

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:** V6.0**B.4 Sponsor's protocol date:** 14/05/2020

⁽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: Clinical Trials & Research Governance
Town/city: 1st Floor, Boundary Brook House, Churchill Drive
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
Town/city Old Road Campus,
Headington
Post code OX3 7LG
Telephone 01865612940
Fax 00000

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

D2. Request for the Ethics CommitteeD.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 applicable⁴:• 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

Town/city Old Road Campus,
Headington

Post code OX3 7LG

Telephone 01865612940

Fax 00000

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: SA5

Version: 1.0

Date: 2020/05/14

E.2 Type of substantial amendmentE.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:

PIS/ICF

PIS/ICF (children)

E.2.4 Amendment to other documents or information: ☒ Yes ☐ No

If yes specify:

SmPC for Kaletra liquid formulation provided

E.2.5 This amendment concerns mainly urgent safety measures already implemented⁵: ☐ Yes ☒ NoE.2.6 This amendment is to notify a temporary halt of the trial⁶: ☐ Yes ☒ NoE.2.7 This amendment is to request the restart of the trial⁷: ☐ 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 AMENDMENT⁹

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)**1.2.1 Main randomisation**

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.

From version 6.0 of the protocol, a factorial design will be used such that eligible participants are randomised to one of the treatment arms in Randomisation A and, simultaneously, to one of the treatment arms in Randomisation B.

Randomisation part A: Eligible patients will be randomly allocated 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.
- 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 rheumatological diseases. It has antiviral activity against SARS-CoV-2 in cell culture.
- Azithromycin: Azithromycin is a macrolide antibiotic with immunomodulatory properties that has shown benefit in inflammatory lung disease.

Randomisation part B: Simultaneously, eligible patients will be randomly allocated between the following treatment arms:

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

Convalescent plasma: Plasma from patients who have recovered from SARS-CoV-2 infection may contain antibodies that can bind to and neutralise the virus. Infusion of convalescent plasma containing high concentrations of neutralising antibody may accelerate clearance of the virus and clinical improvement.

2.4.1 Randomisation part B

For randomisation part B, the randomisation program will allocate patients in a ratio of 1:1 between each of the arms available. If the active treatment is not available at the hospital, the patient does not consent to receive convalescent plasma, or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form and the patient will be excluded from Randomisation part B.

2.7.1 Additional assessment of safety of convalescent plasma

For the first 200 participants in Main Randomization part B (no additional treatment vs. convalescent plasma), the following information will be collected on the following events occurring within the first 72 hours after randomisation:

- Sudden worsening in respiratory status
- Severe allergic reaction
- Temperature >39°C
- Sudden drop in blood pressure requiring urgent medical attention

The Data Monitoring Committee will review unblinded information on these outcomes and advise if, in their view, the collection of such information should be extended to more participants.

In addition, Serious Hazards Of Transfusion (SHOT) reporting will be conducted for all patients receiving convalescent plasma for the full duration of the study.

4.4 Role of the Data Monitoring Committee (DMC)

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.

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 accordingly. Unless this happens, the Steering Committee, Chief Investigator, study staff, investigators, study participants, funders and other partners will remain blind to the interim results until 28 days after the last 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).

As described in section 2.7.1, the DMC will advise if collection of information relating to the safety of convalescent plasma should be extended beyond the first 200 patients enrolled to Main Randomisation phase B (no additional information vs. convalescent plasma).

6.5 Supply of study treatments

For licensed treatments (e.g. lopinavir-ritonavir, corticosteroids, tocilizumab) all aspects of treatment supply, storage, and management will be in accordance with standard local policy and practice for prescription medications. Treatment issue to randomised participants will be by prescription.

For unlicensed treatments, manufacture, packaging and delivery will be the responsibility of the pharmaceutical company and Department of Health and Social Care. Treatment issue to randomised participants will be in accordance with local practice (and may be in line with the processes required for routine prescriptions or compassionate use).

For convalescent plasma, manufacture, packaging, delivery and transfusion staff training will be the responsibility of the relevant UK Blood Service (NHS Blood and Transplant for England, Welsh Blood Service for Wales, Scottish National Blood Transfusion Service for Scotland, and the Northern Ireland Blood Transfusion Service for Northern Ireland). Convalescent plasma will be labelled in accordance with regulatory requirements and the unit will be issued to the ward for a named patient in a bag marked for clinical trial use only. Treatment issue to randomised participants will be by prescription.

Appendix 3:

<u>Convalescent Plasma</u>	<u>Intravenous</u>		
-			<u>5 mL/kg of ABO compatible convalescent plasma intravenous up to standard adult dose of 275 mLs per day on study days 1 and 2.</u>
			-
			<u>Minimum of 12 hour interval between 1st and 2nd units.</u>
			-
			<u>Convalescent plasma for neonates and infants up to one year of age needs to be ordered on a named patient basis from the relevant National Blood Service to ensure the unit meets neonatal requirements.</u>

New wording:

All changes relating to convalescent plasma have been grouped together above (with section numbers [in bold] referring to protocol). All new wording underlined above.

Comments/ explanation/ reasons for substantial amendment:

Convalescent plasma treatment, containing high titres of polyclonal antibody, has been used to treat severe viral pneumonias. Many studies have been small or poorly controlled but have reported beneficial effects in avian influenza, influenza A (H1N1) infections in 1915-1917 and 2009/2010, and seasonal influenza B. More relevant to SARS-CoV-2, a systematic review of convalescent plasma treatment in SARS-CoV infections in 2003 identified eight observational studies that all reported improved mortality associated with the use of convalescent plasma – infected patients received various amounts of convalescent plasma. Recent studies in seasonal influenza A and in MERS-CoV highlight the importance of high avidity and high titre antibodies respectively.

Convalescent plasma therapy has been given to at least 245 COVID-19 patients by the end of February 2020, and, according to a Chinese health official, 91 cases had shown improvement in clinical indicators and symptoms (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). Five small case series (26 patients in total) have been published that report the use of convalescent plasma in people with COVID-19 infection. These studies have reported clinical and radiological improvements after treatment with convalescent plasma. However, these small uncontrolled studies have significant flaws and the reported effects are unreliable. Convalescent plasma is currently being tested in the REMAP-CAP trial among patients on intensive care units.

As in standard care, plasma for infants (children <1 year old) must come from central National Blood Service on a named patient basis which requires transfer of identifiable information from hospital to Blood Service (which is done routinely).

Substantial amendment 2

Previous and new wording:(tracked)

2.7 Collecting follow-up information

The following information will be ascertained at the time of death or discharge or at 28 days after first randomisation (whichever is sooner):

- Vital status (alive / dead, with date and presumed cause of death, if appropriate)
- Hospitalisation status (inpatient / discharged, with date of discharge, if appropriate)
- Use of ventilation (with days of use and type, if appropriate)
- Use of renal dialysis or haemofiltration
- Documented new major cardiac arrhythmia (including atrial and ventricular arrhythmias)

Use of any medications included in the RECOVERY trial protocol (including drugs in the same class)

New wording:

New wording underlined above.

Comments/ explanation/ reasons for substantial amendment:

To collect additional information on potential arrhythmic adverse effects of study treatments. These adverse effects are well-recognised and we wish to quantify them.

Substantial amendment 3

Previous and new wording:(tracked)

3.1 Outcomes

For each pairwise comparison with the 'no additional treatment' arm, the **primary objective** is to provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after first randomisation (with subsidiary analyses of cause of death and of death at various timepoints following discharge).

The **secondary objectives** are to assess the effects of study treatments on duration of hospital stay; the need for (and duration of) ventilation;; and, among patients not on ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO.

Other objectives include the assessment of the effects of study treatments on the need for renal replacement therapy and major cardiac arrhythmias.

Study outcomes will be assessed based on data recorded up to 28 days and up to 6 months after the main randomisation.

New wording:

New wording underlined above.

Comments/ explanation/ reasons for substantial amendment:

To clarify analytical method and to ensure consistency with the Statistical Analysis Plan.

Substantial amendment 4

Previous and new wording:*(tracked)*

9.2 Appendix 2: Drug specific contraindications and cautions

Lopinavir/ritonavir

- Severe hepatic insufficiency*
- Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. This includes alfuzosin, ranolazine, amiodarone, dronaderone, fusidic acid, neratinib, venetoclax, colchicine, astemizole, terfenadine, lurasidone, pimozone, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylethylgonovine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir, lovastatin, simvastatin, lomitapide, avanafil, sildenafil, vardenafil, midazolam, triazolam, ciclosporin, tacrolimus, sirolimus, rivaroxaban and vorapaxar (See Summary of Product Characteristics for more detail). It may be appropriate to temporarily withhold such concomitant medication while the patient is receiving lopinavir/ritonavir. For patients receiving warfarin additional INR monitoring is advised.

Corticosteroid

- Known contra-indication to short-term low-dose corticosteroid.

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 check the QT interval by performing an ECG.

Azithromycin

- Known prolonged QTc interval*
- Co-administration with chloroquine or hydroxychloroquine
- Known hypersensitivity to macrolide or ketolide antibiotic

Tocilizumab

- Known hypersensitivity to tocilizumab.
- Evidence of active TB infection
- Clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)

Convalescent plasma

- Known moderate or severe allergy to blood components (e.g. transfusion-related acute lung injury)*
- Not willing to receive a blood product*

* If these conditions are recorded on the baseline case report form, patients will be ineligible for randomisation to that arm of the study.

New wording:

New wording underlined.

Comments/ explanation/ reasons for substantial amendment:

Additional contraindicated/cautioned medications for lopinavir-ritonavir (requested by MHRA) and additional cautions for tocilizumab.

Standard cautions for blood product usage as recommended by NHSBT.

Substantial amendment 5

Previous and new wording:*(tracked)*

9.3 Appendix 3: Paediatric dosing information

Hydrocortisone (IV) – additional option for Preterm infants with a corrected gestation age of <40 weeks:

0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days

or **Prednisolone (Oral/NG):**

1 mg/kg once daily (max: 40 mg; doses can be rounded as per routine clinical practice)

or **Methylprednisolone sodium succinate (IV):**

0.8 mg/kg once daily (max: 32 mg)

or **Dexamethasone (Oral/NG/IV):**

150 micrograms/kg (as base) once daily (max: 6 mg)

<u>Convalescent Plasma</u>	<u>Intravenous</u>	<u>10 mL/kg of ABO compatible convalescent plasma intravenous up to standard adult dose of 275 mLs per day on study days 1 and 2.</u>
		<u>Minimum of 12 hour interval between 1st and 2nd units.</u>

New wording:

Underlined above. Minor changes in paediatric steroid dosing.

Comments/ explanation/ reasons for substantial amendment:

Previous protocol had 100 mcg/kg (as base) for dexamethasone which was incorrect.

Additional details on convalescent plasma dosing.

Substantial amendment 6

Previous and new wording:(tracked)

We wish to allow lopinavir-ritonavir to be dissolved in water (according to method described by Abbvie) so that it can be delivered to adult patients via nasogastric tube. Currently ventilated patients cannot receive lopinavir-ritonavir as there is no IV formulation and the liquid formulation is not compatible with most nasogastric tubes.

We also wish to use liquid lopinavir-ritonavir (especially for children) which we have now established a supply of. As this is from a third country we enclose quality documents with MHRA submission. We will request that sites label any products sourced from a third country with labels that ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the IMP.

New wording:

Comments/ explanation/ reasons for substantial amendment:

Further justification for this method has been sent directly to MHRA from Abbvie.

Substantial amendment 7

Previous and new wording:(tracked)

Section 4.4: The DMC will review the safety and efficacy analyses among children (age <18 years) both separately and combined with the adult data.

New wording:

Underlined above

Comments/ explanation/ reasons for substantial amendment:

Added to comply with condition placed by MHRA on approval of last amendment.

Substantial amendment 8

Previous and new wording:*(tracked)*

New wording:

Comments/ explanation/ reasons for substantial amendment:

Addition of Kaletra liquid formulation to CTA. As this comes from third country (albeit manufactured in UK) details of MA and QP release also provided (but SmPC will be reference document). This will be labelled at sites to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the IMP.

Substantial amendment 9

Previous and new wording:*(tracked)*

Patients enrolled in the RECOVERY trial and with clinical evidence of a hyper-inflammatory state may be considered for a second randomisation if they meet the following criteria:

- i. Randomised into the RECOVERY trial no more than 21 days ago
- ii. Clinical evidence of progressive COVID-19:
 - a. oxygen saturation <92% on room air or requiring oxygen (or in children (age <18 years), significant systemic disease with persistent pyrexia, with or without evidence of respiratory involvement); and
 - b. C-reactive protein ≥ 75 mg/L

New wording:

Underlined above

Comments/ explanation/ reasons for substantial amendment:

A new "multisystem inflammatory syndrome associated with COVID-19" has been described by RCPCH and cases are identified across UK, Europe and USA. There are now more than 50 children with this syndrome across UK. It is becoming apparent that one of the manifestations of COVID-19 in children appears to be this systemic inflammatory syndrome which does not have any pulmonary involvement unlike adults with COVID-19. However, these children need significant input in Intensive care with potential for significant morbidity and mortality.

After consulting with paediatric working group, we wish to amend the criteria for recruitment into the Tocilizumab arm to include these children.

Substantial amendment 10

Previous and new wording: *(tracked)*

New wording:

Comments/ explanation/ reasons for substantial amendment:

Typographical and other corrections (including unification of reference lists for ease of use).

(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 document¹¹



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: Peter Horby

J.2.3 Date: 2020/05/12

This section was signed electronically by Professor Peter William Horby on 14/05/2020 14:37.

Job Title/Post: Professor of Emerging Infections

Organisation: University of Oxford

Email: peter.horby@ndm.ox.ac.uk

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: Peter Horby

J.3.3 Date: 2020/05/12

This section was signed electronically by Professor Peter William Horby on 14/05/2020 14:37.

Job Title/Post: Professor of Emerging Infections

Organisation: University of Oxford

Email: peter.horby@ndm.ox.ac.uk

- (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.*