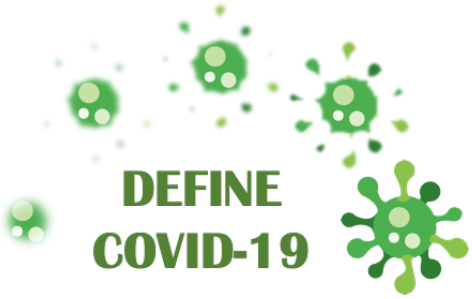
Academic and Clinical Central Office for Research and Development



Rapid Experimental Medicine for COVID-19 Induced Respiratory Failure

PARTICIPANT INFORMATION SHEET

You are being invited to consider whether you agree 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. Ask me or a member of the study team if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

COVID-19 is a new and poorly understood infection. The scientific community needs to develop an understanding of how the body's immune system responds to the virus and to new treatments. We would hope to use this information to develop new ways to treat the virus and assess if they may be effective.

There are no drugs of proven value against COVID-19 although there are several which may turn out to be effective when added to the usual standard of medical care.

The purpose of this study is to determine if new drugs can be useful for patients with COVID-19. These new drugs can take the form of tablets, injections or drugs that can be breathed in (like those in an asthma inhaler). Although these treatments show promise, nobody knows if any of them will turn out to be more effective in helping patients recover than the usual standard of care at your hospital (which all patients will receive). We therefore need to conduct clinical trials to provide information on which treatments may prove to be effective at treating COVID-19.

The trial treatments will be given in addition to the usual care and medication at your hospital. If you decide to take part in the research trial, you will be randomly allocated to receive a trial treatment **or** to continue to receive standard medical care only. Trial treatments will be a drug that can be injected or one taken like an asthma inhaler.

Regardless of whether you are allocated to receive a trial drug or to standard care only, we will ask for repeated samples of your blood (and possibly other samples e.g. nose/throat

fluid and saliva) to see how your body is responding to the virus and any treatments you may be receiving. We will be looking at markers (small molecules in your blood) that show whether your body has had a response to the virus and/or treatments. We may also request to take a scan of your lungs to look at how well they are functioning and responding to treatments or standard care.

Why have I been invited to take part?

You have been admitted to hospital and have tested positive for COVID-19. You will not be included if your attending doctor thinks there is a particular reason you would not be suitable for the trial.

Do I have to take part?

No. It is up to you to decide whether you wish to take part in the research and whether you agree to participate. If you would like to participate you will be given this information sheet to keep and be asked to sign a consent form. However, you will be free to change your mind at any time and without giving a reason. Your medical care will not be affected.

What will happen if I agree to take part?

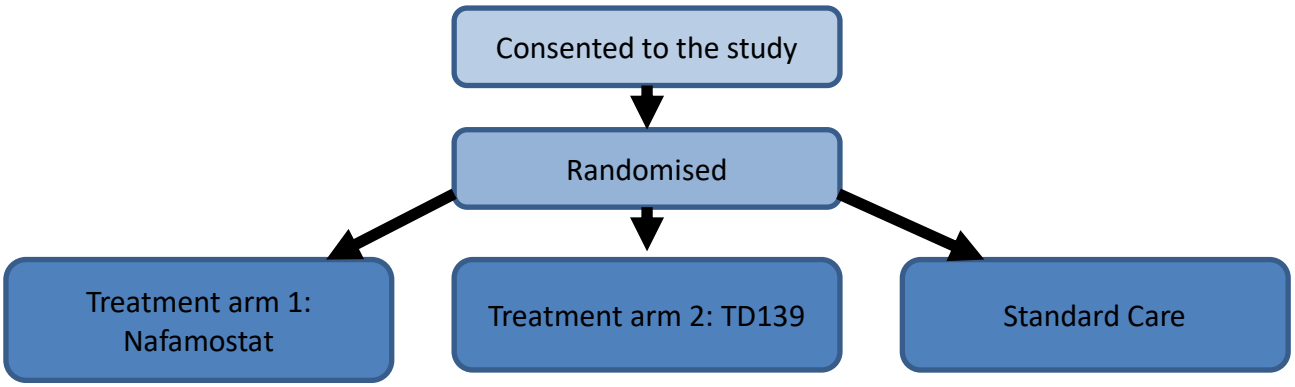
A member of the research team will discuss the study with you and answer any questions you may have. If you consent to participate in this study, a member of the research team will ask you to sign a consent form and you will be given a copy of this information sheet and a summary information sheet to keep. The consent form may be signed in ink or, where this is not possible, completed electronically.

Once the consent form has been signed, the research team will confirm if you are eligible to take part in the trial. We will collect some relevant data from you and from your medical notes. This will include some personal data such as name, date of birth, ethnicity and Community Health Index (CHI) number. The CHI number will be used for administration of the trial and to check your clinical results. If you are of childbearing potential we may ask you to take a urine pregnancy test.

If you are suitable for one or more of the treatments, we will use a computer to allocate you at random (like rolling a dice) to one of the possible trial treatment options or to standard care. In all cases this will include the usual standard of care provided by the hospital. It may also include an additional treatment, which might be given by injection or inhalation. Neither you nor your doctors can choose which of these options you will be allocated.

The two new drugs we are currently testing are called Nafamostat and TD139. Below is a summary of the trial procedures if you are randomised to receive one of these drugs or to

continue with standard care alone. Both Nafamostat and TD139 have been used in patients before and are hoped to reduce the impact of COVID-19.



	Standard Care	Nafamostat	TD139
General			
Type and duration of Treatment	No additional treatment	Continuous IV for 7 days	2 x inhaler for 2 days then 1 x inhaler for 12 days
Duration of research team monitoring and assessment during hospitalisation	16 days	16 days	16 days
At screening			
Urine pregnancy test (if required)	✓	✓	✓
Medical History	✓	✓	✓
Physical Exam	✓	✓	✓
ECG	✓	✓	✓
Blood sampling	✓	✓	✓
Fluid sample from nose and throat	✓	✓	✓
Saliva sample	✓	✓	✓
Continuous Cardiac Monitoring		✓	
Daily for 16 days			
Continuous Cardiac Monitoring		✓	
Vital Signs	✓	✓	✓
Listening to chest sounds	✓	✓	✓
Blood Sampling	✓	✓	✓
Monitoring of blood sugar levels		✓	
Cough Symptom Score			✓
Check how you are feeling	✓	✓	✓
Access to your medical records	✓	✓	✓
Days 1, 3, 5, 8,11 and 15			
Fluid sample from nose and throat	✓	✓	✓
Saliva sample	✓	✓	✓

Medical Imaging			
Baseline Chest X-Ray / CT/CTPA Scan	✓	✓	
Chest X-Ray / CT / CTPA Scan after last dose of trial drug / end of monitoring period	✓	✓	
Follow-up			
Telephone call / Visit at 30, 60 and 90 days	✓	✓	✓
Access to your medical records	✓	✓	✓

Nafamostat is given as a continuous infusion through a drip for 7 days (the drip will be in place for 7 days) and its side effects (seen in a very small percentage of people who have taken this drug) include changes in your blood electrolytes, nausea, an allergic reaction to the ingredients and tissue damage at the infusion site. If you are allocated to this treatment arm, you would be asked to have additional small blood samples of 8mls of blood at roughly 30 minutes before, then 50 minutes, 2 hours and 6 hours after the start of your first infusion. We will try and use an existing line to minimise any bruising or discomfort. We may also ask to monitor your heart using some sticky pads attached to a machine. This drug has been licensed in Japan for over 30 years and is routinely used to treat patients with a blood clotting disorder.

TD139 is given as an inhaler once or twice a day for 14 days and its side effects (seen in a small percentage of people who have taken this drug) are a change in sense of taste and cough. This drug is not licensed at present but has been tested in healthy volunteers and patients with a type of lung disease that results in scarring of the lungs.

Information on your ongoing condition will be collected by the research team throughout your involvement in the trial.

In some instances, information about your health (both prior to, during, and after the trial) may be obtained about you from medical records or databases (including Public Health Scotland, other equivalent bodies, and genetic or other research databases if you have provided samples to them) so that the study team can get more detailed or longer term information about the effects of the study treatments on your health for up to 12 months after the end of your participation.

For more information on how the drugs used in the treatment arms work and information on the DEFINE study and other Edinburgh based COVID-19 studies please see https://www.ed.ac.uk/inflammation-research/clinical-trials/define-covid19. The information available on this website provides more information on the trial in general and does not include any further information on the treatments or tests involved – this is all provided in this information sheet.

What are the possible disadvantages and risks of taking part (all study arms)?

Blood sampling carries a small risk of bruising and discomfort, our doctors and nurses are very experienced in taking blood and will attempt to minimise this. If possible, we will use an existing line to minimise any discomfort.

Collecting samples from the throat and nasal passages can be a bit uncomfortable, this will be done as smoothly as possible and by doctors and nurses experienced in obtaining these samples.

An ECG is quick and painless and involves placing sensors on your skin.

All participants randomised to a treatment will be observed carefully for any side effects; however, there may be potential side-effects that have not previously been seen. These side effects may be mild or serious. Although we do not anticipate this, in some cases, these side effects might be long lasting or permanent and may even be life threatening. If any negative change in your health can be seen to have an association with the treatment we will advise you to stop taking it.

What are the possible disadvantages and risks of the imaging procedures involved (Nafamostat and standard care only)?

If you take part in this study you may have CT scans (these may involve using an injection of a special dye during the scan) and x-rays of your chest. Most of these will be extra to those that you would have if you did not take part. These procedures use ionising radiation to form images of your body and provide your doctor with other clinical information.

Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you from 50% to 50.2%.

What are the potential benefits to taking part?

There is no direct benefit. However, we believe the results of this research may bring potential benefits for similar patients in the future.

Pregnancy or pregnant partner (treatment arms only)

The study treatments have not been tested in pregnancy. A person who is pregnant or breastfeeding cannot take part in this study. If you are a person of child-bearing potential, we will ask you to take a urine pregnancy test. A person of child bearing potential is defined as anyone who has begun menstruation. A post-menopausal person is defined as a person

who is over the age of 45 and has not had a menstrual period for at least 12 months unless they are permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. If necessary and with your permission we may use a blood sample to test hormone levels if we are unsure.

We will request that if it is possible for you to get pregnant that you will confirm you will **use a highly effective method of contraception for 90** days after you stop taking the treatment. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (e.g. oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (e.g. oral, injectable, implantable).
- Intraurine device (IUD)
- Intraurine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

If it's possible for you to get your partner pregnant we request that you confirm you will use a **highly effective method of contraception for 90** days after you stop taking the treatment. Such methods include:

- Condoms
- Sexual abstinence
- Vasectomy (confirmed)

If you were to become pregnant yourself or your partner becomes pregnant up to 90 days after you stop taking the treatment, we would like to follow up you or your partner's pregnancy specific data. We would seek consent separately to do this if this was to occur and as such we request that you notify the research team of pregnancy using contact details below.

Incidental findings

During one of the scans or tests outlined above we may become aware of previously undiscovered medical conditions. These will be reported to the clinical team in charge of your care and any necessary follow up will be undertaken.

What happens if I become more unwell?

With the COVID-19 virus a very small percentage of people may, during the course of the illness, become very unwell and perhaps need help to breathe. If this happens you may be

placed on a ventilator (breathing machine) or have to use a face mask to provide oxygen. If this happens we may need to stop your treatment if it can no longer be administered.

Additionally, if you become very unwell or need a ventilator you may be deemed to have lost capacity as you can no longer speak to the researcher or understand the study and confirm you are happy to proceed with the research trial. In the event of losing capacity, we would like (with your permission) for you to continue to take part in the study, continue (if possible) to keep administering your treatment, and keep collecting your data. We would be available for your personal legal representative (family member or friend) to talk to and voice any concerns regarding your continuing participation in the trial.

Is there any reimbursement for taking part?

No. The results of this study may be used for the future commercial development of new tests and/or therapies. Your participation in this study will not entitle you to benefit financially from the development of any such tests or therapies.

What happens when the study is finished?

The research team will monitor all participants for up to 16 days during hospital admission. After such time, you will remain under the clinical care of your medical team. The research team will then contact you at 30, 60 and 90 days after the 16 days or after you are discharged to check how you are feeling. If you are no longer in the hospital the research team will contact you by phone.

What happens if I don't want to carry on with the study?

You are free to withdraw from the study at **any time** without explanation. Your decision to withdraw from the study will not affect the standard of any treatment you receive now or in the future.

If you decide to withdraw from the study, we will ask you to complete a withdrawal form. You can choose to:

- Stop taking the treatment and allow us to continue collecting data
- Stop taking the treatment and stop all data collection
- Stop all data collection if you have already stopped taking the study treatment or were allocated to standard care.

What if something goes wrong?

If you have a concern about any aspect of this study please contact Professor Kev Dhaliwal, Chief Investigator by email (kev.dhaliwal@ed.ac.uk) or telephone (0131 242 9180) who will do their best to answer your questions.

In the unlikely event that something goes wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for compensation against NHS Lothian but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. If you wish to make a complaint about the study please contact NHS Lothian:

Patient Experience Team
2 – 4 Waterloo Place, Edinburgh, EH1 3EG
0131 536 3370
Email: feedback@nhslothian.scot.nhs.uk

Will information about me be kept confidential?

All personal information that is collected during the course of the research about you will be kept strictly confidential. Any data or samples removed from the hospital and stored will be done so using a unique code. Information concerning you will be collected by an authorised member of the study team and coded to prevent it being recognisable by anyone outside the study team. Data will be stored in a secure location within the University of Edinburgh and transferred anonymously to a secure database at a later date. Data will be retained for 25 years in line with requirements of the funder. Following this time it will be disposed of as confidential material.

With your permission we will notify your GP that you are taking part.

What will happen to any samples taken?

Blood and any excess standard care samples will be stored in a special facility in the University of Edinburgh. After we have used the samples to answer specific research questions, we would like to keep the samples, with your permission, for use in other ethically approved studies focusing on lung disease.

The reason for doing this is to maximise the scientific gain that can be obtained from these samples without having to perform additional procedures on additional patients. Samples will be stored in a linked-anonymous fashion, meaning they will be linked to your data via a code and your personal data will not be stored with the research data or samples.

We may also send small anonymised samples to external laboratories to perform study specific tests that cannot be done at the University or hospital.

Can I access the results of the research?

Should you wish to find out more about the overall results of the study, please contact the research team using HTAF@ed.ac.uk or on 0131 242 9180 referencing the DEFINE COVID-19 study. You can request to receive this information in writing (paper copy), via email, telephone or face to face. Individual results cannot be accessed.

Will my taking part be kept confidential?

Any personal information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage. For details on what data will be held about you and who will hold and store this information please refer to the Data Protection Information Sheet.

What will happen to the results of the research study?

It is our intention that the results of the study will be used for developing ways to treat COVID-19 and other viruses, the results may be published in scientific/medical journals and presented at medical and scientific meetings. You will not be identified in any report/publication.

Your personal data will not be transferred to any external individuals or organisations outside of the University of Edinburgh or NHS Lothian. However, with your consent we may wish to share de-identified data with funders, collaborators and publicly available resources.

Who is organising and funding this study?

This study has been organised by the Centre for Inflammation Research led by Professor Kev Dhaliwal and is co-sponsored by the University of Edinburgh and NHS Lothian.

LifeArc is funding this study. LifeArc is a charity helping to turn promising science into benefits for patients.

NHS Lothian does not benefit financially from this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the safety, rights, wellbeing and dignity of patients. This study has been reviewed and given favourable opinion by this Committee. The NHS Lothian

Research and Development Department and the UK regulator (MHRA) have also given their approval. Additionally, the University of Edinburgh Emergency COVID-19 Research Committee have also reviewed the study and given their permission to proceed.

Is there an independent doctor I can approach for further information?

If you would like to talk to someone who is not involved in the project, we have an independent adviser for this specific purpose. This person is a fully qualified medical practitioner who is there to answer any questions or concerns you may have about the study. He is not in any way involved in the study, but understands all of the medical aspects of this particular project. The contact details are

Professor Adam Hill
Department of Respiratory Medicine
Royal Infirmary of Edinburgh
Edinburgh
EH16 4SA

Phone: 0131 242 1921

Contact for further information
If you would like further information now or at any stage in the future, please do not hesitate to contact us by mail, email or telephone, at:

Professor Kev Dhaliwal
Centre for Inflammation Research
E2.32 Queens Medical Research Institute
47 Little France Crescent
EH16 4TJ
0131 242 9180

Kev.dhaliwal@ed.ac.uk

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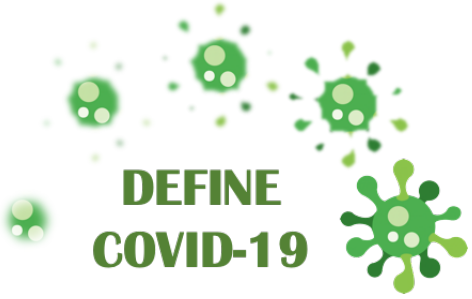

Rapid Experimental Medicine for COVID-19 Induced Respiratory Failure

CONSENT FORM

There is no obligation to take part in the study or agree to the statements below.

Name of Researcher: Professor Kev Dhaliwal

Name of Participant: _____ **Participant ID:** _____

		Please **initial** the box
1	I confirm that I have read and understand the information sheet (Version: Date:) for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	
2	I understand that I am free to change my answers to any of the questions on this form at any time without giving any reason, and that my medical care or legal rights would not be affected in any way by such a decisions.	
3	I understand that I may be randomised to a treatment arm or to standard care. If I to do not wish to continue in the arm I have been allocated to I can withdraw from the study without giving a reason.	
4	I agree that if I lose capacity I wish to continue to take part in the study.	
5	I agree to my GP being informed I am taking part in the study.	
6	I agree that any surplus clinical samples taken as part of standard care may be provided to the research team for analysis as part of this study.	
7	I agree to having blood, saliva and nose/throat fluid samples taken.	

8	I agree to undergo any additional scans that are necessary with the study arm I have been allocated to.	
9	I agree to adhere to the contraceptive advice detailed in the PIS to prevent pregnancy for at least 90 days after the end of treatment. I will inform the study team if I or my partner becomes pregnant within 90 days of the end of treatment.	
10	I confirm that I agree to my data and samples being stored for use in current or future ethically approved studies.	
11	I understand that relevant sections of my medical notes and data collected during the study may be looked at by the trial researchers and individuals from the Sponsor, regulatory authorities or from the NHS organisation, where it is relevant to me taking part in this research.	
12	I give permission for my personal information (including name, date of birth and consent form) to be passed to the University of Edinburgh for administration of the study.	
13	I give permission for my Community Health Index (CHI) number/hospital number to be collected and passed to the University of Edinburgh.	
14	I understand that data collected about me during the study may be converted to anonymised data and may be shared with external funders, collaborators and/or publications.	
15	I understand that the data generated during this study may be used for future commercial development of products and I will not benefit financially from this.	
16	I agree to taking part in the above study	

CONSENT

Name of Participant	Signature	Date
Name of Researcher	**Signature**	**Date**

1x original – into Site File; 1x copy – to Participant (if possible); 1x copy – into medical record