

# An international platform trial for severely ill patients with community-acquired pneumonia or COVID-19

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<b>Registration date</b> 20/07/2020	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 28/10/2025	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.

In 2020, the virus has spread to many countries around the world and neither a vaccine against the virus or specific treatment for COVID-19 has yet been developed. As of April 2020, it is advised that people minimize travel and social contact, and regularly wash their hands to reduce the spread of the virus.

Groups who are at a higher risk from infection with the virus, and therefore of developing COVID-19, include people aged over 70 years, people who have long-term health conditions (such as asthma or diabetes), people who have a weakened immune system and people who are pregnant. People in these groups, and people who might come into contact with them, can reduce this risk by following the up-to-date advice to reduce the spread of the virus.

This study was designed by clinicians who cared for patients and conducted research during the 2009 H1N1 pandemic. Planning for this study started in 2011. For the past several years, the study has been recruiting patients with severe community-acquired pneumonia in the inter-pandemic period. It was designed to adapt to an acute pandemic need: that time has come. The aim of this study is to generate evidence that can be used to reduce mortality (death), ICU resource use and morbidity (illness) in patients who are severely ill from community-acquired pneumonia and/or COVID-19.

### Who can participate?

Critically ill patients from 142 Intensive Care Units who have community-acquired pneumonia or confirmed or suspected COVID-19 infection

### What does the study involve?

The study involves randomly allocating severely ill patients community-acquired pneumonia or

COVID-19 infection to multiple different treatment options. These different treatment groups are then compared to work out the best treatments or combinations of treatments for these patients. The current treatments are: antibiotic treatment, macrolide duration, corticosteroids (closed to recruitment 16/06/2020 in light of the results of the RECOVERY trial), COVID-19 antiviral therapy (no antiviral or lopinavir/ritonavir (Kaletra)), COVID-19 immune modulation (no modulator, interferon-beta, anakinra, sarilumab, or tocilizumab), COVID-19 convalescent plasma (plasma versus no plasma), COVID-19 therapeutic anticoagulation (previously: heparin or standard local antithrombotic treatment; currently: conventional low dose thromboprophylaxis or intermediate dose thromboprophylaxis for patients that have no prior therapeutic anticoagulation; conventional low dose thromboprophylaxis, intermediate-dose thromboprophylaxis, or continuation of therapeutic dose anticoagulation for patients already on prior therapeutic anticoagulation), COVID-19 simvastatin therapy (no simvastatin or simvastatin), vitamin C therapy (no vitamin C or vitamin C), and ACE2 RAS domain (no RAS, angiotensin-converting enzyme inhibitor (ACEi), angiotensin-II receptor blocker (ARB), or ARB in combination with DMX-200, a chemokine receptor-2 (CCR2) inhibitor)

What are the possible benefits and risks of participating?

The treatments being investigated in this study for community-acquired pneumonia are the same as the treatments used in daily practice. The only difference is that the study will randomly determine the treatment received instead of the doctor. The treatments are used to treat other viruses and other immune-related diseases but it is not known if they work well for the new COVID-19 disease. They may offer benefit and improve survival but could also harm. This study will tell us if some treatments are better than others but the researchers cannot guarantee that taking part in this study will benefit participants directly but it will help improve treatment for people with COVID-19 in the future.

Where is the study run from?

Imperial College London and the Intensive Care National Audit and Research Center (ICNARC) (UK)

When is the study starting and how long is it expected to run for?

April 2016 to December 2026

Who is funding the study?

University Medical Center Utrecht (Netherlands)

Who is the main contact?

Unfortunately, this study is not recruiting public volunteers at this time. This is because the researchers are directly identifying participants in certain areas of the hospitals. Please do not contact the research team as they will not be able to respond. For more information about COVID-19 research, visit the Be Part of Research homepage. Any queries should be sent to [ukremap-cap@icnarc.org](mailto:ukremap-cap@icnarc.org).

## Contact information

**Type(s)**

Scientific

**Contact name**

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## Contact details

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## Additional identifiers

### Clinical Trials Information System (CTIS)

2015-002340-14

### Integrated Research Application System (IRAS)

237150

### ClinicalTrials.gov (NCT)

NCT02735707

### Protocol serial number

CPMS 38197, IRAS 237150

## Study information

### Scientific Title

Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP)

### Acronym

REMAP-CAP

### Study objectives

The primary objective of REMAP-CAP is, for patients with severe CAP who are admitted to ICU, to identify the effects of a range for interventions to improve outcome as defined by all-cause mortality at 90 days. During this pandemic the researchers also want to identify the effect of a range for interventions to improve outcome for patients admitted to hospital with acute illness due to suspected or confirmed pandemic infection.

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Approved 30/04/2018, Surrey Borders REC (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)207 104 8104, +44 (0)207 104 8134, +44 (0)207 972 2568; surreyboundaries.rec@hra.nhs.uk), REC ref: 18/LO/0660

### Study design

Randomized; Interventional; Design type: Treatment, Process of Care, Drug

## Primary study design

Interventional

## Study type(s)

Treatment

## Health condition(s) or problem(s) studied

COVID-19 (SARS-CoV-2 infection), influenza and pneumonia

## Interventions

Current interventions as of 23/10/2025:

This is a randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia. This trial aims to identify the effect of a range of interventions on adult ICU patients with severe CAP (and COVID-19 infection) in order to improve patient and hospital outcomes.

Currently available domains:

Antibiotic Domain (pandemic and non-pandemic) If the patient is deemed eligible they will be randomised to receive one of possible five antibiotics/combinations:

1. Ceftriaxone + macrolide (various options; azithromycin preferred)
2. Moxifloxacin or levofloxacin
3. Piperacillin-tazobactam + macrolide
4. Ceftaroline + macrolide
5. Amoxicillin-clavulanate + macrolide

Macrolide Duration Domain (pandemic and non-pandemic):

Patients randomised to the beta-lactam plus macrolide intervention in the antibiotic domain would be randomised to receive either of the following for 14 days or until hospital discharge, whichever occurs first:

1. Short course macrolide (3 days)
2. Extended course macrolide

Corticosteroid Domain open to CAP/Influenza patients (closed to pandemic patients):

A patient will be randomised to either:

1. Intravenous hydrocortisone, 50 mg every 6 h for up to 7 days
2. No hydrocortisone (i.e. no treatment)
3. IV hydrocortisone while in septic shock

Influenza antivirals (non-pandemic):

1. No oseltamivir or other antiviral agent active against influenza
2. 5 days of oseltamivir
3. 10 days of oseltamivir
4. Baloxavir on days 1 and 4
5. Oseltamivir for 5 days + Baloxavir on day 1 and day 4
6. Oseltamivir for 10 days + Baloxavir on day 1 and day 4

## Influenza Immune Modulation (non-pandemic)

1. No Immune Modulation
2. Baricitinib
3. Tocilizumab

## COVID-19 Immunoglobulin therapy (pandemic) (paused to pandemic patients):

1. No immunoglobulin against COVID-19
2. High titer convalescent plasma

## Previous interventions:

### COVID-19 antivirals (pandemic) (closed to pandemic patients):

1. No antiviral for COVID-19 (no placebo) (closed 9th September 2022)
2. Lopinavir/ritonavir (closed 9th September 2022)
3. Hydroxychloroquine (closed 9th September 2022)
4. Hydroxychloroquine + lopinavir/ritonavir (intervention closed 13th July 2020)

### COVID-19 Immune modulation (pandemic) (paused to pandemic patients):

1. No immune modulation for COVID-19 (no placebo) (closed 8th January 2021)
2. Interferon beta-1a (paused 9th April 2021)
3. Anakinra (paused 9th April 2021)
4. Tocilizumab (paused 9th April 2021)
5. Sarilumab (paused 9th April 2021)

### Vitamin C therapy (pandemic and non-pandemic). (Paused in non-pandemic 17th June 2022 and paused in pandemic 16th July 2022)

1. No vitamin C (no placebo)
2. Vitamin C (50 mg/kg IV every 6 h for 16 doses)

### ACE-2 RAS domain (closed to severe patients 27th February 2022 and closed to moderate patients 16th June 2022):

1. No RAS (no placebo)
2. Angiotensin-converting enzyme inhibitor (ACEi)
3. Angiotensin-II receptor blocker (ARB)
4. ARB in combination with DMX-200, a chemokine receptor-2 (CCR2) inhibitor

### COVID-19 Therapeutic anticoagulation (pandemic) (closed 22nd January 2021):

1. Local standard pharmacological venous thromboprophylaxis
2. Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

### COVID-19 Anticoagulation domain (pandemic):

1. No prior therapeutic anticoagulation:
  - 1.1. Conventional low dose thromboprophylaxis (closed 30th November 2022)
  - 1.2. Intermediate dose thromboprophylaxis (closed 30th November 2022)
2. Prior therapeutic anticoagulation:
  - 2.1. Conventional low dose thromboprophylaxis (closed 30th November 2022)
  - 2.2. Intermediate dose thromboprophylaxis (closed 30th November 2022)
  - 2.3. Continuation of therapeutic dose anticoagulation (closed 6th July 2022)

### COVID-19 Simvastatin therapy (pandemic) (closed 9th January 2023):

1. No simvastatin (no placebo)
2. Simvastatin 80 mg/day for 28 days

It is intended that REMAP-CAP will be perpetual. The international steering committee will take responsibility for determining what new questions will be introduced to the trial whether it be new interventions to current domains or new domains.

Most eligible patients for this study will have a reduced level of consciousness due to their illness or due to sedative medication used as part of their treatment and may be unable to give consent at the time of eligibility. Therefore consent will be initially obtained from personal or professional legal representatives and the patient's consent obtained retrospectively once they have recovered and are able to give informed consent themselves.

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Previous interventions as of 16/09/2024:

This is a randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia. This trial aims to identify the effect of a range of interventions on adult ICU patients with severe CAP (and COVID-19 infection) in order to improve patient and hospital outcomes.

Currently available domains:

Antibiotic Domain (pandemic and non pandemic)

If the patient is deemed eligible they will be randomised to receive one of possible five antibiotics/combinations:

1. Ceftriaxone + macrolide (various options; azithromycin preferred)
2. Moxifloxacin or levofloxacin
3. Piperacillin-tazobactam + macrolide
4. Ceftaroline + macrolide
5. Amoxicillin-clavulanate + macrolide

Macrolide Duration Domain (pandemic and non-pandemic)

Patients randomised to the beta-lactam plus macrolide intervention in the antibiotic domain would be randomised to receive either of the following for 14 days or until hospital discharge, whichever occurs first:

1. Short course macrolide (3 days)
2. Extended course macrolide

Corticosteroid Domain (closed to pandemic patients)

A patient will be randomised to either:

1. Intravenous hydrocortisone, 50 mg every 6 h for up to 7 days
2. No hydrocortisone (i.e. no treatment)
3. IV hydrocortisone while in septic shock

Influenza antivirals (non-pandemic):

1. No oseltamivir or other antiviral agent active against influenza
2. 5 days of oseltamivir
3. 10 days of oseltamivir

COVID-19 antivirals (pandemic) (closed to pandemic patients):

1. No antiviral for COVID-19 (no placebo)
2. Lopinavir/ritonavir
3. Hydroxychloroquine
4. Hydroxychloroquine + lopinavir/ritonavir

COVID-19 Immune modulation (pandemic) (paused to pandemic patients):

1. No immune modulation for COVID-19 (no placebo)
2. Interferon beta-1a
3. Anakinra
4. Tocilizumab
5. Sarilumab

COVID-19 Immunoglobulin therapy (pandemic) (paused to pandemic patients):

1. No immunoglobulin against COVID-19 (no placebo)
2. Convalescent plasma (up to two units of convalescent plasma)

Vitamin C therapy (pandemic and non-pandemic) :

1. No vitamin C (no placebo)
2. Vitamin C (50 mg/kg IV every 6 h for 16 doses)

ACE-2 RAS domain:

1. No RAS (no placebo)
2. Angiotensin-converting enzyme inhibitor (ACEi)
3. Angiotensin-II receptor blocker (ARB)
4. ARB in combination with DMX-200, a chemokine receptor-2 (CCR2) inhibitor

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Previous interventions as of 19/04/2021 to 16/09/2024:

This is a randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia. This trial aims to identify the effect of a range of interventions on adult ICU patients with severe CAP (and COVID-19 infection) in order to improve patient and hospital outcomes.

Currently available domains:

Antibiotic Domain (pandemic and non pandemic)

If the patient is deemed eligible they will be randomised to receive one of possible five antibiotics/combinations:

1. Ceftriaxone + macrolide (various options; azithromycin preferred)
2. Moxifloxacin or levofloxacin
3. Piperacillin-tazobactam + macrolide
4. Ceftaroline + macrolide
5. Amoxicillin-clavulanate + macrolide

Macrolide Duration Domain (pandemic and non-pandemic)

Patients randomised to the beta-lactam plus macrolide intervention in the antibiotic domain would be randomised to receive either of the following for 14 days or until hospital discharge, whichever occurs first:

1. Short course macrolide (3 days)
2. Extended course macrolide

Corticosteroid Domain (closed to pandemic patients)

A patient will be randomised to either:

1. Intravenous hydrocortisone, 50 mg every 6 h for up to 7 days
2. No hydrocortisone (i.e. no treatment)
3. IV hydrocortisone while in septic shock

Influenza antivirals (non-pandemic):

1. No oseltamivir or other antiviral agent active against influenza
2. 5 days of oseltamivir
3. 10 days of oseltamivir

COVID-19 antivirals (pandemic) (closed to pandemic patients):

1. No antiviral for COVID-19 (no placebo)
2. Lopinavir/ritonavir
3. Hydroxychloroquine
4. Hydroxychloroquine + lopinavir/ritonavir

COVID-19 Immune modulation (pandemic) (paused to pandemic patients):

1. No immune modulation for COVID-19 (no placebo)
2. Interferon beta-1a
3. Anakinra
4. Tocilizumab
5. Sarilumab

COVID-19 Immunoglobulin therapy (pandemic) (paused to pandemic patients):

1. No immunoglobulin against COVID-19 (no placebo)
2. Convalescent plasma (up to two units of convalescent plasma)

COVID-19 Therapeutic anticoagulation (pandemic) (paused and new interventions now active below):

1. Local standard pharmacological venous thromboprophylaxis
2. Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

Now the COVID-19 Anticoagulation domain (pandemic):

1. No prior therapeutic anticoagulation:
  - 1.1. Conventional low dose thromboprophylaxis
  - 1.2. Intermediate dose thromboprophylaxis
2. Prior therapeutic anticoagulation:
  - 2.1. Conventional low dose thromboprophylaxis
  - 2.2. Intermediate dose thromboprophylaxis
  - 2.3. Continuation of therapeutic dose anticoagulation

COVID-19 Simvastatin therapy (pandemic):

1. No simvastatin (no placebo)
2. Simvastatin 80 mg/day for 28 days

Vitamin C therapy (pandemic and non-pandemic) :

1. No vitamin C (no placebo)
2. Vitamin C (50 mg/kg IV every 6 h for 16 doses)

ACE-2 RAS domain:

1. No RAS (no placebo)
  2. Angiotensin converting enzyme inhibitor (ACEi)
  3. Angiotensin-II receptor blocker (ARB)
  4. ARB in combination with DMX-200, a chemokine receptor-2 (CCR2) inhibitor
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Previous interventions as of 31/07/2020 to 19/04/2021:

This is a randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia. This trial aims to identify the effect of a range of interventions on adult ICU patients with severe CAP in order to improve patient and hospital outcomes.

The eligibility criteria for the trial are applied at two levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomisation into the REMAP-CAP trial as a whole. The second level is that, once eligible for inclusion into the trial, there are additional exclusion criteria for eligibility into the specific domains within the trial. A patient is therefore only eligible for inclusion into a domain once all REMAP-CAP inclusion criteria are met, none of the REMAP-CAP exclusion criteria are present and none of the domain-specific exclusion criteria are present. However, patients who are not eligible for one or more domains can still be enrolled in other domains for which they are eligible. This type of trial allows for broad enrolment but still retains the ability to examine the differences in treatment effects between the various subgroups of patients. It also allows us to evaluate a wide range of treatment options that are used within standard care by embedding it within routine healthcare delivery. The use of Response Adaptive Randomisation within this trial means that the allocation ratios change over time based on accruing outcomes data thereby maximising the number of patients randomised to the interventions which have been shown to be more likely to have better outcomes for patients.

Currently available domains:

#### Antibiotic Domain

If the patient is deemed eligible they will be randomised to receive one of possible five antibiotics/combinations:

- Ceftriaxone + macrolide (various options; azithromycin preferred)
- Moxifloxacin or levofloxacin
- Piperacillin-tazobactam + macrolide
- Ceftaroline + macrolide
- Amoxicillin-clavulanate + macrolide

#### Macrolide Duration Domain

Patients randomised to the beta-lactam plus macrolide intervention in the antibiotic domain would be randomised to receive either:

- Short course macrolide (3 days) or extended course macrolide for 14 days or until hospital discharge, whichever occurs first

#### Corticosteroid Domain

A patient will be randomised to either:

- Intravenous hydrocortisone, 50 mg every 6 h for up to 7 days
- No hydrocortisone (i.e. no treatment)
- IV hydrocortisone while in septic shock

#### Influenza antivirals (non pandemic):

- No oseltamivir or other antiviral agent active against influenza
- 5 days of oseltamivir
- 10 days of oseltamivir

#### COVID-19 antivirals (pandemic):

- No antiviral for COVID-19 (no placebo)

- Lopinavir/ritonavir
- Hydroxychloroquine - Now closed
- Hydroxychloroquine + lopinavir/ritonavir - Now closed

#### COVID-19 Immune modulation (pandemic):

- No immune modulation for COVID-19 (no placebo)
- Interferon beta-1a
- Anakinra
- Tocilizumab
- Sarilumab

#### COVID-19 Immunoglobulin therapy (pandemic):

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma (up to two units of convalescent plasma)

#### COVID-19 Therapeutic anticoagulation (pandemic):

- Local standard pharmacological venous thromboprophylaxis
- Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin

#### COVID-19 Simvastatin therapy (pandemic):

- No simvastatin (no placebo)
- Simvastatin 80 mg/day for 28 days

#### Vitamin C therapy (pandemic and non pandemic) :

- No vitamin C (no placebo)
- Vitamin C (50 mg/kg IV every 6 h for 16 doses)

It is intended that REMAP-CAP will be perpetual. The international steering committee will take responsibility for determining what new questions will be introduced to the trial whether it be new interventions to current domains or new domains.

Because of the emergency nature of the treatment there will be delayed consent. It is important for the selected antibiotics and associated therapies are initiated as quickly as possible. This is why these interventions will be assigned to patients when they are randomised as soon as they are admitted to the ICU.

Most eligible patients for this study will have a reduced level of consciousness due to their illness or due to sedative medication used as part of their treatment and may be unable to give consent at the time of eligibility. Therefore consent will be initially obtained from personal or professional legal representatives and the patient's consent obtained retrospectively once they have recovered and are able to give informed consent themselves.

#### Antibiotic intervention

Patients will be randomly assigned to receive one of the following study interventions. While it is expected that all sites will participate in the ceftriaxone intervention, each site has the option to opt-in to one or more of the remaining four interventions based on local practice and the availability at site:

- Ceftriaxone  $\geq 1$  g IV 24 h
- Moxifloxacin 400 mg IV 24 h or Levofloxacin 750 mg IV 24 h
- Piperacillin-tazobactam  $\geq 4.5$  g IV 8 h
- Ceftaroline 600 mg IV 12h

- Amoxicillin-clavulanate  $\geq 1200$  mg IV 8 h

All patients receiving ceftriaxone, piperacillin-tazobactam, ceftazidime, or amoxicillin-clavulanate will also receive a macrolide. Patients allocated to the moxifloxacin or levofloxacin intervention will not receive a macrolide or any beta-lactam or monobactam agent.

The choice of macrolide will depend on the availability and acceptability of the agents at each site in the following order of preference;

1. IV azithromycin, with switch to enteral azithromycin when appropriate
2. IV clarithromycin, with switch to enteral azithromycin when appropriate
3. Enteral azithromycin
4. Enteral clarithromycin or roxithromycin
5. IV or enteral erythromycin

Sites in which only erythromycin is available are not able to participate in the Macrolide Duration Domain.

The objective of the macrolide domain is to determine the effectiveness of short-course versus extended course of macrolide treatment. The interventions to be compared are:

- Short course macrolide discontinued after 3 days unless there is confirmed or strongly suspected microbiological cause for prolonged administration

- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

Patients will be followed up daily whilst on ICU and routine clinical data recorded.

Patients will be followed up to ascertain survival status at 90 days and at 6 months and their quality of life and disability will be assessed at 6 months.

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Previous interventions:

This is a randomised, embedded, multifactorial adaptive platform trial for community-acquired pneumonia. This trial aims to identify the effect of a range of interventions on adult ICU patients with severe CAP in order to improve patient and hospital outcomes.

The eligibility criteria for the trial are applied at two levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomisation into the REMAP-CAP trial as a whole. The second level is that, once eligible for inclusion into the trial, there are additional exclusion criteria for eligibility into the specific domains within the trial. A patient is therefore only eligible for inclusion into a domain once all REMAP-CAP inclusion criteria are met, none of the REMAP-CAP exclusion criteria are present and none of the domain-specific exclusion criteria are present. However, patients who are not eligible for one or more domains can still be enrolled in other domains for which they are eligible. This type of trial allows for broad enrolment but still retains the ability to examine the differences in treatment effects between the various subgroups of patients. It also allows us to evaluate a wide range of treatment options that are used within standard care by embedding it within routine healthcare delivery. The use of Response Adaptive Randomisation within this trial means that the allocation ratios change over time based on accruing outcomes data thereby maximising the number of patients randomised to the interventions which have been shown to be more likely to have better outcomes for patients.

Currently available domains:

Antibiotic Domain

If the patient is deemed eligible they will be randomised to receive one of possible five antibiotics/combinations:

- Ceftriaxone + macrolide (various options; azithromycin preferred)

- Moxifloxacin or levofloxacin
- Piperacillin-tazobactam + macrolide
- Ceftaroline + macrolide
- Amoxicillin-clavulanate + macrolide

#### Macrolide Duration Domain

Patients randomised to the beta-lactam plus macrolide intervention in the antibiotic domain would be randomised to receive either:

- Short course macrolide (3 days) or extended course macrolide for 14 days or until hospital discharge, whichever occurs first

#### Corticosteroid Domain

A patient will be randomised to either:

- Intravenous hydrocortisone, 50 mg every 6 h for up to 7 days
- No hydrocortisone (i.e. no treatment)

It is intended that REMAP-CAP will be perpetual. The international steering committee will take responsibility for determining what new questions will be introduced to the trial whether it be new interventions to current domains or new domains.

Because of the emergency nature of the treatment there will be delayed consent. It is important for the selected antibiotics and associated therapies are initiated as quickly as possible. This is why these interventions will be assigned to patients when they are randomised as soon as they are admitted to the ICU.

Most eligible patients for this study will have a reduced level of consciousness due to their illness or due to sedative medication used as part of their treatment and may be unable to give consent at the time of eligibility. Therefore consent will be initially obtained from personal or professional legal representatives and the patient's consent obtained retrospectively once they have recovered and are able to give informed consent themselves.

#### Antibiotic intervention

Patients will be randomly assigned to receive one of the following study interventions. While it is expected that all sites will participate in the ceftriaxone intervention, each site has the option to opt-in to one or more of the remaining four interventions based on local practice and the availability at site:

- Ceftriaxone  $\geq 1$  g IV 24 h
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- Piperacillin-tazobactam  $\geq 4.5$  g IV 8 h
- Ceftaroline 600 mg IV 12h
- Amoxicillin-clavulanate  $\geq 1200$  mg IV 8 h

All patients receiving ceftriaxone, piperacillin-tazobactam, ceftaroline, or amoxicillin-clavulanate will also receive a macrolide. Patients allocated to the moxifloxacin or levofloxacin intervention will not receive a macrolide or any beta-lactam or monobactam agent.

The choice of macrolide will depend on the availability and acceptability of the agents at each site in the following order of preference;

1. IV azithromycin, with switch to enteral azithromycin when appropriate
2. IV clarithromycin, with switch to enteral azithromycin when appropriate
3. Enteral azithromycin
4. Enteral clarithromycin or roxithromycin
5. IV or enteral erythromycin

Sites in which only erythromycin is available are not able to participate in the Macrolide Duration Domain.

The objective of the macrolide domain is to determine the effectiveness of short-course versus extended course of macrolide treatment. The interventions to be compared are:

- Short course macrolide discontinued after 3 days unless there is confirmed or strongly suspected microbiological cause for prolonged administration

- Extended course macrolide for 14 days or hospital discharge, whichever occurs first

Patients will be followed up daily whilst on ICU and routine clinical data recorded.

Patients will be followed up to ascertain survival status at 90 days and at 6 months and their quality of life and disability will be assessed at 6 months.

## **Intervention Type**

Drug

## **Phase**

Not Applicable

## **Drug/device/biological/vaccine name(s)**

Ceftriaxone, moxifloxacin or levofloxacin, piperacillin-tazobactam, ceftaroline, amoxicillin clavulanate, hydrocortisone, dexamethasone, azithromycin or clarithromycin or erythromycin or roxithromycin, oseltamivir, baloxavir, baricitinib, tocilizumab, convalescent plasma

## **Primary outcome(s)**

The number of days alive and not requiring ICU organ support measured at day 21. Any death before hospital discharge is recorded as -1 on this ordinal scale. All patients who never receive organ failure support while admitted to an ICU will be coded as 22.

## **Key secondary outcome(s)**

Measured using patient's medical records where not otherwise specified:

1. 28-day all-cause mortality
2. 90-day all-cause mortality
3. ICU mortality censored at 90 days
4. ICU length of stay censored at 90 days
5. Ventilator free days censored at 90 days
6. Hospital length of stay censored at 90 days
7. Destination at time of hospital discharge
8. Readmission to the index ICU during that hospital admission

Where feasible:

1. 6-month all-cause mortality
2. Health-related quality of life measured using EQ5D-5L at 6 months
3. Disability status measured using WHODAS 2.0, 12 item instrument at 6 months

## **Completion date**

31/12/2026

## **Eligibility**

### **Key inclusion criteria**

Current participant inclusion criteria as of 23/10/2025:

1. Adult or paediatric patient (28 days or older) hospitalized with an acute illness due to a lower respiratory tract infection

Domain-specific criteria:

Influenza Strata:

Antiviral domain:

1. Influenza infection has been confirmed by microbiological testing

Corticosteroid domain:

1. If in the Moderate State, receiving some form of supplemental oxygen (simple facemask, lower high-flow oxygen, or non-invasive ventilation)

Immune Modulation:

1. Aged 2 years or older

2. Admitted to ICU and in severe illness state

3. Influenza infection has been confirmed by microbiological testing

4. In the opinion of the treating clinician, the primary contributor to the patient's severe illness is a respiratory tract infection (e.g. not unwell with trauma and happen to have influenza)

CAP Strata:

Antibiotic domain

1. Admitted to ICU with severe CAP

Macrolide domain

1. Patients are eligible for this domain only if they have been allocated a beta-lactam plus macrolide intervention within the Antibiotic domain

COVID Strata:

Immunoglobulin domain

1. Patients are eligible for this domain if SARS-CoV-2 infection is confirmed by microbiological testing

2. Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, corresponding to the APACHE II definitions (Knaus et al., 1985), extended to take into account equivalent forms of immunosuppressant therapy that post-date the APACHE II definitions.

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Previous participant inclusion criteria as of 19/04/2021:

Non-pandemic participants:

1. Adult patient admitted to an ICU for severe CAP within 48 h of hospital admission with both of the following:

1.1. Symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain)

1.2. Radiological evidence of new-onset consolidation (in-patients with pre-existing radiological changes, evidence of new infiltrate)

2. Requiring organ support with one or more of:

2.1. Non-invasive or invasive ventilatory support

2.2. Receiving infusion of vasopressor or inotropes or both

Pandemic participants:

1. Adult patient with confirmed or suspected pandemic infection

Domain-specific criteria:

Antiviral domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Immune modulation domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Immunoglobulin domain:

1. COVID-19 infection is confirmed by microbiological testing

Therapeutic anticoagulation domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Updated anticoagulation domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Antiplatelet domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Simvastatin Domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Vitamin C domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

ACE2 RAS domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Previous participant inclusion criteria:

1. Adult patient admitted to an ICU for severe CAP within 48 h of hospital admission with:
  - 1.1. Symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain); AND
  - 1.2. Radiological evidence of new-onset consolidation (in-patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring organ support with one or more of:
  - 2.1. Non-invasive or invasive ventilatory support
  - 2.2. Receiving infusion of vasopressor or inotropes or both

Domain-specific inclusion:

Corticosteroid domain: as per main protocol

Antiviral domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Immune modulation domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Immunoglobulin domain:

1. COVID-19 infection is confirmed by microbiological testing

Therapeutic anticoagulation domain:

1. COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing
2. Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

28 days

### **Sex**

All

### **Key exclusion criteria**

Current participant exclusion criteria as of 17/10/2025:

Platform Exclusion:

1. More than 14 days has elapsed since admission to hospital
2. If receiving organ failure support in an ICU, more than 48 hours has elapsed since admission to ICU
3. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patients, substitute decision maker or attending physician are not committed to full active treatment
4. Previous participation in this REMAP within the last 90 days
5. Expected to be discharged from this hospital admission within the next 24 hours

Domain Exclusion:

Influenza Strata

Antiviral domain:

1. Patient has already received two or more doses of Oseltamivir or other neuraminidase inhibitors
2. Patient has already received one or more doses of Baloxavir
3. Patient is already receiving, or a clinical decision has been made to commence, an antiviral active against influenza other than Oseltamivir or Baloxavir, or both
4. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Moderate state:

1. More than 96 hours has elapsed since hospital admission

Severe state:

1. More than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU

Intervention specific

1. Known hypersensitivity to Oseltamivir or Baloxavir.
2. Known or suspected pregnancy will result in exclusion from interventions that include Baloxavir

Corticosteroid domain:

1. Known hypersensitivity to any corticosteroid
2. Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jirovecii* or COVID19 pneumonia
3. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Severe state:

1. More than 24 hours have elapsed since ICU admission; if the patient has already been assigned a treatment in another domain in the Moderate State, exclusion will occur if more than 24 hours has elapsed since commencement of sustained organ failure support in an ICU

If in Moderate State, platform exclusion timeframe applies (to be excluded if more than 14 days have elapsed while admitted to hospital)

Immune Modulation domain:

1. SARS-COV-2 infection has been confirmed by microbiological testing
2. Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalisation
3. A neutrophil count  $<1.0 \times 10^9 / L$
4. Confirmed or strongly suspected active mycobacterial infection or invasive fungal infection
5. Patient has already received any dose of one or more of Tocilizumab (or another IL-6 receptor antagonist) or Baricitinib (or another JAK inhibitor) during this hospitalisation or is in long-term therapy with any of these agents prior to this hospital admission
6. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention Exclusion criteria:

1. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
2. Known or suspected pregnancy is an exclusion for Baricitinib (whether known or suspected pregnancy results in exclusion from the tocilizumab intervention depends on local approvals)
3. An ALT or an AST that is  $>5x$  the upper limit of normal is an exclusion for Tocilizumab
4. A platelet count  $< 50 \times 10^9 / L$  is an exclusion for Tocilizumab.
5. A baseline eGFR ( $15 \text{ mL/min}/1.73\text{m}^2$  and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline is an exclusion from Baricitinib.

COVID Strata:

Immunoglobulin domain:

1. Patient has already received treatment with any non-trial prescribed polyclonal antibody therapy (hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this acute illness
2. The treating clinician believes that participation in the domain would not be in the best interests of the patient
3. Known hypersensitivity/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
4. Known previous history of transfusion-related acute lung injury will exclude a patient from receiving high titre plasma
5. Known objection to receiving plasma products will exclude a patient from receiving any plasma components

CAP Strata

Antibiotic domain:

1. Received more than 48 hours of intravenous antibiotic treatment for this index illness
2. More than 24 hours has elapsed since ICU admission
3. Known hypersensitivity to all of the study drugs in the site randomization schedule

A specific antibiotic choice is indicated

1. Suspected or proven concomitant infection such as meningitis
2. Suspected or proven infection with resistant bacteria where agents being trialled would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with Pseudomonas may be suspected but does not

- include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection
- 3. Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count 4 preceding weeks)
- 4. Suspected melioidosis
- 5. Specific microbiological information available to guide specific antibacterial therapy
- 6. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention specific:

- 1. Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include Piperacillin and Amoxicillin
- 2. Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include Ceftriaxone and Ceftazidime
- 3. Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include Piperacillin, Amoxicillin, Ceftriaxone, and Ceftazidime.
- 4. Known hypersensitivity to Moxifloxacin or Levofloxacin will result in exclusion from Moxifloxacin or Levofloxacin intervention.
- 5. Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include Piperacillin, Amoxicillin, Ceftriaxone, and Ceftazidime.
- 6. Known or suspected pregnancy will result in exclusion from Moxifloxacin or Levofloxacin and Ceftazidime interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.

Macrolide domain:

- 1. Agreement to participate in this domain has been declined or has not been requested before the end of study day 5
- 2. There is microbiological confirmation, or the clinician strongly suspects Legionella or any other form of atypical pneumonia.
- 3. Macrolide antibiotics have already been discontinued for more than 36 hours
- 4. The treating clinician believes that participation in the domain would not be in the best interests of the patient

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Previous participant exclusion criteria as of 19/04/2021:

Non-pandemic participants:

- 1. Healthcare-associated pneumonia:
  - 1.1 Prior to this illness, has been an in-patient in any healthcare facility within the last 30 days
  - 1.2. Resident of a nursing home or long term care facility
- 2. Death is deemed imminent or inevitable during this hospital admission and >1 of the patient, substitute decision-maker, or attending physician are not committed to full active treatment
- 3. Previous participation in this REMAP within the last 90 days

Pandemic participants:

- 1. Death is deemed imminent or inevitable during the next 24 h and >1 of the patient, substitute decision-maker, or attending physician are not committed to full active treatment
- 2. Admission to hospital over 14 days ago with acute COVID illness
- 3. Expected to be discharged from hospital today or tomorrow
- 4. Previous participation in this REMAP within the last 90 days

#### Domain-specific criteria:

##### Antibiotic domain:

1. Received >48 h of intravenous antibiotic treatment for this index illness
2. >24 h have elapsed since becoming eligible for this domain
3. Known hypersensitivity to all of the study drugs in the site randomization schedule
4. A specific antibiotic choice is indicated
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient
6. If randomised to a beta-lactam plus macrolide intervention within the antibiotic domain and the treating clinician believes that participation in the domain would not be in the best interests of the patient

##### Corticosteroid domain:

1. An indication to prescribe systemic corticosteroids for a reason other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven pneumocystis jiroveci pneumonia
2. Have received an immunomodulatory dose of systemic corticosteroid therapy for >24 h prior to the time of enrolment. An immunomodulatory dose is defined as >20 mg of hydrocortisone, >5 mg prednisone, >4 mg methylprednisolone or >0.8 mg dexamethasone per 24 h
3. The treating clinician believes that participation in the domain would not be in the best interests of the patient

##### Antiviral domain:

1. >24 h have elapsed since ICU admission
2. Has already received >36 h of treatment with any non-trial prescribed systemic antiviral medication intended to be active against COVID-19 during this hospital admission
3. Has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug
4. In areas where MERS-CoV infection is endemic, laboratory-confirmed MERS-CoV infection
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient
6. Known hypersensitivity to an agent specified as an intervention in this domain
7. Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalization will exclude a patient from receiving that agent
8. Known HIV infection will exclude a patient from receiving lopinavir/ritonavir
9. Known or suspected pregnancy will result in exclusion from any intervention that includes lopinavir/ritonavir or hydroxychloroquine
10. Receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 h prior to assessment of eligibility will exclude a patient from receiving lopinavir/ritonavir
11. High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine

##### Immune modulation domain:

1. >24 h have elapsed since ICU admission
2. Has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission
3. Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization
4. Has been randomized in a trial evaluating an immune modulation agent for proven or

suspected COVID-19 infection, where the protocol of that trial requires ongoing administration of study drug

5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Immunoglobulin domain:

1. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent

2. Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma

3. Known objection to receiving plasma products will exclude a patient from receiving any plasma components

Therapeutic anticoagulation domain:

1. >48 h have elapsed since ICU admission

2. Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual antiplatelet therapy

3. Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation

4. Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial

5. Known or suspected previous adverse reaction to UFH or LMWH including heparin-induced thrombocytopenia (HIT)

6. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Updated anticoagulation domain:

1. >48 h since ICU admission

2. Clinical indication to commence or continue therapeutic dose anticoagulation (not as part of REMAP-CAP therapeutic anticoagulation group)

3. Intention to continue or commence dual antiplatelet therapy

4. Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial

5. Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT).

6. The treating clinician believes that participation in the domain would not be in the best interests of the patient

7. If prior therapeutic anticoagulation, the clinical or laboratory bleeding risk, or both, is sufficient to contraindicate continuation of therapeutic dose anticoagulation with heparin

8. If no prior therapeutic anticoagulation, the clinical or laboratory bleeding risk, or both, is sufficient to contraindicate intermediate dose thromboprophylaxis

9. If no prior therapeutic anticoagulation, and is receiving non-heparin anticoagulation medication (such as a direct acting oral anticoagulant) and the treating clinician believes that cessation and substitution with conventional low-dose thromboprophylaxis is either inappropriate or not possible

Antiplatelet domain:

1. >48 h since ICU admission

2. Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic

- anticoagulation, including intention to continue or commence dual anti-platelet therapy
3. Already receiving antiplatelet treatment or NSAID, or a clinical decision has been made to start antiplatelet or NSAID therapy
  4. Enrolment in a trial evaluating anticoagulation or antiplatelet therapy for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
  5. Aged >75 years
  6. Patients receiving prior therapeutic anticoagulation
  7. Creatinine clearance of <30 ml/min or receiving renal replacement therapy or ECMO
  8. Known hypersensitivity
  9. The treating clinician believes that participation in the domain would not be in the best interests of the patient
  10. P2Y12 Intervention specific exclusion
  11. Known or suspected to be pregnant

#### Simvastatin Domain:

1. >48 h since ICU admission
2. Known severe liver disease
3. Known hypersensitivity to simvastatin
4. Creatinine more than 200 µmol/L (2.26 mg/dL) and not receiving renal replacement therapy
5. Current treatment with medicine that cannot be co-administered with simvastatin
6. Current treatment with any statin or treating clinician intends to commence treatment with any statin
7. Pregnant or breastfeeding.
8. The treating clinician believes that participation in the domain would not be in the best interests of the patient

#### Vitamin C domain:

1. >24 h since ICU admission
2. Patient has received any intravenous vitamin C during this hospitalisation (unless incorporated into parenteral nutrition)
3. Any of the following contraindications to vitamin C therapy:
  - 3.1. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - 3.2. Known allergy to vitamin C
  - 3.3. Known history of symptomatic kidney stones within the past year
4. Has been randomised to a trial evaluating vitamin C, where the protocol of the trial requires ongoing administration of the study drug
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

#### ACE2 RAS domain:

1. >48 h since ICU admission in severe state or >96 h in moderate state
2. Patient is already receiving, or a clinical decision has been made to commence, an ACEi, ARB, direct renin inhibitor, angiotensin-receptor-neprilysin inhibitor, or chemokine receptor modulator
3. Long-term therapy prior to this hospital admission with one or more of ACEi, ARB, direct renin inhibitor, angiotensin-receptor-neprilysin inhibitor, or chemokine receptor modulator
4. Known hypersensitivity to ACEi or ARB, including angioedema
5. Treating clinician believes that administration of ACEi or ARB is inappropriate because of risk for:
  - 5.1. Clinically relevant hypotension or escalation of vasopressor requirements
  - 5.2. Hyperkalemia

6. Known severe renal artery stenosis
7. Patient is known or suspected to be pregnant or breastfeeding
8. Renal impairment with creatinine clearance < 30 ml/min or receiving renal replacement therapy
9. Enrollment in another trial evaluating ACEi, ARB, or other RAS modulator, or any targeted chemokine receptor modulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial
10. If the domain is available at this site in the Moderate State and the patient is being assessed in the Severe state, prior assessment for this domain in the Moderate State
11. The treating clinician believes that participation in the domain would not be in the best interests of the patient
12. ARB + DMX-200 specific exclusions
13. Known severe liver disease or an alanine aminotransferase or an aspartate aminotransferase that is more than 5 times the upper limit of normal
14. Known viral hepatitis
15. Hypersensitivity to repagermanium

Previous participant exclusion criteria:

1. Healthcare-associated pneumonia:
  - 1.1. Prior to this illness, has been an in-patient in any healthcare facility within the last 30 days
  - 1.2. Resident of a nursing home or long term care facility
2. Death is deemed imminent or inevitable during this hospital admission AND one or more of the patient, substitute decision-maker or attending physician are not committed to full active treatment
3. Previous participation in this REMAP within the last 90 days

Patients will be deemed eligible for each treatment domain if they don't meet any of the following domain-specific exclusion criteria

Antibiotic domain:

1. Received more than 48 h of intravenous antibiotic treatment for this index illness
2. More than 24 hours have elapsed since becoming eligible for this domain
3. Known hypersensitivity to all of the study drugs in the site randomization schedule
4. A specific antibiotic choice is indicated
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Macrolide duration domain (if randomised to a beta-lactam plus macrolide intervention within the antibiotic domain):

1. The treating clinician believes that participation in the domain would not be in the best interests of the patient

Corticosteroid domain:

1. An indication to prescribe systemic corticosteroids for a reason other than community-acquired pneumonia (CAP) (or severe sepsis) such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven *Pneumocystis jiroveci* pneumonia
2. Have received an immunomodulatory dose of systemic corticosteroid therapy for more than 24 hours prior to the time of enrolment. An immunomodulatory dose is defined as > 20 mg of hydrocortisone, > 5 mg prednisone, > 4 mg methylprednisolone or > 0.8 mg dexamethasone per 24 hours
3. The treating clinician believes that participation in the domain would not be in the best interests of the patient

#### Antiviral domain:

1. More than 24 hours have elapsed since ICU admission
2. Patient has already received more than 36 hours of treatment with any non-trial prescribed systemic antiviral medication intended to be active against COVID-19 during this hospital admission
3. Patient has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug
4. In areas where MERS-CoV infection is endemic, the patient has laboratory-confirmed MERS-CoV infection
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient
6. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
7. Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalization will exclude a patient from receiving that agent
8. Known HIV infection will exclude a patient from receiving lopinavir/ritonavir
9. Known or suspected pregnancy will result in exclusion from any intervention that includes lopinavir/ritonavir or hydroxychloroquine
10. Receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to assessment of eligibility will exclude a patient from receiving lopinavir/ritonavir
11. High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine

#### Immune modulation domain:

1. More than 24 h have elapsed since ICU admission
2. Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission
3. Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization
4. Patient has been randomized in a trial evaluating an immune modulation agent for proven or suspected COVID-19 infection, where the protocol of that trial requires ongoing administration of study drug
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

#### Immunoglobulin domain:

1. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
2. Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma
3. Known objection to receiving plasma products will exclude a patient from receiving any plasma components

#### Therapeutic anticoagulation domain:

1. More than 48 hours have elapsed since ICU admission
2. Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual antiplatelet therapy
3. Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made

to commence therapeutic anticoagulation

4. Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial

5. Known or suspected previous adverse reaction to UFH or LMWH including heparin-induced thrombocytopenia (HIT)

6. The treating clinician believes that participation in the domain would not be in the best interests of the patient

**Date of first enrolment**

28/05/2019

**Date of final enrolment**

31/12/2026

## **Locations**

**Countries of recruitment**

United Kingdom

England

Australia

Belgium

Canada

Croatia

Finland

France

Germany

Hungary

Ireland

Netherlands

New Zealand

Portugal

Saudi Arabia

Spain

United States of America

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## Sponsor information

**Organisation**  
University Medical Center Utrecht

**ROR**  
<https://ror.org/0575yy874>

## Funder(s)

**Funder type**  
Government

**Funder Name**  
European Commission

**Alternative Name(s)**  
European Union, Comisi3n Europea, Europaische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

**Funding Body Type**  
Government organisation

**Funding Body Subtype**  
National government

**Location**

## Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

## IPD sharing plan summary

Published as a supplement to the results publication

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results for hydrocortisone	06/10/2020	03/09/2020	Yes	No
<a href="#">Results article</a>	results for tocilizumab and sarilumab	25/02/2021	18/03/2021	Yes	No
<a href="#">Protocol article</a>	protocol	01/07/2020	16/07/2020	Yes	No
<a href="#">HRA research summary</a>			26/07/2023	No	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes
<a href="#">Preprint results</a>	results for tocilizumab and sarilumab in preprint	09/01/2021	08/01/2021	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes