Welcome to the Integrated Research Application System

IRAS Project Filter

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

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

Please enter a short title for this project (maximum 70 characters)
RECOVERY-Supportive Care

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. 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

2b. 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)*

- [x] England
- [ ] Scotland
- [x] Wales
- [x] 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?

- [x] IRAS Form
- [x] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

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

( ) Yes (•) No

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

(•) Yes ( ) No

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

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

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

Please see information button for further details.

(•) Yes ( ) No

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

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete

the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

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

○ Yes ◉ No

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

◉ Yes ○ No

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

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

○ Yes ◉ No

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

○ Yes ◉ No

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

○ Yes ◉ No

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

◉ Yes ○ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

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

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

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

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

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:

Ventilation Strategies in COVID-19; CPAP, High-flow, and standard care

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Gavin	Perkins
Post	Chief Investigator/WCTU Director		
Qualifications	MB ChB, MD, FRCP, FFICM, FIMC RCS(Ed)		
ORCID ID	0000 0003 3027 7548		
Employer	University of Warwick		
Work Address	Warwick Clinical Trials Unit		
	The University of Warwick		
	Gibbet Hill Road		
Post Code	CV4 7AL		
Work E-mail	g.d.perkins@warwick.ac.uk		
* Personal E-mail	g.d.perkins@warwick.ac.uk		
Work Telephone	02476 750479		
* Personal Telephone/Mobile	02476 750479		
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
	Mr	Scott	Regan
Address	Warwick Clinical Trials Unit		
	University of Warwick, Gibbet Hill Campus		
	Coventry		
Post Code	CV4 7AL		
E-mail	S.Regan@warwick.ac.uk		
Telephone	02476151301		
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):	26/19-20
Sponsor's/protocol number:	26/19-20
Protocol Version:	1.0
Protocol Date:	01/04/2020
Funder's reference number (enter the reference number or state not applicable):	TBC
Project website:	TBC

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): ISRCTN00000000
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

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

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of

specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

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

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 as a new coronavirus, resulting in a current global pandemic of respiratory illness, Coronavirus Disease 2019 (COVID-19). This illness can cause serious breathing difficulties and it is important to provide ventilatory (lung or respiratory system) methods to support the patient to breathe. Deciding which form of ventilatory support for patients with COVID-19 is the most effective is critical to ensure the best therapy is given to patients and to protect vital UK critical care resources and NHS organisations. The trial will also have the potential to provide information on the global ventilation practice for patients with COVID-19.

This trial will look at three different approaches to providing ventilatory support to patients suspected or confirmed COVID-19, all of which are currently in use in clinical practice at present; High Flow Nasal Oxygen (HFNO), Continuous Positive Airway Pressure (CPAP), and standard care involving regular oxygen therapy. We will see which is more effective in relation to survival of patients and intubation (tube inserted in to patient's throat to help them breathe).

There is currently little evidence to support the use of HFNO or CPAP compared to standard care in patients with COVID-19. This trial will also look at other important outcomes in patients whilst they are in hospital such as how long it takes to intubate a patient, time to death, survival in critical care and hospital stay and length of critical care and hospital stay up until 30 days or hospital discharge, whichever comes later.

The trial is a multi-centre randomised controlled trial taking place in 40 hospital sites in the UK with the aim to recruit 4,002 patients. The trial will take place over a period of 18 months.

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.

MAIN ETHICAL ISSUES: CONSENT, CONFIDENTIALITY AND SAFETY

1) ETHICAL CONSIDERATIONS

The trial will recruit patients in UK-based hospitals in England, Wales, and Northern Ireland, many of whom will lack capacity to consent due to the nature of the underlying disease process.

Obtaining informed consent from patients will not be possible at the time of enrolment for the following reasons:
1. Patients will be deteriorating clinically with acute respiratory impairment. The resulting hypoxia, and the urgent nature with which treatment needs to be provided that limits available time, will preclude the ability to undertake a full, informed consent process and guarantee sufficient patient understanding of the information provided.
2. It is not practical or appropriate to consult a personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk of viral transmission to those involved. Significant limitations have been placed on the visitation of COVID-19 patients and therefore a personal consultee will not immediately be available, and to attempt contact via telephone will delay treatment. Pressures on clinical services will make it impractical to identify an appropriate medical practitioner.

We believe the most appropriate way to proceed is to use an emergency research model outlined in the Mental Capacity Act and to seek approval for its use by a Research Ethics Committee. We have carefully considered the framework for such a waiver of consent, developed by Davies et al (2014) in conjunction with the National Research Ethics Service. Importantly, our approach includes offering, where the clinical condition of the patient allows, brief information about the trial to participants and providing them with the opportunity to decline participation. This will be recorded on the baseline data collection form. Where a patient objects at this point they will not be entered into the study, and this will be captured through screening. It is also important to highlight that all of the interventions proposed in the trial (CPAP, HFNO, and standard care) are existing standards of care currently employed in clinical

practice; we are not investigating any experimental interventions in this trial.

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation, namely the Mental Capacity Act 2005 (England, Wales and Northern Ireland) as a proportion of patients will lack capacity, and Warwick Standard Operating Procedures (SOPs). We will apply separately for ethical approval to a REC flagged for trials involving patients without capacity in England. All data will be stored securely and held in accordance with the Data Protection Act 2018.

2) CONFIDENTIALITY

We are seeking approval from the Confidentiality Advisory Group (CAG) to use section 251 of the NHS Act 2006 and its current Regulations, the Health Service (Control of Patient Information) Regulations 2002 to access patient identifiable information prior to consent. The NHS Act 2006 and the regulations enable the common law duty of confidentiality to be temporarily lifted so that confidential patient information can be transferred to the applicant (CI researcher) without the discloser (NHS site) being in breach of the common law duty of confidentiality. We present the potential risks, mitigations and benefits of this approach below.

The main risk for access patient identifiable information from clinical records relates to a breach of trust/confidentiality through access to clinical records. We are mitigating the risk by: (1) collecting the minimum amount of data to address this research question, (2) providing a brief summary of the trial to the patient beforehand if they have mental capacity, to opt-out if they wish, (3) retrospectively retrieving patient consent or consultee agreement for ongoing delivery of the intervention and ongoing data collection, 4) collecting and submitting anonymised data only to WCTU if a patients dies prior to regaining capacity and before consultee agreement can be sought, and (5) ensuring staff collecting the data will have a duty of confidentiality through a contract with the hosting NHS Trust.

The direct benefits to current and future patients will ensure an optimum strategy is identified to manage COVID-19 patients and primarily reduce the need for intubation, with additional important benefits for healthcare resource utilisation. Considering the risks, mitigations and benefits we assess the overall risks from this to be justified.

The research requires the research team to access the following identifiable information from the patient's clinical records
1) NHS Number
2) DOB
3) Postcode
4) Initials

The information will be linked by NHS number to:
1) ICNARC
2) NHS Digital (or equivalent in devolved nations)
3) REMAP-CAP and RECOVERY trials; two other COVID-19 clinical trials currently prioritised for conduct during the COVID-19 pandemic

Our approach seeks to balance respect for the patients right to information in their medical record being treated confidentially, an urgent public health interest and need in obtaining an unbiased sample to achieve a valid research outcome, and consideration of practicable alternatives to obtaining consent.

3) SAFETY
It is essential that treatment (as per the study arms) is initiated as soon as possible. Delays in treatment initiation may place the patient at risk and increase the likelihood of the need for intubation and invasive mechanical ventilation and increase the risk of death. Delays may therefore make study interventions appear less effective by reducing any observed treatment effect. Therefore, the emergency consent research model outlined in the Mental Capacity Act will minimise risk and ensure the safety of those involved. No additional tests or investigations will be required to assess eligibility.

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
- [x] Randomised controlled trial
- [ ] Other (please specify)

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

The primary objective of this trial is to determine if CPAP or HFNO is clinically effective compared to standard care in relation to intubation (inserting a tube inside a patient's throat to help them breathe) and mortality in patients with confirmed or suspected COVID-19.

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

The secondary objectives for this study are to assess in-hospital patient data in terms of their stay. This will include:
- Intubation rates
- Time to intubation
- Time to death (mortality)
- Mortality in critical care
- Mortality in hospital stay
- Mortality at 30 days
- Length of stay in critical care
- Length of stay in hospital

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

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 as a novel coronavirus, resulting in a current global pandemic of respiratory illness, Coronavirus Disease 2019 (COVID-19). Using very recent World Health Organization (WHO) data on the total number of deaths up to 1 March 2020, death rates of 5·6% for China and 15·2% outside of China have been reported.

COVID-19 can range from having no symptoms to patients being critically ill and ultimately death. A common complication of advanced COVID-19 is severe respiratory failure requiring oxygen and ventilation therapies to help patients breathe. Patients often decline quickly, with high respiratory rate (rapid breathing) and falling oxygen levels.

Ventilation support is vital for the management for COVID-19 patients who have respiratory difficulties. Reports from China, the source of the pandemic, indicate patients with COVID-19 often experience hypoxic respiratory failure which is when there is not enough oxygen in your blood, although true global figures are unclear. That said, there is evidence that patients have received treatment to help this with high-flow nasal oxygen (HFNO), continuous positive airways pressure (CPAP), non-invasive positive pressure ventilation (NIV), and invasive mechanical ventilation.

Already the potential impact of the respiratory symptoms associated with COVID-19 on UK critical care units can be appreciated; with many patients requiring invasive mechanical ventilation.

Potentially very high numbers of patients will require ventilation support. The ability for the UK critical care hospital settings to be able to deliver this places a huge pressure on existing services with a small amount of resources. The excess demand on limited ventilator availability and critical care bed capacity is being seen across the world, in particular in neighbouring European countries.

Determining the most effective form of ventilatory support for patients with COVID-19 is therefore essential to ensure

the best therapy is delivered to patients, and to protect UK vital critical care resources and NHS organisations. Findings from this trial will also have the potential to inform global ventilation practice for patients with COVID-19.

Review of the current evidence highlights that whilst there is some evidence to support current ventilation options compared to standard oxygen therapy for patients with COVID-19, there is little evidence to guide the effectiveness of these interventions especially HFNO versus CPAP versus standard care oxygen therapy prior to intubation and invasive mechanical ventilation. Current evidence also comes from the general Acute Respiratory Failure (ARF) patient population as there is no COVID-19 specific data. Evidence on the effectiveness of these interventions is important to ensuring that critically ill patients with COVID-19 are treated in the best way to help with their breathing requirements and that the need to intubate a patient is minimised.

This trial will compare the effects of HFNO and CPAP against standard care (standard care is regular ward level oxygen therapy). Due to the uncertainty around its a0pplicability to the COVI-19 population and the clinical nature of respiratory impairment patients. This trial will provide important data to clarify current national recommendations on the preferred mode of non-invasive respiratory support.

We have also reviewed the experiences to date from other countries treating COVID-19 patients. A study in China found HFNO and invasive mechanical ventilation was the main supportive treatment for these critically ill patients. It is very worrying the demand for therapy to help patients breathe will outweigh the ability to provide it to patients. There is a huge lack of equipment to deliver ventilation methods and specialist training is also required to meet the demands. Therefore, the absolute need to reduce the number of patients requiring intubation is vital.

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.*

Primary objective

The primary objective of this trial is to determine if Continuous positive airway pressure (CPAP) or High Flow Nasal Oxygen (HFNO) is clinically effective compared to standard care in relation to intubation and mortality in patients with confirmed or suspected COVID-19.

Participant identification and screening

During the study recruitment period, hospital research teams will, on a regular basis, attend or contact hospital clinical areas caring for patients with known or suspected COVID-19. Teams will liaise with clinical staff to identify individuals with respiratory impairment (high breathing rates, and falling oxygen levels making it difficult for the patient to breathe) that may be eligible for enrolment. Based on this referral, the research team will formally assess eligibility of the patient against trial inclusion and exclusion criteria. No additional tests or investigations will be required for assessing eligibility.

All clinical trials have an inclusion and exclusion criteria referred to as the eligibility criteria which are used to assess whether it is safe and suitable for a patient to enter in to a trial. The hospital research team will assess whether an identified patient is suitable for the trial using the eligibility criteria set out in the protocol. This assessment can be carried out by any member of clinical staff (doctors and nurses) who have been given this responsibility. No further tests or investigations will be needed after this to assess a patient's eligibility.

Consent

An emergency research consent process will be used to enrol patients in to the trial. Following this, information such as patient demographics, pre-existing health conditions, temperature at hospital admission and COVID-19 diagnosis status will be recorded.

Interventions

When the patient enters the trial they be will randomly allocated to receive either CPAP, HFNO, or standard care. Patients in all three treatment groups will be intubated and receive invasive mechanical ventilation when clinically required. The three treatment arms are described here.

Continuous Positive Airway Pressure
CPAP will be administered according to local protocol/guidelines. Details of initial settings (PEEP and FiO2) will be recorded on the CRF. Administration of CPAP will not be protocolised and left to clinical discretion for management.

CPAP is machine that pumps oxygen through a mask that covers the nose and mouth. The oxygen is pumped at a set

pressure that helps to keep the airways open in patients with low oxygen levels and breathing difficulties. This increases the level of oxygen in the lungs. Because the oxygen is pumped at a high pressure, the mask needs to fit tightly over the nose and mouth to prevent any leaking. The mask is held in place with straps that go around the head and attach to the mask. CPAP can be used to avoid the need for a breathing tube and ventilator (breathing machine) in the intensive care unit.

High Flow Nasal Oxygen
HFNO will be administered according to local protocol/guidelines. Administration of HFNO will not be protocolised and left to clinical discretion for management. HFNO is a way of giving humidified (moistened) and warmed oxygen via prongs (cannuale) that sit in the nose. The oxygen is delivered at high flow (very quickly) that can be helpful for patients with low oxygen levels and breathing difficulties. In patients needing high amounts of oxygen, HFNO can be more comfortable than a tight fitting mask. HFNO can be used to avoid the need for a breathing tube and ventilator in the intensive care unit.

Standard care
Standard care will comprise regular ward level oxygen therapy according to local protocol/guidelines, and excludes escalation to CPAP and HFNO. Administration of regular oxygen therapy will not be protocolised and left to clinical discretion for management Regular oxygen therapy involves oxygen delivered via a normal face mask or prongs (cannulae) in the nose. However, oxygen would be pumped at a slower rate than in the other two treatments.

The patient will receive treatment up until the point of death, intubation, or until a decision has been made that there is no ongoing need for treatment.

Data collection and follow-up

During this time information will be collected from the patients hospital record to monitor how the patient is and their survival status. The patients will undergo regular in-hospital reviews at least weekly until day 30 or hospital discharge, whichever comes later.

Data collection and entering patients in to the trial will be completed by the Research Delivery Team at the hospital site. They will be aware of what treatment the patient is receiving. The coordinating trial team at Warwick Clinical Trials Unit will not be aware of which intervention a participant has had.

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

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

Give details of involvement, or if none please justify the absence of involvement.
Three members of Royal College of Anaesthetist Patient Carer Public Involvement Engagement (PCPIE) were approached to give their opinion on research question, study design, appropriateness of emergency waiver of consent and patient facing documents. PCPIE members were unanimous in their support for the research question and considered the study to be highly relevant to patients and public. They opined that it is critical and urgent to find the optimal breathing support for patient to avoid invasive ventilation and improve patient survival. They were also particularly supportive of the adaptive pragmatic study design and planned rapid dissemination of study results. Emergency waiver of consent was considered both appropriate in a very difficult and time critical situation and sensitive in limiting burden to patient and family.
Furthermore, we also consulted with an independent member of the Clinical Research Ambassador Group, University Hospitals Birmingham NHS Foundation Trust with extensive experience of contributing to emergency care trials. This PPI colleague was supportive and confirmed our approach of emergency consent given the challenging clinical circumstances and urgency with which treatment of potential benefit should be delivered to patients, advising that they felt it would be considered acceptable to patients and members of the public. Planned use of data without consent was also agreed as being necessary, and acceptable.

In addition, investigating optimum ventilation practice was prioritised in a 2014 James Lind Alliance Priority Setting Partnership for intensive care research involving patients and family representatives, and subsequently in a NIHR critical care research priority setting survey. We will continue to engage patients and family members at later stages of the trial conduct where possible, such as dissemination of findings.

A14-2. Have you tested the acceptability of using patient identifiable data in this study without consent?

Please give details.
We have engaged, at urgent notice, support from PPI colleagues who have confirmed they agree with the acceptability of using patient identifiable data in this study without consent.

Further detail is given in response to A14-1.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

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

Select all that apply:

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

Gender: Male and female participants

Lower age limit: 18 Years

Upper age limit:	No upper age limit

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

1. Adults ≥ 18 years
2. Admitted to hospital with suspected or proven COVID-19
3. FiO2 >0.4 and SpO2 <94%
4. Plan for escalation to intubation if needed

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

1. Planned intubation and mechanical ventilation imminent within 1 hour
2. Known or clinically apparent pregnancy
3. Any absolute contraindication to CPAP or HFNO
4. Decision not to intubate due to ceiling of care or withdrawal of care anticipated
5. Equipment for both CPAP and HFNO not available

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 following enrolment	1	0	40	Local clinicians and researchers delegated by PI. Procedure completed on hospital ward/discharge location.
Eligibility assessment	1	0	10	PI or delegate during hospital admission
Baseline characteristics and demographics	1	0	10	Delegated member of the research team

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
Continuous positive airway pressure (CPAP)	1	1	4 days	Clinical personnel e.g. doctor, nurse, physiotherapist
High flow nasal oxygen (HFNO)	1	1	4 days	Clinical personnel e.g. doctor, nurse, physiotherapist
Standard care (regular oxygen therapy)	1	1	4 days	Clinical personnel e.g. doctor, nurse, physiotherapist

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?

All clinical outcomes for the trial will be measured to 30 days following randomisation or hospital discharge, whichever comes later.

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.

Some people receiving continuous positive airway pressure (CPAP) do not like the feeling of the tight fitting mask, and sensation of the high flow of oxygen. This latter point is the same for patients receiving high-flow nasal oxygen (HFNO) as well. For example, it can make some people feel claustrophobic. CPAP may also make the patient feel sick and cause them to vomit (in case some of the extra oxygen being pumped via the machine goes into the stomach). The tight fitting mask may cause some pressure sores around the nose and mouth.

Care will be taken to ensure the best fit of the CPAP and HFNO equipment, with close monitoring of patients by clinical staff to quickly identify any adverse effects that patients may experience, and adjustments made to resolve the problems.

If the patient is allocated to receive oxygen via a standard mask this is unlikely to cause any problems except possible dryness of the mouth/nose.

These symptoms may cause a burden on participants but are part of ventilation methods currently used in critical care settings as part of standard care treatment.

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?

All three treatment arms are current treatment options available to patients in clinical practice. In this trial, we are aiming to determine which is the most effective. There may be an individual benefit to patients participating in the study, but we cannot guarantee this.

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.*

Not applicable.

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

There are no additional anticipated risks for the researchers themselves.

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).*

During the study recruitment period, hospital research teams will, on a regular basis, attend or contact hospital clinical areas caring for patients with known or suspected COVID-19. Teams will liaise with clinical staff to identify individuals with acute hypoxaemic respiratory failure that may be eligible for enrolment. Based on this referral, the research team will formally assess eligibility of the patient against trial inclusion and exclusion criteria. No additional tests or investigations will be required for assessing eligibility.

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:
Potential participants can only be identified through screening of their medical history. These procedures will be completed in line with Good Clinical Practice (GCP), the Data Protection Act (2018) and Caldicott Principles.

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.*

Local clinicians and research team members will be selected during a formal process of site selection and site setup for experience and familiarity with GCP. Local site members will be delegated screening tasks, according to their experience and skills, by an experienced local PI. Support for ensuring the quality of these procedures will be provided through the experienced team at Warwick CTU. Ongoing monitoring procedures will identify any difficulties and the WCTU team will work with the local PI to ensure all procedures are in line with strict operating procedures.

Members of the clinical care and research teams will handle this data confidentially and will only use the data for the purposes of screening and recruitment to the trial. The use of medical records is included in the transparency information in the Information Sheets for patients and legal representatives. Patients, or their consultee, can also withdraw from further data collection from their medical records using the contact details specified in the Information Sheets.

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

◉ Yes ○ No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

○ Yes ◉ No

If No, and your application involves identifiable patient information, application should be made to the Confidentiality Advisory Group (CAG) to process identifiable information of patients in England and Wales without consent – see guidance notes.

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

○ Yes ◉ No

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

Obtaining informed consent from patients will not be possible at the time of enrolment for the following reasons:
1. Patients will be deteriorating clinically with acute respiratory impairment. The resulting hypoxia, and the urgent nature with which treatment needs to be provided that limits available time, will preclude the ability to undertake a full, informed consent process and guarantee sufficient patient understanding of the information provided.
2. It is not practical or appropriate to consult a personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk of viral transmission to those involved. Significant limitations have been placed on the visitation of COVID-19 patients and therefore a personal consultee will not immediately be available, and to attempt contact via telephone will delay treatment. Pressures on clinical services will make it impractical to identify an appropriate medical practitioner.

We believe the most appropriate way to proceed is to use an emergency research model outlined in the Mental Capacity Act and to seek approval for its use by a Research Ethics Committee. We have carefully considered the framework for such a waiver of consent, developed by Davies et al (2014) in conjunction with the National Research Ethics Service. Importantly, our approach includes offering, where the clinical condition of the patient allows, brief information about the trial to participants and providing them with the opportunity to decline participation. This will be recorded on the baseline data collection form. Where a patient objects at this point they will not be entered into the study, and this will be captured through screening. It is also important to highlight that all of the interventions proposed in the trial (CPAP, HFNO, and standard care) are existing standards of care currently employed in clinical practice; we are not investigating any experimental interventions in this trial.

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.

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

We believe the most appropriate way to proceed is to use an emergency waiver of consent model, approved by a Research Ethics Committee. Obtaining informed consent from patients will not be possible at the time of enrolment for the following reasons:
1. Patients will be deteriorating clinically with acute respiratory impairment. The resulting hypoxia, and the urgent nature with which treatment needs to be provided that limits available time, will preclude the ability to undertake a full, informed consent process and guarantee sufficient patient understanding of the information provided.
2. It is not practical or appropriate to consult a personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk of viral transmission to those involved. Significant limitations have been placed on the visitation of COVID-19 patients and therefore a personal consultee will not immediately be available, and to attempt contact via telephone will delay treatment. Pressures on clinical services will make it impractical to identify an appropriate medical practitioner.

The patient will be enrolled into the trial under deferred consent once they meet all eligibility criteria. Following enrolment, the participant will be followed up regularly by the hospital research team. In participants that regain capacity, the site research team will approach the participant and provide verbal information about the trial. They will also be provided with the written participant information sheet, and given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form.

In participants that do not regain capacity, an approach will be made to a personal consultee or professional consultee at the earliest reasonable practical opportunity. This will likely be several days after the initial enrolment. The initial approach should ideally be made to a personal consultee. However, this will likely be precluded due to visiting restrictions, in which the opinion of a professional consultee will be sought. The professional consultee will be a registered medical practitioner that is independent of the trial. The consultee will be provided with a verbal explanation of the trial and a copy of the written participant information sheet and cover note. If the consultee does not

know of any objection to research participation expressed by the participant, they will be asked to complete the consultee agreement form, which will be counter-signed by a member of the site research team.

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, anonymised data will be collected and submitted to Warwick Clinical Trials Unit.

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

A30-3. Why is it not practicable for either the researcher's organisation, or the current holder of the information required by the researcher, to seek or obtain patient consent for proposed use of patient identifiable information?

In most cases, patient identifiable information may be processed and used before consent can be obtained from the patient or their personal or professional consultee. Many of the patients with suspected or confirmed COVID-19 infection will lack capacity, primarily due to acute confusion secondary to hypoxia and infection. It therefore may not be possible to consult with or obtain prospective consent directly from the research participant.

Once the initial emergency has passed, consent for continuation in the trial and continued use of patient identifiable data will be sought from the patient professional or (if they have not already consented). If the patient regains capacity while in hospital, they will be informed about their participation and asked for verbal consent for continued data collection.

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

As per A30, due to the urgent need to initiate treatment and the context in which the trial will operate, we do not consider it practical or appropriate to consult a personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk to those involved.

We believe the only practical way to proceed is to use an emergency waiver of consent model.

Following enrolment, the participant will be followed up regularly by the hospital research team. In participants that regain capacity, the site research team will approach the participant and provide verbal information about the trial. They will also be provided with the written participant information sheet, and given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form.

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?

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with national NIHR-supported co-enrolment guidelines. There are many current examples of successful co-enrolment between UK critical care studies, facilitated by these guidelines.

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)*

We will provide alternative arrangements where possible, to facilitate enrolment of patients who might not adequately understand verbal explanations in English, or who have special communication needs. However this may be challenging in the current circumstances under which this trial will be conducted, and the pressures on clinical

services may mean that these facilities are not available. In which case, enrolment of these patients may not be possible.

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?

We will work with local Welsh sites experienced in recruiting patients to research in the acute hospital setting. Sites will be supported in any additional costs in preparing written translations of the PIS and consent documents. We will ask local sites to arrange the translations in accordance with the availability of GCP trained staff who will be available to be involved in the research process.

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?

Should there be any subsequent amendment to the final protocol, which might affect the patient's participation in the trial, then these will be discussed with the participant or their consultee and, if applicable, continuing consent will be obtained using an amended consent form.

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
- [ ] 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
  - [x] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [x] Laptop computers

Further details:
Warwick Clinical Trials Unit for monitoring and data collection, including sharing with NHS Digital and ICNARC to meet the objectives of the Trial. Warwick CTU will oversee data sharing with any other external organisations should this arise.

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

Personal identifying consent forms and demographic details will be held in research site files, which will be stored in locations which are restricted to research team access. Patient identifiable data will only be transmitted to Warwick Clinical Trials Unit from participating sites via a secure online web portal, designed by the WCTU Programming Team. Access to this online web portal will be restricted to authorised members of the research team, via individual logins and IP addresses. Identifiable data will be held in a separate table within the trial database so that access can be further restricted to only
individuals who require it. Any paper forms with patient identifiable information will be held in secure locked filing cabinets within a restricted access area at participating centres.

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.*

All trial staff and investigators will adhere to General Data Protection Regulation (GDPR) and the Data Protection Act 2018. The University of Warwick is registered on the Data Protection Act Register. Access to patient's personal data will be limited to the trial staff, investigators and regulatory authorities. Databases will only be accessed by authorised personnel using individual user accounts. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant number, not by name. Only anonymised data will be available to statisticians for data analysis. Participants will not be identified in any trial reports or publications.

A39. Please specify whether identifiers will be held in the same database as the clinical data, or in a separate database and linked through a unique study or case number. *If held separately, please specify how and at what point the separation will occur. If held in the same database, will the identifiers be encrypted? If so, specify what will be encrypted and who will continue to have access.*

Patient identifiers will be held in the same database as the clinical data, but in a separate table linked through a unique study number. The trial database is encrypted and held on a secure server at the University of Warwick. Access to the table containing patient identifiable data will be restricted to members of the trial team who require access e.g. undertaking data linkage work.

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.*

Personal data will be accessed initially by members of the research team at participating sites, who may sit outside of the patient's direct care team, for screening, recruitment and data collection purposes. Personal data will then be entered onto the trial database via the online web portal, which will be accessed at the University of Warwick Clinical Trials Unit by members of the coordinating centre trial team. WHAT IS THE REASON FOR THIS? The data that will be collected, the purposes and who will have access to that data is specified in the Patient
Information sheet. Statement confirming understanding of this are included on the patient and legal representative consent forms.

MONITOR
REMAP-CAP
ANY OTHER ANALYSES?

Storage and use of data after the end of the study

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

The data will be analysed by statisticians at Warwick Clinical Trials Unit, University of Warwick.

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

	Title	Forename/Initials	Surname
	Professor	Gavin	Perkins
Post	Chief Investigator/Warwick Clinical Trials Unit Director		

Qualifications	MB ChB, MD, FRCP, FFICM, FIMC RCS(Ed)
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Work Telephone	02476750479
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:
Access to personal data at participating centres may be required for the purposes of sponsor audit or inspection by the regulatory authorities, and must be stored for a period of 10 years or longer if required as per WCTU Standard Operating Procedures. Please note patient identifiable data will be deleted as soon as possible once no longer required (i.e. once communication with patients/legal representatives and data linkage work is complete).

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

Years: 10
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.*

The local Principal Investigators will maintain all records and documents regarding the conduct of the study. These will be archived by the site for at least 10 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at the secure archive facilities used by WCTU. This archive shall include all trial databases and associated meta-data encryption codes. Only the trial research team will have authority to access this data if required. The records will be archived for at least 10 years from the close of the study.

INCENTIVES AND PAYMENTS

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

○ Yes ◉ No

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

○ Yes ◉ No

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

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

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

○ Yes ◉ No

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

PUBLICATION AND DISSEMINATION

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

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

◉ Yes ○ No

Please give details, or justify if not registering the research.
The trial will be registered with the International Standard Randomised Control Number (ISRCTN) database.

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

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

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

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

Participants will not be identified in any trial reports or publications.

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.
A summary of the results will be made available on the trial website at the appropriate time (following publication in a scientific journal).

5. Scientific and Statistical Review

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

- ☑ Independent external review
- ☐ Review within a company
- ☑ Review within a multi−centre research group
- ☑ Review within the Chief Investigator's institution or host organisation
- ☑ 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:
Peer review for this protocol will initially be provided by the Department of Health and Social Care and the NIHR Urgent Public Health prioritisation group. .

Leading experts in this field of research are co-applicants/co-investigators on the trial and have contributed to the trial protocol.

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

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

The primary outcome is a composite outcome comprising intubation or mortality within 30 days. Mortality will be reported from hospital records up until discharge and tracked after discharge using the NHS Digital tracking service, hospital records and GP records. Intubation will be obtained from hospital data.

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

Secondary outcomes relating to effectiveness include:
- Intubation rates
- Time to intubation
- Time to death (mortality)
- Mortality in critical care (level 2/3)
- Mortality in hospital stay
- Mortality at 30 days
- Length of stay in critical care (level 2/3)
- Length of stay in hospital

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:	4002
Total international sample size (including UK):	4002
Total in European Economic Area:	4002

Further details:

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.*

In our sample size calculation, we have assessed both outcome measures from the literature and taken the largest in terms of the incidence, to ensure we have maximum power and sample size for our study. Therefore taking the data primarily from Baud et al1 and from the CEBM2 to be representative of usual care and assuming a conservative incidence of 15% for the composite outcome of intubation or mortality on the usual care arm, and using a two-sided 5% significance level, a total of 4002 patients (1334 across 3 arms) would give 90% power to detect an odds ratio of 0.67, corresponding to a reduction from 15% to 10.5% in the composite events rate, allowing for the 4 interim analyses as detailed below. Our comparisons will be based on CPAP versus standard care and HFNO versus standard care.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Providing the patient meets the eligibility criteria above, they will be randomly assigned to one of three interventions. A simple and secure, web-based and allocation concealed randomisation system will be established by the programming team at Warwick Clinical Trials Unit. A computer-generated randomisation sequence will be generated by the minimisation method and patients will be randomised in a ratio of 1:1:1 to either standard care: CPAP: HFNO. Patients will be stratified by site, gender (M/F), and age (<50, >=50 years). In the event that the web-based system

cannot be used, an emergency interactive voice response (IVR) randomisation system will also be in place. If a patient has been randomised and found to be ineligible or the device is not available, they will be included in the analysis on an intention-to-treat basis. Any data already collected will be retained and included in the analysis unless otherwise indicated.

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 statistical analysis will be based on intention to treat and will be conducted in line with the CONSORT statement. For the overall analyses, numbers of events will be assessed using the logistic regression unadjusted and adjusted for important predictors, such as previous morbidities, age and gender) and results will be presented using odds ratios (with 95% confidence intervals). At the interim stages, the numbers of events will be analysed using the latter methods and compared to the p-value critical values given in Table 1. A final p-value and treatment effect estimate will be calculated adjusting for the interim analyses using the methods described by Jennison and Turnbull, Fairbanks and Madsen and, Emmerson and Fleming. Intubation rates and mortality at 30 days will be assessed using the logistic regression models (both for adjusted and unadjusted analyses) and summarised using odds ratio (with 95% confidence intervals). Continuous secondary data will be presented using summary statistics and analysed using parametric or non-parametric methods depending on the distribution of the data.

We will conduct a compliers average cause effect (CACE) analysis to assess the effect on the non-compliance to the allocation interventions (for all three interventions or two, if one is dropped).

We anticipate no or very little missing data. However, in the case of missingness, we will use multiple imputation techniques (ICE procedures) to assess the missingness mechanisms.

Interim analyses are planned following the recruitment of every 1000 participants. It is proposed to conduct pairwise comparisons, each with standard care as a one-sided group-sequential test with an overall one-sided type I error rate of 0.025.

At each interim analysis the number of events (intubation or mortality) observed will be used to calculate an information time for each of the pairwise comparison given by the number of events observed in these two arms divided by the number expected at the end the of study. Stopping limits will be calculated using the spending function approach, with the type I error spent at a look with information fraction t set to be 0.025t. As decisions to stop an arm for futility, either relative to standard care or to other arms, will be based on advice from the DMC, no binding futility rule has been assumed.
Assuming 1334 patients per arm (4002 overall) gives a power of 90% to detect a hazard ratio of 0.67, corresponding to a reduction from 15% to 10.5% in the composite event rate. The group-sequential design means that the trial is more likely to stop early if the interventions are more effective than standard care. The expected duration of the trial in terms of the number of events required for different effect sizes (assuming a control event rate of 15%) is shown in Figure 2. If the event rate for an intervention is 10.5%, with a standard care rate of 15%, the expected number of patients per arm is reduced to 824.

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
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Title	Forename/Initials	Surname
Professor	Paul	Dark

Post	Co-Investigator
Qualifications	
Employer	University of Manchester
Work Address	Division of Infection, Immunity, and Respiratory Medicine NIHR Manchester Biomedical Research Centre Faculty of Biology, Medicine and Health, Unviersity of Manchester
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Title	Forename/Initials	Surname
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Title	Forename/Initials	Surname
Professor	Nicholas	Hart

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Fax	
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Title	Forename/Initials	Surname
Professor	Ranjit	Lall

Post	Co-Investigator
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Employer	University of Warwick
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Title	Forename/Initials	Surname
Professor	Anita	Simonds

Post	Co-Investigator

Qualifications	
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Title	Forename/Initials	Surname
Professor	Nigel	Stallard

Post	Co-Investigator
Qualifications	
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Title	Forename/Initials	Surname
Dr	Joyce	Yeung

Post	Co-Investigator
Qualifications	
Employer	University of Warwick
Work Address	Warwick Clinical Trials Unit (WCTU) The University of Warwick, Gibbet Hill Road Coventry
Post Code	CV4 7AL
Telephone	02476 574880
Fax	
Mobile	
Work Email	J.Yeung.4@warwick.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry

Commercial status: Non-Commercial

- ◯ Medical device industry
- ◯ Local Authority
- ◯ Other social care provider (including voluntary sector or private organisation)
- ◯ Other

If Other, please specify:

Contact person

Name of organisation	University of Warwick
Given name	Jane
Family name	Prewett
Address	Research and Impact Services, University House, University of Warwick
Town/city	Coventry
Post code	CV4 8UW
Country	UNITED KINGDOM
Telephone	02476575732
Fax	
E-mail	sponsorship@warwick.ac.uk

A65. Has external funding for the research been secured?

Please tick at least one check box.

- ☑ 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	Department of Health and Social Care
Address	39 Victoria St Westminster London
Post Code	SW1H 0EU

Telephone 020 7210 4850
Fax
Mobile
Email

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

Amount: 1,400,000.00

Duration
Years: 1
Months: 6

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
NIHR COVID-19: Urgent Public Health

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
	Mr	Nick	Denyer
Organisation	University Hospital Birmingham NHS Foundation Trust		
Address	MIDRU Building, R&D Department		
	Birmingham Heartlands Hospital		
	Bordesley Green East, Birmingham		
Post Code	B9 5SS		
Work Email	nick.denyer@uhb.nhs.uk		
Telephone	+44 (0) 121 424 1633		
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:

West Midlands

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: 03/04/2020
Planned end date: 02/10/2021
Total duration:
Years: 1 Months: 6 Days: 0

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 40

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	34
☑ NHS organisations in Wales	3
☐ NHS organisations in Scotland	
☑ HSC organisations in Northern Ireland	3
☐ 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: 40

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?

A monitoring plan will be produced in line with the level of risk identified in the risk assessment. Appropriate WCTU staff members shall carry out central monitoring of trial data on an ongoing basis. Data being recorded on the eCRF allows assessment of protocol compliance. The TMG will regularly assess serious adverse event data and protocol non-compliances.
On-site monitoring will not be feasible in this trial, due to restrictions on non-essential staff visiting hospitals with COVID-19 patients. A risk-based approach to off-site monitoring will be developed through discussion with the trial sponsor, that takes account of the challenging circumstances in which this trial will operate and the extreme pressure that will be placed on hospital staff.

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?

A DMC will be appointed comprising of two independent clinicians with experience in clinical trials and an independent statistician. They will be provided with interim reports with outcome measures, when data are available on 1000 patients, at 4 time points in the study. One of the independent clinicians will have experience in undertaking clinical trials in emergency or acute care. The DMC charter will be based on the DAMOCLES study group template. Its roles will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; making recommendations as to whether to drop any arm from the study for futility, either relative to standard care or to other arms; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies.

Membership of the DMC will be confirmed. DMC meetings will also be attended by the Chief Investigator and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician. The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

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

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

The trial will be an adaptive (group-sequential), pragmatic, randomised controlled, open-label, multi-centre, effectiveness trial to determine if the use of CPAP or HFNO reduces intubation or death (mortality), within 30 days. We will test each of the intervention against standard care, and if required, drop one of the interventions if there is evidence of harm or ineffectiveness. We will do this using formalised interim analysis statistical rules and the results will be assessed by the Independent Data Monitoring Committee and the Trial Steering Committee at each interim point.

A76. Insurance/ indemnity to meet potential legal liabilities

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

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

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes.

Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

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

The University of Warwick has public and product liability insurance with a limit of indemnity of no less than £10m to cover negligent acts resulting in damage injury or death it is legally liable for subject to policy terms and conditions.

The University of Warwick has professional indemnity insurance with a limit of indemnity of no less than £2m to cover breaches of duty subject to policy terms and conditions.

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 <u>design</u> of the research? *Please tick box(es) as applicable.*

<u>Note:</u> Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

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

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

The University of Warwick has public and product liability insurance with a limit of indemnity of no less than £10m to cover negligent acts resulting in damage injury or death it is legally liable for subject to policy terms and conditions.

The University of Warwick has professional indemnity insurance with a limit of indemnity of no less than £2m to cover breaches of duty subject to policy terms and conditions.

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 <u>conduct</u> of the research?

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

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

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

The University of Warwick has public and product liability insurance with a limit of indemnity of no less than £10m to cover negligent acts resulting in damage injury or death it is legally liable for subject to policy terms and conditions.

The University of Warwick has professional indemnity insurance with a limit of indemnity of no less than £2m to cover breaches of duty subject to policy terms and conditions.

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

If Yes, please give details of the compensation policy:
Insurer: Newline
Policy number: WIBCLT18365
Clinical Trial Insurance Specific Trial Policy in accordance with ABPI guidelines.

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

B. All research other than CTIMPs

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

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

Suspected or confirmed COVID-19.

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

There is an urgent need to determine the optimum strategy to manage COVID-19 patients with worsening respiratory failure. This proposal has been commissioned by the NIHR to answer a research question that is considered to be of high priority by the UK clinical community. There are perceived benefits to each study intervention, and each is in widespread use across the NHS. However, there is ongoing uncertainty as to the optimum approach.

Obtaining informed consent from patients will not be possible at the time of enrolment for the following reasons:
1. Patients will be deteriorating clinically with acute respiratory impairment. The resulting hypoxia, and the urgent nature with which treatment needs to be provided that limits available time, will preclude the ability to undertake a full, informed consent process and guarantee sufficient patient understanding of the information provided.
2. It is not practical or appropriate to consult a personal consultee or independent registered medical practitioner prior to enrolment without placing the potential participant at risk of harm from delaying treatment. These processes will also not be feasible or safe to undertake in order to minimise risk of viral transmission to those involved. Significant limitations have been placed on the visitation of COVID-19 patients and therefore a personal consultee will not immediately be available, and to attempt contact via telephone will delay treatment. Pressures on clinical services will make it impractical to identify an appropriate medical practitioner.

We believe the most appropriate way to proceed is to use an emergency research model outlined in the Mental Capacity Act and to seek approval for its use by a Research Ethics Committee. We have carefully considered the framework for such a waiver of consent, developed by Davies et al (2014) in conjunction with the National Research Ethics Service. Importantly, our approach includes offering, where the clinical condition of the patient allows, brief information about the trial to participants and providing them with the opportunity to decline participation. This will be recorded on the baseline data collection form. Where a patient objects at this point they will not be entered into the study, and this will be captured through screening. It is also important to highlight that all of the interventions proposed in the trial (CPAP, HFNO, and standard care) are existing standards of care currently employed in clinical practice; we are not investigating any experimental interventions in this trial.

B3. 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?

Sites will be selected on the basis of established NIHR Clinical Research Network staff infrastructure, training and research capacity to perform procedures to consent adults lacking capacity in an acute care environment and where procedures for Nominated Consultees are already in place. Local clinicians and/or research nurses/practitioners, who have up-to-date GCP training and knowledge of the patient's condition and treatment will assess their capacity to give consent. Ongoing monitoring will repeatedly consider patients capacity to give consent for themselves where a Personal or Nominated Consultee has provided Declaration/Assent for their inclusion.

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

(●) Yes ( ) No

If Yes, please indicate the nature of this benefit. You may refer back to your answer to Question A24.

As per A24

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

◉ Yes ○ No

If Yes, please explain how the research will achieve this:

The sample size is designed to include a representative sample of hospitalised patients with COVID-19 infection receiving ventilation. The results will, therefore, be generalisable to this group of patients.

B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

○ Yes ◉ No

Questions B7 and B8 apply to any participants recruited in England and Wales.

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research.
- Personal consultee- throughout the NHS, significant limitations have been placed on the visitation of COVID-19 patients. On this basis, a personal consultee will not be immediately physical available for consultation. Waiting for a personal consultee to attend the hospital would place the consultee at risk of infection and cause treatment delays.
- Professional consultee- due to COVID-19, there will be extreme pressure on UK health services. In this context, we consider it impractical for hospital research teams to identify an appropriate medical practitioner to act as a professional consultee without delaying treatment.

In participants that do not regain capacity, an approach will be made to a personal consultee or professional consultee at the earliest reasonable practical opportunity. This will likely be several days after the initial enrolment. The initial approach should ideally be made to a personal consultee. However, this will likely be precluded due to visiting restrictions, in which the opinion of a professional consultee will be sought. The professional consultee will be a registered medical practitioner that is independent of the trial. The consultee will be provided with a verbal explanation of the trial and a copy of the written participant information sheet and cover note. If the consultee does not know of any objection to research participation expressed by the participant, they will be asked to complete the consultee agreement form, which will be counter-signed by a member of the site research team.

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, anonymised data will be collected and submitted to Warwick Clinical Trials Unit.

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?

◉ Yes ○ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, 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 advice from a consultee as soon as practicable thereafter.

There is an urgent need to determine the optimum strategy to manage COVID-19 patients with worsening respiratory failure.

There are perceived benefits to each study intervention, and each is in widespread use across the NHS. However, there is ongoing uncertainty as to the optimum approach. Eligible participants will be critically unwell and may lack capacity as part of their underlying condition (e.g. acute confusion due to hypoxia/ sepsis). These individuals are an important COVID-19 group that are potentially at greater risk of deterioration.

We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research.
- Personal consultee- throughout the NHS, significant limitations have been placed on the visitation of COVID-19 patients. On this basis, a personal consultee will not be immediately physical available for consultation. Waiting for

a personal consultee to attend the hospital would place the consultee at risk of infection and cause treatment delays.
- Professional consultee- due to COVID-19, there will be extreme pressure on UK health services. In this context, we consider it impractical for hospital research teams to identify an appropriate medical practitioner to act as a professional consultee without delaying treatment.

It is essential that treatment (as per the study arms) is initiated as soon as possible. Delays in treatment initiation may place the patient at risk, and increase the likelihood of the need for tracheal intubation and increase the risk of death. Delays may therefore make study interventions appear less effective by reducing any observed treatment effect. A personal or professional consultee may have capacity, but consultation is impractical due to the urgent need to commence treatment and research context. We will subsequently ask for patient consent or consultee agreement for ongoing delivery of the intervention (if applicable) and ongoing data collection.

Questions B7-2 and B8-2 apply to any participants recruited in Northern Ireland.

B7-2. What arrangements will be made to consult a close relative or close friend able to advise on the inclusion of the participant and on their likely wishes?

We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research.
- Personal consultee- throughout the NHS, significant limitations have been placed on the visitation of COVID-19 patients. On this basis, a personal consultee will not be immediately physical available for consultation. Waiting for a personal consultee to attend the hospital would place the consultee at risk of infection and cause treatment delays.
- Professional consultee- due to COVID-19, there will be extreme pressure on UK health services. In this context, we consider it impractical for hospital research teams to identify an appropriate medical practitioner to act as a professional consultee without delaying treatment.

In participants that do not regain capacity, an approach will be made to a personal consultee or professional consultee at the earliest reasonable practical opportunity. This will likely be several days after the initial enrolment. The initial approach should ideally be made to a personal consultee. However, this will likely be precluded due to visiting restrictions, in which the opinion of a professional consultee will be sought. The professional consultee will be a registered medical practitioner that is independent of the trial. The consultee will be provided with a verbal explanation of the trial and a copy of the written participant information sheet and cover note. If the consultee does not know of any objection to research participation expressed by the participant, they will be asked to complete the consultee agreement form, which will be counter-signed by a member of the site research team.

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, anonymised data will be collected and submitted to Warwick Clinical Trials Unit.

B8-2. Is it possible that a participant might need to be treated urgently as part of the research before it is possible to consult with a close relative or close friend?

(●) Yes ( ) No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants.

There is an urgent need to determine the optimum strategy to manage COVID-19 patients with worsening respiratory failure.

There are perceived benefits to each study intervention, and each is in widespread use across the NHS. However, there is ongoing uncertainty as to the optimum approach. Eligible participants will be critically unwell and may lack capacity as part of their underlying condition (e.g. acute confusion due to hypoxia/ sepsis). These individuals are an important COVID-19 group that are potentially at greater risk of deterioration.

We have carefully considered the feasibility of seeking agreement from a personal or professional consultee in the context of this research.
- Personal consultee- throughout the NHS, significant limitations have been placed on the visitation of COVID-19 patients. On this basis, a personal consultee will not be immediately physical available for consultation. Waiting for a personal consultee to attend the hospital would place the consultee at risk of infection and cause treatment delays.
- Professional consultee- due to COVID-19, there will be extreme pressure on UK health services. In this context, we consider it impractical for hospital research teams to identify an appropriate medical practitioner to act as a

professional consultee without delaying treatment.

It is essential that treatment (as per the study arms) is initiated as soon as possible. Delays in treatment initiation may place the patient at risk, and increase the likelihood of the need for tracheal intubation and increase the risk of death. Delays may therefore make study interventions appear less effective by reducing any observed treatment effect. A personal or professional consultee may have capacity, but consultation is impractical due to the urgent need to commence treatment and research context. We will subsequently ask for patient consent or consultee agreement for ongoing delivery of the intervention (if applicable) and ongoing data collection.

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

Following enrolment, the participant will be followed up regularly by the hospital research team. In participants that regain capacity, the site research team will approach the participant and provide verbal information about the trial. They will also be provided with the written participant information sheet, and given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form.

In participants that do not regain capacity, an approach will be made to a personal consultee or professional consultee at the earliest reasonable practical opportunity. This will likely be several days after the initial enrolment. The initial approach should ideally be made to a personal consultee. However, this will likely be precluded due to visiting restrictions, in which the opinion of a professional consultee will be sought. The professional consultee will be a registered medical practitioner that is independent of the trial. The consultee will be provided with a verbal explanation of the trial and a copy of the written participant information sheet and cover note. If the consultee does not know of any objection to research participation expressed by the participant, they will be asked to complete the consultee agreement form, which will be counter-signed by a member of the site research team.

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, anonymised data will be collected and submitted to Warwick Clinical Trials Unit.

On occasion, participant consent or personal/ professional consultee agreement may not be obtained prior to hospital transfer or discharge. In this circumstance, the site research team will attempt to contact the participant or their consultee (if it is known that the participant lacks mental capacity) at their place of residence to seek agreement. Up to three attempts to contact the participant will be made. Given the urgent need to answer this research questions, minimal personal identifiable data (NHS number, date of birth, postcode) will be submitted contemporaneously to Warwick Clinical Trials Unit. In the event that a trial participant declines consent to continue in the trial, personal identifiable data will be deleted. Information collected about the participant up to the point of withdrawal will be retained for analysis.

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

Following enrolment, the participant will be followed up regularly by the hospital research team. In participants that regain capacity, the site research team will approach the participant and provide verbal information about the trial. They will also be provided with the written participant information sheet, and given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form.

On occasion, participant consent or personal/ professional consultee agreement may not be obtained prior to hospital transfer or discharge. In this circumstance, the site research team will attempt to contact the participant or their consultee (if it is known that the participant lacks mental capacity) at their place of residence to seek agreement. Up to three attempts to contact the participant will be made. Given the urgent need to answer this research questions, minimal personal identifiable data (NHS number, date of birth, postcode) will be submitted contemporaneously to Warwick Clinical Trials Unit. In the event that a trial participant declines consent to continue in the trial, personal identifiable data will be deleted. Information collected about the participant up to the point of withdrawal will be retained for analysis.

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

The urgency of the treatment precludes the opportunity for potential participants to be given detailed study information and for them to make an informed decision about enrolment. Where the clinical condition of the patient allows, brief information about the trial will be given to participants and providing them with the opportunity to decline participation.

Following enrolment, the participant will be followed up regularly by the hospital research team. In participants that regain capacity, the site research team will approach the participant and provide verbal information about the trial. They will also be provided with the written participant information sheet, and given adequate time to review the information sheet and ask questions. Due to ongoing concerns regarding risk of infection transmission, verbal consent only will be sought and documented on a study form.

B12-1. What will be the criteria for withdrawal of participants?

Participants may be withdrawn from the trial intervention at the discretion of the investigator and/or Trial Steering Committee due to safety concerns. Participants, or their professional consultee on their behalf, may request to be withdrawn from the trial at any time without prejudice. Patients or professional consultee who decline consent will be logged on the database from the point that they communicate their intention to the trial team and no further contact will be made. Data already collected will be retained and included in the analysis. The information sheet explains the trial and the data that will be collected. Patients and personal consultees will be informed that the research team will continue to collect data remotely as per the protocol until the end of the trial, unless they explicitly withdraw their consent for this.

B12-2. Where a participant is recruited urgently, and later withholds their consent or is withdrawn or dies before consent / consultation can take place, what provisions will apply to the study data collected up to that point?

In the event that the participant dies prior to regaining capacity and before consultee agreement can be sought, anonymised data will be collected and submitted to Warwick Clinical Trials Unit.

In rare circumstances, participant consent or personal/ professional consultee agreement may not be obtained prior to hospital discharge. In this circumstance, the site research team will contact the participant or their consultee (if it is known that the participant lacks mental capacity) at their place of residence to seek agreement. Up to three attempts to contact the participant will be made. In the event that no response is received, anonymised data will be collected and submitted to Warwick Clinical Trials Unit.

Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

Patients will be continually assessed by their clinical team as part of routine care, any signs of distress will be dealt with by the clinical team.

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant? *This question applies to England, Wales and Scotland only – please see guidance notes for further information.*

GCP trained researchers, together with the local treating clinical team, are obliged to identify the existence of any advance decisions or statements as part of recruitment/consent considerations. Any information in an advance decision or statement will be respected. If the advanced decision is contrary to completing the study protocol the patient will not be recruited, if the advance decision becomes known following recruitment and continuation in the study would be contrary to their wishes, they would be withdrawn and all collected data discarded.

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

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 Prof Gavin Perkins on 01/04/2020 17:06.

Job Title/Post:	Professor
Organisation:	University of Warwick
Email:	g.d.perkins@warwick.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.

   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.*

7. 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.

8. 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 Mrs Jane Prewett on 01/04/2020 17:08.

Job Title/Post:	Head of Research Governance
Organisation:	University of Warwick
Email:	jane.prewett@warwick.ac.uk