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)
TACTIC- E (COVID-19)

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)
TACTIC- E (COVID-19)

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

REC Name:

REC Reference Number: **Submission date:**

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

mulTi-Arm Therapeutic study in pre-ICu patients admitted with Covid-19 – Experimental drugs and mechanisms

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

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

Given name	Joseph
Family name	Cheriyan
Qualification (MD...)	MBCHB, MA (Cantab), FRCP
ORCID ID	
Institution name	Cambridge University Hospitals NHS Foundation Trust
Institution department name	Experimental Medicine & Immuno Therapeutics, ACCI, Level 3, Box 98
Street address	Hills Road
Town/city	Cambridge
Post Code	CB2 0QQ
Country	UNITED KINGDOM
Work E-mail	jc403@medschl.cam.ac.uk

* Personal E-mail	jc403@medschl.cam.ac.uk
Work Telephone	01223256653
* Personal Telephone/Mobile	01223256653
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
	Miss	Natalia	Igosheva
Address	Level 6, Coton House		
	Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital		
	Hills Road,		
Post Code	CB2 0QQ		
E-mail	cctureguIatory@addenbrookes.nhs.uk		
Telephone	01223349760		
Fax			

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):	A095607
Sponsor's/protocol number:	TACTIC-E
Protocol Version:	1.0
Protocol Date:	27/05/2020
Funder's reference number (enter the reference number or state not applicable):	not applicable
Project website:	www.tactictrial.net

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):	NCT04393246
European Clinical Trials Database (EudraCT) number:	2020-002229-27

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.
TACTIC-R (IRAS 282213) Multiarm Therapeutic study in pre-ICU patients admitted with COVID-19 - Repurposed Drugs

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.*

The COVID-19 pandemic is caused by a novel coronavirus (SARS-Cov-2). It is estimated that it will cause a significant number of deaths in the UK alone due to the complications that can arise in older patients and those with other comorbidities. While there are no current vaccines, prophylactic or therapeutic agents of proven efficacy, several medications licensed for patients with autoimmune disease can be used to prevent overactivation of the immune response in severe COVID-related disease.
TACTIC-E is a randomised, parallel arm, open-label, platform trial of potential disease modifying therapies in patients with late stage 1/stage 2 COVID-19-related disease, with a diagnosis based either on a positive assay or high suspicion of COVID-19 infection by clinical and radiological assessment.
TACTIC-E is part of the TACTIC programme of research that will look at repurposing drugs and experimental drugs in the management of COVID-19 related complications.
The aim TACTIC-E trial is to determine if a novel immunomodulatory intervention reduces the composite progression of patients with COVID-19-related disease to organ failure or death.
The trial will have 2 treatment arms and a comparator arm using the following drugs: Dapagliflozin and Ambristentan (administered together) and EDP1815. The comparator is standard of care treatment.

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.

All patients will receive the best standard of care according the current treatment guidelines at the time of recruitment. TACTIC-E subjects will also be randomised to either no additional therapy, or one of the trial interventional arms. The patient selection criteria (including the risk score) ensure that participants are enrolled who are at significant risk of clinical deterioration, providing justification for the risks associated with the proposed therapies.

COVID19 preferentially affects older adults, and such patients frequently present with delirium during infections. This patient population is essential to include in research to ensure external validity of findings. However some participants may not have the capacity to consent to this trial. In patients lacking capacity, a legal representative will be sought. In cases where no personal legal representative is available, then an independent clinician will be nominated to act as Legal Representative to fulfil this role. Further consent will then be sought with the patient if they recover sufficiently.

The investigational medicinal products:
Ambristentan is licensed for treating pulmonary arterial hypertension in adult patient. Efficacy has also been shown in idiopathic pulmonary arterial hypertension and in pulmonary arterial hypertension associated with connective tissue disease. The drug is metabolised by the liver, and has a favourable pharmacokinetic profile with minimal risk of drug interactions with common medications co-prescribed in COVID19. The side effects of Ambrisentan are established in other disease areas, and have been carefully reviewed before inclusion in TACTIC-E. The most relevant effect is reduced blood pressure. However, in stage 2 COVID19 disease (the time between the initial mild viral symptoms and before progression to ventilatory failure), very few patients have significant haemodynamic instability. Data from King's College Hospital showed only 8% of admissions were hypotensive on presentation. In addition, patients with COVID19 will have close clinical monitoring, with dosing of Ambrisentan taking place in hospital, mitigating the potential of this side effect to cause harm.

Dapagliflozin is licensed for treatment of insufficiently controlled type 2 diabetes mellitus. The drug is metabolised by the kidneys, and has a favourable pharmacokinetic profile, with minimal risk of drug interactions with common medications co-prescribed in COVID19. Similar to Ambrisentan, an important consideration is the risk of volume depletion with Dapagliflozin, which can cause a mild diuresis. Studies from patients with cardiac failure have provided reassurance about the safety of the drug in the context of unstable fluid balance. However, similar to the discussion for Ambrisentan, the key mitigation to this risk is the concurrent vital sign monitoring that will be ensured for all participants.

Both Ambrisentan and Dapagliflozin will be used outside of licensing for this trial.

In addition, one of the treatment arms in the trial will study EDP1815. EDP1815 is an orally administered non-live pharmaceutical preparation of a single strain of a human commensal bacteria, Prevotella histicola. it has been selected for its ability to modulate immune system responses. Pre- clinical findings have suggested that EDP1815, despite being gut restricted, can modulate systemic immune biology, and this unique profile and mechanism makes EDP1815 an ideal candidate for the TACTIC-E trial. As EDP1815 is a monoclonal microbial product, concerns around drug interactions, pharmacokinetic interactions or metabolism are not an issue. Data from use in autoimmune disease (psoriasis) demonstrate excellent safety profiles with no issues around tolerability. EDP1815 is currently unlicensed.

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.*

To determine if a specific intervention reduces the composite of progression of patients with COVID-19-related disease to organ failure or death.

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

To identify the pharmacodynamic effects of therapies on biomarkers known to be associated with progression of CRC.

To identify pharmacodynamic effects of the therapies based on their mechanisms of action.

To determine if a specific intervention reduces severity of disease as assessed by the 7-point ordinal scale.

To determine if a specific intervention reduces incidence of the individual endpoints of the composite.

To assess the safety and efficacy of the different arms.

To identify the pharmacodynamic effects of therapies on relevant biomarkers

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

There is currently no protocolised treatment for COVID-19 related disease and there is still limited data on drug efficacy.
Due to the rapid increase in COVID-19 positive cases in the UK alone, it is likely that the National Health System will be overwhelmed and might result in failure to deliver optimum health care. In older adults and patients with preexisting comorbidities this may result in severe complications that may require admission to ICUs.
This trial aims to reduce the number of admissions to ICU by tackling the immune response to COVID-19 at an early disease stage and decrease the likelihood of aggravating patient condition by assessing different medications in a platform study.
Several medications that are used to treat patients with autoimmune disease such as rheumatoid arthritis, act by modulating the immune response. An abberant activation of the immune system can cause further collateral damage and result in acute respiratory distress syndrome (ARDS), organ failure and possible death.
Some studies have already contemplated modulating the immune response, however this has the potential to cause more harm to the patient rather benefit. It remains unknown what causes the aberrant activation of the immune system, so the use of the chosen drugs with a good safety profile will target multiple pathways to avoid this. Mode of action of these immunomodulators has already shown some effectiveness against coronavirus outbreak in 2012.

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.*

This trial is a randomised, parallel arm, open label platform study with 2 treatment arms and a comparator arm.

The aim of the trial is to modify immune response in COVID-19 positive patients to prevent organ damage and reducing the need for transfer to ICU.

The different available arms for this trial are:

Arm 1: EDP1815 in addition to standard of care

Arm 2: Ambrisentan and Dapagliflozin in addition to standard of care

Arm 3: Standard of care (including approved antiviral therapies)

TACTIC-E is part of the TACTIC programme of research. This design would allow flexible features such as dropping treatments for futility, declaring one or more treatments superior to standard of care, or adding new treatments to be tested during the course of a trial.

Screening (day -2 to day -1)
After discussing the study with the research team and having any questions answered the participants will be asked to provide informed consent prior to any study procedures being carried out. In line with other urgent COVID -19 trials such as RECOVERY if the patient lacks capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or delerium), 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. Participants that are contemplated for the trial will be those that are admitted to hospital. Assessments will include review of medical history and whole medical record, clinical examination, medication review, blood tests, pregnancy test (if required), chest x-ray (extracted from medical records) and eligibility check for inclusion and exclusion criteria. Chest x-ray will be an optional assessment. They will then be randomised into one of the available arms. Screening and baseline visits can be done on the same day, with treatment commencing on the same day where possible.

Baseline (day -2 to day -1)
Several data points will be collected: days since onset of symptoms, demographics, anthropomorphic data, current position on 7-point ordinal scale, COVID-19 RTPCR result if available, extraction of clinical data from medical records and research blood samples where units have capability.
At selected sites, optional research samples may be taken for assays of biomarkers of response at this visit including but not confined to immunological and genomic transcriptomic and cellular analyses for future analysis.

Treatment phase (Day 2-14, treatment will begin on Day 1)
On the ward several data points will be collected (vital signs from medical records, current position on 7-point ordinal scale, COVID-19 RTPCR results if available, extraction of clinical data form medical records and review of adverse events). Additionally; on days 2, 6 and 14 (+/- 2 days) or discharge, there will be a research blood sampling where units have capability and record of days since onset of symptoms). Assessments on Day 14 or discharge will be done where
feasible.

Follow up (28 days, and 3 months)
28 days after screening visit and 3 months after baseline visit, the patients will be assessed again. Several data points will be collected (discharge status, return to normal function status, mortality status, days since onset of symptoms and review of adverse events). If possible this visit will be done via telephone.

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
- [ ] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The protocol and research processes were widely circulated among frontline NHS staff during its development.

Feedback was collated and incorporated into the Protocol and PIS-ICF where appropriate.

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
- [x] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [x] Infection
- [x] 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
- [x] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

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

To be included in the trial the participant must:
• be aged 18 or over
• have clinical picture strongly suggestive of COVID-19-related disease (with/without positive COVID-19 test) AND
- Risk count (as defined above) >3
OR
- Risk count >=3 if it includes “Radiographic severity score >3”
• be considered an appropriate subject for intervention with immunomodulatory or other disease modifying agents in the opinion of the investigator
• Is able to swallow capsules/tablets

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

The presence of any of the following will preclude participant inclusion:

• Inability to supply direct informed consent from patient or from Next of Kin or Independent Healthcare Provider on behalf of patient
• Invasive mechanical ventilation at time of screening
• Contraindications to study drugs, including hypersensitivity to the active substances or any of the excipients
• Currently on any of the study investigational medicinal products
• Concurrent participation in an interventional clinical trial (observational studies allowed)
• Patient moribund at presentation or screening
• Pregnancy at screening
• Unwilling to stop breastfeeding during treatment period
• Known severe hepatic impairment (with or without cirrhosis)
• Stage 4 severe chronic kidney disease or requiring dialysis (i.e. Cockcroft Gault estimated creatinine clearance < 30 ml /min)
• Inability to swallow at screening visit
• Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of a safety concern.
• Patient is taking a systemic immunosuppressive agent such as, but not limited to, oral steroids, methotrexate, azathioprine, ciclosporin or tacrolimus, unless these are given as part of COVID standard of care treatment.
• Type 1 diabetes
• Known idiopathic pulmonary fibrosis
• Previous hospital admission with ketoacidosis
• History of symptomatic heart failure within 3 months of admission
• Sustained blood pressure below 90/60 mmHg at admission
• Metabolic acidosis defined as pH< 7.25 (or venous bicarbonate <15 mmol/l) AND ketones > 3.0 mmol/L
• Alanine transaminase and/or aspartate transaminase (ALT and/or AST) > 3 times the upper limit of normal (only one needs to be measured)

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	30 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Demography/anthropomorphic data/ medical history/medication history	1	0	10 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Adverse events review	16	0	10 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
7-point ordinal scale	14	0	2 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.

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
Vital signs	14	0	15 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
COVID-19 RT-PCR	14	0	5 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Blood sampling (baseline)	1	1	5 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Research blood sampling (optional)	4	0	5 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Pregnancy test (blood/urine)	1	0	5 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Height and weight	1	0	10 mins	Principal investigator or suitably qualified and delegated member of research team. This will
EDP1815 administration	14	0	5 mins	Oral dose taken by trial participant in hospital
Dapagliflozin administration	14	0	5 mins	Oral dose taken by trial participant in hospital
Ambristentan administration	14	0	5 mins	Oral dose taken by trial participant in hospital
Physical examination	1	0	15 mins	Principal investigator or suitably qualified and delegated member of research team. This will take place at the hospital.
Venous blood gas (pH) or venous bicarbonate : Screening for all	15	0	10	Principal investigator or

patients & thereafter for Ambrisentan + Dapagliflozin arm only			mins	suitably qualified and delegated member of research team. This will take place at the hospital.
Blood ketone POC: Screening for all patients & thereafter for Ambrisentan + Dapagliflozin arm only	15	0	10 mins	Principal investigator or suitably qualified and delegated member of research team. This will

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

○ Yes ◉ No

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

The total trial duration for each participant will be approximately 90 days (+/- 7 days) in total. The trial primary endpoint will be assessed at day 14/discharge/primary endpoint met whichever is sooner. Follow up will continue up to 3 months to capture secondary endpoints.

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.

Irrespective of participation in this trial an admission for COVID-19 disease comes with significant morbidity and mortality.
The trial procedures have been designed to be as minimally intrusive as possible so as not to interfere with the patients care. The patients will undergo a blood test at screening and research blood sampling at baseline, day 2,6 and 14. This is minimally invasive and may only cause some mild discomfort and possibly some bruising.

Ambristentan side effects: headache, peripheral oedema, fluid retention, anaemia, dizziness, cardiac failure, palpitations, low blood pressure, flushing, nosebleeds, difficulty breathing, upper respiratory congestion, nausea, vomiting, diarrhoea, abdominal pain, constipation, increased liver enzymes (transaminases), chest discomfort or pain, lack of energy, fatigue, hypersensitivity reactions, e.g. angioedema (swelling under the skin) rash, itchiness, fainting, autoimmune hepatitis, liver injury.

Dapagliflozin: hypoglycaemia (when used with insulin), genital infections, urinary tract infections, dizziness, rash, back pain, painful or difficult urination, increased urine output, blood test results which show an increase in haematocrit (increase in the volume of red blood cells in your whole blood), decrease in creatinine renal clearance, which indicates kidney function, or dyslipidaemia (changes in the fat concentrations), dehydration, hypotension and thirst, dry mouth and constipation, nocturia, genital pruritus, and blood test results which show an increase in blood creatinine and urea levels, which indicate kidney function and decreased weight, diabetic ketoacidosis , fournier's gangrene, angioedema (swelling under the skin).

EDP1815: There is no systemic absorption of the bacteria and hence no specific side effects have been described with EDP 1815.

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 is no guarantee that participants will benefit from taking part in this trial. Currently, 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.*

At the end of trial participation, participants will revert back to standard of care as per local policy. Administration of the investigational drug will not be continued outside the trial.

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

Due to the infection pathway of COVID-19 there is a risk to the researchers to get infected themselves. It will be ensured that researchers have access to PPE as per local trust policy.

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 patients will be identified by an attending clinician upon arrival to the participating hospital if they are strongly suspected to be or are COVID-19 positive. Suitable patients will be approached and referred to the research team if appropriate. This may be achieved by reviewing inpatient medical notes (by a member of the clinical team or suitably qualified, delegated team member) or by discussion with clinical teams regarding their inpatients. Patients will be referred to the research team if they are interested in participating in this clinical trial.

There will be study advertisements placed in clinical areas, web-based (online/generic Trust emails/newsletters) and social media platforms. Research team members who are also direct care team members will monitor admissions, electronic track boards in the emergency department and admissions ward and may receive COVID result alerts to identify potential participants.

All trial documentation will also be uploaded onto the trial website and will be accessible by members of public.

The trial may also receive media coverage in the form of newspaper articles, video recorded interviews etc.

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:
The direct clinical care team of a potential participant will review medical notes, blood results, monitor admissions and electronic track boards in the emergency department in order to assess eligibility.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Potential participant's information will only be accessible by those members of the trial team that are part of the direct care team and by the clinical care team who admit patients regularly ie the Acute Medicine department. No personal data will leave the hospitals. All data will be pseudoanonymised to protect participant's confidentiality. Patients will be given a unique trial identification number that will be used in place of their identifiable information. All investigators and trial site staff involved in this trial will comply with the requirements of the Data Protection Act 2018 and Trust Policies

with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

○ Yes ◉ No

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

◉ Yes ○ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Posters will be put up throughout the main site and participating sites to inform patients of the possibility of joining the trial.

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

The patients will first be approached by the attending clinical team who will inform the trial team to contact the patient. The trial team will outline and explain the aims of the trial and provide a copy of the patient information sheet to the patient.

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.

The patient will be given the patient information sheet before a member of the trial team (investigator or designee) will obtain informed consent. This will only be done once the patient has been given time to read, and discuss with relatives/friends, the REC approved patient information sheet. Ideally, they should be given a minimum of 12 hours but due to potential rapid deterioration of the patient this may be less. Informed consent will only be taken from the patient after a fully informed discussion.
In cases where the patient lacks capacity to provide written consent due to the severity of their medical condition or prior disease, consent may be obtained from a relative acting as the legal representative of the patient or from an independent healthcare provider. Legal representative will receive a thorough explanation of the trial and will be able to make a decision on behalf of the patient. Further consent from the patient will be sought if they recover sufficiently. Any new information which becomes available that might affect the patient´s decision to remain in the trial will be communicated to the participant/legal representative as soon as possible.

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

If a patient is too ill to provide written consent a legally designated representative (a relative/friend/health care professional not involved in the trial) can provide written consent.

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?

Participants will ideally be given 12 hours to consider taking part in the trial. However, due to the acute nature of COVID-19 this may be 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 are allowed to take part in observational studies at the same time as taking part in TACTIC-E.

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, an interpreter (eg. professional translator or close relative) will be used.

Patient information sheet and consent forms will only be available in 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?

The primary language of communication of all NHS staff in the UK is English. Therefore, given the emergency situation that the UK is experiencing, it was not considered an efficient use of resources at this time. However, if requested, Welsh translation services are available.

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?

In the event of new information becoming available during the course of the trial which may affect a patient's willingness to continue in the trial, the principal investigator or suitably qualified, delegated member of the trial team will contact them at the earliest opportunity and provide the information verbally. Once the updated patient information sheet has been approved by the REC, the patient will be provided with this document and if appropriate, asked to re-consent to the trial.

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
- [x] Electronic transfer by magnetic or optical media, email or computer networks
- [x] Sharing of personal data with other organisations
- [x] 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:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [ ] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
The Clinical Trials Monitor will require access to participant's medical records as part of their routine monitoring duties conducted on behalf of the Sponsor. In the event of a Sponsor led audit or CA Inspection, the authorised individual will also require access to the participant's medical records in the course of their duties.
With the exception of communications within the research team about specific participants and their visits, treatment or data, the data transferred will be pseudoanonymised.
Participants may provide a variety of contact information to the research team for study related communication. This will be held in strictest confidence.
Personal data will be recorded in screening/enrolment logs and with results of some assessments (e.g. laboratory reports). Such data will be accessible only by members of the research team who will respect patient confidentiality at all times. Some personal health related data, such as pregnancies and serious adverse reactions may be shared with other organisations in the UK and abroad.
Participants medical records (held on NHS computers) will include references to their participation in this study.

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

Personal data will be stored within a secure area within the local centers with access limited to employees of the clinical trials unit and clinical study team (Investigator or Designee). Where personal data is stored electronically it will be stored on password protected central secure server.

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.*

Each participant will be allocated a unique trial number at trial entry and will be identified by this number and date of birth on all trial related documentation throughout the course of the trial and data analysis process, with the exception of enrollment logs, prescriptions etc.
Any data transfer will be done according to the NHS Code of Practice on Confidentiality and local Trust data protection policies and procedures.
All investigators and trial site staff involved in this trial will comply with the requirements of the Data Protection Act 2018 and Trust Policies with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

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.*

Medical records and personal data of the participants will be accessed by members of direct clinical care team and also the research study team in order to provide appropriate care and to contact participants as deemed necessary (eg. phone calls to remind participant of follow up appointment/requirements.).

Participants will provide informed consent for all delegated members of the research team to access their data.

Clinical trial monitors and authorised representatives of the sponsor and MHRA will access personal data as part of their review of study information.

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?

Anonymised data will be analysed by the trial statistician. Any data transferred will be done according to the NHS Code of Practice on Confidentiality and local Trust data protection policies and procedures.

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

Title	Forename/Initials	Surname
Dr	Joseph	Cheriyan

Post	Consultant Clinical Pharmacologist/Assoc Lecturer
Qualifications	MBCHB, MA (Cantab), FRCP
Work Address	Cambridge University Hospitals NHS Foundation Trust Experimental Medicine & Immuno Therapeutics, Addenbrooke's Hospital ACCI, Level 3, Box 98
Post Code	CB2 0QQ
Work Email	jc403@medschl.cam.ac.uk
Work Telephone	01223256653
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

If longer than 12 months, please justify:
Personal data included in the Trial Master File and electronic CRF's will be stored for the duration of the trial and then archived in accordance with the current Sponsor's retention policy and applicable regulatory requirements. Principal investigators at their relevant institutions will act as local custodians for the data, and should refer to their Trust's policy for the records retention in terms of access to patients medical records.

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

Years: 5
Months: 0

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.*

Once the trial has started, the research data will be stored securely and centrally by the Cambridge Clinical Trials Unit during the trial. Once trial
has ended, all trial related documentation and data will be archived in accordance with the Sponsor's SOPs, Policies and Procedures.
All trial related documentation as part of the investigator site file and data will be archived in accordance with the participating site's standard operating procedures. These procedures state suitable locations to be specified at the time of archiving with limited access to named members of the research team only.
The co-ordination team at Cambridge Clinical Trials Unit will be responsible for the archiving of the Trial Master File

and each participating site will be responsible for archiving their own site file.

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.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

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 has been registered on ClinicalTrials.gov (NCT04393246) and will also be registered on ISRCTN and EudraCT register.

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:*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [x] Publication on website
- [x] Other publication
- [x] 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?

Identifiable personal data will not be part of published results.

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.
Participants will be sent a simplified summary of the trial at the end of the research once data has been collected and analysed.

5. Scientific and Statistical Review

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

- [x] Independent external review
- [x] Review within a company
- [x] 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:
It was devised by a steering group of experts.

It has gone through a separate review in the process of funding applications to the Astrzeneca and Evelo Biosciences.

We also have independent external reviews from Profs Ritter and Cockcroft - enclosed with this application.

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

☑ 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
	Dr	Simon	Bond
Department	Cambridge Clinical Trials Unit		
Institution	Cambridge University Hospitals NHS Foundation Trust		
Work Address	Hills Road		
	Cambridge		
Post Code	CB2 0QQ		
Telephone	01223596475		
Fax			
Mobile			
E-mail	simon.bond@addenbrookes.nhs.uk		

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

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

Time to incidence (up to Day 14) of any one of the following:

o Death
o Invasive mechanical ventilation
o ECMO
o Cardiovascular organ support (balloon pump or inotropes/ vasopressors)
o Renal failure (Cockcroft-Gault estimated creatinine clearance <15 ml /min), haemofiltration or dialysis

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

• Biomarkers thought to be associated with progression of COVID-19: Ferritin, CRP, D-Dimer, neutrophil to lymphocyte ratio, LDH
• Change in clinical status as assessed on 7-point ordinal scale compared to baseline
• Time to each of the individual endpoints of the composite primary outcome measure
• Proportion of patients with adverse events of special interest in each arm
• SpO2/FiO2
• Time to Sp02 >94% on room air (excluding chronically hypoxic individuals)
• Time to first negative SARS-CoV2 PCR
• Duration of oxygen therapy (days)
• Duration of hospitalisation (days)
• All-cause mortality at day 28
• Time to clinical improvement (defined as >2 point improvement from day 1 on 7-point ordinal scale)

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:	1407
Total international sample size (including UK):	1407
Total in European Economic Area:	1407

Further details:
There is not a fixed sample size for this study and futility analyses will be performed to minimise the number of subjects exposed to potentially inefficacious compounds. As the agents in this study are either novel (pre-approval) or novel combinations of approved agents, a biomarker based futility analysis will be assessed to provide a very early stopping criteria. The point at which this early biomarker futility analysis can be performed will be determined during the study.

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.*

There is not a fixed sample size for this study and the only predetermined aspect is to perform an interim analysis after approximately 125 patients are recruited to each of the two active arms. Given the randomisation ratios, we would expect 375 patients to be recruited at the time of the interim analysis. Thereafter, the DMC has the ability to recommend which arms are to continue or to allow additional arms, and for how many subsequent patients to recruit before the next interim analysis. Provisionally, there will be a second interim after approximately 229 patients per active arm, and potentially then a third interim after approximately 469 per active arm, to be agreed or modified with the DMC at each preceding interim analysis.

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 randomised using a central web-based randomisation service initially in a 1 (arm 1):1 (arm 2):1 (arm 3) ratio to one of the following treatment arms (each in addition to standard of care (SoC).

Arm 1: EDP1815 in addition to standard of care

Arm 2: Ambrisentan and Dapagliflozin in addition to standard of care

Arm 3: Standard of care (including approved antiviral therapies)

If a patient meets drug-specific exclusion criteria for any of the active treatment arms then they can be randomised to one of the remaining arms as long as they meet any additional drug specific inclusion/exclusion criteria.

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.

The primary endpoint will compare the experimental treatments to control using Cox proportional hazards, adjusting for important baseline prognostic predictors (age, gender, ethnicity, radiological severity score, underlying health condition, neutrophils, CRP, and recruiting site). Estimates, 95% confidence intervals and p-values will be provided for the treatment effects on the hazard ratio (HR) scale. The main analyses will be conducted by the trial statistician following the intention-to-treat principle.

Secondary endpoints will be analysed using a similar regression methodology, as suitable for the nature of the endpoint (binary, categorical, continuous, time-to-event).

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
	Dr	James	Galloway
Post	Senior Lecturer and Honorary Consultant Rheumatologist		
Qualifications	MBChB, MSc, CHP, MRCP, PhD		
Employer	King's College London		
Work Address	Faculty of Life Sciences and Medicine Guy's Campus King's College London		
Post Code	SE1 1UL		
Telephone			
Fax			
Mobile			
Work Email	james.galloway@nhs.net		

	Title	Forename/Initials	Surname
	Dr	Frances	Hall
Post	Consultant Rheumatologist		
Qualifications	M.A.oxon, B.M., B.Ch., F.R.C.P.(UK), D.Phil		
Employer	Cambridge University Hospitals NHS Foundation Trust		
Work Address	Box 194, Hills Road Cambridge		
Post Code	CB2 0QQ		
Telephone			
Fax			
Mobile			
Work Email	frances.hall@addenbrookes.nhs.uk		

	Title	Forename/Initials	Surname
	Professor	Ian	Wilkinson
Post	Professor of Therapeutics & Hon Consultant Clinical Pharmacologist		
Qualifications	BA, BM BCh, MA, MRCP, DM, FRCP		
Employer	Cambridge University Hospitals NHS Foundation Trust		
Work Address	Experimental Medicine & Immuno Therapeutics, Addenbrooke's Hospital		
Post Code	CB2 0QQ		
Telephone	01223336806		
Fax			
Mobile			
Work Email	ibw40@medschl.cam.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Andrew	Cope
Post	Versus Arthritis Professor of Rheumatology Head, Centre for Rheumatic Disease		
Qualifications	BSc, MBBS, PhD, FRCP, HFEA		

Employer	King's College London
Work Address	Faculty of Life Sciences and Medicine Guy's Campus King's College London
Post Code	SE1 1UL
Telephone	
Fax	
Mobile	
Work Email	andrew.cope@kcl.ac.uk

Title	Forename/Initials	Surname
Professor	David	Jayne

Post	Professor of Clinical Autoimmunity
Qualifications	MD, FRCP, FRCPE, FMedSci
Employer	Cambridge University Hospitals NHS Foundation Trust
Work Address	Hills Road
Post Code	CB2 0QQ
Telephone	01223245151
Fax	
Mobile	
Work Email	dj106@medschl.cam.ac.uk

Title	Forename/Initials	Surname
Professor	Iain	McInnes

Post	Versus Arthritis Professor of Rheumatology, and Director of Institute of Infection, Immunity and Inflammation
Qualifications	
Employer	University of Glasgow
Work Address	120 University Place Glasgow
Post Code	G12 8TA
Telephone	
Fax	
Mobile	
Work Email	Iain.McInnes@glasgow.ac.uk

Title	Forename/Initials	Surname
Dr	Michalis	Kostapanos

Post	Consultant in Acute Medicine
Qualifications	MD, PhD, FRSPH
Employer	Cambridge University Hospitals NHS Foundation Trust
Work Address	Addenbrooke's Hospital ACCI Hills Road, Cambridge
Post Code	CB2 0QQ
Telephone	
Fax	

Mobile	
Work Email	mk828@medschl.cam.ac.uk

Title	Forename/Initials	Surname
Dr	Edward	Banham-Hall

Post	Consultant in Acute and General Medicine
Qualifications	MRCP, PhD
Employer	Cambridge University Hospitals NHS Foundation Trust
Work Address	Hills Road
Post Code	CB2 0QQ
Telephone	
Fax	
Mobile	
Work Email	edward.banham-hall@addenbrookes.nhs.uk

Title	Forename/Initials	Surname
Mrs	Anita	Chhabra

Post	Lead Clinical Trials Pharmacist (Oncology)
Qualifications	
Employer	Cambridge University Hospitals NHS Foundation Trust
Work Address	Addenbrooke's Hospital Hills Road
Post Code	CB2 0QQ
Telephone	01223245151
Fax	
Mobile	
Work Email	anita.chhabra@addenbrookes.nhs.uk

Title	Forename/Initials	Surname
Miss	Sonakshi	Kadyan

Post	Clinical Trials Coordinator
Qualifications	B.Tech, MRes
Employer	Cambridge University Hospitals NHS Foundation Trust
Work Address	Hills Road
Post Code	CB2 0QQ
Telephone	01223349007
Fax	
Mobile	
Work Email	sonakshi.kadyan@addenbrookes.nhs.uk

Title	Forename/Initials	Surname
Professor	Iain	McInnes

Post	Muirhead Chair of Medicine, Versus Arthritis Professor of Rheumatology, and Director of Institute of Infection, Immunity and Inflammation
Qualifications	

Employer	University of Glasgow
Work Address	Sir Graeme Davies Building, 120, University Place Glasgow
Post Code	G12 8TA
Telephone	
Fax	
Mobile	
Work Email	Iain.McInnes@glasgow.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	Cambridge University Hospitals NHS Foundation Trust
Given name	Stephen
Family name	Kelleher
Address	Research & Development, Box 277, Addenbrooke's Hospital
Town/city	Hills
Post code	CB2 0QQ
Country	UNITED KINGDOM
Telephone	01223348491
Fax	
E-mail	research@addenbrookes.nhs.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	Evelo Biosciences Inc.
Address	620 Memorial Drive Cambridge
Post Code	MA 02139
Telephone	
Fax	
Mobile	
Email	

Funding Application Status: ◉ Secured ○ In progress

Amount: £600,000

Duration
Years: 2

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

Organisation Astrazeneca PLC
Address 1 Francis Crick Ave
Trumpington, Cambridge

Post Code CB2 0AA
Telephone
Fax
Mobile
Email

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

Amount: £ 1,160,000.00

Duration
Years: 2
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

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
Ms	Lucy	Bennett

Organisation Cambridge University Hospitals NHS Foundation Trust
Address Hills Road
Cambridge

Post Code CB2 0QQ

Work Email	lucy.bennett@addenbrookes.nhs.uk
Telephone	01223348468
Fax	
Mobile	

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

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

Eastern

For more information, please refer to the question specific guidance.

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

Planned start date: 01/06/2020
Planned end date: 30/05/2022
Total duration:
Years: 1 Months: 11 Days: 30

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

Planned start date: 01/06/2020
Planned end date: 30/05/2022
Total duration:
Years: 1 Months: 11 Days: 30

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)

The end of trial is 18 months after LPLV.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

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

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 14

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:*

☑ NHS organisations in England	12
☑ NHS organisations in Wales	1
☑ NHS organisations in Scotland	1
☐ HSC organisations in Northern Ireland	
☐ 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:	14

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 sponsor has an established monitoring programme for all sponsored clinical trials. This trial will be routinely monitored and may also be selected for routine or targeted auditing if necessary. A monitoring plan will be produced describing all the planned monitoring for the trial.

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?

The trial will have an Independent Data Monitoring Committee that at regular intervals will determine
a) If there is clear evidence of efficacy in any arm; in this case the DMC may recommend that the data are published and the agent provided in the care pathway for CRC.
b) If there is a safety signal in any arm; in this case, the DMC may recommend termination of the relevant arm and addition of a new arm.

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?

Treatment arms may be discontinued due to lack of efficacy or safety concerns in which case all subjects currently being dosed will stop dosing of randomised IMP and no more subjects will be randomised to that 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.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

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.

- [x] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

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.

- [x] 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 Forxiga 10mg (Dapagliflozin)

PR2 Ambrisentan

PR3 EDP1815

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

Trade name:
Forxiga 10mg (Dapagliflozin)
EV Product Code
Name of the MA holder:
AstraZeneca AB
MA number (if MA granted by a Member State):
EU/1/12/795/007 28 film-coated tablets
Is the IMP modified in relation to its MA?

○ Yes ◉ No ○ Not Answered

Which country granted the MA?
EUROPEAN UNION
Is this the Member State concerned with this application?

○ 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

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	Forxiga 10mg (Dapagliflozin)
Product code where applicable	
ATC codes, if officially registered	A10BK01
Pharmaceutical form (use standard terms)	Film-Coated Tablet
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	14 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	10 mg per day
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	140 mg milligram(s)
Route of administration (relevant to the maximum dose):	Oral Use

Routes of administration for this IMP

Oral 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):	Dapagliflozin
CAS number:	461432-26-8
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C21H25ClO6

Chemical/biological description of the Active Substance	Dapagliflozin is a highly potent , selective and reversible inhibitor of SGLT2.
Strength	
Concentration unit:	mg milligram(s)
Concentration type:	equal
Concentration number (only use both fields for range):	10

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. Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

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

Trade name:
EV Product Code
Name of the MA holder:
MA number (if MA granted by a Member State):
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?

Is this the Member State concerned with this application?
○ 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
If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group
◉ Yes ○ No ○ Not Answered
If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

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	Ambrisentan
Product code where applicable	
ATC codes, if officially registered	C02KX02
Pharmaceutical form (use standard terms)	Film-Coated Tablet
Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
Maximum duration of treatment of a subject according to the protocol	14 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 per day
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	70 mg milligram(s)
Route of administration (relevant to the maximum dose):	Oral Use

Routes of administration for this IMP

Oral 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):	ambrisentan
CAS number:	177036-94-1
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C22H22N2O4
Chemical/biological description of the Active Substance	Ambrisentan is an Endothelin receptor antagonist, and is selective for the type A endothelin receptor.
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. Ambrisentan is an orally active, propanoic acid-class, ERA selective for the endothelin A (ETA) receptor. Endothelin plays a significant role in the pathophysiology of PAH.

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

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	EDP1815
Product code where applicable	
ATC codes, if officially registered	
Pharmaceutical form (use standard terms)	Capsule
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	14 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	1.6 x 10^11 cells (2 capsules) TWICE A DAY (3.2 X 10^11 Cells per day)
Specify per day or total	◉ per day ◯ total ◯ Not Answered
Specify total dose (number and unit)	
Route of administration (relevant to the maximum dose):	

Routes of administration for this IMP

Oral 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):	EDP1815
CAS number:	
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	
Chemical/biological description of the Active Substance	EDP1815 is a pharmaceutical preparation of a strain of Prevotella histicola.This is new class of therapeutic agent known as monoclonal microbials.
Strength	
Concentration unit:	
Concentration type:	equal
Concentration number (only use both fields for range):	8.0 x 10^10 cells per capsule

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. EDP1815 is an orally administered microbe which exerts systemic anti-inflammatory effects by modifying the activity of immune cells which are resident in the small intestine.it has been shown to increase secretion of antiinflammatory
cytokines, such as interleukin (IL)-10 and IL-27, while inducing minimal production of pro-inflammatory cytokines such as IL-6, tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ), thereby reducing immune activation and inflammation

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	Quay Pharmaceuticals Ltd
Address	Quay House, 28 Parkway Deeside Ind Park
Town/city	Flintshire
Post code	CH5 2NS
Country	UNITED KINGDOM

Give the manufacturing authorisation number
MIA(IMP) Number: MIA(IMP) 20300

If no authorisation, give the reasons:

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

IMP
PR3

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Blood samples will be obtained from participants in the trial

2. Who will collect the samples?

Principal investigator or suitably qualified delegate e.g. research nurse

3. Who will the samples be removed from?

- [x] Living donors
- [ ] The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?

(•) Yes ( ) No

In future research?

(•) Yes ( ) No ( ) Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

( ) Yes (•) No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*

( ) Yes (•) No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*

(•) Yes ( ) No

If Yes, say who will have access to the code and personal information about the donor.

Participants will be assigned a unique trial number at screening and this number will be used on all trial samples. Only authorized members of the trial team will have access to the code and personal information about the donor.

In a form in which the donor could be identifiable to researchers?

( ) Yes (•) No

9. What types of test or analysis will be carried out on the samples?

Blood samples (optional at sites depending on local logistics and/or NHS resources): biomarker analysis.

10. Will the research involve the analysis or use of human DNA in the samples?

◉ Yes ○ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

○ Yes ◉ No

12. If so, will arrangements be made to notify the individuals concerned?

○ Yes ○ No ◉ Not applicable

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Participants on this trial will be assigned a unique trial number. This number and date of birth will be used as an identifier for all samples collected from them. Only authorised staff will have access to the code and personal information about the donor.
Samples will be securely stored in freezers located in the participating sites for analysis later. Only personnel authorised by the Chief Investigator or Principal Investigator (participating sites only) will be responsible for the storage and access to these samples and the samples will only be released for analysis after first seeking approval of the Chief Investigator.
Stored samples may be analysed to fulfill exploratory endpoints as part of this trial or may be used in other ethically approved research with the patient's consent. A Trial Procedures Manual will also be produced to describe how samples are processed, stored and analysed for this trial.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☑ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☑ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☑ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

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 or suspected 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.*

There is no guarantee that participants will benefit from taking part in this trial. Currently, there are no known therapies that improve outcomes in COVID-19 disease

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 for which participants will 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 enrollment into the study. However, if the patient lacks capacity to give consent due to the severity of their medical condition, 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.

For those patients whose legal representative is not immediately available, a suitable clinician independent from the research team, can give consent on behalf of the patient to proceed with randomisation and consequent treatment. Consent will be sought from the legal representative or directly form 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 in mind potential visiting restrictions to COVID-19 cases). Legal representatives will be kept informed about the
situation throughout the hospital stay. This will be done by telephone call or other mutually acceptable form of communication due to restrictions on visiting and high infection risk. If at any stage the legal representative chooses to withhold consent then the patient will be withdrawn from the trial without giving reasons and without prejudicing his/her further treatment

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.

Due to the acute setting and potential severity of illness, and the need for urgent intervention we will only provide the approved PIS and discuss any issues arising verbally. Where patients lack capacity we will seek consent from a relative or the doctor involved in their clinical care.

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

Same withdrawal criteria will apply to all patients as established in the protocol

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?

As per standard guidelines for intention to treat analysis we will include these data in the analysis - as to avoid introducing bias.

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 Middle name Family name Email	Edward Banham-Hall edward.banham-hall@addenbrookes.nhs.uk
	Organisation name	CAMBRIDGE UNIVERSITY HOSPITALS NHS FOUNDATION TRUST	Qualification (MD...)	MRCP, PhD
	Address	CAMBRIDGE BIOMEDICAL CAMPUS HILLS ROAD CAMBRIDGE	Country	UNITED KINGDOM
	Post Code	CB2 0QQ		
	Country	ENGLAND		
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Helen Parfrey hp22@cam.ac.uk
	Organisation name	ROYAL PAPWORTH HOSPITAL NHS FOUNDATION TRUST	Qualification (MD...)	BA, BM BCh, CCST, PhD, FRCP
	Address	PAPWORTH EVERARD CAMBRIDGE CAMBRIDGESHIRE	Country	UNITED KINGDOM
	Post Code	CB23 3RE		
	Country	ENGLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Andrew Cope andrew.cope@kcl.ac.uk
	Organisation name	GUY'S AND ST THOMAS' NHS FOUNDATION TRUST	Qualification (MD...)	BSc, MBBS, MRCP, PhD, FRCP
	Address	ST THOMAS' HOSPITAL WESTMINSTER BRIDGE ROAD	Country	UNITED KINGDOM

	LONDON
Post Code	SE1 7EH
Country	ENGLAND

IN4

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename	Andrew
Middle name	
Family name	Ustianowski
Email	andrew.ustianowski@pat.nhs.uk
Qualification (MD...)	MBChB, PhD, FRCP
Country	UNITED KINGDOM

Organisation name	PENNINE ACUTE HOSPITALS NHS TRUST
Address	TRUST HEADQUARTERS NORTH MANCHESTER GENERAL HOSPITAL DELAUNAYS ROAD, CRUMPSALL MANCHESTER
Post Code	M8 5RB
Country	ENGLAND

IN5

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename	Michele
Middle name	
Family name	Bombardieri
Email	m.bombardieri@qmul.ac.uk
Qualification (MD...)	MD, PhD, FRCP
Country	UNITED KINGDOM

Organisation name	BARTS HEALTH NHS TRUST
Address	THE ROYAL LONDON HOSPITAL 80 NEWARK STREET LONDON
Post Code	E1 2ES
Country	ENGLAND

IN6

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Forename	Muhammad
Middle name	
Family name	Nisar
Email	muhammad.nisar@ldh.nhs.uk
Qualification (MD...)	MBBS, MRCP, FRCP
Country	UNITED KINGDOM

Organisation name	LUTON AND DUNSTABLE UNIVERSITY HOSPITAL NHS FOUNDATION TRUST
Address	LEWSEY ROAD LUTON

Post Code	LU4 0DZ
Country	ENGLAND

IN7

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	BASILDON AND THURROCK UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	BASILDON HOSPITAL NETHERMAYNE BASILDON
Post Code	SS16 5NL
Country	ENGLAND

Forename	Simon
Middle name	
Family name	Godwin
Email	godwin.simon@btuh.nhs.uk
Qualification (MD...)	MBBS, MD, MRCP, CCT, FRCP
Country	UNITED KINGDOM

IN8

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	MID ESSEX HOSPITAL SERVICES NHS TRUST
Address	BROOMFIELD HOSPITAL COURT ROAD CHELMSFORD
Post Code	CM1 7ET
Country	ENGLAND

Forename	Emese
Middle name	
Family name	Balogh
Email	Emese.Balogh@meht.nhs.uk
Qualification (MD...)	MD, PhD
Country	UNITED KINGDOM

IN9

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST
Address	FREEMAN HOSPITAL FREEMAN ROAD HIGH HEATON NEWCASTLE UPON TYNE
Post Code	NE7 7DN

Forename	Arthur
Middle name	
Family name	Pratt
Email	arthur.pratt@newcastle.ac.uk
Qualification (MD...)	BSc, MBChB , MRCP, PhD
Country	UNITED KINGDOM

Country ENGLAND

IN10

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	JAMES PAGET UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
Address	LOWESTOFT ROAD GORLESTON GREAT YARMOUTH
Post Code	NR31 6LA
Country	ENGLAND

Forename	Damodar
Middle name	
Family name	Makkuni
Email	damodar.makkuni@jpaget.nhs.uk
Qualification (MD...)	FRCP
Country	

IN11

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	NHS Greater Glasgow and Clyde
Address	J B Russell House Gartnavel Royal Hospital 1055 Great Western Road Glasgow Glasgow Scotland
Post Code	G12 0XH
Country	SCOTLAND

Forename	Iain
Middle name	
Family name	McInnes
Email	Iain.Mcinnes@glasgow.ac.uk
Qualification (MD...)	BSc, MBChB, MRCP, PhD, FRCP, FRSE, FRCP, FMedSci
Country	UNITED KINGDOM

IN12

◉ NHS/HSC Site
○ Non-NHS/HSC Site

Organisation name	CARDIFF & VALE UNIVERSITY LHB
Address	WOODLAND HOUSE MAES-Y-COED ROAD CARDIFF
Post Code	CF14 4HH
Country	WALES

Forename	Jonathan
Middle name	
Family name	Underwood
Email	jonathan.underwood@wales.nhs.uk
Qualification (MD...)	MBBS, MRCP, DipHIV, PhD
Country	UNITED KINGDOM

IN13

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST
Address	DENMARK HILL
	LONDON
Post Code	SE5 9RS
Country	ENGLAND

Forename	James
Middle name	
Family name	Galloway
Email	james.galloway@kcl.ac.uk
Qualification (MD...)	MBChB, MSc, CHP, MCP, PhD
Country	UNITED KINGDOM

IN14

(●) NHS/HSC Site
( ) Non-NHS/HSC Site

Organisation name	LEEDS TEACHING HOSPITALS NHS TRUST
Address	ST. JAMES'S UNIVERSITY HOSPITAL
	BECKETT STREET
	LEEDS
Post Code	LS9 7TF
Country	ENGLAND

Forename	Sinisa
Middle name	
Family name	Savic
Email	s.savic@leeds.ac.uk
Qualification (MD...)	MBBS, MSc, PhD, FRCPath, MRCP
Country	UNITED KINGDOM

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 Dr JOSEPH CHERIYAN on 27/05/2020 17:36.

Job Title/Post:	Consultant Clinical Pharmacologist & Physician
Organisation:	Cambridge University Hospitals NHS Foundation Trust
Email:	jc403@cam.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 Dr Natalia Igosheva on 27/05/2020 17:54.

Job Title/Post:	Clinical Trials Officer
Organisation:	Cambridge University Hospitals NHS FT
Email:	natalia.igosheva@addenbrookes.nhs.uk