliminary results reported)
2. 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) (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, preliminary results reported)
4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)

Main randomisation part B:
Simultaneously with randomisation part A or C (if appropriate)

1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units).
2. Synthetic neutralising antibodies for participants aged ≥12 years only: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation

Main Randomisation Part C:
Simultaneously with randomisation part A or B (if appropriate)
Aspirin: 150 mg by mouth (or nasogastric tube) or per rectum once daily until discharge, for adults ≥18 years old.

Second randomisation for patients with progressive COVID-19:

Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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 and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 25/09/2020:

RECOVERY is a randomised trial among people hospitalised for 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 corticosteroids (for children only) vs azithromycin vs intravenous immunoglobulin (children only). In a factorial design, eligible patients are allocated simultaneously to no additional treatment vs convalescent plasma vs synthetic neutralising antibodies. The study allows a subsequent randomisation for patients with progressive COVID-19 (evidence of hypoxia [or in children a hyper-inflammatory state] and raised inflammatory markers): 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration
Main randomisation part A:
1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 h for 10 days or until discharge (treatment arm closed, preliminary results reported)
2. 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) (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, preliminary results reported)

4. Azithromycin 500 mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)

Main randomisation part B:
1. Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) intravenous per day on study days 1 (as soon as possible after randomisation) and 2 (with a minimum of 12-h interval between 1st and 2nd units).
2. Synthetic neutralising antibodies for participants aged ≥12 years only: A single dose of REGN10933 + REGN10987 8 g (4 g of each monoclonal antibody) in 250 ml 0.9% saline infused intravenously over 60 min +/- 15 min as soon as possible after randomisation

Second randomisation for patients with progressive COVID-19:
Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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 and equivalent bodies, and to relevant research databases (e.g. UK Biobank, Genomics England, ISARIC-4C and PHOSP-COVID).

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Previous intervention as of 21/08/2020:

RECOVERY is a randomised trial among people hospitalised for 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 corticosteroids (for children only) vs azithromycin vs intravenous immunoglobulin (children only). 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 hypoxia [or in children a hyper-inflammatory state] and raised inflammatory markers): 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration
Main randomisation part A:
1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge (treatment arm closed, preliminary results reported)

2. 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) (treatment arm closed to adults, preliminary results reported)
Corticosteroid (in children ≤44 weeks gestational age, or >44 weeks gestational age with PIMS-TS only) in the form of hydrocortisone or methylprednisolone sodium succinate (see protocol for dose and duration)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, preliminary results reported)
4. Azithromycin 500mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days
5. Intravenous immunoglobulin (IVIg) for children >44 weeks gestational age and <18 years with PIMS-TS only (see protocol for dose)

Main randomisation part B:
Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) 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).

Second randomisation for patients with progressive COVID-19:
Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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).

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Previous intervention as of 02/07/2020:

RECOVERY is a randomised trial among people hospitalised for 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 corticosteroids (for children only) 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 hypoxia [or in children a hyper-inflammatory state] and raised inflammatory markers): 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration
Main randomisation part A:
1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge (treatment arm closed, preliminary results reported)
2. 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) (treatment arm closed to adults, preliminary results reported)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing) (treatment arm closed, preliminary results reported)
4. Azithromycin 500mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days

Main randomisation part B:
Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) 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).

Second randomisation for patients with progressive COVID-19:
Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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).

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Previous intervention as of 27/05/2020:

RECOVERY is a randomised trial among people hospitalised for 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 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 hypoxia [or in children a hyper-inflammatory state] and raised inflammatory markers): 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration
Main randomisation part A:
1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge
2. 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)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing)
4. Azithromycin 500mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days

Main randomisation part B:
Convalescent plasma: Single unit of ABO compatible convalescent plasma (275 ml +/- 75 ml) 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).

Second randomisation for patients with progressive COVID-19:
Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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).

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Previous intervention as of 07/05/2020:

RECOVERY is a randomised trial among people hospitalised for 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 corticosteroids vs hydroxychloroquine vs azithromycin. The study allows a second randomisation for patients with progressive COVID-19 (evidence of hypoxia and a 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

Drug dosage and duration
First (main) randomisation:
1. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge
2. 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)
3. Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing)
4. Azithromycin 500mg: by mouth (or nasogastric tube) or intravenously once daily for 10 days

Second randomisation for patients with progressive COVID-19:
Tocilizumab by intravenous infusion with the dose determined by body weight (see protocol for dosing).

Dosing for children provided in the protocol.

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

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).

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Original intervention:

RECOVERY is a randomised trial among adults hospitalised for 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.

RECOVERY has an adaptive trial design. The interim trial results will be monitored by an independent Data Monitoring Committee (DMC). The DMC will 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.

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.

Drug dosage and duration:
Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge.
Interferon-β1a: Nebulized solution of IFN-β1a 6 MIU (0.5ml of a solution containing 12 MIU/ml) once daily for 10 days or until discharge.
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).
Hydroxychloroquine: by mouth for a total of 10 days (see protocol for timing and dosing)

All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner). Data from routine healthcare records (including linkage to medical databases held by organisations such as NHS Digital) will allow subsidiary analyses of the effect of the study treatments on particular non-fatal events, the influence of pre-existing major co-morbidity (e.g. diabetes, heart disease, lung disease), and longer-term outcomes (e.g. 6-month survival) as well as in particular sub-categories of patient.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
COVID-19 arms: Lopinavir + ritonavir, interferon-β1a, corticosteroids (dexamethasone, hydrocortisone, prednisolone or methylprednisolone sodium succinate), hydroxychloroquine, azithromycin, tocilizumab, convalescent plasma, intravenous immunoglobulin (IVIg), colchicine , tocilizumab, synthetic neutralising antibodies REGEN-COV (casirivimab + imdevimab, REGN-COV2, REGN-10933 + REGN-10987), aspirin, baricitinib, anakinra, dimethyl fumarate, empagliflozin, sotrovimab, molnupiravir, Paxlovid (nirmatrelvir + ritonavir) Influenza arms: Baloxavir marboxil, oseltamivir, low dose corticosteroids (dexamethasone) Community-acquired pneumonia arms: low dose corticosteroids (dexamethasone)

Primary outcome(s)
Current primary outcome measure as of 04/12/2023:

COVID-19 and community-acquired pneumonia:
The primary objective is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after randomisation.
Influenza:
The co-primary objectives are to provide reliable estimates of the effect of study treatments on:
(a) all-cause mortality at 28 days after randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge) and
(b) time to discharge alive from hospital.
Holm’s procedure will be used to control the family-wise error rate across these two co-primary

outcomes at 5%
Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records.

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Previous primary outcome measure as of 07/05/2020:

All-cause mortality at 28 days after randomisation. Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records.

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Previous primary outcome measure:

Number of hospitalised patients who died within 28 days of randomisation, data collected via a secure web-based case report form

Key secondary outcome(s))

Current secondary outcome measures as of 04/12/2023:

COVID-19 and community-acquired pneumonia:
The secondary objectives are to assess the effects of study treatments on:
(a) Number of days stay in hospital (time to discharge alive within the first 28-days)
(b) Among patients not on invasive mechanical ventilation at baseline, the number of patients with a composite endpoint of death or need for invasive mechanical ventilation or ECMO

Influenza:
The secondary objective is to assess the effects of study treatments on the composite endpoint of death or need for invasive mechanical ventilation or ECMO among patients not on invasive mechanical ventilation at baseline.
Other outcome measures (for all types of pneumonia):
(a) Number of patients who needed any ventilation and (for invasive mechanical ventilation) the number of days it was required
(b) Number of patients who needed renal replacement therapy
(c) Number of patients who had thrombotic events
Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records. Study outcomes will be assessed based on data recorded up to 28 days and at other time-points e.g. 6 months and 18-months after randomisation.

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Previous secondary outcome measures as of 03/02/2021:

1. Number of days stay in hospital
2. Among patients not on invasive mechanical ventilation at baseline, the number of patients with a composite endpoint of death or need for invasive mechanical ventilation or ECMO

Other outcome measures:
3. Number of patients who needed any ventilation and (for invasive mechanical ventilation) the

number of days it was required
4. Number of patients who needed renal replacement therapy
5. Number of patients who had thrombotic events

Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records. Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after randomisation.

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Previous secondary outcome measures as of 09/11/2020:

1. Number of days stay in hospital
2. Among patients not on invasive mechanical ventilation at baseline, the number of patients with a composite endpoint of death or need for invasive mechanical ventilation or ECMO

Other outcome measures:
3. Number of patients who needed ventilation and the number of days it was required
4. Number of patients who needed renal replacement therapy
5. Number of patients developing new major cardiac arrhythmias

Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records. Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after randomisation.

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Previous secondary outcome measures as of 25/09/2020:

1. Number of days stay in hospital
2. Among patients not on invasive mechanical ventilation at baseline, the number of patients with a composite endpoint of death or need for invasive mechanical ventilation or ECMO

Other outcome measures:
3. Number of patients who needed ventilation and the number of days it was required
4. Number of patients who needed renal replacement therapy
5. Number of patients developing new major cardiac arrhythmias

Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records. Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after the main randomisation.

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Previous secondary outcome measures as of 02/07/2020:

1. Number of days stay in hospital
2. Among patients not on mechanical ventilation at baseline, the number of patients with a composite endpoint of death or need for mechanical ventilation or ECMO

Other outcome measures:
3. Number of patients who needed ventilation and the number of days it was required

4. Number of patients who needed renal replacement therapy
5. Number of patients developing new major cardiac arrhythmias

Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records. Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after the main randomisation.

Previous secondary outcome measures as of 27/05/2020:

1. Number of days stay in hospital
2. Number of patients who needed ventilation and the number of days it was required
3. Among patients not on ventilation at baseline, the number of patients with a composite endpoint of death or need for mechanical ventilation or ECMO

Other outcome measures:
4. Number of patients who needed renal replacement therapy
5. Number of patients developing new major cardiac arrhythmias

Data collected via a secure web-based case report form wherever possible, or otherwise via linkage to electronic health records. Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after the main randomisation.

Original secondary outcome measures:

1. Number of days stay in hospital
2. Number of patients who needed ventilation and the number of days it was required, within 28 days of randomisation
3. Number of patients who needed renal replacement therapy, within 28 days of randomisation

Data collected via a secure web-based case report form. All randomised participants are to be followed up until death, discharge from hospital or 28 days after randomisation (whichever is sooner).

Completion date
30/06/2036

Eligibility

Key inclusion criteria
Current inclusion criteria as of 04/12/2023:

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

(i) Hospitalised
(ii) Pneumonia syndrome
In general, pneumonia should be suspected when a patient presents with:
a) typical symptoms of a new respiratory tract infection (e.g. influenza-like illness with fever and

muscle pain, or respiratory illness with cough and shortness of breath); and
b) objective evidence of acute lung disease (e.g. consolidation or ground-glass shadowing on X-ray or CT, hypoxia, or compatible clinical examination); and
c) alternative causes have been considered unlikely or excluded (e.g. heart failure).
However, the diagnosis remains a clinical one based on the opinion of the managing doctor (the above criteria are just a guide).
(iii) One of the following diagnoses:
a) Confirmed SARS-CoV-2 infection (including patients with influenza co-infection)
b) Confirmed influenza A or B infection (including patients with SARS-CoV-2 co-infection)
c) Community-acquired pneumonia with planned antibiotic treatment (excluding patients with suspected or confirmed SARS-CoV-2, influenza, active pulmonary tuberculosis or Pneumocystis jirovecii pneumonia)
(iv) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

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Previous inclusion criteria as of 28/03/2022:

1. Hospitalised
2.Viral pneumonia syndrome. In general, viral pneumonia should be suspected when a patient presents with:
2.1. typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough AND
2.2. compatible chest X-ray findings (consolidation or ground-glass shadowing) AND
2.3. alternative causes have been considered unlikely or excluded (e.g. heart failure, bacterial pneumonia).
However, the diagnosis remains a clinical one based on the opinion of the managing doctor.
3. SARS-CoV-2 infection (clinically suspected or laboratory-confirmed)
4. 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

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Previous inclusion criteria as of 07/05/2020:

1. Hospitalised
2. SARS-CoV-2 infection (clinically suspected or laboratory-confirmed)
3. 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

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Previous inclusion criteria:

1. Aged at least 18 years
2. Hospitalised
3. SARS-CoV-2 infection

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
All

Sex
All

Key exclusion criteria
Current exclusion criteria as of 04/12/2023:

Participants will be excluded if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see Protocol Appendix 2; section 8.2, Appendix 3; section 8.3 for children, and Appendix 4 for pregnant and breastfeeding women), or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient. For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial.

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Previous exclusion criteria as of 07/05/2020:

Participants will be excluded if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see Protocol Appendix 2; section 8.2 and Appendix 3; section 8.3 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.

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Previous exclusion criteria:

1. Patients will be excluded if they have a 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
2. In addition, if the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms, then the patient will be excluded from randomisation to that arm

Date of first enrolment
19/03/2020

Date of final enrolment
30/06/2026

Locations

Countries of recruitment

United Kingdom

England

Ghana

India

Nepal

South Africa

Viet Nam

Study participating centre
Nuffield Department of Population Health
University of Oxford
Richard Doll Building
Old Road Campus
Roosevelt Drive
Oxford
United Kingdom
OX3 7LF

Study participating centre
Eijkman Oxford Clinical Research Unit (EOCRU)
Eijkman Institute for Molecular Biology
Jl. P. Diponegoro No. 69
Jakarta
Indonesia
10430

Study participating centre
Clinical Trial Unit, Oxford University Clinical Research Unit-Nepal
Patan Academy of Health Sciences
Kathmandu
Nepal
-

Study participating centre
Oxford University Clinical Research Unit
Centre for Tropical Medicine
764 Vo Van Kiet
District 5

Ho Chi Minh City
Viet Nam
-

Study participating centre
Indian Council of Medical Research
Division of Epidemiology and Communicable Diseases
Ramalingaswami Bhavan
Ansari Nagar
New Delhi
India
110029

Study participating centre
Kumasi Center for Collaborative Research in Tropical Medicine
Kwame Nkrumah University of Science and Technology (KNUST)
Southend Asuogya Road
Kumasi
Ghana
-

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
NIHR Oxford Biomedical Research Centre

Alternative Name(s)
NIHR Biomedical Research Centre, Oxford, OxfordBRC, OxBRC

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, Gates Learning Foundation, William H. Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Funder Name
Department for International Development

Alternative Name(s)
DFID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Health Data Research UK

Funder Name
Medical Research Council Population Health Research Unit

Funder Name
NIHR Clinical Trials Unit Support Funding

Funder Name
NIHR Health Protection Research Unit in Emerging and Zoonotic Infections

Funder Name
Foreign, Commonwealth and Development Office

Alternative Name(s)
Foreign, Commonwealth & Development Office, Foreign, Commonwealth & Development Office, UK Government, FCDO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Flu Lab

Results and Publications

Individual participant data (IPD) sharing plan
RECOVERY data will be made available via the Infectious Diseases Data Observatory (IDDO). Researchers will be able to apply via the IDDO Data Access process - https://www.iddo.org/covid19/data-sharing/accessing-data

IPD sharing plan summary
Available on request

Study outputs

	Date	Date	Peer	Patient-

Output type	Details	created	added	reviewed?	facing?
Results article	Dexamethasone results	25/02/2021	20/07/2020	Yes	No
Results article	Lopinavir–ritonavir results	01/10/2020	06/10/2020	Yes	No
Results article	Hydroxychloroquine results	19/11/2020	09/11/2020	Yes	No
Results article	Azithromycin results	13/02/2021	03/02/2021	Yes	No
Results article	Convalescent plasma results	29/05/2021	23/07/2021	Yes	No
Results article	Tocilizumab results	01/05/2021	23/07/2021	Yes	No
Results article	Colchicine results	18/10/2021	21/10/2021	Yes	No
Results article	Aspirin results	17/11/2021	24/11/2021	Yes	No
Results article	Casirivimab and imdevimab results	12/02/2022	14/02/2022	Yes	No
Results article	Baricitinib results	30/07/2022	02/08/2022	Yes	No
Results article	Results for higher-dose corticosteroids in COVID-19 inpatients who were hypoxic but not receiving ventilatory support	12/04/2023	17/04/2023	Yes	No
Results article	Empagliflozin results	18/10/2023	23/10/2023	Yes	No
Results article	Immunomodulatory therapy results	22/01/2024	30/01/2024	Yes	No
Results article	Dimethyl fumarate results	31/01/2024	09/02/2024	Yes	No
Results article	RECOVERY baseline characteristics and outcomes compared with a reference popluation		02/07/2024	Yes	No
Results article	Higher dose corticosteroids results	12/02/2025	05/03/2025	Yes	No
Results article	Molnupiravir or nirmatrelvir-ritonavir results	15/05/2025	19/05/2025	Yes	No
Results article	Sotrovimab results	01/09/2025	01/09/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Preprint results	Tocilizumab results	11/02/2021	12/02/2021	No	No
Preprint results	Non-peer-reviewed convalescent plasma results	10/03/2021	18/03/2021	No	No
Preprint results	Non-peer-reviewed results for REGEN-COV (casirivimab and imdevimab)	16/06/2021	23/07/2021	No	No
Preprint results	Non-peer-reviewed results for aspirin	08/06/2021	23/07/2021	No	No
Preprint results	Non-peer-reviewed results for colchicine	18/05/2021	21/10/2021	No	No
Preprint results	Baricitinib results	03/03/2022	28/03/2022	No	No

Preprint results	Dimethyl fumarate results	25/09/2022	28/12/2022	No	No
Preprint results	Higher-dose dexamathasone results	17/12/2022	28/12/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes