Evaluation of new or repurposed treatments for COVID-19

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Evaluation of new or repurposed treatments for COVID-19: protocol for the phase Ib/IIa DEFINE trial platform

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ABSTRACT

Introduction COVID-19 is a new viral-induced pneumonia caused by infection with a novel coronavirus, SARS-CoV-2. At present, there are few proven effective treatments. This early-phase experimental medicine protocol describes an overarching and adaptive trial designed to provide safety data in patients with COVID-19, pharmacokinetic (PK)/pharmacodynamic (PD) information and exploratory biological surrogates of efficacy, which may support further development and deployment of candidate therapies in larger scale trials of patients positive for COVID-19.

Methods and analysis Define is an ongoing exploratory multicentre-platform, open-label, randomised study. Patients positive for COVID-19 will be recruited from the following cohorts: (a) community cases; (b) hospitalised patients with evidence of COVID-19 pneumonitis; and (c) hospitalised patients requiring assisted ventilation. The cohort recruited from will be dependent on the experimental therapy, its route of administration and mechanism of action. Randomisation will be computer generated in a 1:1:n ratio. Twenty patients will be recruited per arm for the initial two arms. This is permitted to change as per the experimental therapy. The primary statistical analyses are concerned with the safety of candidate agents as add-on therapy to standard of care in patients with COVID-19. Secondary analysis will assess the following variables during treatment period: (1) the response of key exploratory biomarkers; (2) change in WHO ordinal scale and National Early Warning Score 2 (NEWS2) score; (3) oxygen requirements; (4) viral load; (5) duration of hospital stay; (6) PK/PD; and (7) changes in key coagulation pathways.

Ethics and dissemination The Define trial platform and its initial two treatment and standard of care arms have received a favourable ethical opinion from Scotland A Research Ethics Committee (REC) (20/SS/0066), notice of acceptance from The Medicines and Healthcare Products Regulatory Agency (MHRA) (EudraCT 2020-002230-32) and approval from the relevant National Health Service (NHS) Research and Development (R&D) departments (NHS Lothian and NHS Greater Glasgow and Clyde). Appropriate processes are in place in order to be able to consent adults with and without capacity while following the necessary COVID-19 safe procedures. Patients without capacity could be recruited via a legal representative. Witnessed electronic consent of participants or their legal representatives following consent discussions was established. The results of each study arm will be submitted for publication in a peer-reviewed journal as soon as the treatment arm has finished recruitment, data input is complete and any outstanding patient safety follow-ups have been completed. Depending on the results of these or future arms, data will be shared with larger clinical trial networks, including the Randomised Evaluation of COVID-19 Therapy trial (RECOVERY), and to other partners for rapid roll-out in larger patient cohorts.

Trial registration number ISRCTN14212905, NCT04473053.

Strengths and limitations of this study

- The trial is as flexible as possible to ensure a broad range of patients can be recruited and candidate therapies can be added or removed as evidence emerges.
- The team are collecting real-world data of medications at an early stage of their use in COVID-19 across the full spectrum of disease, allowing the administration of different treatment formulations (inhaled vs oral vs intravenous).
- The simultaneous collection of clinical outcomes as well as exploratory endpoints including clinical biomarkers, flow cytometry, pharmacokinetic/pharmacodynamic and thromboelastography allows further characterisation and elucidation of the temporal immunoinflammatory cascade in COVID-19 to inform on future therapy selection.
- This is a phase Ib/IIa platform study and thus the primary endpoint is clinical safety, therefore our anticipated numbers will be too small to allow for definitive data on efficacy.
- Define is an experimental medicine platform, currently restricted to three clinical sites and so the generation of data will be slower than that of larger platforms with access to a greater number of patients.

INTRODUCTION

COVID-19 is a new viral-induced pneumonia caused by infection with a novel coronavirus, SARS-CoV-2. This highly contagious, zoonotic infection was first identified in Wuhan,

China, in late 2019[1] and its emergence has led to a global pandemic with a significant impact on health, society and the economy.

The majority of those infected with SARS-CoV-2 have asymptomatic or mild infection; however, 10%–20% of non-immunised individuals will require admission to hospital with hypoxaemic respiratory failure requiring oxygen therapy and possibly ventilatory support.[2] Risk factors for severity include increased age, obesity and medical history such as diabetes and hypertension.[3] Genetic predisposition is now known to play a role[4] and much of the lung damage is driven by a surge of inflammatory mediators. Mortality rate among hospital inpatients is felt to be as high as 20%.[5] By September 2021, over 4.5 million individuals worldwide have died of COVID-19. To date, there are few proven treatments with significant impact on mortality, and despite multiple successful vaccination developments it is expected that the virus will become endemic in the population, with significant levels of disease activity for years to come.

Define is a phase Ib/IIa experimental medicine trial. This protocol describes an overarching and adaptive trial designed to provide safety, pharmacokinetic (PK)/pharmacodynamic (PD) information and exploratory biological surrogates of efficacy which may support further development and deployment of candidate therapies in larger scale trials of patients positive for COVID-19 receiving normal standard of care.

Given the spectrum of clinical disease, community-based infected patients or hospitalised patients can be included. Products requiring parenteral administration will only be investigated in hospitalised patients. Patients will be divided into cohorts as described below. Participants may be recruited from all three of the study cohorts, depending on the experimental therapy, its route of administration and mechanism of action.

Candidate therapies can be added to the protocol and previous candidates removed from further investigation as evidence emerges. The trial will be monitored by an independent data monitoring committee (DMC) to ensure patient safety.

Each candidate cohort will include a small cohort of patients randomised to candidate therapy or existing standard of care management dependent on disease stage at entry. Each treatment arm will recruit up to 20–30 patients to provide safety data, and PK-PD profile of potential therapeutic agents against COVID-19.

As COVID-19 follows a variable clinical path in individual patients, the protocol is designed to enable inclusion of patients across the disease stages. The trial is intended to provide mechanistic data from patients receiving standard of care therapy and from patients treated with the therapy candidates. The study will enable delivery of PK information and effects of standard of care and candidate agents on surrogate biomarkers of the disease process and the specific drug target.

METHODS AND ANALYSIS

This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[6]

Trial design

Define is an exploratory multicentre-platform, open-label, randomised study. This experimental medicine platform trial encompasses early-phase studies, and the identification of major safety signals is the primary objective. Each candidate therapy will include a small cohort of patients randomised to the candidate therapy or existing standard of care management dependent on disease stage at entry. Twenty patients will be recruited per arm for the initial two arms. This is permitted to change as per the experimental therapy. Randomisation will be computer generated and patients randomised in a 1:1:1:n ratio using a minimisation procedure based on sex, age, body mass index and a history of diabetes.

The proposed ‘hybrid’ platform (multiple interventions) and basket-type (multiple phenotypes) randomised trial is early phase to investigate biomarker response relevant to demonstrating COVID-19 clinical activity in repurposed drugs. As such, formal sample size calculations which would be mandatory for a confirmatory phase III randomised trial are neither feasible nor appropriate. An indicative sample size, considering the comparison of one active drug against control, each with n=20 per group, and assuming 5% missing data, would give 80% power at a one-sided 10% level of significance, using a two-sample t-test, to detect an effect size of 0.7 in the difference of means in the biomarker between active and control.

Usually, the biomarker will be a continuous measure and the treatment effect estimated via a linear model which will adjust for baseline covariates highly correlated with the primary outcome, including possibly the baseline measurement of the primary outcome biomarker.

The study will not be powered for subgroup analyses. Safety data will be analysed on the as-treated data set (anyone who initiated on randomised treatment) and will be presented descriptively. Randomisation will involve computer-generated minimisation using a ratio of 1:1:1 across arms and there is no blinding. There are multiple interventions across several cohorts on the COVID-19 pathway (from community based, to breathless in hospital, to ventilation with different intensities), with potentially different primary outcomes. Hence, it is not practicable to produce bespoke minimisation algorithms for every possibility, so instead we will base the minimisation algorithm on what is currently known about risk factors associated with admission to intensive care unit or death. The minimisation will include a random element (set at 20%) to increase unpredictability of allocation.

Cohorts

Patients with confirmed SARS-CoV-2 infection with relevant COVID-19 symptoms or signs will be recruited into this trial. As SARS-CoV-2 has a range of clinical

Cohort 1A	Community (primary care) patients with confirmed COVID-19
Cohort 1B	Community (primary care) patients with confirmed COVID-19 with new changes on CXR or CT scan compatible with COVID-19 and deemed 'high-risk' of hospitalisation or death*
Cohort 2A	Hospitalised confirmed COVID positive patients with new changes on CXR or new changes on CT compatible with COVID-19 but not requiring supplemental oxygen,
Cohort 2B	Hospitalised confirmed COVID positive patients with: new changes on CXR or new changes on CT compatible with COVID-19 and requiring supplemental oxygen ,
Cohort 3	Hospitalised patients with confirmed COVID-19 requiring assisted ventilation (including non-invasive and mechanical ventilation)

Figure 1 Cohorts of patients considered for participation in Define. *High risk is defined as over 50 years of age with comorbidities. CXR, chest x-ray.

manifestations, representatives of three target patient cohorts will be included in this trial, as seen in figure 1. Participants may be recruited from one or more of these cohorts, depending on the experimental therapy under investigation. While the study will approach patients with suspected COVID-19 and conduct screening assessments, only patients who are confirmed SARS-CoV-2 positive will be randomised.

In terms of future studies, we anticipate additional standard of care arms may be required, given the evolving nature of the treatment modalities in COVID-19 in response to other clinical trials.

Eligibility criteria

Eligible participants were hospital inpatients over the age of 16 with confirmed SARS-CoV-2 infection within 14 days of a positive test. Exclusion criteria include pregnancy, lactation and the inability to reliably take or tolerate modes of treatment delivery, or if the patient was receiving anticoagulation, antiplatelet therapies or potassium-sparing diuretics which could not reasonably be withheld. Patients were also excluded if they had a current or recent history of severe, uncontrolled cardiac disease (New York Heart Association Functional Classification class IV), diabetes mellitus, renal impairment (estimated glomerular filtration rate (eGFR) <30 or ongoing dialysis) or hepatic impairment (alanine transaminase (ALT) >5 ×upper limit of normal), anaemia with an Hb <80, platelets (PLT) <50, hyponatraemia with an Na <120 or K+ >5.0. Coenrolment with a Clinical Trial of an Investigational Medicinal Product will not be permitted.

See online supplemental file 1 for the Define patient information sheet and consent form as an example of the information and standard consent form given to the participants.

Concomitant treatment

Any drug required for the normal clinical care of these patients will be permitted, although as-treatment assets are added to the Define platform interactions with candidate therapies and will be reviewed on a case-by-case basis.

Adverse events

Participants in all arms will be instructed to contact the research team at any time after consent to study participation if any symptoms develop. For all participants, all adverse events (AE) that occur from the time of consent until 90 days after the final dose of investigational medication will be recorded in the case report form or AE log. In the case of an AE, the investigator should initiate the appropriate treatment according to their medical judgement. Clinical data and disease progression will be documented via linkage to control participants' medical records. All AEs that are not related to the patient's underlying condition or clinical interventions will be recorded following consent.

Patient and public involvement

There is an active patient representative in the Define Trial Steering Group. They have provided important feedback on logistical issues raised during the course of the first two treatment arms. Their contribution and feedback is ongoing regarding the design of the next arm of the trial, and how information is presented to the potential patients. Results will be disseminated to study participants on request.

Trial status

The recruitment for the first two treatment arms and a standard of care arm of Define was completed in January 2021. The first patient was recruited in September 2020. Nafamostat mesylate, a synthetic protease inhibitor, and GB0139, an inhaled galectin-3 inhibitor, were examined. Further arms are currently in preparatory stages.

Objectives and endpoints

Primary

The primary outcome is to evaluate the safety and tolerability of candidate agents as add-on therapy to Standard of Care in patients with COVID-19. Safety will be assessed using daily:

- Haematological and biochemical safety laboratory investigations.

Full blood count, urea, creatinine, sodium, potassium, alanine transaminase, aspartate transaminase, alkaline phosphatase, coagulation screen (including activated partial thromboplastin time, prothrombin time, International normalised ratio, fibrinogen), glucose.
- Physical examination (if clinically relevant).
- Vital signs.
  Blood pressure, heart rate, respiratory rate, oxygen saturations, oxygen requirement, temperature.
- ECG readings.
- AEs.

Secondary

- To explore the PK/PD or appropriate surrogate of bioavailability of the proposed trial treatments in patients with COVID-19.
- Assess the response of key exploratory biomarkers during treatment period. Evaluate the change from baseline values for key exploratory biomarkers of target engagement for each treatment.
- To evaluate the improvement or deterioration of patients in each treatment arm using the WHO ordinal scale and National Early Warning Score 2 (NEWS2) score.
- To evaluate the number of oxygen-free days (eg, duration (days) of oxygen use and oxygen-free days).
- To evaluate ventilator-free days and incidence and duration of any form of new ventilation use. This will be measured in duration (days) of ventilation and ventilation-free days. Incidence of any form of new ventilation use and duration (days) of new ventilation use.
- Change in the ratio of the oxygen saturation to fraction of inspired oxygen concentration (SpO_2/FiO_2). SpO_2/FiO_2 will be measured daily from first dose to day 15, hospital discharge or death.
- To evaluate SARS-CoV-2 viral load. Qualitative and quantitative PCR determination of SARS-CoV-2 in saliva samples while hospitalised on days 1, 3, 5, 8, 11 and 15 and oropharyngeal/nasal swab on the same days if tolerated.
- To evaluate time to discharge and duration to discharge following treatment.
- To evaluate the use of renal dialysis or haemofiltration for each treatment arm.

Follow-up

All discharged patients will undergo follow-up to assess for AEs at 30, 60 and 90 days.

Data collection and analysis

The biomarker variables will be mostly continuous measures and the treatment effect estimated via a linear model which will adjust for baseline covariates highly correlated with the primary outcome, including possibly the baseline measurement of the primary outcome biomarker.

The study will not be powered for subgroup analyses and these will be exploratory on a limited number of subgroups prespecified in the study protocol.

Due to the small sample sizes there will be no formal adjustment for missing data, and the primary analysis set—appropriate for early-phase proof of signal studies—could be a suitably defined per-protocol set (eg, those that were compliant with their randomised medications).

Safety data will be analysed on the as-treated data set (anyone who initiated on randomised treatment) and will be presented descriptively.

The independent DMC will review accumulating data, unblinded to the randomised groups. Their first and foremost responsibility will be the safety of the participants, and the committee may terminate the study at any time on the grounds of safety.

Data management

The principal investigator is responsible for the quality of the data recorded at each investigator site.

All investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information). Access to personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

Appropriate representatives from the patient community were involved in the design of the study and the participant-facing documents were reviewed and commented on. This was carried out over email and via online meetings. A suitably experienced lay patient representative is on the Trial Steering Committee.

ETHICS AND DISSEMINATION

The Define trial platform and its initial two treatment and standard of care arms have received a favourable ethical opinion from Scotland A Research Ethics Committee (REC) (20/SS/0066), notice of acceptance from The Medicines and Healthcare Products Regulatory Agency (MHRA) (EudraCT 2020-002230-32) and approval from the relevant National Health Service (NHS) Research and Development (R&D) departments (NHS Lothian and NHS Greater Glasgow and Clyde).

For the Define trial, a number of ethical and safety considerations have been addressed.

- The Define trial recruits adults with severe COVID-19 symptoms who are often incapacitated. The selection and enrolment of adults with incapacity will take place within the legal framework described in Adults with Incapacity (Scotland) Act 2000 and Medicines

for Human Use (Clinical Trials) Regulations 2004. During the pandemic, relatives were not allowed to visit the hospital so the majority of consent for adults with incapacity will be undertaken over the phone. This is a well-practised method of obtaining consent and will be undertaken following all necessary guidance and with a set of instructions to ensure the personal legal representative has all the appropriate information and safeguarding in place. In rare cases, if no appropriate personal legal representative can be found, and it is believed to be in the best interests of the patient, consent from a professional legal representative may be sought. This is a person not connected with the trial who is either the doctor primarily responsible for the patient's medical treatment or is a person nominated by the relevant healthcare provider.

- If potential participants feel unable to or the physical signing of the consent form could increase potential transmission of COVID-19, a consent form completed by a member of the research team and witnessed by an independent member of the staff was acceptable. This has so far not been used.
- Trial treatments have been extensively tested preclinically and in patients prior to Define. All necessary safety information regarding the treatments is available to the research team and will be referred to in case of any serious safety event. All risks relating to the treatments will be carefully explained to both patients and their representatives.
- Inclusion and exclusion criteria will carefully considered to avoid exposing patients to undue risk.
- All appropriate approvals will be in place prior to the start of recruitment.

Ownership of the data arising from this study resides with the study team. Scientific publications and the sharing of clinical data generated as part of this trial are crucial to better understanding COVID-19 and developing new treatments. As such, the results of each study arm will be submitted for publication in a peer-reviewed journal as soon as the treatment arm has finished recruitment, data have been cleaned and any outstanding patient safety follow-ups completed. Depending on the results of these or future arms, data will be shared with larger clinical trial networks, including Randomised Evaluation of COVID-19 Therapy trial (RECOVERY), and to other partners for rapid roll-out in larger patient cohorts.

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Contributors KD, JWD, JN, AA, NH, OK and CM designed the study and contributed to the study protocol. EG, TQ, AB, JA, VY and JM contributed to the study protocol and all study-related approvals. EG and TQ wrote the manuscript. All authors reviewed and approved the manuscript.

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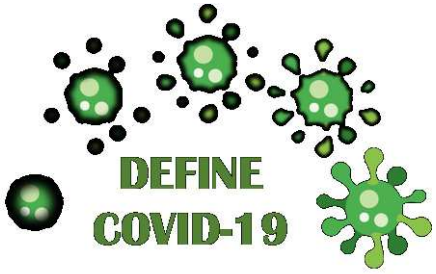

DEFINE - Evaluating therapies for COVID 19

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.

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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, or it is suspected that you have COVID-19 but are awaiting test results to confirm. 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. Randomisation will not take place until we have a positive COVID-19 test result confirmed. If, after providing consent, your test result is negative we will withdraw you from the research.

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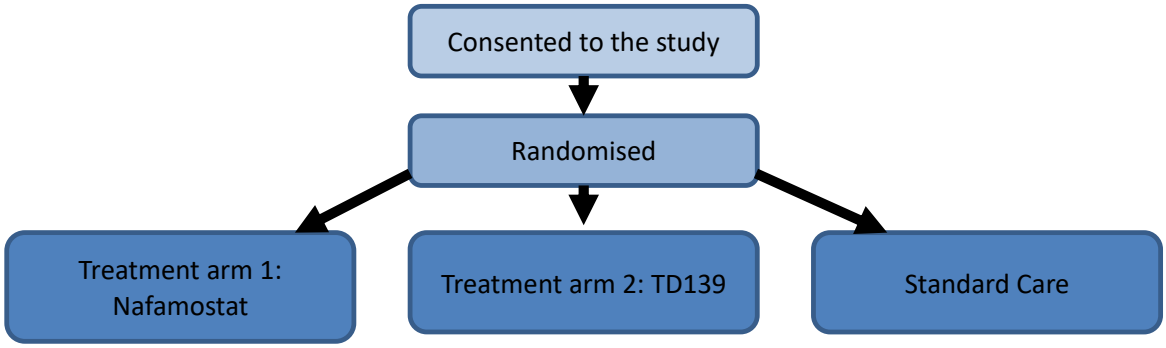

The two new drugs we are currently testing are called Nafamostat and TD139. Both Nafamostat and TD139 have been used in patients before and are hoped to reduce the impact of COVID-19

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 prior to commencing the Nafamostat infusion and then again 6-36 hours after the infusion was started. 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. TD139 is not suitable for people who have a lactose intolerance, if you are affected by this type of intolerance we will be unable to recruit you to the study. 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.

As Nafamostat is an anti-coagulant (i.e. stops the blood from clotting), there is a small risk that you may experience bleeding. If any unexpected bleeding was to occur, doctors will be able to stop it very quickly as the drug only remains in your system for a very short period of time.

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.

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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 may be 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.

We also ask that if you are randomised to receive Nafamostat that you do not undergo sperm or egg donation whilst taking part in the trial.

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

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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
Consultant 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

accord
Academic and Clinical Central Office for Research and Development
NHS Lothian

DEFINE COVID-19

DEFINE – Evaluating therapies for COVID-19

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 my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care and/or legal rights being affected.	
3	I agree that if I lose capacity I wish to continue to take part in the study.	
4	I agree to my GP being informed I am taking part in the study.	
5	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.	
6	I agree to having blood, saliva and nose/throat fluid samples taken.	
7	I agree to undergo any additional scans that are necessary with the study arm I have been allocated to.	
8	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.	

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9	I confirm that I agree to my data and samples being stored for use in current or future ethically approved studies.	
10	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.	
11	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.	
12	I give permission for my Community Health Index (CHI) number/hospital number to be collected and passed to the University of Edinburgh.	
13	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.	
14	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.	
15	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

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