Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
RECOVERY trial

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

( ) Yes (●) No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA? ○ Yes ◉ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product? ○ Yes ◉ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ○ Yes ◉ No

b) Will you be taking new human tissue samples (or other human biological samples)? ○ Yes ◉ No

c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Which applications do you require?

- ☑ IRAS Form
- ☑ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☐ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

○ Yes ◉ No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

◉ Yes ○ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
RECOVERY trial

Please complete these details after you have booked the REC application for review.

REC Name:
Cambridge East

REC Reference Number:

Submission date:
13/03/2020

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Randomised Evaluation of COVID-19 Therapy (RECOVERY)

A3-2. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	Peter
Family name	Horby
Qualification (MD...)	MBBS PhD FRCP
ORCID ID	0000 0002 9822 1586
Institution name	University of Oxford
Institution department name	Nuffield Department of Medicine
Street address	New Richards Building, Old Road Campus, Headington
Town/city	Oxford
Post Code	OX3 7LG
Country	UNITED KINGDOM

Work E-mail	peter.horby@ndm.ox.ac.uk
* Personal E-mail	
Work Telephone	01865 612940
* Personal Telephone/Mobile	07785 604877
Fax	

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	NA	NA	CTRG
Address	1st Floor, Boundary Brook House		
	Churchill Drive		
	Headington, Oxford		
Post Code	OX3 7GB		
E-mail	ctrg@admin.ox.ac.uk		
Telephone	00000		
Fax	00000		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	not available
Sponsor's/protocol number:	NDPHRECOVERY
Protocol Version:	1.0
Protocol Date:	13/03/2020
Funder's reference number (enter the reference number or state not applicable):	pending
Project website:	

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):	
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	2020-001113-21

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Background: In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19, a disease induced by the novel coronavirus SARS-CoV-2 that emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that several possible treatments should be evaluated, including Lopinavir-Ritonavir, Interferon β, corticosteroids, and Remdesivir. These groups also advised that other treatments will soon emerge that require evaluation. A World Health Organization (WHO) expert group issued broadly similar advice.

Eligibility and randomisation: This protocol describes a randomised trial among adults hospitalised for confirmed COVID-19. Eligible patients are randomly allocated between several treatment arms, each to be given in addition to the usual standard of care in the participating hospital: No additional treatment vs Lopinavir-Ritonavir vs Interferon β1b vs low-dose corticosteroids. For patients for whom not all the trial arms are appropriate or at locations where not all are available, randomisation will be between fewer arms.

Outcomes: The main outcomes will be in-hospital death, discharge, and need for ventilation. For the main analyses, follow-up will be censored at 28 days after admission. Additional information on longer term outcomes may be collected through review of medical records or linkage to medical databases such as those managed by NHS Digital and equivalent organisations in the devolved nations.

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A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

PURPOSE & DESIGN: It is likely that the UK will face a significant epidemic of COVID-19 in the coming weeks, and many hundreds (if not thousands) of people may die from this disease. There are currently no known treatments that improve outcomes for this condition, so this trial will compare the efficacy of three (or possibly more) potential therapies to see if they improve major outcomes (including survival and requirement for ventilation). The therapies were recommended by the UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG). Because of the short timelines to prepare this trial, patients have not been involved.

RECRUITMENT: The trial will recruit adults who are admitted to hospital with proven COVID-19 disease. They will be approached by their managing doctors who will either discuss the trial and receive informed consent or - with the patient's agreement - introduce them to a trials practitioner who will discuss the trial and enter the patient, if appropriate.

ELIGIBILITY CRITERIA: These are deliberately very broad to ensure the trial is as large as possible so that the results are as reliable as possible. The eligibility criteria only exclude people for whom their managing doctor thinks participation in the trial would not be in their best interests. If certain study treatments are not appropriate for an

individual (eg, because of the known contraindications for the treatment) then this treatment can be excluded from the randomisation options for that individual.

CONSENT: Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation), then consent may be obtained from a relative acting as the patient's legally designated representative. Further consent will then be sought with the patient if they recover sufficiently.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomization and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

RISKS, BURDENS & BENEFITS: The mortality rate of COVID-19 in the UK population is currently not known, but in similar countries (eg, Italy) up to 30% of admitted patients develop severe disease (eg, require ventilation or die). There are no proven therapies for this condition. Two of the study treatments (lopinavir-ritonavir and low-dose corticosteroids) are in routine clinical use in other conditions and the side-effect profile well-known (and mild). The other arm (interferon β1b) is not currently licensed, but other forms of interferon are used already in other conditions (including treating other viral diseases).

Participation will not place undue burden on participants; they will receive their study treatment once or twice daily by mouth or by nebuliser. Follow-up information will be collected at a single timepoint (about 28 days after randomisation) and any further data will be captured by linkage with routinely-collected data held elsewhere in the NHS.

CONFIDENTIALITY: Participants will be identified and invited by their treating medical teams. All information will be stored on secure computer systems and will not be shared with third parties in an identifiable format.

CONFLICT OF INTEREST: There is no relevant conflict of interest. The Chief Investigator is Chair of the UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) which was involved in determining the treatments to be studied. Because of the short timelines to prepare this trial, patients have not been involved.The adapative design of the trial means that if any one treatment arm is definitely inferior in terms of major clinical outcomes then it will be recommended that that arm will be discontinued. Conversely, if compelling evidence emerges that any one treatment arm is definitely superior, then that information would inform treatment recommendations for future patients with COVID-19. Furthermore, new trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial

☐ Other (please specify)

A8. Type of medicinal trial:

☑ Clinical trial of an unlicensed investigational medicinal product

☑ Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new target population, new dosage schemes, new administration route, etc.)

☐ Clinical trial of a licensed medicinal product used according to the SmPC

☐ Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

Human pharmacology (Phase I)	○ Yes	◉ No
Therapeutic exploratory trial (Phase II)	◉ Yes	○ No
○ Therapeutic exploratory trial (Phase II)		
◉ Therapeutic exploratory trial including comparison with the standard treatment regimen (Phase II/III)		
Therapeutic confirmatory trial (Phase III)	◉ Yes	○ No
Therapeutic use trial (Phase IV)	○ Yes	◉ No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The primary objective is to provide reliable estimates of the effect of study treatments on in-hospital death (with subsidiary analyses of cause of death).

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

The secondary objectives are to assess the effects of study treatments on duration of hospital stay and on need for (and duration of) ventilation or renal replacement therapy.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

In 2019 a novel coronavirus-induced disease (COVID-19) emerged in Wuhan, China. A month later the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the aetiological agent. The clinical manifestations of COVID-19 range from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure. As many patients do not progress to severe disease the overall case fatality rate per infected individual is low, but hospitals in areas with significant community transmission have experienced a major increase in the number of hospitalized pneumonia patients, and the frequency of severe disease in hospitalised patients can be as high as 30%. The progression from prodrome (usually fever, fatigue and cough) to severe pneumonia requiring oxygen support or mechanical ventilation often takes one to two weeks after the onset of symptoms. The kinetics of viral replication in the respiratory tract are not well characterized, but this relatively slow progression provides a potential time window in which antiviral therapies could influence the course of disease. There are currently no approved anti-viral or host-directed treatments for COVID-19. This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

Initially randomization will be between four treatment arms:

1. No additional treatment: There are currently no approved anti-viral or host-directed treatments for COVID-19.

2. Lopinavir-Ritonavir: Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor, which is combined with ritonavir to increase lopinavir's plasma half-life.

3. Interferon β1b: Interferons belong to the family of cytokines and have antiviral and immunoregulatory effects. Interferons (IFNs) are licensed for use in multiple sclerosis, leukaemia, lymphoma, and viral hepatitis. IFNs have shown activity against SARS and MERS CoVs.

4. Low dose corticosteroids: Favourable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial in the treatment of severe acute respiratory viral infections, including COVID-19, SARS and MERS.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The RECOVERY trial will test four different treatments among adult patients hospitalised with COVID-19 disease. Each experimental arm will be compared to the 'no additional treatment' arm with the null hypothesis that there is no difference in outcome between the two.

A randomised controlled trial design has been chosen as it is the most reliable way to assess the effects of treatment. The trial is not blinded and there is no placebo because it is not practical to blind in a four-arm trial and it would add significant complexity to a trial that will need to operate in a very busy clinical environment. It is also not necessary as the primary outcome is death.

The control arm is 'no additional treatment' because there are no known treatments that influence outcomes in COVID-19 disease. All participants in the trial will receive the best available standard care available in their institution.

Participants will be recruited at the time of admission or shortly thereafter. They will receive the study treatments by prescription from a doctor as part of their routine care. There will be a single follow-up contact at about 28 days after randomisation when information on the small number of primary and secondary outcomes will be collected.

It is intended that all patients admitted with proven COVID-19 disease will be invited to participate.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
Due to the short timescales required for this application it has not been possible to involve patients yet. However, we intend to involve them as the trial is established and have at least one patient representative on the trial steering committee.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular

- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [x] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Patients are eligible for the study if all of the following are true:

(i) Aged at least 18 years
(ii) Hospitalised
(iii) Confirmation of SARS-CoV-2 infection by PCR
(iv) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

In addition, if the attending clinician believes that there is a specific contra-indication (see Appendix 2; section 8.2) to one of the active drug treatment arms, then the patient will not be excluded from randomisation to that arm.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Participants may be excluded from receiving one or more of the possible randomised options if their medical history suggests that a treatment may be contraindicated.

Lopinavir-ritonavir: severe hepatic insufficiency.

Inhaled interferon-beta1b: severe depressive illness; severe hepatic insufficiency.

Dexamethasone: none.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed consent	1	0	15 minutes	Managing doctor or research practitioner/nurse. At bedside.
Baseline questionnaire	1	0	10 minutes	Managing doctor or research practitioner/nurse. At bedside or with medical records.
Randomisation	1	0	1 minute	Managing doctor or research practitioner/nurse. At computer in clinical area.
Follow-up assessment at about 28 days	1	0	5 minutes	Managing doctor or research practitioner/nurse. At bedside, by telephone or with medical records.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Lopinavir-ritonavir tablet (if assigned to this arm)	20	0	1 minute	Administered as part of routine care.
Interferon beta-1b nebuliser (if assigned to this arm)	10	0	5 minutes	Administered as part of routine care.
Dexamethasone tablet (if assigned to this arm)	10	0	1 minute	Administered as part of routine care.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

(●) Yes ( ) No

If Yes, please give details, explain the risks and justify the need to withhold the intervention or procedure:

If a participant is assigned a treatment which potentially interacts with their usual medication, their doctors (and pharmacists) will review the situation and guide modifications to both the study treatment and use of concomitant medication. The doctor may decide whether it is appropriate to stop such medications temporarily to allow the patient to complete the course of their assigned intervention.

A21. How long do you expect each participant to be in the study in total?

Participants will have a follow-up assessment conducted at about 28 days after randomisation (or sooner if they are discharged before then).

Participants may be linked with routinely-held data registries (for example, those held by NHS Digital or similar bodies in the devolved nations) so longer-term follow-up information can be collected for up to 10 years.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Admission with COVID-19 disease carries a significant morbidity and mortality irrespective of participation in this trial. The trial procedures have been designed to be as minimally intrusive as possible so that they interfere with the participant's care as little as possible.

The study treatments do have side-effects, including:
1. lopinavir-ritonavir: diarrhoea, nausea and vomiting
2. interferon beta1b: decreased white blood cell count, hypertonia, flu-like symptoms, chest pain
3. dexamethasone: disorder sleep pattern, elevated mood, increased blood sugar, increased blood sodium.

Participants would be monitored for such side-effects and symptomatic treatment may be given if required.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

There are no known therapies that improve outcomes in COVID-19 disease.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

It would not be appropriate for participants to continue to receive their study treatment after the end of the trial as it is an acute treatment for an acute condition.

A26. What are the potential risks for the researchers themselves? *(if any)*

Caring for patients with COVID-19 poses a risk to the researchers who may contract the infection. However, involvement in this trial does not modify that risk at all.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified by their managing medical teams who will offer them participation in the trial. They may be able to discuss the trial in detail and seek informed consent, or introduce the participant to a research practitioner who will do this.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

They will be approached by their managing medical teams during their routine care.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation), then consent may be obtained from a relative acting as the patient's legally designated representative. Further consent will then be sought with the patient if they recover sufficiently.

If you are not obtaining consent, please explain why not.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomization and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Because of the acute nature of COVID-19 potential participants will be given as long as possible to consider participation, but this may only be a few hours or less.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

◉ Yes
○ No
○ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Participants in other research studies will be eligible as long as the other study does not prohibit participation in other clinical trials of investigational medicinal products. The RECOVERY trial aims to be as large and inclusive as possible so no unnecessary exclusion criteria are planned.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

If possible, consent will be sought using an interpreter (either a professional translator or a close relative). Given the large range of possible languages it is not possible to provide the information leaflet and consent form in languages other than English.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

If requested the participation information leaflet may be provided in Welsh. However, this may not be possible from the beginning of the trial due to the short timelines involved.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Participant contact details will be collected at the time of randomisation. Given the short duration of study treatment (10 days) it is unlikely that new information will emerge while they are taking treatment. However, the interim trial results will be monitored by a Data Monitoring Committee (DMC). If, at any stage, evidence emerges that any one treatment arm is definitely inferior in terms of major clinical outcomes then it will be recommended that that arm will be discontinued.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [ ] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [ ] Export of personal data outside the EEA
- [x] Use of personal addresses, postcodes, faxes, emails or telephone numbers
- [ ] Publication of direct quotations from respondents
- [ ] Publication of data that might allow identification of individuals
- [ ] Use of audio/visual recording devices
- [x] Storage of personal data on any of the following:
  - [ ] Manual files (includes paper or film)
  - [ ] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers

☐ Private company computers

☐ Laptop computers

Further details:
Participants will be approached by the managing medical team and consent will be sought by them or an associated research practitioner. Participants will be informed that their data will be stored on university computers and that it may be shared with other organisations (in an anonymised format).

In order to link participants with routinely-collected data (for example those held by NHS Digital) it will be necessary to share the identifiable details of the trial participants with NHS Digital, but this will be done in a highly-secure manner.

A37. Please describe the physical security arrangements for storage of personal data during the study?

All study data will be stored on computer servers within the University of Oxford or subcontracted by them (for example, from Amazon Web Services). All such machines are kept physically secure with access limited to personnel with appropriate permission. If data are held on a third party server (eg, AWS) then the contract will include strict security requirements.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Nuffield Department of Population Health computers are in a secure building protected by a firewall. All NDPH employees agree to maintain confidentiality at all times as part of their employment contract with the University of Oxford, and all other staff employed by Trusts will have similar clauses in their contracts. Access to study data will require a username and password combination (i.e. an electronic signature) and will be audited. Study staff only have access to data appropriate to their role.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

In addition to their direct care team, study personnel based at the Nuffield Department of Population Health (University of Oxford) will also have access to their personal data. These data will be processed under the legal basis of work for the public good, but participants will also have provided consent for their data to be stored and processed by the university.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be analysed by programmers and statisticians based in the Nuffield Department of Population Health, University of Oxford.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Prof	Martin	Landray
Post	Professor of Clinical Trials & Epidemiology		
Qualifications	BM BCh, FRCP, PhD		
Work Address	Big Data Institute		
	Old Road Campus, Headington		
	Oxford		
Post Code	OX3 7LF		
Work Email	martin.landray@ndph.ox.ac.uk		

Work Telephone
Fax

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years
- ○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 25
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

Data will be stored on servers based physically in the University of Oxford. Physical and electronic access will be controlled by the principal investigators and the most up-to-date security measures will be employed.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
The trial will be registered on at least one clinical trial registry, but due to the short setup timelines this has not been done in advance of this application.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- ☑ Peer reviewed scientific journals
- ☐ Internal report
- ☑ Conference presentation
- ☑ Publication on website
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

No participants will be identifiable from the published results. Due to the size of the trial it is very unlikely that there will be any small enough numbers presented that could potentially lead to identification, but this will be monitored and suppressed if necessary.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.
We will inform participants by publishing a lay summary of the research on the trial website which participants may request by e-mailing the trial team.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- ☐ Independent external review
- ☐ Review within a company

- [ ] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The protocol has been developed rapidly by the chief investigator and the trials unit (based in separate departments within the University of Oxford). The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised that a number of treatments should be evaluated, including Remdesivir, Lopinavir-Ritonavir, Interferon β, and low-dose corticosteroids. These groups also advised that other treatments will soon emerge that require evaluation. A World Health Organization (WHO) expert group issued broadly similar advice.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [ ] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Prof	Richard	Peto
Department	Nuffield Department of Population Health		
Institution	University of Oxford		
Work Address	Clinical Trial Service Unit, Richard Doll Building		
	Old Road Campus, Headington		
	Oxford		
Post Code	OX3 7LF		
Telephone	01865743743		
Fax			
Mobile			
E-mail			

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

In-hospital mortality.

A58. What are the secondary outcome measures?*(if any)*

Cause-specific mortality.
Duration of hospitalisation.
Need for ventilation.
Need for renal replacement therapy.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:

Total international sample size (including UK):

Total in European Economic Area:

Further details:
The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

See answer to A59.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Eligible patients will be randomized using a central web-based randomization service (without stratification or minimization) in a 2:1:1:1 ratio to one of the following treatment arms (in addition to usual care):

Arm 1: No additional treatment
Arm 2: Lopinavir-Ritonavir
Arm 3: Interferon-beta-1a
Arm 4: Corticosteroid

If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated for this patient, then this fact is to be recorded via the web-based IT system prior to randomization and random allocation will then be between the remaining arms (in a 2:1:1 or 2:1 ratio).

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Comparisons will be made between all participants randomized to a particular drug treatment arm vs. all participants randomized to the No additional treatment arm, irrespective of whether they received all, some or none of their allocated treatment (i.e. intention-to-treat [ITT] analyses).

For time-to-event analyses, survival analytic methods will be used to evaluate the time to the first event during the entire study period using the log-rank test.

Multiple testing will not formally be taken into account but due allowance will be made in their interpretation, taking into account the nature of events and evidence from other studies. Tests of heterogeneity or trend will generally be used to assess disparity in efficacy among different subgroups (e.g. men vs. women; age <50, ≥50<70, ≥70).

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Prof	Martin	Landray
Post	Professor of Clinical Trials & Epidemiology		
Qualifications	BM BCh, FRCP, PhD		
Employer	University of Oxford		
Work Address	Big Data Institute		
	Old Road Campus, Headington		
	Oxford		
Post Code	OX3 7LF		
Telephone	00000		
Fax	00000		
Mobile	00000		
Work Email	martin.landray@ndph.ox.ac.uk		

	Title	Forename/Initials	Surname
	Prof	Richard	Haynes
Post	Professor of Renal Medicine & Clinical Trials		
Qualifications	DM FRCP		
Employer	Clinical Trial Service Unit, Oxford University		
Work Address	CTSU, Richard Doll Building, Old Road Campus		
	Roosevelt Drive, Headington		
	Oxford		
Post Code	OX3 7LF		
Telephone	01865 743743		
Fax	01865 743985		
Mobile	07779099061		
Work Email	richard.haynes@ctsu.ox.ac.uk		

	Title	Forename/Initials	Surname
	Ass Prof	Ed	Juszczak
Post	Director, National Perinatal Epidemiology Unit Trials Unit		
Qualifications	PhD		
Employer	University of Oxford		
Work Address	National Perinatal Epidemiology Trials Unit		
	Richard Doll Building, Old Road Campus		
	Headington, Oxford		
Post Code	OX3 7LF		
Telephone	00000		
Fax	00000		
Mobile	00000		
Work Email	ed.juszczak@ndph.ox.ac.uk		

A64. Details of research sponsor(s)

A64-1. Sponsor

SP1

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University of Oxford
Given name	NA
Family name	NA
Address	Clinical Trials & Research Governance, 1st Floor, Boundary Brook House, Old Road, Headington
Town/city	OXFORD
Post code	OX3 7GB
Country	UNITED KINGDOM
Telephone	00000
Fax	00000
E-mail	ctrg@admin.ox.ac.uk

Legal representative in the European Economic Area for the purpose of this trial

A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal representative

Contact person

Name of organisation	
Given name	
Family name	
Address	
Town/city	
Post code	
Country	
Telephone	
Fax	
E-mail	

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (•) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	UK Research & Innovation
Address	Polaris House, North Star Avenue SWINDON
Post Code	SN2 1FL
Telephone	07590 464767
Fax	
Mobile	
Email	joanna.jenkinson@mrc.ukri.org

Funding Application Status: (•) Secured ( ) In progress

Amount: £2,106,034

Duration
Years:
Months: 18

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
Covid-19 Rapid Research Call

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

( ) Yes (•) No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	XX	XX	OUHFT Research and Development Dept
Organisation	Oxford Radcliffe Hospitals NHS Foundation Trust		
Address	Joint Research Office		
	Second Floor, OUH Cowley		
	Unipart House Business Centre, Garsington Rd, OXFORD		
Post Code	OX4 2PG		
Work Email	ouhtma@ouh.nhs.uk		
Telephone	00000		
Fax	00000		
Mobile	00000		

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 20/03/2020
Planned end date: 30/09/2030
Total duration:
Years: 10 Months: 6 Days: 11

A69-2. How long do you expect the study to last in all countries?

Planned start date: 20/03/2020
Planned end date: 30/09/2030
Total duration:
Years: 10 Months: 6 Days: 11

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

All randomised participants are to be followed up until death, discharge from hospital or 28 days post-randomisation (whichever is sooner). Longer term follow-up will be sought through linkage to electronic healthcare records and medical databases including those held by NHS Digital, Public Health England and equivalent bodies. The end of the study is the date of the final data extraction from NHS Digital (anticipated to be 10 years after the last patient is enrolled).

A71-1. Is this study?

○ Single centre
◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [x] England
- [x] Scotland
- [x] Wales
- [x] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study 120

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

[x] NHS organisations in England	100
[x] NHS organisations in Wales	5
[x] NHS organisations in Scotland	10
[x] HSC organisations in Northern Ireland	5
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Joint health and social care agencies (eg community mental health teams)	
[ ] Local authorities	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent (private or voluntary sector) organisations	
[ ] Educational establishments	
[ ] Independent research units	
[ ] Other (give details)	
Total UK sites in study:	120

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The focus will be on those factors that are critical to quality (i.e. the safety of the participants and the reliability of the trial results). Remedial actions would be determined by the totality of the monitoring evidence, so that the focus remains on issues with the potential to have a substantial impact on the safety of the study participants or the reliability of the results.

The study will be conducted in accordance with the principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and relevant local, national and international regulations. Any serious breach of GCP in the conduct of the clinical trial will be handled in accordance with regulatory requirements. Prior to initiation of the study at each LCC, the CCO will confirm that the LCC has adequate facilities and resources to carry out the study. LCC lead investigators and study clinic staff will be provided with training materials.

In the context of this epidemic, visits to hospital sites is generally not appropriate since it increases the risks of spreading infection. In exceptional circumstances, the CCO may arrange monitoring visits to LCCs as considered appropriate based on perceived training needs and the results of central statistical monitoring of study data.42,43 The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, to help LCC staff to resolve any local problems, and to provide extra training focussed on specific needs. No routine source data verification will take place as study data is obtained directly from participants.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

Yes. During the study, interim analyses of all study data will be supplied in strict confidence to the independent DMC. The DMC will request such analyses at a frequency relevant to the emerging data from this and other studies.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The DMC will independently evaluate these analyses and any other information considered relevant. The DMC will determine if, in their view, the randomised comparisons in the study have provided evidence on mortality that is strong enough (with a range of uncertainty around the results that is narrow enough) to affect national and global treatment strategies. In such a circumstance, the DMC will inform the Trial Steering Committee who will make the results available to the public and amend the trial arms accoordingly. Unless this happens, the Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the interim results trial results until the 28 days after the end of the studylast patient has been randomised for a particular intervention arm (at which point analyses may be conducted comparing that arm with the no additional treatment arm).

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

See attached confirmation of insurance.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided

through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

See attached confirmation of insurance.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

◉ Yes ○ No ○ Not sure

Part B Section 1: Investigational Medicinal Products

Information on each IMP.

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable.
If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.
Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question 13 using the navigation screen.

Investigational medicinal products

PR1 Lopinavir/ritonavir

PR2 Dexamethasone

PR3 Interferon beta-1a

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ◯ No ◯ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

14-3. IMPD submitted:

Full IMPD

◯ Yes ◉ No ◯ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Lopinavir/ritonavir
Product code where applicable	
ATC codes, if officially registered	J05AR10
Pharmaceutical form (use standard terms)	Coated Tablet
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment	

of a subject according to the protocol	10 days

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total: ◯ per day ◯ total ◯ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed	400/100 mg	
Specify per day or total	◉ per day ◯ total ◯ Not Answered	
Specify total dose (number and unit)	800/200	mg milligram(s)
Route of administration (relevant to the maximum dose):	Oral Use	

Routes of administration for this IMP

Oral Use
Nasogastric Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Lopinavir
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	200

Active Substance 2

Name of active substance (INN or proposed INN if available):	Ritonavir
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	50

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes ○ No ○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes ◉ No ○ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Viral protease inhibitor

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR2**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ◯ No ◯ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

14-3. IMPD submitted:

Full IMPD
◯ Yes ◉ No ◯ Not Answered

Simplified IMPD
◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
◉ Yes ◯ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Dexamethasone
Product code where applicable	
ATC codes, if officially registered	H02AB02
Pharmaceutical form (use standard terms)	Syrup
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	10 days

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total: ◯ per day ◯ total ◯ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed	5 mg
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	50 mg milligram(s)
Route of administration (relevant to the maximum dose):	Oral Use

Routes of administration for this IMP

Oral Use
Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Dexamethasone
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	5

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	(●) Yes ( ) No ( ) Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	( ) Yes (●) No ( ) Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	( ) Yes (●) No ( ) Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	( ) Yes (●) No ( ) Not Answered
Radiopharmaceutical medicinal product?	( ) Yes (●) No ( ) Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	( ) Yes (●) No ( ) Not Answered
Plasma derived medicinal product?	( ) Yes (●) No ( ) Not Answered
Extractive medicinal product?	( ) Yes (●) No ( ) Not Answered
Recombinant medicinal product?	( ) Yes (●) No ( ) Not Answered
Medicinal product containing genetically modified organisms?	( ) Yes (●) No ( ) Not Answered
Herbal medicinal product?	( ) Yes (●) No ( ) Not Answered

Homeopathic medicinal product? ◯ Yes ◉ No ◯ Not Answered

Another type of medicinal product? ◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Immune response modulation.

Is it an IMP to be used in a first-in-human clinical trial? ◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR3**
Investigational medicinal product category:
Test IMP

14. STATUS OF THE IMP
If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◉ Yes ◯ No ◯ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

14-3. IMPD submitted:

Full IMPD
◉ Yes ◯ No ◯ Not Answered

Simplified IMPD
◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
◯ Yes ◉ No ◯ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Interferon beta-1a
Product code where applicable	
ATC codes, if officially registered	L03 AB07
Pharmaceutical form (use standard terms)	
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	10 days

Dose allowed

First dose for first-in-human clinical trial		
Specify per day or total:	◯ per day ◯ total ◯ Not Answered	
Specify total dose (number and unit)		
Route of administration (relevant to the first dose):		
Maximum dose allowed	6 million international units	
Specify per day or total	◉ per day ◯ total ◯ Not Answered	
Specify total dose (number and unit)	60	million IU million international units
Route of administration (relevant to the maximum dose):	Inhalation Use	

Routes of administration for this IMP

Inhalation Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Interferon beta-1a
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	

Strength

Concentration unit:	million IU million international units
Concentration type:	equal
Concentration number (only use both fields for range):	6

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	◉ Yes	○ No	○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	○ Yes	◉ No	○ Not Answered
Is this a:			
Advanced Therapy IMP (ATIMP) [1]	○ Yes	◉ No	○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes	◉ No	○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes	◉ No	○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes	◉ No	○ Not Answered
Plasma derived medicinal product?	○ Yes	◉ No	○ Not Answered
Extractive medicinal product?	○ Yes	◉ No	○ Not Answered
Recombinant medicinal product?	○ Yes	◉ No	○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes	◉ No	○ Not Answered
Herbal medicinal product?	○ Yes	◉ No	○ Not Answered

Homeopathic medicinal product?	◯ Yes ◉ No ◯ Not Answered
Another type of medicinal product?	◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Antiviral agent

Is it an IMP to be used in a first-in-human clinical trial?	◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

Information on Placebo

13. Is there a placebo:

○ Yes ◉ No

Index of Sites where the qualified person certifies batch release

14. IMPs and placebos for which no responsible site needs to be identified:

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Finished IMP
PR1

Finished IMP
PR2

This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. In the case of multiple sites indicate the product certified by each site.

15. Identify who is responsible in the Community for the certification of the finished IMPs.
Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2. of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial.

RS1

Manufacturer

Organisation	Synairgen Research Ltd
Address	Tremona Road
Town/city	Southampton
Post code	SO16 6YD
Country	UNITED KINGDOM

Give the manufacturing authorisation number

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP
PR3

Part B: Section 6 - Adults unable to consent for themselves

A. Clinical trials of investigational medicinal products

In this sub-section, an adult means a person aged 16 or over.

A1. What clinical condition(s) will the participants have? *The trial must relate directly to this condition.*

Confirmed SARS-CoV-2 infection by PCR

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

○ Yes ◉ No

A3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

Treating clinician at NHS site. They will use clinical training and experience to determine capacity.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? *You may refer back to your answer to Question A24.*

It is possible that one or more of the treatment arms might be associated with improved outcomes, in which case the participants assigned to such arms may benefit.

Participants will also benefit from the knowledge that they are contributing to a major project that is addressing a key health challenge.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

◉ Yes ○ No

If Yes, please give an assessment below. You may refer back to your answers to Questions A22 and A23. Highlight any risk, burden or discomfort specific to these participants. Justify in relation to the potential benefits.

Admission with COVID-19 disease carries a significant morbidity and mortality irrespective of participation in this trial. The trial procedures have been designed to be as minimally intrusive as possible so that they interfere with the participant's care as little as possible.

The study treatments do have side-effects, including:
1. lopinavir-ritonavir: diarrhoea, nausea and vomiting
2. interferon beta1b: decreased white blood cell count, hypertonia, flu-like symptoms, chest pain
3. dexamethasone: disorder sleep pattern, elevated mood, increased blood sugar, increased blood sodium.

Participants would be monitored for such side-effects and symptomatic treatment may be given if required.

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation), then consent may be obtained from a relative or independent healthcare practitioner acting as the patient's legally designated representative. Further consent will then be sought with the patient if they recover sufficiently.

A7. Is it possible that a participant requiring urgent treatment might need to be recruited into the trial before it is possible to identify and seek consent from a legal representative?

◉ Yes ○ No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or a legal representative as soon as practicable thereafter.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort39), patients who lack capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomization and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

A8. What arrangements will be made to continue to consult legal representatives during the course of the research where necessary?

If it was not possible to seek consent from the participant or their legal representative at time of randomisation, this consent would be sought as soon afterwards as possible (bearing on mind potential visiting restrictions to COVID-19 cases).

A9. Will steps be taken to provide information about the trial to participants, according to their capacity of understanding, and to consider the wishes of participants capable of forming an opinion?

◉ Yes ○ No

If Yes, give details.

The person taking consent (managing clinician or trial practitioner) will provide information at a level that the individual can understand.

A10-1. What will be the criteria for withdrawal of participants?

A decision by a participant that they no longer wish to continue receiving study treatment should not be considered to be a withdrawal of consent for follow-up. However, participants are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, data that have already been collected and incorporated in the study database will continue to be used.

A10-2. Where a participant is recruited prior to consent being obtained, and consent is later withheld or the participant dies before consent can be given, what provisions will apply to the study data collected up to this point?

Any data collected up to that point would be used, but no further data would be collected.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site		Investigator Name	
IN1	(●) NHS/HSC Site ( ) Non-NHS/HSC Site		Forename	Peter
			Middle name	
			Family name	Horby
	Organisation name	OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST	Email	peter.horby@ndm.ox.ac.uk
	Address	JOHN RADCLIFFE HOSPITAL HEADLEY WAY HEADINGTON OXFORD OXFORDSHIRE	Qualification (MD...)	MB BS 1992 University of London
			Country	UNITED KINGDOM
	Post Code	OX3 9DU		
	Country	ENGLAND		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.

10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- (●) Chief Investigator
- ( ) Sponsor
- ( ) Study co-ordinator
- ( ) Student
- ( ) Other – please give details
- ( ) None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☑ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Peter William Horby on 13/03/2020 17:07.

Job Title/Post:	Professor of Emerging Infections
Organisation:	University of Oxford
Email:	peter.horby@ndm.ox.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.

7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

9. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Clinical Trial and Research Governance CTRG Sponsorship on 13/03/2020 17:27.

Job Title/Post:	Heather House
Organisation:	University of Oxford
Email:	