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)

4a. Will you be seeking data from Hospital Episode Statistics (HES) or the Secondary Uses Service (SUS)?

○ Yes ◉ No

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

SUBSTANTIAL AMENDMENT FORM [1]

NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

For official use:

Date of receiving the request:	Grounds for non acceptance/negative opinion:
	Date:
Date of start of procedure:	Authorisation/ positive opinion:
	Date:
Competent authority registration number of the trial:	Withdrawal of amendment application:
Ethics committee registration number of the trial:	Date:

To be filled in by the applicant:

*This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.*

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted:

United Kingdom

A.2 Notification for authorisation to the competent authority: ☑

A.3 Notification for an opinion to the ethics committee: ☑

(1) Cf. Section 3.7.b of the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (OJ, C82, 30.3.2010, p.1) hereinafter referred to as 'detailed guidance CT-1'.

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP? [2] ○ Yes ◉ No

B.2 EudraCT number: 2020-001113-21

B.3 Full title of the trial: Randomised evaluation of COVID-19 therapy

B.4 Sponsor's protocol code number: NDPHRECOVERY

B.4 Sponsor's protocol version number: 3.0

B.4 Sponsor's protocol date: 07/04/2020

(2) Cf. Section 3.7. of the detailed guidance CT-1

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor

Organisation:	University of Oxford
Contact Given name:	Heather
Contact Family name:	House
Address:	1st Floor, Boundary Brook House, Churchill Drive
Town/city:	Headington, Oxford
Post code:	OX3 7GB
Telephone:	00000
Fax:	00000
E-mail:	ctrg@admin.ox.ac.uk

C.2 Legal representative [3] of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)

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

(3) As stated in Article 19 of Directive 2001/20/EC.

D APPLICANT IDENTIFICATION, (please tick the appropriate box)

D1. Request for the competent authority

D.1.1 Sponsor	☐
D.1.2 Legal representative of the sponsor	☐
D.1.3 Person or organisation authorised by the sponsor to make the application.	☑

D.1.4 Complete below:

Name of organisation	University of Oxford
Contact Given name	Peter
Contact Family name	Horby
Address	New Richards Building, Old Road Campus, Headington
Town/city	Oxford
Post code	OX3 7LG
Telephone	01865612940
Fax	

E-mail	peter.horby@ndm.ox.ac.uk

D2. Request for the Ethics Committee

D.2.1 Sponsor ☐

D.2.2 Legal representative of the sponsor ☐

D.2.3 Person or organisation authorised by the sponsor to make the application. ☐

D.2.4 Investigator in charge of the application if applicable[4]:

- Co-ordinating investigator (for multicentre trial): ☑
- Principal investigator (for single centre trial): ☐

D.2.5 Complete below:

Name of organisation	University of Oxford
Given name	Peter
Family name	Horby
Address	New Richards Building, Old Road Campus, Headington
Town/city	Oxford
Post code	OX3 7LG
Telephone	01865612940
Fax	
E-mail	peter.horby@ndm.ox.ac.uk

(4) According to national legislation.

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1 Sponsor's substantial amendment information for the clinical trial concerned:

Code Number: SA2
Version: 1.0
Date: 2020/04/07

E.2 Type of substantial amendment

E.2.1 Amendment to information in the CT application form ◉ Yes ○ No

E.2.2 Amendment to the protocol ◉ Yes ○ No

E.2.3 Amendment to other documents appended to the initial application form ◉ Yes ○ No

If yes specify:
Participant Information Sheet and Informed Consent Form

E.2.4 Amendment to other documents or information: ○ Yes ◉ No

If yes specify:

E.2.5 This amendment concerns mainly urgent safety measures already implemented[5]: ○ Yes ◉ No

E.2.6 This amendment is to notify a temporary halt of the trial[6]: ○ Yes ◉ No

E.2.7 This amendment is to request the restart of the trial[7]: ○ Yes ◉ No

(5) Cf. Section 3.9. of the detailed guidance CT-1.
(6) Cf. Section 3.10. of the detailed guidance CT-1
(7) Cf. Section 3.10. of the detailed guidance CT-1

E.3 Reasons for the substantial amendment:

E.3.1 Changes in safety or integrity of trial subjects	○ Yes	◉ No
E.3.2 Changes in interpretation of scientific documents/value of the trial	○ Yes	◉ No
E.3.3 Changes in quality of IMP(s)	○ Yes	◉ No
E.3.4 Changes in conduct or management of the trial	◉ Yes	○ No
E.3.5 Change or addition of principal investigator(s), co-ordinating investigator	○ Yes	◉ No
E.3.6 Change/addition of site(s)	○ Yes	◉ No
E.3.7 Other change	○ Yes	◉ No
E.3.7.1 If yes specify:		
E.3.8 Other case	○ Yes	◉ No
E.3.8.1 If yes specify:		

E.4 Information on temporary halt of trial:[8]

E.4.1 Date of temporary halt		
E.4.2 Recruitment has been stopped	○ Yes	○ No
E.4.3 Treatment has been stopped	○ Yes	○ No

E.4.4 Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment

E.4.5 Briefly describe:

Justification for a temporary halt of the trial *(free text)*:

The proposed management of patients receiving treatment at time of the halt *(free text)*:

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text)*:

(8) Cf. Section 3.10. of the detailed guidance CT-1

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9]

Please use this section to detail each substantial amendment which is being notified. If you are notifying more than one substantial amendment, please use the "Add Amendment" button as required

Substantial amendment 1

Previous and new wording:*(tracked)*

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

1. Aged at least 18 years
2. Hospitalised
3. SARS-CoV-2 infection <u>(clinically suspected or laboratory confirmed)</u>

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

New wording underlined.

New wording:

Comments/ explanation/ reasons for substantial amendment:

We wish to include participants with suspected SARS-CoV-2 infection as well as proven, because
(i) testing may not be done on patients presenting with classic syndrome
(ii) testing may be falsely negative in some patients, especially with more advanced disease
(iii) waiting for positive test results introduces delay (sometimes 1-2 days) before patients can be enrolled and receive treatment.

Substantial amendment 2

Previous and new wording:*(tracked)*

Addition of azithromycin as a new arm to the trial (replacing inhaled interferon beta).

New wording:

Comments/ explanation/ reasons for substantial amendment:

It was not possible to acquire a reliable supply of inhaled interferon beta for the trial and it is not clear that production could be scaled up if results were positive to provide large-scale treatment.

The government's Chief Scientific Adviser considered other treatments that would be suitable for testing (on basis of scientific rationale and scalability if results were positiv) and recommended to the trial steering committee to consider azithromycin.

Substantial amendment 3

Previous and new wording:*(tracked)*

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) <u>or prior disease (e.g. dementia)</u>, then consent may be obtained from a relative acting as the patient's legally designated representative or independent doctor.

New wording underlined.

New wording:

Comments/ explanation/ reasons for substantial amendment:

We wish to include patient's with dementia as we do not wish to deny them access to possible benefits of treatment (especially as they may not receive more intensive care during the epidemic). As relatives cannot attend hospital with the patient we wish to use legal representative route for consent.

Substantial amendment 4

Previous and new wording:*(tracked)*

The primary objective is to provide reliable estimates of the effect of study treatments on ~~in-hospital~~ all-cause mortality at 28 days after the main randomisation

New text underline, previous text now removed struck-through

New wording:

Comments/ explanation/ reasons for substantial amendment:
To facilitate interpretation of results and analyses, we wish to include all deaths within 28 days of randomisation, not just those occuring in hospital. The linkage that has been established with NHS Digital and other similar registries allows capture of deaths occuring after discharge.

Substantial amendment 5

Previous and new wording:*(tracked)*

Corticosteroid in the form of dexamethasone administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days. In pregnancy, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone.

-

New wording underlined.

New wording:

Comments/ explanation/ reasons for substantial amendment:
In order to facilitate recruitment of pregnant women (who are risk of COVID-19) we wish to allow flexibility in type of corticosteroid used as prednisolone/hydrocortisone are considered preferable in pregnancy.

Substantial amendment 6

Previous and new wording:*(tracked)*

Previous wording:

Comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment (“intention-to-treat” 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, taking discharge without the relevant event as implying safety from it.

The scope for multiple treatment comparisons will be taken into account in multiple pairwise tests. Due allowance will be made in the interpretation of all analyses, 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).

New wording:
Comparisons will be made between all participants randomised to the different treatment arms, irrespective of whether they received their allocated treatment (“intention-to-treat” analyses).

For time-to-event analyses, each treatment group will be compared with the no additional treatment group using

the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted (with associated log-rank p-values). For binary outcomes where the timing is unknown, the odds ratio and absolute risk difference will be calculated with confidence intervals and p-value reported. For the primary outcome, death within 28 days of randomisation, discharge alive before 28 days will assume safety from the event (in the absence of additional data confirming otherwise).

Pairwise comparisons will be made between each treatment arm and the no additional treatment arm (reference group). Since not all treatments may be available or suitable for all patients, those in the no additional treatment arm will only be included in a given comparison if, at the point of their randomisation, they could alternatively have been randomised to the active treatment of interest. The effect of allocation to each treatment (versus no treatment) will be calculated for each of the contributing strata, and an inverse-variance-weighted meta-analysis of those results will be done to provide an overall estimate of the pairwise difference. Adjustment for multiple treatment comparisions due to the multi-arm design will be made using the Dunnett test.

Pre-specified subgroup analysis will be conducted for the primary outcome using the statistical test for interaction (or test for trend where appropriate) for the following: disease severity; time since onset of symptoms; sex; age group).

Comments/ explanation/ reasons for substantial amendment:

The Statistical Analysis Plan has been developed more fully so the protocol has been updated to be consistent. For the avoidance of doubt, this was done blind to any study outcome data.

Substantial amendment 7

Previous and new wording:*(tracked)*

Typographical and administrative updates.

New wording:

Comments/ explanation/ reasons for substantial amendment:

Clarifications and corrections.

(9)Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

Type of change:

G.1.1 Addition of a new site

G.1.1.1 Principal investigator (provide details below)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.2 Removal of an existing site

G.1.2.1 Principal investigator (provide details below)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.3 Change of co-ordinating investigator (provide details below of the new coordinating investigator)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.3.6 Indicate the name of the previous co-ordinating investigator:

G.1.4 Change of principal investigator at an existing site (provide details below of the new principal investigator)

Given name
Middle name(if applicable)
Family name
Qualification (MD...)
Professional address

G.1.4.6 Indicate the name of the previous principal investigator:

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

H.1 Change of e-mail contact for feedback on application*

H.2 Change to request to receive an .xml copy of CTA data ○ Yes ◉ No

H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ○ Yes ○ No

H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):

H.2.2 Do you want to receive this via password protected link(s)[10]? ○ Yes ○ No

If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)

H.2.3 Do you want to stop messages to an email for which they were previously requested? ◯ Yes ◯ No

H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:

(*This will only come into effect from the time at which the request is processed in EudraCT).

(10) This requires a EudraLink account. (See eudract.emea.europa.eu for details)

I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

I.1 Cover letter	☑
I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)	☐
I.3 Entire new version of the document[11]	☑
I.4 Supporting information	☑
I.5 Revised .xml file and copy of initial application form with amended data highlighted	☑
I.6 Comments on any novel aspect of the amendment if any :	

(11) Cf. Section 3.7.c. of the detailed guidance CT-1

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

J.1 I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable)

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY*(as stated in section D.1):* ☑

J.2.1 Signature [12]: .....

J.2.2 Print name: Heather House

J.2.3 Date: 2020/04/07

J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE *(as stated in section D.2)*: ☑

J.3.1 Signature [13]: .....

J.3.2 Print name: Heather House

J.3.3 Date: 2020/04/07

(12) On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
(13) On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.