**INVESTIGATOR SITE HEADED PAPER**

**Investigator: [Name]**

**Patient Information Sheet**

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

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. Take time to decide whether or not you wish to take part. Thank you for reading this.

**What is the purpose of the study?**

You are invited to take part in the REMAP-CAP research study. This is because you are suffering from pneumonia possibly or known to be caused by a new Coronavirus. This disease is called COVID-19. Pneumonia (lung infection) is an important, common health problem. Some patients with pneumonia are admitted to the Intensive Care Unit (ICU). These patients have severe pneumonia. The treatment for pneumonia patients is generally based on national and international guidelines. The evidence on which these guidelines are based, often comes from research conducted with patients admitted to a different hospital department than the ICU. As COVID-19 is a new disease it is not clear whether these guidelines are suitable for these seriously ill patients.

The aim of this study is to investigate which of these treatment options are best for patients admitted to ICU with severe pneumonia.

**What medical treatments are being investigated?**

In this project several different treatments are being compared at the same time. These treatments can be subdivided into the following six different types of treatment: 1) use of COVID-19 antiviral medication; 2) use of COVID-19 immune modulation; 3) choice of antibiotic; 4) duration of macrolide treatment; 5) supportive treatment; and 6) Use of influenza antiviral medication. This hospital is currently, taking part in the following treatments:

**1. Use of COVID-19 antiviral medication.** When a patient has pneumonia caused by the Coronavirus, some doctors will prescribe antiviral medications that may work against COVID-19. Doctors use these antiviral medications in other situations, but 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. The participant will only receive these treatments if they have pneumonia that is believed or known to be caused by the Coronavirus. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, that treatments with unknown benefit should only be given in a clinical trial. *[delete if not taking part in the COVID-19 antiviral domain]*

**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. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, that treatments with unknown benefit should only be given in a clinical trial.

**3. Choice of antibiotic.** All patients that have pneumonia are given antibiotics to help fight infection, but some doctors give different antibiotics. This project is comparing [insert number] combinations of antibiotics in this hospital: *to be adjusted for each hospital*

Amoxicillin-clavulanate + clarithromycin

Ceftriaxone + clarithromycin

Piperacillin-tazobactam + clarithromycin

Ceftaroline + clarithromycin

Moxifloxacin or levofloxacin

The doctors in this ICU have chosen to have these options available in the study as all of these options are known to be safe and effective to treat pneumonia. If you are not in the study, it is very likely that the doctors would treat you with one of these options. However, it is not known which option is best.

**4. Duration of macrolide treatment.** Macrolide antibiotics are used to treat some types of pneumonia but also have some anti-inflammatory actions. Most doctors give macrolide antibiotics to most patients with pneumonia but stop after a few days. It has been suggested that longer treatments may provide beneficial anti-inflammatory effects. In this research project, stopping the macrolide antibiotic after three days will be compared with continuing it for up to 14 days. *[delete if not taking part in macrolide treatment domain]*

**5. Supportive treatment - 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 (is in “septic shock”). At this site, this study evaluates:

No corticosteroids

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”.

*[delete if not taking part in hydrocortisone domain]*

**6. Use of influenza antiviral medications.** When a patient 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 study evaluates:

No Oseltamivir

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.

*[delete if not taking part in antiviral domain]*

**Why have I been chosen?**

You have been asked to take part in this study as you have been admitted to ICU for pneumonia possibly or known to be caused by COVID-19. Because you are unwell and showing signs of lung infection, you have been prescribed antibiotics, and possibly breathing support. 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 1200 patients in total, admitted to different hospitals within the UK.

**What does participation in this research involve?**

It is up to you to decide whether or not to take part. If you do decide to take part in the study, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, 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 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.

It is important for the treatment of your pneumonia that the selected antibiotics and other treatments are started as quickly as possible. This is why these treatments will already be assigned (‘randomized’) to you when you are admitted to the 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 and no additional tests will be performed.

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 side effects to expect?**

Different types of antibiotics and hydrocortisone and antivirals *[delete if not participating in hydrocortisone / antiviral domain]* 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 oral mucus membrane and the tongue, deteriorating vision, deafness, anorexia, 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.

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 tests muscle stiffness, numbness of the skin, and increased risk of infection. *[delete if not participating in immune modulation domain]*

Hydrocortisone may have the following side effects:  
High blood pressure, fluid retention, nausea, increased risk of infection, high blood pressure, general discomfort (malaise) and hypersensitivity. *[delete if not participating in hydrocortisone domain]*

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 drugs if needed.

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

The treatments being investigated in this study include many that are the same as the treatments used in daily practice (antibiotics, steroids and oseltamivir). The only difference is that the study will randomly determine which treatment you receive instead of your doctor. The treatments for COVID-19 are used to treat other viruses and other immune-related diseases and have been suggested as possible treatment 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 pneumonia including 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…………………………………………., contact details at end). The normal National Health Service complaints mechanisms are also available to you.

**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 di-identified study data on servers based on servers in Sydney Australia. This identifiable 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](mailto:privacy@umcutrecht.nl).

**[NHS site name]** will collect information from you and your medical records for this research study in accordance with the sponsor’s instructions.

**[NHS site name]** will keep your name, NHS number and contact details confidential and will not pass this information to UMC Utrecht. **[NHS site name]** 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 data will be collected on servers in Sydney Australia which will collect personal identifiable 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). 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.

**[NHS site name]** 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](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/)**.**

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.com](http://www.remapcap.com).

**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 the Intensive Care National Audit and Research Center (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 person listed below. They will give you advice about who you can talk to for independent advice.

|  |  |
| --- | --- |
| **Local Contact** | **Local address** |
|  |  |

**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:

**Study Investigators Contact details**

|  |  |
| --- | --- |
| **Study Investigator** |  |
| **Study Nurse** |  |
| **Day time Telephone** |  |
| **Emergency Telephone** |  |

**CONSENT FORM FOR PATIENTS ABLE TO GIVE CONSENT**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 **9th April 2020 Version 1.2** 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.
* 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 hydrocortisone domain. *[delete if not taking part in hydrocortisone treatment domain]*
* I agree to take part in the influenza antiviral domain.  *[delete if not taking part in influenza antiviral treatment 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.

|  |  |
| --- | --- |
| Patient | Person responsible for collecting the informed consent |
| *Date:*  *Signature:*  *Printed Name:* | *Date:*  *Signature:*  *Printed Name:* |