Study Title: An observational study of the relationship between pressure-volume curves and recruitability of the lung in mechanically ventilated critically ill patients with respiratory failure

Internal Reference Number **/ Short title:** Recruitment manoeuvres in critically ill patients

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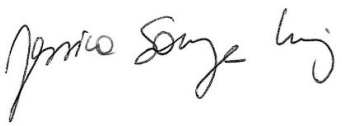

Conflict of interest statement:

The University has applied/ hold patents in relation to the measuring apparatus to be deployed in this application. Peter A Robbins has an interest in these applications/patents.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

KEY CONTACTS

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Clinical Trials Unit	Not applicable
Statistician	Not applicable
Committees	REC Reference: 22/SC/0127 South Central - Oxford C Research Ethics Committee REC Email: oxfordc.rec@hra.nhs.uk

LAY SUMMARY

Diseases of the lungs can be life-threatening. Conditions affecting the lungs can prevent oxygen being effectively transferred from the air to the blood, and the carbon dioxide removed from the blood and breathed out into the air.

Conditions that affect the lungs may progress over a long period of time and are called chronic conditions. Patients with such conditions are particularly vulnerable to sudden deterioration when they become unwell with acute illnesses, for example pneumonia. In this situation specialist treatments in an Intensive Care Unit (ICU) are often required to try to help the patient recover from the illness. However, previously fit and well individuals can also become very unwell with acute illnesses and need support on an ICU, as has been well illustrated by the COVID-19 pandemic.

The specialist treatments available on ICU are described as organ support. To support the failing lung, a process denominated as respiratory failure, patients may need to be sedated and have a tube placed in their windpipe so that a mechanical ventilator can take over their breathing until they have recovered enough to breathe again on their own.

Mechanical ventilation via a breathing tube is a very abnormal situation that is far removed from normal breathing in healthy people. One problem that occurs, both as a result of how mechanical ventilators work, and the underlying disease affecting the patient, is that parts of the lung tissue tend to collapse down, sometimes called 'atelectasis'. Over time this reduces the amount of the lung that is able to transfer oxygen and carbon dioxide effectively and can also progress to pneumonia.

One procedure that is often used in ICU is called a 'recruitment manoeuvre'. There are various different ways of performing these, but all involve briefly inflating the patient's lungs with enough pressure to try to open up the collapsed areas of lung. However, we do not fully understand many aspects of this process, including some of the most fundamental aspects of the change in the functioning of the heart and lungs that occur during and after such a manoeuvre is performed.

In this longitudinal observational study, we wish to study patients with respiratory failure who are receiving mechanical ventilation. We will collect cardiopulmonary data over the course of a day on the ICU. During this period, some patients will be assessed to determine whether they may benefit from a recruitment manoeuvre. This assessment is made using a pressure-volume curve for the patient's lung, which is obtained by briefly varying the ventilator settings. However, this assessment is not perfect, and we wish to study further which features of the pressure-volume curve predict a successful recruitment. We will do this by making an assessment of the volume of the lung before and after the recruitment manoeuvre is performed.

A better understanding of how to predict the effects of a recruitment manoeuvre can then inform future interventional studies aiming to determine how and when such manoeuvres should be performed in critically ill patients.

SYNOPSIS

Study Title	An observational study of the relationship between pressure-volume curves and recruitability of the lung in mechanically ventilated critically ill patients with respiratory failure
Internal ref. no. / short title	Recruitment manoeuvres in critically ill patients
Study registration	NCT05508724 (ClinicalTrials.gov)

Sponsor	University of Oxford | Research Governance, Ethics & Assurance Team Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB		
Funder	University of Oxford | Internal Funds Sherrington Building, Sherrington Road, Oxford OX1 3PT		
Study Design	Observational study		
Study Participants	Critically ill adult patients with respiratory failure receiving invasive mechanical ventilation on an Intensive Care Unit		
Sample Size	60		
Planned Study Period	3 years		
Planned Recruitment period	01/05/2022 to 01/05/2025		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To determine whether parameters derived from the airway pressure-volume curve predict changes in static measures of lung volume in response to recruitment manoeuvres	Functional residual capacity	Before and after recruitment manoeuvre
Secondary	To determine if and how anatomic dead space and ventilatory inhomogeneity changes in response to recruitment manoeuvres	1. Anatomic dead space 2. Standard deviation for ventilation inhomogeneity across the lungs	Before and after recruitment manoeuvre.
Intervention(s)	No interventions additional to routine clinical care		
Comparator	Within patient changes in lung parameters before and after a recruitment manoeuvre in a given patient		

ABBREVIATIONS

CT	Computerised Tomography
CRF	Case Report Form
GCP	Good Clinical Practice
HME	Heat and Moisture Exchange
HRA	Health Research Authority
ICU	Intensive Care Unit
NHS	National Health Service
OGA	Optical Gas Analyser
PV	Pressure-Volume
REC	Research Ethics Committee
RI	Recruitment-to-Inflation Ratio
RM	Recruitment manoeuvre
SOP	Standard Operating Procedure
VILI	Ventilator-induced Lung Injury

BACKGROUND AND RATIONALE

Critical care units provide supportive therapies to help patients survive a period of life-threatening illness. Among such treatments, mechanical ventilation constitutes an essential asset to assist in patient recovery from respiratory failure and to provide airway protection in neurologically compromised patients. The need for mechanical ventilation is more often driven by respiratory failure than a need for neuroprotection (1,2). In excess of 100,000 adult patients are mechanically ventilated in UK ICUs annually (3), and this number has risen considerably recently due to the emergence of the COVID-19 pandemic.

Respiratory failure may be triggered by pulmonary (e.g., pneumonia, acute respiratory distress syndrome, interstitial fibrosis) or extra-pulmonary (e.g., sepsis, shock) disturbances. The abnormal function of the cardiorespiratory system in these critical conditions results in carrying degrees of hypoxaemia and hypercapnia, leading to the need for respiratory support by mechanical ventilation (4).

In patients undergoing mechanical ventilation for respiratory failure, the lung is characterized by a much-enhanced tendency to collapse. This collapse worsens hypoxaemia, and increases the stress and strain applied to those regions of the lung that remain aerated, leading to ventilator-induced lung injury (VILI) (5). Re-aeration of non-aerated lung (recruitment) improves oxygenation (6) and prevents VILI (7). For this reason, some clinicians employ recruitment manoeuvres following intubation, or subsequently during their ICU stay. However, it remains unclear which patients benefit from this intervention, at what time point(s) it is most beneficial, and the underlying mechanisms.

It is recognised that the volume of lung that is potentially recruitable (recruitability) varies widely from patient to patient (8,9), being influenced by: (i) the underlying disease precipitating respiratory failure (pulmonary versus extrapulmonary injury) (10); (ii) the distribution of lung injury (lobar versus non lobar); and (iii) the time from initiation of lung injury (11).

An ability to assess recruitability is a pre-requisite for a rational recruitment strategy and selecting parameters for mechanical ventilation. The gold standard to assess recruitability involves performing a CT scan at two different levels of inspiratory pressure and assessing the mass of lung tissue (grams) that transitions from a non-aerated to an aerated state (9). This is not feasible in everyday clinical practice since it is time consuming, requires transfer of a critically ill patient to the radiology suite, and involves a significant exposure to ionising radiation. An alternative is to use some measure of the change in lung volume between the different pressure levels, but this is not the same as a change in non-aerated lung mass and indeed the two measures may not even be correlated (12).

It has been suggested that certain parameters derived from a low-flow inflation and deflation pressure-volume (PV) curve might be useful in the prediction of lung recruitability (17,18). When a sustained inflation recruitment manoeuvre is performed, the increase in volume evident on the curve should theoretically give a measure of the volume recruited during the manoeuvre (18,19). Based on a similar PV curve principle, recruitment-to-inflation ratio (RI) was developed as a single-breath assessment of lung recruitability (20). However, these strategies for the bedside assessment of recruitability have received limited validation and currently provide only a qualitative analysis, whereby the patient's lungs will be considered to have either a high or a low potential of recruitment. Finally, electric impedance tomography has been advocated by some as an alternative tool to assess recruitment (13-16) but has not been widely adopted into clinical use.

The decision as to whether or not to perform a recruitment manoeuvre in a given patient currently relies on individual consultant preference and clinical judgement, leading to variation within medical practice. Due to an inadequate understanding of the full physiological effects associated with this intervention, it can be difficult to decide whether lung recruitment is likely to prove useful for a given patient. For example, a recruitment manoeuvre that increases lung volume is more likely to be beneficial if it results in an even inflation of a larger alveolar volume than if it arises purely as an increase in dead space.

To date, there is no consensus regarding recruitment manoeuvres and the existing guidance is limited. As stated in contemporary joint guidance (21) from the Faculty of Intensive Care Medicine and Intensive Care Society: "The evidence supporting the role of recruitment manoeuvres was so poor and the concept so ill-defined that we were unable to make a recommendation. By contrast, the American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine group has given a conditional recommendation, albeit with low-to-moderate confidence."

The broad objective of this prospective, observational study is to gain a better understanding of how to predict the effects of recruitment manoeuvres in patients who are being mechanically ventilated for respiratory failure. The opportunity to examine this area more closely than has previously been possible, arises from the development of technology to make highly precise measurements of respiratory exchange non-invasively in these patients: the Optical Gas Analyser (OGA) (22,23). By employing small, transient variations in gas tensions well within those observed during the normal care of such patients, this approach can provide much more detailed physiological information relating to the lung (22,23). By way of example, an increase in end-expiratory lung volume following an inflation manoeuvre can be partitioned between the change relating to the dead space volume and the change relating to the alveolar volume. Furthermore, the measurements also quantify how evenly the lung inflates and deflates during a breathing cycle, and thus changes in ventilation heterogeneity before and after an inflation manoeuvre may also be assessed.

A better understanding of the cardiorespiratory changes that occur in mechanically ventilated patients after a recruitment manoeuvre is performed will aid future studies seeking to determine which patients can benefit from them, when, and why. This will – we hope – ultimately lead to better medical care and improved ICU survival rates.

OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To determine whether parameters derived from the airway pressure-volume curve predict changes in static measures of lung volume in response to recruitment manoeuvres.	Functional residual capacity	Before and after recruitment manoeuvre.
Secondary Objective To determine if and how anatomic dead space and ventilatory inhomogeneity change in response to recruitment manoeuvres	1. Anatomic dead space 2. Standard deviation for ventilation inhomogeneity across the lungs	Before and after recruitment manoeuvre.

STUDY DESIGN

This is a prospective, longitudinal, observational study in 60 critically ill, intubated, and ventilated patients. Adult patients who have undergone intubation and mechanical ventilation due to respiratory failure will be enrolled at the Royal Berkshire Hospital ICU. Once a patient is enrolled, we will insert the OGA into the ventilation circuit. The device will be connected to the ventilator circuit for up to 12 hours.

All patients will receive routine clinical care, which may include assessing PV curves and performing recruitment manoeuvre or manoeuvres if felt to be indicated by the treating clinician. Both the measurement of PV curves and the performance of recruitment manoeuvres are considered as part of standard medical care, and will not be conducted as part of the ethics permission (the proposed study is observational). We anticipate that both the measurement of the PV curves and the conduct of the recruitment manoeuvres will normally be performed in accordance with the ventilator manufacturer's (Hamilton Medical) recommendations (https://www.hamilton-medical.com/dam/jcr:2be7809a-1f5e-4c4f-93fc-2377d664c087/PV-Tool-user-guide-en-10067117.00.pdf). However, as previously outlined, we recognise that the evidence base for how to perform PV curves is limited, and that some clinicians may choose to use a different approach, for example a recruitment-to-inflation ratio (20), for their standard clinical care.

Ventilation parameters derived from the airway pressure-volume curve obtained prior the recruitment manoeuvre will be analysed to determine associations with static measures of lung volumes recorded by the OGA before and after the manoeuvre is performed. Additionally, potential

changes in absolute dead space and lung inhomogeneity will be registered by the device before and after recruitment manoeuvre.

Since many other interventions performed in critically ill patients may affect the parameters of interest, data will be collected continuously for the duration of attachment of the OGA, not merely immediately before and after a recruitment manoeuvre. This will allow separation of the effects of the recruitment manoeuvre itself from other interventions the patient may simultaneously be receiving, such as infusion of vasoactive drugs or volume resuscitation. Such interventions are routinely and continuously captured by the electronic clinical information system in use in the ICU.

PARTICIPANT IDENTIFICATION

Study Participants
60 adult patients receiving mechanical ventilation on ICU due to respiratory failure.

Inclusion Criteria
- Male and female, aged 18 years or above
- Receiving mechanical ventilation via an endotracheal tube on ICU

Exclusion Criteria
The participant may not enter the study if ANY of the following apply:

- Consultee indicates patient would be likely to decline enrolment
- Patient is receiving palliative care
- Language barriers prevent sufficiently good communication with patient or consultee for full consent to be obtained

PROTOCOL PROCEDURES

Recruitment
Suitable patients will be identified to the research team by the clinical team responsible for the patient. A member of the research team will then make an approach to obtain consent and confirm patient's eligibility for the study. The patient's data will not pass outside of the clinical team to the research team before consent has been obtained.

Screening and Eligibility Assessment
As this is an observational study, no randomisation or additional screening procedures will be necessary.

Informed Consent
Patients will be unable to give informed consent due to alterations in consciousness caused by illness and therapeutic sedation, which is necessary to facilitate mechanical ventilation. Practice will therefore be as directed by the Mental Capacity Act 2005 (MCA). Advice will be sought from an appropriate consultee either in person or via telephone call to determine if the patient would be likely

to agree to enrolment. If the consultee deems the patient would not wish to be involved care will continue as normal. If the consultee believes the patient would have agreed to participate, they will be enrolled in the study. Those patients who survive and regain capacity during their hospital admission will be tracked onto a ward after their discharge from ICU and be visited by a member of the study team, who will explain that they participated in this observational study after advice had been sought from the consultee. Written confirmation will be sought at that time, endorsing that the patient consents the use of the already collected data in the way set out in the patient information sheet (PIS). If the patient does not wish his/her data to be used these will be erased without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

All the patients in the study will lack the capacity to give informed consent at the time of enrolment, since this work involves exclusively critically ill individuals who are intubated and receiving mechanical ventilation. The design of the study is such that there will be time to seek the views of a personal consultee as detailed in the MCA. If a personal consultee cannot be identified, a professional consultee, independent of the treating and study teams, will be sought. If no consultee can be identified the patient will not be enrolled.

A copy of the signed Informed Consent will be given to the participant or to the consultee acting on participant's best interest. The original signed form will be retained at the study site.

Description of study interventions, comparators and study procedures

The study is observational in nature and therefore there are no interventions additional to routine clinical care.

Description of study procedures

Attachment of the OGA to the ventilator circuit

Once a patient is included in the study, the OGA will be connected to the ventilator circuit. The OGA (when attached to a heat and moisture exchange filter) introduces a small additional dead space of 75ml into the ventilator circuit, which can be compensated for when configuring ventilator settings. Additionally, at present the device is configured to work with a ventilator circuit which uses heat and moisture exchange (HME) filters, rather than those using active humidification. The ICUs in which this study will be developed currently use active humidifiers, though other units may routinely use HMEs. Previous research has shown that the use of HME is efficient and safe for up to 48 hours (24-27). Therefore, for the duration of the study the humidification system will be changed from an active humidifier to an HME. The time required to acquire the data will only be of the order of 12 hours.

Data collection by OGA

To allow the OGA to acquire certain physiological data during the study it will be necessary slightly to vary the tension of oxygen and carbon dioxide for short periods. The changes involved will be of a lesser magnitude than those often seen due to natural variation over time in critically ill patients. The FiO2 will be increased by around 20% from baseline for several minutes; this is a far more modest increase than is seen with the practice of pre-oxygenation – a transitory increase in FiO2 to 100% – performed regularly in ICU patients to make certain routine interventions safer. The end-tidal CO2 level will also briefly be varied by around 1 kPa. Data collection will occur in the following timepoints:

- Before and after a PV curve determination
- Before and after recruitment manoeuvre(s);

Before and after a period of time when no intervention was performed;

No additional procedures will be performed
Regarding laboratory blood tests, mechanically ventilated patients routinely undergo many blood samples each day. For this study, no additional blood sampling will be performed. Laboratory data and arterial blood gases will be collected from samples performed as part of routine clinical care.

Study visit
Data acquisition takes place on a single day for a period of no more than 12 hours, which starts immediately after the attachment of the OGA.

For those patients undergoing a recruitment manoeuvre, this will be performed according to the current Royal Berkshire Hospital ICU SOP for the procedure.

Prior to performing a recruitment manoeuvre, a low flow inflation and deflation PV curve or a recruitment-to-inflation ratio assessment may be recommended by the ICU clinician in charge of the care of the patient, in which case OGA measurements will be obtained before and after these procedures.

Withdrawal of Participants
Patients surviving and regaining capacity prior to hospital discharge will have the option to decline the use of already collected data and withdraw from the study.

Should a consultee change their mind about a patient's participation, they would be free to withdraw the patient, except in the situation where the patient had regained capacity to make the decision for themselves.

Withdrawal can also occur if the clinician responsible for the care of the participant requests it or if palliative care is instituted for the participant.

The reason for withdrawal will be recorded in the CRF.

Definition of End of Study
The end of study is the date of the last study day of the last participant.

SAFETY REPORTING

Definition of Serious Adverse Events
A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

STATISTICS AND ANALYSIS

Description of the Statistical Methods

This is an observational study. The primary outcome measure is the observation of whether and by how much functional residual capacity changes following a recruitment manoeuvre, compared with that predicted based on airway pressure-volume curve analysis. The FRC measurements will be obtained from the gas exchange measurements from the OGA (28) by fitting a lung model to the data as has been previously described. A comparison of observed versus predicted FRC increase will be made using linear (Pearson's) and non-linear (Spearman's) correlation analysis. The relationship between the parameters relating to the airway pressure-volume curve analysis and the secondary outcome measures (changes in dead space and inhomogeneity) will be explored through regression.

Sample Size Determination

The primary outcome measure is the increase in functional residual capacity following a recruitment manoeuvre, compared with that predicted based on airway pressure-volume curve analysis. To power the study, we chose the minimum proportion of one variable that is explained by the second variable (r^2) to be 0.36, which corresponds to a correlation coefficient of 0.6. To detect this (when the comparator is no correlation) with $\beta=0.2$ and $\alpha=0.05$, we need to study 19 patients (28). However, not all patients recruited will subsequently undergo recruitment manoeuvres. If we assume that one in three patients will undergo at least one recruitment manoeuvre during the 12-hour period of the study, then this provides an overall study size of 60 patients.

Analysis populations

All the patients enrolled will be included in the analyses.

The Level of Statistical Significance

The level of significance which will be used is $\alpha<0.05$.

Procedure for Accounting for Missing, Unused, and Spurious Data

Spurious data from the OGA arising from matters such as leaks around the endotracheal cuff, are readily recognised through the loss of recorded nitrogen balance. Such data will be treated as missing in the analysis – no imputation is involved.

DATA MANAGEMENT

Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Data Recording and Record Keeping

Security of data collection, handling, transfer, storage and use is a key component of this study and central to the continuing integrity and viability of this research project. Data will be collected in ICU by staff trained in high quality handling and secure procedures. All other information and data will be stored electronically. The security of the database is maintained by the following principles:

(i) Access to clinical and personal data in the database will be limited to the CI, named research staff, and clinicians (typically research fellows, research nurses and data entry staff). Access will be secure and password protected. The research individuals will maintain confidentiality and be trained in database care.

(ii) All identifiable data (name, hospital number and address) will be stored in one database and all clinical and research data will stored in a separate database. The databases are linked by a key file. When data are downloaded for analysis identifiable data will not be included and individuals will only be identified by their study number.

(iii) Hamilton researchers will have access only to specific pseudo-anonymised data which will be encrypted and password protected before being shared via a GDPR and ISO-27001 compliant Microsoft Sharepoint. Data encompasses clinical information and measurements acquired from both the ventilator (weight, height, analytical respiratory curves, and lung mechanics assessment) and the Optical Gas Analyser (measurements of gas and water vapour pressures, volumes, flows, temperatures, balances, and oxygen consumption over time). The specified data will have no commercial intent.

(iv) The number of staff having access to all fields of the database will be limited. It is also permitted for appropriate regulating bodies and ethics committees to have direct access to the source documents and data.

(v) Responsible members of the University of Oxford or the Royal Berkshire NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

No identifiable, personal data will be retained centrally by the University of Oxford.

QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Risk assessment

The Optical Gas Analyser is an instrument that has been constructed by the University of Oxford. It is not a commercially licensed medical device. The following points relate to the risk assessment for using the device:

Disconnection

Insertion of the OGA into the breathing circuit increases the number of connections, and therefore the possibility that the breathing circuit becomes disconnected. This risk will be mitigated by ensuring an initial secure connection of the OGA and due to the fact that mechanically ventilated patients are under constant supervision.

Electrical safety

The unit is fully enclosed and all external metalwork is grounded with the exception of the connections going to the head which are isolated (as requested by the hospital). Inside the unit all the mains connections are fully insulated and all other voltages after the power supply are less than 20V. The unit has been Portable Appliance Tested to ensure it is safe.

Laser safety

All of the lasers used in the optical gas analyser are class 1 (i.e. emission below hazardous levels) as calculated according to section 5 of BS EN 60825-1:2014. In addition, engineering measures have been taken to prevent individuals gaining access to the beam. The beams are fully enclosed within the head, cabling and main unit. If the covers are removed, the beams remain fully enclosed because everything is fibre coupled. Finally, there is an interlock on the fibre cable between the main unit and the head such that if the cable is disconnected the lasers turn off. This is a hardware interlock and cannot be overridden.

Study monitoring

Not applicable.

Study Committees

There will be no oversight committees in place, as it is an observational study.

PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Other Ethical Considerations

Ethical considerations regarding participants who are unable to consent for themselves are detailed in the section “Informed Consent”.

Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

Transparency in Research

The study will be registered at clinicaltrials.gov once it has been ethically approved.

Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic databases, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants’ personal data.

Expenses and Benefits
Study participation is not associated with any additional expense or inconvenience for patients and no remuneration will be offered.

FINANCE AND INSURANCE

Funding
The study is funded by the University of Oxford.

Insurance
The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

Contractual arrangements
Appropriate contractual arrangements will be put in place with all third parties.

PUBLICATION POLICY
The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the University of Oxford. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Sub Amend 1	1.2	28/07/2023	Dr Jessica Luiz	(1) Increase the sample size to 60 participants. The increase will ensure the study is not underpowered. (2) Add 4 new researchers from a third party to the study team. Having commenced the study we have been approached by Hamilton Medical, the manufacturer of mechanical ventilators used routinely at the study site, who have offered to provide access to data routinely collected by the

				ventilator to which we would not otherwise have access. The facility to add these additional data to those already specified in the protocol will greatly enhance the scientific value of the study. (3 & 4) Allow next of kin to provide remote advice about consent over the phone. Having commenced the study we have found that the current consent process has in some cases delayed enrolment such that periods of care of most interest to us are not being captured. This is often the case for recruitment manoeuvers, as they are frequently performed with some urgency. If a family member is not immediately available in person to approach, we would propose an approach where the study is discussed over the telephone with the next of kin, and remote assent is confirmed upon completion of remote consent form by researcher. Following this, restrospective consent will be requested from participants as they regain capacity, as already described in the existing protocol. (5) Alter consent forms and information sheets

				accordingly to reflect the changes proposed in (1), (2),(3), and (4). (6) Alter study protocol accordingly to reflect the changes proposed in (1), (2), (3), and (4).
Sub Amend 2	1.3		Dr. Jessica Luiz	Extension of study duration from 2 to 3 years.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).