

Participant Information Sheet and Consent (Prior to Enrolment)



COVID-19: Pandemic infection is either suspected or proven

Interventional Study - Adult providing own consent prior to enrolment

Title	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
Short Title	REMAP-CAP
Protocol Number	X 17-0199
Project Sponsor	Monash University
Coordinating Principal Investigator	Professor Steven Webb
Principal Investigator	Dr Hergen Buscher
Location	St Vincent's Hospital St Vincent's Hospital, Sydney

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have a condition called pneumonia, which is an infection of the lungs caused by a new Coronavirus. The disease is called COVID-19.

Most patients with pneumonia due to COVID-19 who are being treated in an Intensive Care Unit (ICU) will receive many different treatments, as many as 20 or 30 different treatments, that act together to treat both the infection and its effects on the body. For this research project:

- Several treatments may be tested, at the same time, in the same patient.
- We will tell you if you are not eligible for all options that are tested in the study.
- You can choose the parts of the study you participate in.
- Because COVID-19 is a new disease, doctors don't already know which treatments work best and the side effects of some treatment options.
- The study looks at its results as it goes and uses the results so that new patients in the study have a better chance of getting better treatments.
- The different treatment options are tested to tell which are the best. The study only tests options where it is not known which treatments are best.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. The drugs used in this study are approved in Australia for treating other diseases however they are not approved for the treatment of pneumonia caused by COVID-19. This study

will be conducted under the Therapeutic Goods Administration (TGA) Clinical Trials Notification (CTN) Scheme. This allows the investigators to use these products for medical research purposes once the research has been assessed and approved by an authorised Human Research Ethics Committee (HREC).

2 About this Information Sheet and Consent Form

This Participant Information Sheet/Consent Form tells you about the research project. It explains the treatments involved and how it is determined which treatments you will receive. Knowing what is involved will help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether to take part, you might want to talk about it with a relative, friend or the doctors who are treating you.

Participation in this research is voluntary. If you don't wish to take part, you do not have to. If you choose not to participate, you will receive the best treatment the doctors can provide.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it, you are telling us that you:

- Understand what you have read
- Agree to take part in the research project
- Agree to have the treatments that are described, so long as your doctor thinks they are appropriate
- Agree to the use of information about you and your health, as described.

You will be given a copy of this Participant Information and Consent Form to keep.

3 What is the purpose of this research?

The purpose of this research is to study drugs that might improve survival and recovery for patients with pneumonia caused by COVID-19. This study might not directly benefit you but may lead to the development of treatment options for patients like you. As explained later, the trial uses a technique to use information from patients already enrolled in the trial to increase the likelihood that you will receive treatments that are effective.

We understand that being a patient with pneumonia can be very concerning. The doctors and the team associated with this research project are dedicated to giving you the best possible treatments.

In general, patients with pneumonia receive many different treatment options as part of standard care but doctors aren't always sure which of these treatments are best.

All medications used in this research project are already available and used routinely to treat patients with pneumonia.

In this project, different aspects of treatment are being evaluated:

- 1. COVID-19 – use of antiviral agents.** Some antiviral medicines may work against COVID-19. Doctors don't know if any of them work or what side effects they may have. At this site, this project evaluates:

Lopinavir/ritonavir (also known as Kaletra)

No agent antiviral agent that is intended to be active against COVID-19

The doctors in this ICU have chosen these options because they don't know which option is best. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, treatments with unknown benefit should only be administered in a clinical trial. The use of antivirals is not a usual treatment, so this evaluation is a "new treatment". The antiviral drugs listed above are not approved by the TGA for COVID-19 and may not be beneficial to you.

One clinical trial has already evaluated Lopinavir/ritonavir for COVID-19 infection. This trial did not report benefit. However, the trial occurred in patients who are different to you, because they were not as sick as you. The other study may also have not had enough patients to show benefit. The other study may not be a good indicator of whether the treatment works.

- 2. COVID-19 - use of immune modulation agents.** The immune system consists of cells and proteins that fight off infection but if the immune system is over-active it can cause harm to the you. There are some medicines that may work against COVID-19 by controlling damage caused by the immune system. Doctors don't know if any of them work or what side effects they may have. At this site, this project evaluates:

Interferon-beta 1a

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. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, treatments with unknown benefit should only be administered in a clinical trial. The use of immune modulation is not a usual treatment, so this evaluation is a "new treatment". The immune modulation drugs listed above are not approved by the TGA for COVID-19 and may not be beneficial to you.

- 3. Whether to use hydrocortisone.** Hydrocortisone is an anti-inflammatory medication. Some doctors believe it helps reduce inflammation in the lungs and elsewhere in the body, and that this helps the body to recover. Other doctors disagree and don't use the medicine, and others use the medicine only when a patient is very unwell, that is if the patient is in "septic shock". At this site, this project evaluates:

A fixed duration of treatment with hydrocortisone

Hydrocortisone given only when the patient is in "septic shock"

The doctors in this ICU don't know which treatment is best but believe all options are safe and reasonable. Therefore, the choice of whether to use hydrocortisone or not is comparing different types of "standard care".

- 4. Choice of antibiotic.** All participants who doctors think have pneumonia are given antibiotics, but doctors give different antibiotics. At this site, this project evaluates the following antibiotics:

Ceftriaxone and a macrolide

Amoxicillin-clavulanate and a macrolide

Moxifloxacin or Levofloxacin

The doctors in this ICU have chosen to have these options available in the study because all of these options are known or believed to be safe and effective. If the participant is not in the study, it is very likely that the doctors would have treated them

with one of these options. However, it is not known which option is best. The choice of antibiotic evaluates different types of “standard care”. The doctors in this ICU will be asked to consider whether the above antibiotics are appropriate for your individual medical presentation.

5. Duration of macrolide treatment. The medicine, Azithromycin, is a macrolide antibiotic that also has some anti-inflammatory actions. Most doctors give Azithromycin to most participants with pneumonia but stop after a few days. However, if it's stopped early the participant may not benefit from its anti-inflammatory effect. In this research project, stopping Azithromycin after a few days will be compared with continuing it for up to 14 days. The longer course of Azithromycin is not a usual treatment, so this evaluation is a “new treatment”.

6. Use of influenza antiviral medications. When a participant has pneumonia caused by an influenza virus, some doctors will prescribe a drug called Oseltamivir, an antiviral medication. Some doctors do not routinely use Oseltamivir, and those who do may prescribe it for different lengths of time. At this site, this project evaluates:

Oseltamivir for five days

Oseltamivir for ten days

The doctors in this ICU have selected these options because they do not know which of them is best, but believe that all of these options are safe and effective. Therefore, these options are different types of “standard care”. The participant will only receive these treatments if they have pneumonia that is believed or known to be caused by Influenza.

4 How is this study being paid for?

This study is happening in Australia, New Zealand, Europe and Canada. In Australia, the research is being coordinated by the Australian and New Zealand Intensive Care Research Centre at Monash University on behalf of a large group of ICU doctors, nurses, and other health professionals known as the Australian and New Zealand Intensive Care Society Clinical Trials Group.

This research has been funded by the Australian government through a grant from the National Health and Medical Research Council (NHMRC).

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.

No money is paid directly to individual researchers or doctors.

5 What does participation in this research involve?

This research project is called a Platform Trial. The design means that the researchers analyse the results as the trial occurs rather than just at the end of the trial. The longer the study is going on for the more information the researchers can work with. This means that people who participate in the study once it has been running for a while have a better chance of getting a better treatment.

During the study your doctor will know what treatment you are getting at all times (that is they are not ‘blinded’). This means your doctor can change your treatment if they need to.

Your doctor has already decided that all treatment options that you might receive in the study are appropriate and suitable for you.

There are no additional costs from being in the research. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

6 What do I have to do?

In hospital

Some of the treatments you receive will be determined by the study but all other treatments and tests will be those that you needed anyway. No additional tests, examinations or samples of blood are required for this research study. Members of the research team will collect information about you from your medical record and put this information in a database so it can be analysed.

Following discharge from hospital

Either you or your relative or friend will be contacted by a trained research co-ordinator by telephone at approximately 3 months after you started in the study. This phone call is to determine how well you are recovering and should take no longer than 5 minutes.

At approximately 6 months after you started in the study a phone call will also be made to you, your relative or friend to collect information about your recovery. The trained research coordinator will ask you about your quality of life including whether you are able to walk, look after yourself and how you are generally going. It is expected this phone call will take no more than 10 minutes. In order for this phone call to take place, we will ask you to supply contact phone numbers. The questions may be mailed a few weeks before the phone call to save some time during the call.

7 Other relevant information about the research project

We plan to conduct this research study at approximately 30 hospitals in Australia and New Zealand, 50 hospitals in Europe and 10 hospitals in Canada and enrol a total of 7,100 participants over the first 4 years.

8 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Please be assured that your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your medical treatment or your relationship with those treating you or your relationship with St Vincent's Hospital.

9 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. If you decide not to participate your doctor will choose your treatment (but will not have access to the results of the study).

10 What are the possible benefits of taking part?

We cannot guarantee that you will receive any benefits from being a participant in this research.

11 What are the possible risks and disadvantages of taking part?

Medical treatments often 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 side effects. As these are all drugs that have been used in other diseases previously, the doctors and nurses who will be caring for you while in the ICU are trained to recognise the risks associated with them. If side effects occur and the doctor thinks it is best to stop that treatment that is what will happen.

More information about the known side effects of medications in the COVID-19 antiviral and COVID-19 immune modulation components are listed in the Appendix at the end of this sheet.

If you could be pregnant or are breast feeding the study will only give treatment options that are recommended for use in these situations.

12 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research team, in combination with a group of independent doctors and research experts (known as the Data Safety Monitoring Board) may decide how best to take this new information into account.

13 What if I withdraw from this research project?

You can decide to withdraw from the project at any time without having to give a reason. Please notify a member of the research team if you wish to withdraw.

Even if your participation in the study stops, the de-identified information obtained for the whole study period is critical to determining the study question. We would request that we continue to collect data on treatment received whilst in ICU and information on your health status for up to 90 days from the day you entered the study.

Part 2 How is the research project being conducted?

14 What will happen to information about me?

By signing the consent form you agree to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Information relating to the study will be kept indefinitely. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Your health records and any relevant study information obtained, are subject to inspection (for the purpose of verifying the procedures and the data) by the authorised representatives of the Sponsor, Monash University, the institution relevant to this Participant Information Sheet, St Vincent's Hospital, or as required by law.

The data collected in this study will be analysed at Monash University in Melbourne, Victoria, by members of the REMAP-CAP research team. Participants in many other countries are being included in this study and your data may be shared with other members of the REMAP-CAP research team located in other countries. The data collected in this study may also be joined with

data from other studies to help reach answers more quickly or with more accuracy. The data from this study will be used to determine if treatments work and results from the study will be used to help the design of future research on COVID related treatment.

Research information will be collected by the research staff at St Vincent's Hospital from your medical record. This study information will be kept in a locked filing cabinet or on a password protected computer in the secure research office at St Vincent's Hospital which is only accessible to the research staff. Your research information will be sent to the coordinating centre at Monash University. The research study results will be held securely at the coordinating centre.

Information about participant's who are admitted to ICUs in Australia is submitted to the national ICU Registry, the Adult Patient Database which is managed by the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation. We will identify your ICU admission(s) at this hospital in the Adult Patient Database and information available from this database, which can include data obtained from other sources such as hospital admission data and statutory registries, will be provided to the research team. No personal identifying data will be provided by the Adult Patient Database to the research team. The value of this information is that it provides additional information about episodes of ICU care and can be used to provide information about outcomes into the future. The custodian of data submitted to the Adult Patient Database is the Director of this ICU and data will only be provided with their agreement.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified. The study website www.remapcap.org will provide updates on the studies progress and publications.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or New South Wales privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in Section 14 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

15 Complaints and compensation

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In addition, you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You do not give up any legal rights to compensation by participating in this study.

16 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the approved by Sydney Local Health District (RPAH Zone). This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X 17-0199.

17 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor Dr Hergen Buscher on 02 83822036 or any of the following people:

Clinical contact person

Name	Claire Reynolds
Position	Research Coordinator
Telephone	0283822174
Email	Claire.reynolds@svha.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Research Office Manager
Telephone	02 83824960
Email	SVHS.research@svha.org.au

APPENDIX 1: Potential Adverse Events

Reported adverse events for Lopinavir/ritonavir (kaletra) include:

- Diarrhoea, which is common
- Nausea
- Rash
- Elevated liver enzymes
- Inflammation of the pancreas
- Increased blood lipid levels
- Heart rhythm disturbances
- Interaction with other medicines (which the treating doctor has been told about by the trial).

Reported adverse events for Anakinra include:

- New infections
- Low blood counts including white cells (help fight infections) and platelets (help stop bleeding)
- Headaches

Clinical trials of anakinra have been conducted in ICU patients. Adverse events were no more common in patients receiving anakinra.

Reported adverse events for IFN-beta1a include:

- Mood problems including depression
- Elevated liver enzymes
- Serious allergic reactions
- Rash
- Low blood counts including white cells (help fight infections), red (blood cells that carry oxygen to the body), and platelets (help stop bleeding)
- Seizures
- Making heart function worse
- Cause or make worse autoimmune disease such as inflammatory bowel disease, type I (juvenile) diabetes, thyroid disease
- Clinical trials of IFN beta 1a have been conducted in ICU patients. The only adverse event that was more common in patients who received IFN beta 1a was fever.

A clinical trial of IFN beta1a reported possible complications in patients who received IFN beta1a and corticosteroids. It is not known if these complications are real, it is only a possibility, but the complication was worse survival. In this study the trial may lead some patients to receive both IFN beta1a and a corticosteroid. The statistics in the trial are carefully analysing this possibility and the investigators will rapidly stop this combination in the trial if patient outcomes are worse.

Consent Form - Adult providing own consent (prior to enrolment)

COVID-19: Pandemic infection is either suspected or proven

Title	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
Short Title	REMAP-CAP
Protocol Number	X 17-0199
Project Sponsor	Monash University
Coordinating Principal Investigator	Professor Steven Webb
Principal Investigator	Dr Hergen Buscher
Location	St Vincent's Hospital

Consent Agreement

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to St Vincent's Hospital concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I acknowledge that any regulatory authorities may have access to my medical records **specifically related** to this project to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project:

Use of COVID-19 antiviral treatment	☐ Yes	☐ No
Use of COVID-19 immune modulation therapy	☐ Yes	☐ No
Use of hydrocortisone	☐ Yes	☐ No
Choice of antibiotic	☐ Yes	☐ No
Duration of macrolide treatment	☐ Yes	☐ No
Use of influenza antiviral medications	☐ Yes	☐ No

I understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Declaration by Participant

Name of Participant (please print) _____	
Signature _____	Date and time _____

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher [†] (please print) _____	
Signature _____	Date and time _____

[†] A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Form for Withdrawal of Participation - Adult providing own withdrawal

COVID-19: Pandemic infection is either suspected or proven

Title	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
Short Title	REMAP-CAP
Protocol Number	X 17-0199
Project Sponsor	Monash University
Coordinating Principal Investigator	Professor Steven Webb
Local Principal Investigator	Dr Hergen Buscher
Location	St Vincent's Hospital

Declaration by Participant

I wish to withdraw from participation in the following aspects of the above research project:

Use of COVID-19 antiviral treatment	☐ Withdraw	☐ Continue
Use of COVID-19 immune modulation therapy	☐ Withdraw	☐ Continue
Use of hydrocortisone	☐ Withdraw	☐ Continue
Choice of antibiotic	☐ Withdraw	☐ Continue
Duration of macrolide treatment	☐ Withdraw	☐ Continue
Use of influenza antiviral medications	☐ Withdraw	☐ Continue

I understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with St Vincent's Hospital.

Name of Participant (please print) _____

Signature _____

Date and time _____

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher[†] (please print) _____

Signature _____

Date and time _____

[†] A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project. Note: All parties signing the consent section must date their own signature.