

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 <sup>1</sup>**

**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:**



*(<sup>1</sup>) 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?** <sup>2</sup> ☐ 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:** 2.0

**B.4 Sponsor's protocol date:** 20/03/2020

*(<sup>2</sup>) 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 <sup>3</sup> 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:

*(<sup>3</sup>) 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  
Contact Given name  
Contact Family name  
Address  
Town/city  
Post code  
Telephone  
Fax  
E-mail

**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<sup>4</sup>:• Co-ordinating investigator (for multicentre trial): ☐• Principal investigator (for single centre trial): ☐

D.2.5 Complete below:

Name of organisation

Given name

Family name

Address

Town/city

Post code

Telephone

Fax

E-mail

*(4) According to national legislation.***E SUBSTANTIAL AMENDMENT IDENTIFICATION****E.1 Sponsor's substantial amendment information for the clinical trial concerned:**

Code Number: SA1

Version: 1.0

Date: 2020/03/20

**E.2 Type of substantial amendment**E.2.1 Amendment to information in the CT application form ☒ Yes ☐ NoE.2.2 Amendment to the protocol ☒ Yes ☐ NoE.2.3 Amendment to other documents appended to the initial application form ☒ Yes ☐ No

If yes specify:

Participant Information Leaflet

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<sup>5</sup>: ☐ Yes ☒ NoE.2.6 This amendment is to notify a temporary halt of the trial<sup>6</sup>: ☐ Yes ☒ NoE.2.7 This amendment is to request the restart of the trial<sup>7</sup>: ☐ Yes ☒ No*(5) Cf. Section 3.9. of the detailed guidance CT-1.**(6) Cf. Section 3.10. of the detailed guidance CT-1*

<sup>(7)</sup> 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:  
Addition of fifth arm in randomisation to include hydroxychloroquine.  
Other minor changes to protocol.
- E.3.8 Other case ☐ Yes ☒ No
- E.3.8.1 If yes specify:

**E.4 Information on temporary halt of trial:<sup>8</sup>**

- 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*):

<sup>(8)</sup> Cf. Section 3.10. of the detailed guidance CT-1

**F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT<sup>9</sup>**

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)*

New wording underlined.

**1.2 Treatment Options**

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.

Randomisation may be between the following treatment arms (although not all arms may be available at any one time):

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

**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. Lopinavir-Ritonavir has shown activity against SARS and MERS CoVs.

**Interferon b:** Interferons (IFNs) are cytokines with antiviral and immunoregulatory effects. They are licensed for use in multiple sclerosis, leukaemia, lymphoma, and viral hepatitis. IFNs have shown activity against SARS and MERS CoVs.

**Low dose corticosteroids:** Favourable immune response modulation by low-dose corticosteroids might help treat severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS.

**Hydroxychloroquine:** Hydroxychloroquine, a derivative of chloroquine, has been used for many decades to treat malaria and rheumatic diseases. It has antiviral activity against SARS-CoV-2 in cell culture.

**New wording:**

Hydroxychloroquine: Hydroxychloroquine, a derivative of chloroquine, has been used for many decades to treat malaria and rheumatic diseases. It has antiviral activity against SARS-CoV-2 in cell culture.

**Comments/ explanation/ reasons for substantial amendment:**

Hydroxychloroquine has been recommended by World Health Organisation to be tested within large-scale trials of COVID-19. UK Department of Health has secured a supply which means it is now feasible to include it in RECOVERY protocol.

**Substantial amendment 2****Previous and new wording:***(tracked)***2.1 Eligibility**

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

1. Aged at least 18 years
2. Hospitalised
3. ~~Confirmation of SARS-CoV-2 infection by PCR~~
4. 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 be excluded from randomisation to that arm.

**New wording:**

As above.

**Comments/ explanation/ reasons for substantial amendment:**

Other diagnostic tests are rapidly becoming available for SARS-CoV-2 which may replace PCR so we do not wish to require a test which may not be done routinely. Later on in outbreak diagnostic tests may not be required and COVID-19 may become a clinical diagnosis.

**Substantial amendment 3****Previous and new wording:***(tracked)*

## 2.4 Randomisation

**Arm 5: Hydroxychloroquine** by mouth for a total of 10 days as follows:

Timing	Total dose	E.g. using 155 mg tablets
Initial	775 mg	5 tablets
+ 6 hours	775 mg	5 tablets
+ 12 hours	310 mg	2 tablets
+ 24 hours	310 mg	2 tablets
Every 24 hours thereafter for 9 days	310 mg	2 tablets

**New wording:**

As above

**Comments/ explanation/ reasons for substantial amendment:**

This is standard dosing for hydroxychloroquine when used to treat infections.

**Substantial amendment 4****Previous and new wording:***(tracked)*

New text underlined.

6.4 Local Clinical Centres The study will be conducted at multiple hospitals (Local Clinical Centres) within the UK. At each LCC, a lead investigator will be responsible for trial activities but much of the work will be carried out by medical staff attending patients with COVID-19 within the hospital and by hospital research nurses, medical students and other staff with appropriate education, training, and experience.

**New wording:**

, medical students and other staff with appropriate education, training, and experience.

**Comments/ explanation/ reasons for substantial amendment:**

As discussed with MHRA assessor we wish to allow a broad range of staff (including medical students) as long as they have appropriate education, training and experience.

**Substantial amendment 5****Previous and new wording:***(tracked)***Appendix 2****Inhaled interferon-b-1a**

Severe hepatic insufficiency

~~Severe depressive illness~~

### **Hydroxychloroquine**

- Known prolonged QTc interval

Caution: Co-administration with medications that prolong the QT interval (e.g. macrolides, quinolones) is not an absolute contraindication, but it may be appropriate to monitor the QT interval.

#### **New wording:**

Hydroxychloroquine

Known prolonged QTc interval

Caution: Co-administration with medications that prolong the QT interval (e.g. macrolides, quinolones) is not an absolute contraindication, but it may be appropriate to monitor the QT interval.

#### **Comments/ explanation/ reasons for substantial amendment:**

We wish to remove the severe depression contraindication for inhaled interferon. This is because this side-effect typically takes many months to develop during a long-term course of interferon (e.g. for hepatitis C). A short-term course of topical treatment is very unlikely to cause any mood disturbance and our expert advice has been to remove this contraindication.

We have added information for hydroxychloroquine to this appendix.

### **Substantial amendment 6**

#### **Previous and new wording:***(tracked)*

n/a

#### **New wording:**

n/a

#### **Comments/ explanation/ reasons for substantial amendment:**

We have now launched our trial website ([www.recoverytrial.net](http://www.recoverytrial.net)). All information in the "Patient FAQ" section is directly taken from the approved participant information sheet.

### **Substantial amendment 7**

#### **Previous and new wording:***(tracked)*

n/a

#### **New wording:**

n/a

#### **Comments/ explanation/ reasons for substantial amendment:**

In addition to the above changes, a number of administrative changes have been made to the protocol including:

+ adding the trial website information

+ adding trial registration details

A number of typographical errors have also been corrected.

<sup>(9)</sup>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)<sup>10</sup>?

☐ 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](http://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<sup>11</sup>



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 <sup>12</sup>: .....

J.2.2 Print name: Heather House

J.2.3 Date: 2020/03/23

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

J.3.1 Signature <sup>13</sup>: .....

J.3.2 Print name: Heather House

J.3.3 Date: 2020/03/23

(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.