

REMAP-CAP

Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia for COVID-19



Investigator: **Matt Wise**

Patient Information Sheet - Overview

You are invited to take part in the REMAP-CAP research study. This is because you are unwell possibly or known to be due to a new coronavirus, COVID-19. This virus causes pneumonia (lung infection) and other illnesses, and is an important health problem.

We are continuing to test different treatments that may be beneficial for patients to ensure we provide the best possible treatment for you. In this information sheet we have listed each treatment available at your hospital, including any potential benefits and risks. If you are happy to participate, you will be allocated by chance (called randomised) to at least one of these treatment options, but you and we will not know which treatment choice you will receive before this.

Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. This sheet tells you the purpose of this study, what will happen to you if you take part and provides more detailed information about how the study will be carried out. Ask us if there is anything that is not clear or if you would like more information and discuss it with others if you wish.

If you do not wish to be part of this study, no further information will be collected about you for the trial and the doctors will continue to provide you with whatever medical treatment is needed. Thank you for reading this.

Important things to know

- You have been admitted to hospital with COVID-19 and it is important to treat you as soon as possible
- COVID-19 is a new disease and we need to know which treatments are best
- You may be eligible to receive a number of different treatments
- These treatments will be randomly chosen for you by a computer system (by chance)
- All treatments and a list of their possible benefits and risks are included in this information sheet
- All your data will be kept confidential
- We will follow up with you in 6 months and ask you to complete a questionnaire
- You can withdraw from this study at any time and you will continue to receive the local standard treatments and care

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Information about the research

What is the purpose of the study?

The treatment for patients with pneumonia and other severe infections is generally based on national and international guidelines that guide healthcare professionals to choose the best treatments from the evidence available. As COVID-19 is a new disease it is not clear what the right treatments are. Treatment guidelines and recommendations from the World Health Organisation are that, for COVID-19, treatments with unknown benefit should only be given in a clinical trial.

The aim of this study is to investigate which of these treatment options are best for patients admitted to hospital or the intensive care unit (ICU) with suspected or confirmed COVID-19 infection.

What medical treatments are being investigated?

In this study, several different treatments are being compared at the same time. These treatments, which are available at your hospital, for COVID-19 can be put into the following different groups:

If you are being treated in the intensive care unit (ICU):

- 1) antiviral medication; 2) immune modulation; 5) immunoglobulin therapies; 6) Vitamin C Therapy;
- 7) Simvastatin Therapy; 8) Anticoagulation Therapies, and 9) Antiplatelet therapy

Why have I been chosen?

You have been asked to take part in this study as you have been admitted to hospital or ICU due to known or suspected COVID-19. We know that treating patients early in this situation provides the best opportunity for medications to work well and so we need to include patients as soon as possible after they become unwell. We are planning to study about 1000 patients in total, admitted to different hospitals within the UK. We are also working closely with research partners internationally.

What does participation in this research involve?

It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not affect the standard of care you receive.

This is a randomised study. Randomisation is a process that can be compared to tossing a coin. Sometimes we need to make comparisons to see which way of treating patients is the best. People are put into groups by chance and then compared. The groups are selected by a computer which has no information about the individual – i.e. so patients are put into the groups by chance. Each group has a different treatment and these are compared.

Additionally, this study is an 'adaptive' study. This means that the chances of being assigned to any of the treatment options may change on the basis of the study results, in favour of the most promising treatment. Neither you nor your doctors will be informed of these changes in randomisation. This study assesses multiple different types of treatment. You may be eligible for all of them or only some of them, depending on your individual clinical condition. It is important for the treatment of your pneumonia that the

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treatments are started as quickly as possible. This is why these treatments may have already be assigned ('randomized') to you when you are admitted to hospital or ICU. The doctor or researcher will explain the study and ask for your consent for participation. If you do not consent to participate in the study, no further data will be collected from you. The treatment that was previously started will be continued or will be changed if your doctor thinks this is necessary.

If you do consent to participate in the study, you will continue to be treated with the treatments already started. Various routine data collected from you throughout your hospital stay as part of routine care will be used for the study. If the doctors feel that your condition changes they can change your treatments as necessary.

What do I have to do?

You do not need to do anything for the study. A researcher will collect data from you for the study, and you will not notice anything. The data collected for the study are already collected as part of your daily and ongoing medical care. With your permission, we will also use routinely collected data held by either the Case Mix Programme, the national clinical audit of UK critical care units, run by the Intensive Care National Audit & Research Centre (ICNARC) or by NHS Digital. These data will include information regarding your health that will be important to answer the objectives of the study and will include, data from this and future hospital stays and survival data. We would also like to contact you in 6 months' time with a short telephone call to ask about your quality of life and wellbeing.

If you do not wish to be part of this study, no further information will be collected about you for the trial and the doctors will continue to provide you with whatever medical treatment is needed.

What are the possible advantages and disadvantages of participating in this study?

The treatments that we are testing for COVID-19 are used to treat other viruses and other immune-related diseases, but we do not know 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 we cannot guarantee that taking part in this study will benefit you directly but it will help improve treatment for people with COVID-19 in the future.

All medical treatments can cause side effects. The risks from side effects are similar if you choose not to be in the study. Your doctor will know what treatment you are receiving at all times, and so the doctors will be looking out for any side effects.

What if something goes wrong?

University Medical Center Utrecht (UMCU) (The trial sponsor) holds insurance policies which apply to this study. If in the unlikely event you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that UMCU is at fault.

This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action.

If you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the local Investigator (Dr Wise, contact details at end). The normal National Health Service complaints mechanisms are also available to you.

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Will information from this study be kept confidential?

Yes. This is a large global trial and we will follow the law by making sure your information is kept private and secure. UMC Utrecht is the sponsor for this study based in the Netherlands. We will be using information from you and your medical records in order to undertake this study and UMC Utrecht will act as the data controller for this study. This means that they are responsible for looking after your information and using it properly. UMC Utrecht will be storing de-identified study data on servers based in Sydney Australia. This information will be kept for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting privacy@umcutrecht.nl.

Cardiff and Vale UHB will collect information from you and your medical records for this research study in accordance with the sponsor's instructions.

Cardiff and Vale UHB will keep your name, NHS number and contact details confidential and will not pass this information to UMC Utrecht. **Cardiff and Vale UHB** will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from UMC Utrecht and regulatory organisations may look at your medical and research records to check the accuracy of the research study. UMC Utrecht will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Minimal randomisation and clinical data will be collected on servers in Sydney Australia which will collect some personal information about you for this global study. This information will include your initials, date of birth and gender and basic eligibility health information. The information will be held securely with strict arrangements about who can access the information. With your permission, in order that we can contact you in 6 months and identify you in the Case Mix Programme database (as outlined above) your hospital will provide your name, telephone number and NHS number to ICNARC (based in the UK), alongside some additional clinical data. Once you have been identified, the trial team will share your postcode, date of birth and NHS number (held by the Case Mix Programme), along with your name with NHS Digital. This will enable NHS Digital to provide us with information as described above.

Cardiff and Vale UHB will keep identifiable information about you from this study for 15 years after the study has finished. When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the [UK Policy Framework for Health and Social Care Research](#).

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This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance. It is necessary for us to process your data as described to allow us to perform a task in the public interest (lawful basis).

What will happen to the results of the research study?

The study stops for you once you have completed your 6 month follow up telephone conversation with a member of the clinical research team. You will not be personally informed about the results of the study. The results of this study will be presented at medical meetings and published in scientific journals. Only anonymous group information and no personal information will be presented. If you are interested in the results you will be able to look them up after the trial has finished. The website link where you can see the overall results will be: www.remapcap.org.

Who is organising and funding the research?

The Coordinating Principal Investigator for this study is Professor Marc Bonten, at the University Medical Center Utrecht, Netherlands. This research has received funding from the EU FP7-HEALTH-2013 INNOVATION-1 Grant as part of the global PREPARE consortium. The cost of some treatments for immune modulation for COVID-19 may be covered by pharmaceutical companies that make these products. These pharmaceutical companies have no involvement in the design, analysis, or reporting of results from the trial. The UK Principal Investigator is Professor Anthony Gordon at Imperial College London, and the UK Trial Coordinating Centre is ICNARC, Napier House, 24 High Holborn, London WC1V 6AZ.

Who has reviewed the study?

All research involving patients in the NHS is looked at by an independent group of people called a Research Ethics Committee. This study has been reviewed and approved by the **London- Surrey Borders HRA Ethics Committee**.

Who can I contact for independent research information?

If you have any questions about being in a research study, you can contact the Trust's Patient Advice Liaison Service (PALS). They will give you advice about who you can talk to for independent advice.

Local PALS office telephone number	Local PALS office address
02920 744095 concerns@wales.nhs.uk	Concerns Team University Hospital of Wales Cardiff CF14 4XW

Further information

Thank you for considering participation in this study. If you have any questions about this research, the local study staff will be more than happy to answer them. Their contact details are:

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Study Investigators Contact details

Study Investigator	Dr Matt Wise
Study Nurse	Critical Care Research Team
Day time Telephone	02920743608
Emergency Telephone	02920746800

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CONSENT FORM FOR PATIENTS ABLE TO GIVE CONSENT (Hospital level)

Patient Study ID		Site #	
Name of Research Doctor			

Please initial each box if you agree with the following:

I, (forename and surname)..... freely agree to take part in the study.

- I confirm that I have read and understood the patient information sheet dated 1st October 2020 v1.7 for the above study and have been able to ask questions which have been answered fully.
- I agree to take part in the therapeutic anticoagulation domain
- I agree to take part in the antiplatelet domain
- I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
- I understand my identity will never be disclosed to any third parties and any information collected will remain confidential.
- I agree that my medical records and other personal data generated during the study may be examined by representatives of the sponsor (UMC Utrecht), by people working on behalf of the sponsor, and by representatives of Regulatory authorities, ICNARC and NHS Digital where it is relevant to my taking part in this research.
- I agree that I will not seek to restrict the use to which the results of the study may be put.
- I understand I will be contacted by ICNARC in six months to ask about my quality of life and wellbeing. *[delete if not taking part in follow-up aspect]*
- I understand that minimal randomisation data collected about me will be transferred outside of the EEA.

<p>Patient</p> <p>Date:</p> <p>Signature:</p> <p>Printed Name:</p> <p>Witness Consent (in the event the patient cannot sign)</p> <p>Date:</p> <p>Signature:</p> <p>Printed Name:</p>	<p>Person responsible for collecting the informed consent</p> <p>Date:</p> <p>Signature:</p> <p>Printed Name:</p>
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Treatments available at this ICU

1. Use of COVID-19 antiviral medication. When a patient has known or suspected COVID-, some doctors will prescribe antiviral medications. These antiviral medications work in other situations, but we don't know if any of them work against COVID-19 or not. At this site, this study evaluates:

- Lopinavir/ritonavir (also known as Kaletra)
- No antiviral medication intended to be active against COVID-19

The doctors in this ICU have selected these options because they do not know which treatment option is best.

2. Use of COVID-19 immune modulation. There are some medicines that may work in COVID-19 disease by altering the patient's immune response to the virus. These drugs are used in other diseases to alter inflammation and the body's immune response but we don't know if any of them work in COVID-19. At this site, this study evaluates:

- Interferon-beta 1a
- Anakinra
- Tocilizumab
- Sarilumab
- No agent that is intended to modulate the immune response

The doctors in this ICU have chosen these options because they don't know which option is best.

5a. Use of COVID-19 Immunoglobulin Therapy (standard sampling) COVID-19 immunoglobulin therapy is a blood-based treatment, giving patients antibodies to help fight infection. Antibodies are found in plasma, which is the liquid part of blood. It contains a mixture of proteins including antibodies, clotting factors, and natural anticoagulants. Convalescent plasma is plasma collected from volunteers who have recovered from COVID-19, which contains antibodies to help fight COVID-19. At this site the study evaluates:

- No Immunoglobulin Therapy
- Convalescent Plasma

Convalescent plasma has been used to treat other viruses in the past but doctors are unsure if giving it to people with COVID-19 will be beneficial. Part of this study includes taking additional blood and respiratory samples when you enter the study, the blood sample will take 6mls (just over 1 teaspoon) of blood. These samples will be transported to a central laboratory for testing. All samples collected from you under this study will be used within this study or in other ethically approved studies.

You will only receive these treatments if you have pneumonia that is believed or known to be caused by the Coronavirus.

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6. Vitamin C therapy. It has been suggested that high doses of vitamin C may be useful to treat infection and the inflammation often seen in sepsis and especially COVID-19. However, there is no clear evidence of benefit for this treatment yet.

The following interventions will be available:

- No vitamin C (no placebo)
- Intravenous Vitamin C for 4 days

7. Simvastatin therapy. Statins are commonly used to lower cholesterol and lower the risks of heart attacks or strokes. One of these drugs, simvastatin has also been shown to reduce inflammation and therefore may be beneficial to treat COVID-19.

The following interventions will be available:

- No simvastatin (no placebo)
- Simvastatin

8. Anticoagulation therapy – ICU level. All critically ill patients are at risk of developing blood clots in their legs that can move to the lungs and cause severe breathing problems. It is usual to give small doses of blood “thinners” (heparin drugs) to try and prevent these clots. Patients with COVID-19 appear to be at even higher risk of developing blood clots. Therefore, patients may require higher doses of these drugs to “thin” the blood even more. But this could increase the risk of bleeding and therefore doctors are uncertain which strategy is best. At this site, this study evaluates:

- Standard low dose (prophylactic / preventative) heparin
- Treatment (higher) dose heparin

9. Antiplatelet Therapy. Blood clots that develop in arteries are common in hospitalised patients with COVID-19 and antiplatelet therapy is commonly used in treating this. These drugs have been shown to prevent the development of blood clots and inflammation and therefore may be beneficial in the treatment of COVID-19

The following interventions will be available:

- No antiplatelet (no placebo)
- Aspirin
- P2Y12 inhibitor (Clopidogrel, Prasugrel or Ticagrelor)

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Possible side effects

Different types of antibiotics are used as part of the study. These medications are used as part of normal care, and the side effects are minimal, but these drugs can still give side effects. The antibiotics and antivirals used as part of this study may have the following side effects:

Diarrhoea, dizziness, headache, stomach ache, tingling sensations, nausea, vomiting, heartburn, unpleasant taste, inflammation of the mouth and the tongue, deteriorating vision, deafness, loss of appetite, low blood sugar, itching, skin rash, joint pain, fatigue, vein inflammation, general anaemia, cardiac arrhythmia, excessive sweating, shortness of breath, sleepiness, anxiety and confusion, and nervousness.

These side-effects are similar for most different antibiotics and antivirals.

Immune modulators may have the following side effects:

Headache, runny nose, vomiting, diarrhoea, nausea, rash, fever, chills, fatigue, night sweats, bruising, muscle cramp, muscle and joint pain/stiffness, injection site reactions (e.g. bruising/pain), increased blood cholesterol level, decrease in white blood cells and/or platelets, changes in liver function tests, muscle stiffness, numbness of the skin, and increased risk of infection.

Convalescent plasma has been used to treat other viral infections, but its effects are not known in people with COVID-19. However, the risk that a standard plasma transfusion may make you ill is very low. A plasma transfusion may have the following side-effects:

Allergic reactions (rash, fever, chills) or increased difficulty breathing. These reactions are usually mild and are easily treated with medicines such as paracetamol and antihistamines, or by slowing down or stopping the plasma transfusion.

Vitamin C may potentially cause kidney stones.

Simvastatin is a medicine used to lower cholesterol and the risks of heart attacks or strokes and may have the following side effects:

Muscle aches, pains, tenderness or weakness, and temporary changes in liver blood tests.

Heparin is a blood thinner that can prevent and treat blood clots but it can also increase the risk of bleeding. This can be minor, e.g. bruising, but sometimes can be more severe, e.g. require a blood transfusion.

Aspirin is commonly used to treat pain, fever and inflammation. Common side effects are nausea, vomiting or stomach pain. Common side effects of P2Y12 inhibitors are stomach pain, bleeding, dizziness and chest pain.

Other rare side effects may occur (in less than 1% of people) but the doctors and nurses looking after you will watch carefully for these possible effects and treat them as necessary and even stop the treatment if needed.

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CONSENT FORM FOR PATIENTS ABLE TO GIVE CONSENT (ICU)

Patient Study ID		Site #	
Name of Research Doctor			

Please initial each box if you agree with the following:

I, (forename and surname)..... freely agree to take part in the study.

- I confirm that I have read and understood the patient information sheet dated 1st October 2020 v1.7 for the above study and have been able to ask questions which have been answered fully.
- I agree to take part in the COVID-19 antiviral domain. *[delete if not taking part in COVID-19 antiviral treatment domain]*
- I agree to take part in the COVID-19 immune modulation domain. *[delete if not taking part in COVID-19 immune modulation treatment domain]*
- I agree to take part in the antibiotic domain. *[delete if not taking part in antibiotic treatment domain]*
- I agree to take part in the macrolide domain. *[delete if not taking part in macrolide treatment domain]*
- I agree to take part in the immunoglobulin therapy domain. *[delete if not taking part in immunoglobulin therapy domain]*
- I agree that my blood and respiratory samples can be retained by researchers as part of the study. *[delete if not taking part in immunoglobulin therapy domain]*
- I agree that these samples can be donated as a gift to researchers for future research purposes. *[delete if not taking part in immunoglobulin therapy domain]*
- I agree that DNA and RNA from my blood sample will be analysed to determine whether any genetic factors have made me susceptible to severe infection. *[delete if not taking part in immunoglobulin therapy domain]*
- I agree to take part in the therapeutic anticoagulation domain *[delete if not taking part in therapeutic anticoagulation domain]*
- I agree to take part in the Antiplatelet domain *[delete if not taking part in Antiplatelet domain]*
- I agree to take part in the Vitamin C domain *[delete if not taking part in Vitamin C domain]*
- I agree to take part in the Simvastatin domain *[delete if not taking part in Simvastatin domain]*
- I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
- I understand my identity will never be disclosed to any third parties and any information collected will remain confidential.
- I agree that my medical records and other personal data generated during the study may be examined by representatives of the sponsor (UMC Utrecht), by people working on behalf of the sponsor, and by

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representatives of Regulatory authorities, ICNARC and NHS Digital where it is relevant to my taking part in this research.

- I agree that I will not seek to restrict the use to which the results of the study may be put.
- I understand I will be contacted by ICNARC in six months to ask about my quality of life and wellbeing. [delete if not taking part in follow-up aspect]
- I understand that minimal randomisation data collected about me will be transferred outside of the EEA.

Patient

Date:

Signature:

Printed Name:

Witness Consent (in the event the patient cannot sign)

Date:

Signature:

Printed Name:

Person responsible for collecting the informed consent

Date:

Signature:

Printed Name:

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