DOMAIN PROTOCOL

The Awake Prone Study:
Awake prone positioning in patients with acute hypoxaemic respiratory failure not due to COVID-19: A randomised controlled trial

To be read in conjunction with CoReCCT Master Protocol.

CoReCCT (Confederation of Respiratory Critical Care Trials)

Trial registration number:	TBC
Sponsor:	University of Warwick
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This protocol has regard for current Health Research Authority guidance and content.

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Master protocol title	CoReCCT: Confederation of Respiratory Critical Care Trials	
Domain protocol title	Awake prone positioning in patients with acute hypoxaemic respiratory failure not due to COVID-19: A randomised controlled trial	
Internal ref. number (or short title)	Awake Prone	
Domain Design	Multi-centre, pragmatic, individual patient randomised, open-label, parallel group trial, and economic evaluation	
Domain participants	Hospitalised adults with acute hypoxaemic respiratory failure ($SpO_2 \leq 94\%$ on ≥40% supplemental oxygen) not due to COVID-19 and deemed suitable for tracheal intubation in event of physiological deterioration	
Planned sample size	1708	
Treatment Duration	From randomisation to recovery (maximum of 120 hours from randomisation in intervention group)	
Follow-up Duration	6 months following randomisation	
Planned Trial Period	1st January 2024 to 31st December 2027	
	Objectives	Outcome Measures
Domain Primary Outcome	To evaluate the effect of awake prone positioning on need for tracheal intubation within 30 days of randomisation	Tracheal intubation within 30 days of randomisation
Domain Secondary outcomes	To evaluate the effect of awake prone positioning on mortality, length of hospital stay, length of critical care stay, health-related quality, time to tracheal intubation, need for non-invasive respiratory support, and duration of invasive mechanical ventilation	As above

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
CoReCCT	Confederation of Respiratory Critical Care Trials
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HRQoL	Health-Related Quality of Life
ICE	Inter-current events
ICNARC	Intensive Care National Audit & Research Centre
IRAS	Integrated Research Application System
NICE	National Institute of Health and Care Excellence
NIHR HTA	National Institute of Health and Care Research Health Technology Assessment
PI	Principal Investigator
PPI	Patient and Public Involvement
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Tracheal intubation and delivery of invasive ventilation on the critical care unit is a life-saving intervention. Each year in the UK, over 60,000 adults receive invasive ventilation.[1] Illnesses that impair oxygenation, such as pneumonia and sepsis, are the most common reason for an adult needing invasive ventilation.[2]

Most people (66%) that receive invasive ventilation survive to leave hospital.[1] However, underlying this survival, are extremely important long-term physical, psychological, and social effects that impact on quality of life.[3 4] A recent systematic review of 48 studies reported that quality of life in critical care survivors was markedly worse than age- and sex-matched controls.[4] Furthermore, there are important healthcare costs associated with needing invasive ventilation with each day of care costing around £1500.[5 6]

There is a strong clinical and public interest in identifying strategies that might safely reduce the need for tracheal intubation and invasive ventilation.

In patients that are invasively ventilated on an intensive care unit, the use of prone positioning (lying on one's front) has been shown to reduce mortality, leading to it being supported by UK and international clinical guidelines.[7-9] The landmark PROSEVA randomised controlled trial showed that in 466 patients with severe acute respiratory distress syndrome (ARDS) patients placed in the prone position for at least 16 hours/ day, compared to standard care, had significantly lower 28-day mortality (hazard ratio 0.39, 95% confidence interval 0.25 to 0.63).[10] The use of prone positioning in invasively ventilated patients is, however, used in less than 20% of patients with severe ARDS, likely due, in part, to implementation challenges including risks of turning (e.g. accidental extubation) and the high number of staff required to safely turn a patient (at least five).[2 11-13]

The COVID-19 pandemic and associated urgent need to identify strategies that might avoid the need for invasive ventilation drove interest in the concept of use of prone positioning prior to intubation (awake prone positioning).[14] In contrast to prone positioning in invasively ventilated patients, awake prone positioning is more straightforward to implement. In many cases, the patient may turn independently or with the assistance of a single nurse.

Prior to the pandemic, small published case series studies reported an association between awake prone positioning and improved oxygenation.[15 16] Early studies in patients with COVID-19 showed a similar benefit, leading to the rapid conduct of a number of randomised controlled trials.[17 18]

Experience in the COVID-19 pandemic drove widespread uptake in the use of awake prone positioning, such that doctors, nurses, and physiotherapists throughout acute hospitals are comfortable with its use. Awake prone positioning is an extremely attractive intervention- it is easy, safe, and free to implement.

1.2 Existing knowledge

There is consistent evidence that awake prone positioning is associated with improvements in oxygenation.[19-23] However, the mechanism for this improvement seems to differ between patients that are invasively ventilated and patients who are not invasively ventilated.[23] Across a range of patient presentations, physiological studies show that the improvement in oxygenation in awake prone positioning in patients who are not invasively ventilated is likely primarily driven by improved recruitment of specific lung regions and by homogenising distribution of ventilation, although there are some inconsistent findings across studies.[20-23] There is also evidence from one study that awake prone positioning may increase oesophageal pressure, potentially increasing the risk of self-inflicted lung injury.[20]

In 2022, a systematic review and meta-analysis summarised the evidence on the use of awake prone positioning in patients with COVID-19.[24] The review identified 17 trials (2931 patients), of which six trials were originally published as a meta-trial.[19] High certainty evidence showed that awake prone positioning, compared with standard care, reduced the risk of tracheal intubation (relative risk 0.83, 95% confidence interval 0.73 to 0.94, I^2=0%), whilst moderate certainty evidence showed that awake prone positioning, compared with standard, did not reduce the risk of mortality (relative risk 0.90, 95% confidence interval, 95% CI 0.76-1.07, I^2=0%). Awake prone positioning did not reduce ventilator-free days, critical care length of stay, hospital length of stay, or escalation of oxygen therapy type (all low- moderate certainty evidence). Four sub-group analyses were performed (duration of awake prone positioning, baseline hypoxaemia severity, baseline care setting, baseline use of non-invasive respiratory support), but the p-value for interaction was not significant for all interactions. There were few adverse events reported across all studies. In a Bayesian analysis, awake prone positioning was found to reduce the risk of tracheal intubation with a high probability across a range of priors.

A key concern with the implementation of awake prone positioning is how well it might be tolerated by patients, potentially contributing to a reduced effect if poorly tolerated. Data from observational studies and randomised controlled trials provide evidence of a dose-response with increased duration associated with increased benefit.[25 26]

Clinical guidelines, including those developed by the National Institute of Health and Care Excellence (NICE), support the use of awake prone positioning only in patients with acute hypoxaemic respiratory failure due to COVID-19.[27 28 29] These guidelines highlight the need for further research on the effectiveness of awake prone positioning in patients with acute hypoxaemic respiratory failure that is not caused by COVID-19.

Our clinical trial registry search (December 2023) identified three planned or ongoing clinical trials of awake prone positioning in a similar target population, which had a sample size of over 100 participants (NCT05698004; NCT05990101; NCT04142736/ ISRCTN11536318).[30] The sample size of these studies ranges from 244 to 650 patients and all three studies were specifically recruiting from the Intensive Care Unit. In line with previous observational studies showing an association between early initiation of awake prone position and improved outcome, Awake Prone will start awake prone positioning as early as possible in the patient journey and, therefore, hopefully avoid the need for critical care unit admission, which is a key secondary outcome.[31]

1.3 Research question

In hospitalised adults with acute hypoxaemic respiratory failure not due to COVID-19 and who are deemed suitable for tracheal intubation, is an awake prone positioning strategy compared with standard care clinically- and cost-effective?

1.4 Need for a trial

Avoiding intubation, when safe to do so, is a key goal for patients and clinicians. Our discussions with patients and members of the public in preparing this trial confirm that they highly value the avoidance of tracheal intubation and invasive ventilation, both due to the actual experience being unpleasant and its long-term consequences.[3 4 32]

Intensive care research prioritisation exercises highlight the importance of research that identifies strategies to prevent lung injury in patients receiving invasive ventilation.[33 34] Our planned study will directly address this knowledge gap by evaluating the effectiveness of an intervention (awake prone positioning) in preventing the need for invasive ventilation.

The recent European Society of Intensive Care Medicine ARDS guidelines and an international expert panel have highlighted the urgent need for a randomised controlled trial of awake prone positioning in patients who do not have COVID-19.[28 29]

Our Patient, Public Involvement Engagement (PPIE) work has endorsed the importance of the study question.

1.5 Ethical considerations

The Awake Prone trial will evaluate the clinical and cost-effectiveness of awake prone positioning in patients with acute hypoxaemic respiratory failure. The trial intervention is likely to be most effective when initiated as early as possible after the potential participant meets trial eligibility criteria. We have developed an easy-read participant information leaflet to supplement the standard participant information leaflet, which will help to clearly and quickly communicate information about the trial to potential participants. Some potential participants may lack mental capacity due to their underlying condition. It is important that these individuals are included as these individuals may be most unwell and potentially be most likely to benefit from the trial intervention. For this reason, we have developed a consent process which will facilitate the inclusion of individuals lacking mental capacity that aligns with national legislation across the UK. We will adopt in full the NIHR INCLUDE Impaired Capacity to Consent Framework (co-applicant Dark was contributor) to support the inclusion of this patient group.[35]

Our experience is that under-served communities in clinical research, as defined by NIHR's INCLUDE project, frequently present for NHS care as an emergency.[6] Our trial design will offer participation to those most likely to benefit from the proposed intervention in acute, unscheduled NHS care hospital settings. Our recruitment processes will support recruitment across all patient groups, including those whose first-language is not English.[357] We will follow recommendations within NIHR INCLUDE guidance and the equality-diversity-

inclusion strategy document (2022-2027).[35] This has included trial design and protocol review; trial steering group membership; PPI; and will include trial inclusion and trial result dissemination.

The trial will conform to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.[38] It will be conducted in accordance with UK legislation, such as the Mental Capacity Act 2005, Mental Capacity Act (Northern Ireland) 2016, and University of Warwick Standard Operating Procedures (SOPs).

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Cons*olidated *S*tandards *o*f *R*eporting *T*rials) statement.[39]

1.7 Confederation of Respiratory Critical Care Trials

Awake Prone sits as one domain within the Confederation of Respiratory Critical Care Trials (CoReCCT). The confederation was established as a novel concept to group a range of respiratory critical care trials with an overarching aim to streamline trial delivery across areas such as governance, contracting, and data collection. The overriding objective is to improve deliverability by minimising burden on participating sites and participants.

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

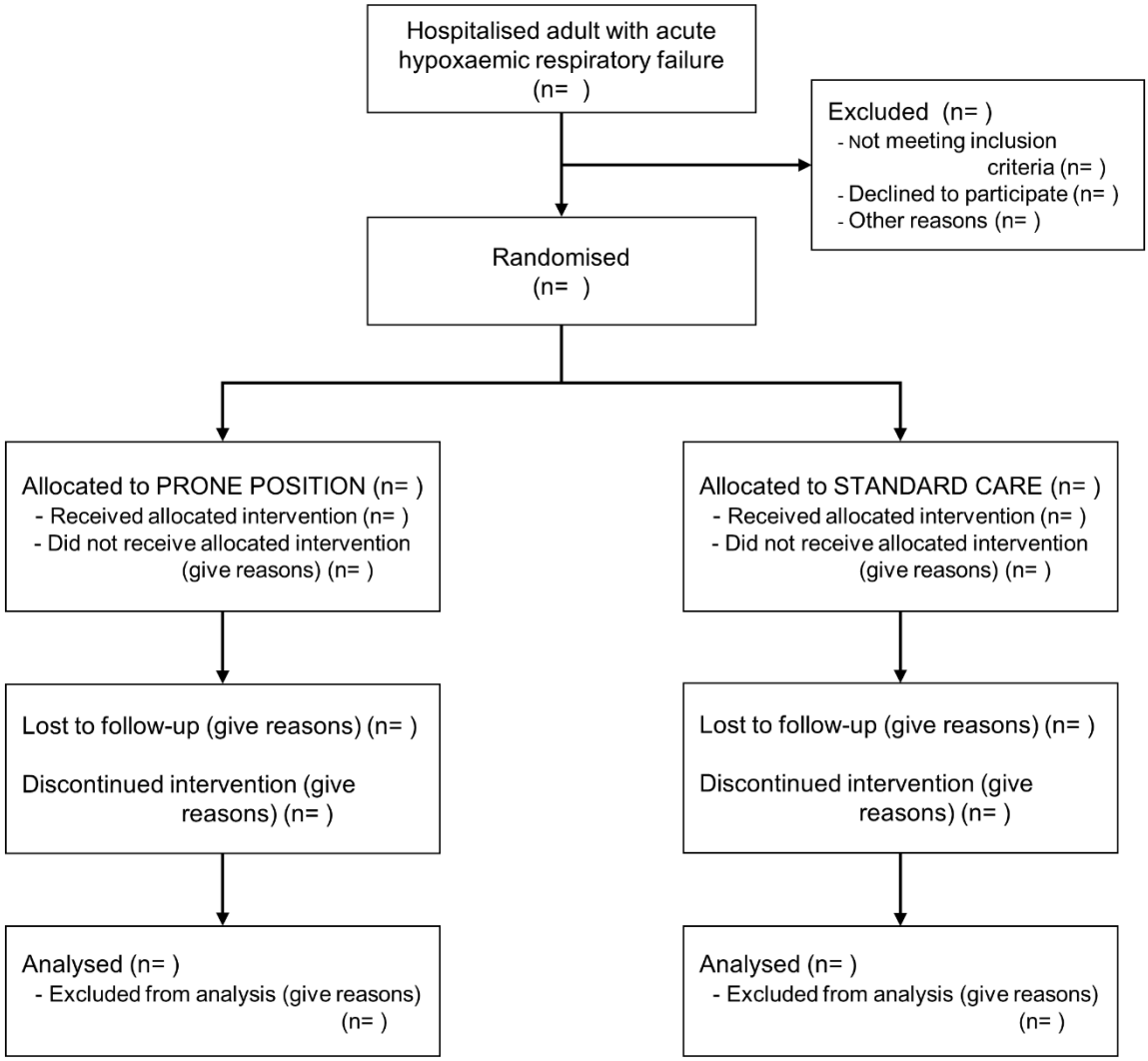
We will conduct a multi-centre, pragmatic, individual patient randomised, open-label, parallel group trial to evaluate the clinical- and cost-effectiveness of awake prone positioning in patients with acute hypoxaemic respiratory failure.

Hospitalised adult patients with acute hypoxaemic respiratory not due to COVID-19, and who are deemed suitable for tracheal intubation in the event of physiological deterioration, will be randomised in a 1:1 ratio to either awake prone positioning or standard care. The trial will include an internal pilot (8 months duration) during which we will test the detailed trial procedures, data collection and confirm the feasibility of recruitment. Patients will be followed up for 6 months post-randomisation to assess their quality of life and to collect cost data for the economic evaluation.

The trial will be conducted across at least 60 hospitals in the UK. A list of trial sites will be available on the study registration page. A trial flow diagram is included as figure one.

The trial will incorporate a study within a trial to explore strategies for monitoring treatment adherence.

Figure 1: Trial Flow Diagram



2.2 Aims and objectives

2.2.1 Primary objective

The primary objective of this trial is to evaluate the clinical effectiveness of awake prone positioning in non-intubated adults with acute hypoxaemic respiratory failure not due to COVID-19, measured by our primary outcome of tracheal intubation within 30 days.

2.2.2 Secondary objective

Secondary objectives of the trial are to:

- Evaluate the effect of awake prone positioning in non-intubated adults with acute hypoxaemic respiratory failure not due to COVID-19 on mortality, quality of life, and hospital length of stay.
- To determine the cost-effectiveness of awake prone positioning in non-intubated adults with acute hypoxaemic respiratory failure not due to COVID-19

2.3 Outcome measures

The primary trial outcome is the incidence of tracheal intubation within 30 days of randomisation.

Our primary outcome of tracheal intubation is the start of the process of invasive ventilation. This reflects a new phase of critical illness/ deterioration, which patients and clinical staff avoid when safe to do so, due to its long-term effect on patient well-being. Tracheal intubation is commonly used as an outcome in studies of pre-intubation interventions, such as awake prone positioning in COVID-19 and non-invasive respiratory strategies.[24 36]

A criticism of tracheal intubation as an outcome is that it may be subject to performance bias.[41-43] The decision to perform tracheal intubation and commence invasive mechanical ventilation is a complex clinical decision that incorporates the patient's current physiology, illness trajectory, and patient wishes. [37]
To mitigate potential concerns that the outcome of tracheal intubation may be influenced by performance bias, we will collect physiological criteria prior to tracheal intubation to enable us to assess whether there is any evidence of a different threshold for tracheal intubation being adopted across the study arms.

Our secondary outcomes and their timing align, where appropriate, to the critical care ventilation core outcome set and other clinical trials planned in this clinical area.[38] To optimise trial efficiency, we will use routine data sources (e.g. Hospital Episode Statistics (HES), Intensive Care National Audit and Research Centre (ICNARC)) for outcome collection, wherever feasible.

2.3.1 Efficacy

The primary outcome is the incidence of tracheal intubation within 30 days of randomisation. This does not include tracheal intubation where it is used only to facilitate an operation or procedure.

Secondary outcomes are:

- Length of critical care stay (days), from randomisation
- Length of hospital stay (days), from randomisation
- Time to tracheal intubation (days)
- Time to admission to critical care (hours/days)
- Duration of non-invasive respiratory support (days)
- New requirement for non-invasive respiratory support (yes/no)
- Duration of invasive ventilation during hospital stay
- Mortality (hospital discharge/ 2 months/ 6 months)
- Health related quality of life- EQ-5D-5L (2 months/ 6 months)
- Pre-specified complications that occur between randomisation and 5 days*

* See section 4.1 for Pre-Specified Complications List

2.3.2 Safety

Reportable safety events are described in section 7 of the CoReCCT Master Protocol.

2.3.3 Health economic outcomes

The primary health economic outcome is Incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS and personal social services (PSS).

Secondary health economic outcomes are:

- Cost of critical care stay (level 2/3 days)
- Cost of hospital stay
- Utilisation of NHS and PSS resources after discharge
- Incremental cost per tracheal intubation avoided
- Probability of cost-effectiveness at £20,000 and £30,000 per QALY.

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet all the inclusion criteria and none of the exclusion criteria:

2.4.1 Inclusion criteria

- Adult (age $\geq$18 years) hospitalised patient who is not intubated
- Acute hypoxaemic respiratory failure, defined as sustained $SpO_2 \leq 94\%$ whilst receiving ≥40% supplemental oxygen
- Deemed suitable for tracheal intubation in event of physiological deterioration

2.4.2 Exclusion criteria

- Hypoxaemia fully explained by acute pulmonary oedema due to heart failure
- Patient unwilling to attempt awake prone positioning
- Contraindication to awake prone positioning
- COVID-19 pneumonitis as primary cause of respiratory failure
- Invasive mechanical ventilation during current hospital admission (except where provided only to facilitate a procedure or operation)

2.5 Participant identification / Screening

Staff will identify potential participants in appropriate clinical areas, such as emergency departments, critical care units, acute wards, respiratory support units, and acute medical units. Potential processes for identifying patients includes referrals, screening in clinical areas, or review of electronic health systems using appropriate queries. We anticipate that screening will be a continuous process as patients may become eligible during their hospital stay. We will work with each participating site to support the development of local strategies to optimise screening in their hospital, based on factors such as available technology and clinical areas at their site which can safely deliver awake prone positioning.

Screening information will be entered on to a trial web application, hosted by Warwick Clinical Trials Unit (WCTU). This will capture anonymised data on the numbers of patients meeting inclusion criteria for the trial but not entered into the trial along with the reasons for non-enrolment. These data are important to understand the generalisability of the recruited patient population.

Screening of patients will involve reviewing personal identifiable information. This may be undertaken by a member of the patient's existing clinical care team, or by a member of the hospital research team, depending on local arrangements. Screening and eligibility assessment may be undertaken by any individual clinically competent to undertake that role, as delegated by the principal investigator. It is anticipated that this process may be undertaken at any time of day or night, provided appropriately trained staff members are available.

Patients may be receiving conventional oxygen therapy or any non-invasive respiratory support strategy (high-flow nasal oxygen/ non-invasive ventilation/ continuous positive airway pressure) at the time of the eligibility assessment.

There are no specific tests or investigations required to determine eligibility, beyond those that are performed as part of routine care. Trial eligibility criteria are based on peripheral oxygen saturations. In patients with darker skin pigmentation, pulse oximeters may give erroneously high readings.[39 405,46] As such, where appropriate, clinical teams may choose to base the eligibility assessment on arterial oxygen saturations recorded on an arterial blood gas that has been collected as part of standard care. A COVID-19 test is not required to determine eligibility. Where a patient has a positive COVID-19 test, they may still be eligible where COVID-19 is not deemed to be the primary cause of respiratory failure (e.g. hospital-acquired pneumonia).

The individual assessing eligibility will consider whether there is any contraindication to awake prone positioning that would make it unsafe to perform. This may include patient factors, such as open abdominal wounds or unstable spine fracture, or contextual factors, such as inadequate staffing. If the patient is deemed to be eligible, then they will be approached for consent to participate.

Confirmation that all eligibility criteria are met will be entered on to the trial web application prior to the patient being randomised.

2.6 Site Staff Training

A programme of training will be provided to individuals at hospital sites with responsibility for the assessment of eligibility criteria and randomisation of participants. We will develop web-based training resources that enable site staff to complete training at a time convenient to them. If it is more convenient to specific individuals, training may be provided in person or via video conferencing. This training may be delivered by WCTU staff or by the site principal investigator, or a member of the site team that has been approved to deliver training by the principal investigator. Each hospital site will maintain a training completion log.

We will develop a bespoke training package for clinical members of staff that may be involved in supporting participants to turn into the prone position or who have responsibility for caring for individuals whilst they are in the prone position.

2.7 Informed consent

Our approach to the consent in this trial is based on maximising patient choice and ensuring the trial recruits a participant population that is representative of individuals with the target condition.

The target population for this trial is individuals with acute hypoxaemic respiratory failure. Low levels of oxygen in the blood can cause confusion and affect capacity to make decisions. Based on our experience in previous trials in broadly similar conditions, we anticipate that most potential participants will have capacity to make decisions about trial enrolment.[41] However, those that lack capacity are likely to be those individuals with the greatest severity of disease and are therefore at highest risk of tracheal intubation. Exclusion of these individuals would potentially reduce trial generalisability.

On this basis, we propose, in line with relevant UK mental capacity legislation, to seek agreement from an appropriate consultee in patients that lack capacity. The assessment of mental capacity will be made by the site research team in collaboration with the clinical team and recorded in the clinical record.

Participant consent or consultee agreement is required prior to randomisation.

2.7.1 Individuals with mental capacity

For individuals with mental capacity, a member of the site research team will make an initial approach as soon as possible after the individual has been identified as being potentially eligible for the trial. The research team member will provide a verbal overview, that includes the trial rationale and trial procedures. They will then provide information in a written format.

We recognise that potential trial participants will be acutely unwell. We have developed a layered approach to information provision that enables individuals to access the information that they need about the trial in targeted and easy-to-digest formats:

- Main participant information leaflet- this provides key information about the trial and explains what participation means to the potential participant,
- Data information leaflet- this provides information about the way in which participant's data are managed and what they can do if they have concerns or something goes wrong,
- An easy-read information leaflet which covers all aspects of the trial in an easily digestible format.

All potential participants will be provided with the main participant information leaflet and data information leaflet. Site research staff will decide on an individual basis whether or not to use easy-read information leaflet.

The individual will be given adequate time to consider participation in the trial. This will include the opportunity to ask questions. The participant information leaflet will, however, make clear to the participant that if the trial intervention is clinically effective, it is likely to be most beneficial when started early. Individuals may decline to participate without giving any reason and without it influencing their care.

If the individual is willing to participate, their consent will be recorded on a consent form, which is signed by both the participant and research team member. The consent form may be signed physically or, where this option is available, digitally. If the individual patient is physically incapable of completing the consent form, witnessed verbal consent will be sought from the participant, and this will be documented on the consent form. For these individuals, the research team member will annotate each box on the consent form to indicate consent to that item.

If required, translation services will be used to support the consent process. For a limited number of the most common languages used in the UK, Warwick Clinical Trials Unit will provide translations of study information leaflets.

Following the trial pilot period, the information leaflet will be amended to include information about the study within a trial (SWAT). The research team will explain to the individual whether they are potentially eligible to also participate in the SWAT. The consent form will contain an additional box for the participant to record their agreement for participation in the SWAT. Individuals may choose to participate in the main trial without participating in the SWAT. Individuals may not participate in the SWAT if they have declined to participate in the main trial.

2.7.2 Individuals lacking mental capacity

A key consideration for trial delivery and which forms part of the eligibility criteria is participant willingness to attempt awake prone positioning. We anticipate that even where the participant lacks mental capacity, they will be able to communicate their willingness to attempt awake prone positioning. To enable individuals to communicate their wishes, the research team member will provide very brief information, such as:

- You are currently needing a high amount of oxygen to help your breathing.
- We are currently doing a research study to work out if lying on your tummy will help you get better.
- Would it be OK if we spoke to your family/ doctors about including you in this study?
- If you took part in the research, would you be willing to try lying on your tummy? [Pictures from the easy-read information leaflet may be used to help explain this]. We would ask you to do this for several hours at a time.
- We will give you more information about the study when you are feeling better.

If an individual is unable to respond or states that are unwilling to attempt awake prone positioning, then they would not be eligible for the trial. Where an individual lacks mental

capacity, but expresses a willingness to attempt awake prone positioning, the process outlined in sections 2.7.2.1 or 2.7.2.2 will be followed.

2.7.2.1 Process for England, Wales and Northern Ireland for individuals lacking mental capacity

For individuals lacking mental capacity, the site research team will identify and approach a personal consultee, such as a relative, friend or partner, that is willing to be consulted about trial participation. The consultation process will follow that described in section 2.7.1, except that the consultee will additionally be provided with a covering statement summarising the role of the consultee. The consultee will be asked to provide their opinion about the individual's wishes and feelings if they had capacity. If the consultee feels that the individual would be willing to participate, then the consultee will be asked to record this opinion on the consultee declaration form, which will be counter-signed by a member of the site research team. The form may be signed physically or, where this option is available, digitally.

Consultation with the personal consultee may take place either in-person or by telephone. For telephone consultations, the member of the site research team will need to ensure that the consultee has access to a copy of the consultee covering statement and participant information leaflet (e.g. through e-mail or web-link). Where there is no option to sign the declaration form digitally, witnessed verbal consent will be sought and the consultee's opinion will be recorded on a paper form by the member of the site research team.

If a personal consultee cannot be identified or is not available, then the site research team will seek the opinion of a professional consultee, who will be a registered medical practitioner that is not connected to the study. The process for personal consultees, as detailed above, will be followed. Where agreement from a professional consultee is initially obtained, the opinion of a personal consultee should be sought at the earliest practical opportunity.

2.7.2.2 Process for Scotland for individuals lacking mental capacity

For individuals lacking mental capacity, the site research team will identify and approach the individual's nearest relative/guardian or welfare attorney. The consultation process will follow that described in section 2.7.1, except that the relative/guardian or welfare attorney will additionally be provided with a covering statement summarising their role. They will be asked to provide their opinion about the individual's wishes and feelings if they had capacity. If they feel that the individual would be willing to participate, then they will be asked to record this t on the nearest relative/guardian or welfare attorney consent form, which will be counter-signed by a member of the site research team. The form may be signed physically or, where this option is available, digitally.

Consultation with the nearest relative/guardian or welfare attorney may take place either in-person or by telephone. For telephone consultations, a member of the site research team will need to ensure that the nearest relative/guardian or welfare attorney has access to a copy of the appropriate covering statement and participant information leaflet (e.g.

through e-mail or web-link). Where there is no option to sign the consent form digitally, the decision will be recorded on a paper form by the member of the site research team.

If a relative/guardian or welfare attorney cannot be identified or is not available, then the individual would not be eligible for trial participation.

2.7.2.3 Process where the participant does not regain mental capacity- England, Scotland, Wales, and Northern Ireland

If the participant does not regain mental capacity (e.g. due to death or persistent neurological impairment), then the opinion of the consultee will continue to be followed.

2.7.2.4 Process where the participant regains mental capacity- England, Wales, and Northern Ireland

Once the participant has regained mental capacity, an approach should be made for their consent for ongoing trial participation. At this time, the trial intervention will likely be complete so the focus of such an approach will be on the participant's willingness to complete follow-up questionnaires. A specific follow-up participant information leaflet has been developed to support this process. In the event that the participant regains mental capacity *during* the intervention, then the main participant information leaflet will be used.

A member of the site research team will approach the participant at the earliest practical opportunity after they have regained mental capacity. The research team member will provide a verbal overview, that includes the trial rationale, trial procedures, and details of the trial follow-up. They will then provide information in a written format through the appropriate participant information leaflet.

The individual will be given adequate time to consider participation in the trial. This will include the opportunity to ask questions.

If the individual is willing to participate, their consent will be recorded on a consent form, which is signed by both the participant and research team member. The consent form may be signed physically or, where this option is available, digitally. If the patient is physically incapable of completing the consent form, verbal consent only will be sought from the participant and this will be documented on the consent form. The research team member will annotate each box on the consent form to indicate consent to that item.

If the participant declines further trial participation, the research team member will ask the participant if they are happy for data collected up until that point to be kept. The participants preference will be recorded on the withdrawal CRF. If site staff are unable to ask participants this question (e.g. the participant is transferred to a different hospital), a reasonable attempt must be made to gain this information. Where attempts are unsuccessful, data already collected will be retained to prevent bias from loss of data for this participant population.

There is no requirement to reaffirm consent in Scotland.

2.8 Randomisation

2.8.1 Randomisation

Following consent or consultee agreement, eligible patients will be individually randomised in a 1:1 ratio to either awake prone positioning or standard care. Randomisation will be stratified by hospital site and care setting (critical care or other). A web-based randomisation system will be used to ensure allocation concealment.

The allocation sequence will be generated by the study statistician.

Participants will be randomised sequentially as they become eligible for randomisation. The participant's randomisation information, including allocation and trial number, will be recorded in their clinical record.

2.8.2 Post-randomisation withdrawals, exclusions and moves out of region

Participants, or their consultee on their behalf, may request to be withdrawn from the trial at any time without prejudice. Those that choose to withdraw from the trial intervention will continue to be followed-up as per the trial protocol, unless consent for this is explicitly withdrawn by the participant (or consultee if the participant lacks capacity).

In the event that a participant is transferred to another hospital, intervention delivery will usually stop at the point of transfer. The recruiting hospital will liaise with the new hospital to facilitate collection of follow-up data.

Due to the nature of the trial primary outcome, timing of assessment, and our experience in previous trials, we anticipate that we will achieve high-rates of follow-up for the primary outcome.[41-44] Follow-up rates will be monitored by the Trial Management Group (TMG).

In the event that a randomised participant is later found to be ineligible, they will continue to be followed-up and will be included in study analyses.

2.9 Trial treatments / intervention

Both the intervention and comparator group will receive standard care, such as antibiotics and fluids, as directed by the clinical team. In line with the pragmatic nature of the trial, any escalation or de-escalation of standard treatment will be at the discretion of the clinical team, including oxygen therapy titration and use of non-invasive respiratory strategies, such as high-flow nasal oxygen or continuous positive airway pressure.

Trial treatments may be delivered in any clinical setting in the acute hospital that is deemed clinically safe by the participant's clinical team. Such settings may include acute medical admissions units, critical care units, respiratory support units, acute medical wards, and acute surgical wards.

Trial patients in both arms will be at risk of physiological deterioration. The frequency of physiological monitoring (e.g. blood pressure, respiratory rate, peripheral oxygen

saturations) will be determined by the participant's clinical team in line with their local clinical guidelines. Physiological targets such as SpO_2 and PaO_2 will be determined by the local clinical team. It is expected that in most cases, trial participants being cared for outside the critical care unit will be referred to the hospital critical care outreach team, where this service is available.

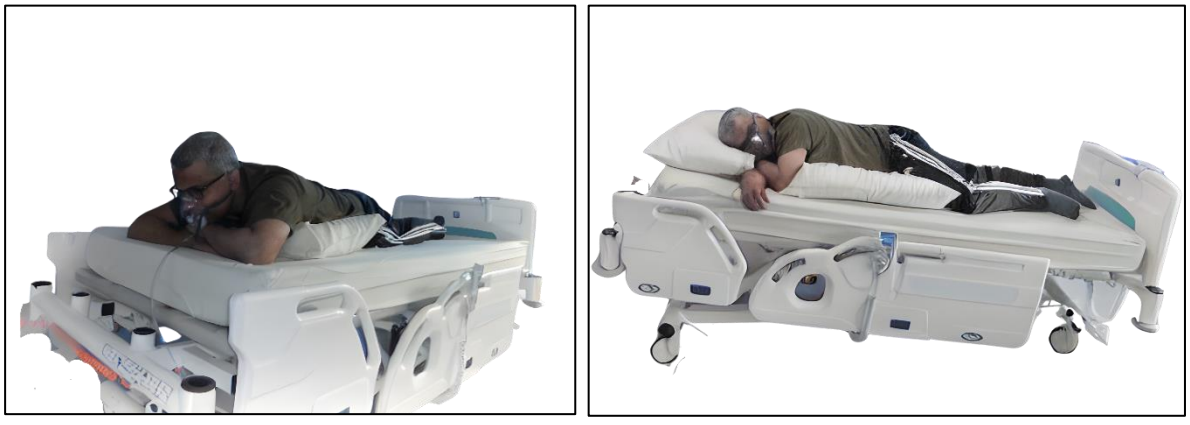
2.9.1 Intervention- awake prone positioning

The intervention is to be applied as below over a maximum of 5 days / 120 hours from randomisation. The target daily duration for awake prone positioning is ≥ 8 hours per 24-hour period. This may be achieved through a single long period of awake prone positioning or several shorter periods. We expect any shorter period to last at least one-hour.

Participants will lie in prone position as long and frequently as feasible, as soon as possible after randomisation (see figure two). Instructions to the patient on intervention adherence will be provided by the hospital research/ clinical team and reinforced by the clinical team at regular intervals.

Following randomisation, a healthcare professional will assist the participant to turn on their side and then face down ensuring that they are predominantly on their chest rather than on their side (figure two). Arms can be positioned wherever is most comfortable for the participant. The participant will have additional support as needed to optimise comfort (e.g. pillow under the chest). A patient call bell will be given to the participant, in line with standard practice, to ensure that they can contact a staff member for assistance when needed. If the patient cannot tolerate lying wholly on their chest, then the participant will be permitted to lie in a 3/4 prone position (figure two).

Figure 2: Images of full-prone and 3/4 prone position



We carefully considered the optimum daily target for awake prone positioning, noting that in observational studies a treatment duration of 6-8 hours/ day seems to be a key cut-off for treatment efficacy.[25 26] However, the recent systematic review and meta-analysis of awake prone positioning in COVID-19 found no evidence of an interaction in a sub-group analysis of treatment duration.[24] The large meta-trial of awake prone positioning in COVID-

19 targeted a duration of 16 hours/ day, but the actual median delivered duration was 5 hours.[19] To determine our target treatment duration, we worked with PPI collaborators and attempted to strike a balance between a duration that was likely to be perceived as feasible and acceptable to participants, whilst ensuring that the target duration was potentially beneficial, based on the COVID-19 literature.

The intervention will continue until one of the following criteria are met:

- 120 hours from randomisation,
- Tracheal intubation,
- Participant recovery,*
- Participant decision to stop intervention,
- Development of contraindication to awake prone positioning,
- Participant transferred to care setting where intervention could not be delivered, or
- Participant transferred to another hospital.

* The time-point of recovery will be determined by the treating clinician in partnership with the participant. This will be individualised to the participant and will commonly be based on both objective criteria (e.g. amount of supplemental oxygen and peripheral oxygen saturations, such as SpO_2 of 94% or more whilst receiving ≤ 35% supplemental oxygen) and subjective criteria (e.g. breathlessness). To meet criteria for recovery, it is expected that any clinical improvement is sustained after moving to a semi-recumbent position.

2.9.2 Control- standard care

The control arm will be usual care, as currently used across participating hospitals, namely a semi-recumbent position with 30^o-90^o head elevation. Physiotherapy or nursing staff may also recommend that participants lie with a slight side tilt as part of standard care for pressure area relief and, in some cases, to support drainage of pulmonary secretions. Any use of the full prone or 3/4 prone position will be recorded.

2.9.3 Compliance/contamination

We anticipate that individuals randomised to the awake prone positioning may find the position uncomfortable. To support participants with continuing with the awake prone position, site staff will be encouraged to adopt strategies to support compliance, such as:

- Working with the patient to identify which time periods are best suited for them to spend in the awake prone position,
- Regular comfort checks,
- Feedback of any clinical improvements.

Each day, we will record the amount of time that an individual has spent in the awake prone position (full-prone or 3/4 prone) in the preceding 24 hours. In our study within a trial, we will explore different strategies for monitoring compliance.

2.10 Blinding

Due to the nature of the trial interventions, it is not possible to blind hospital staff members or patients to treatment allocation.

2.11 Co-enrolment into other trials

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with national NIHR-supported co-enrolment guidelines.[53] There are many current examples of successful co-enrolment between UK critical care studies, facilitated by these guidelines.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table one summarises the trial schedule of events and timing of data collection.

Table 1: Trial Assessments

	Timing of assessment				
	Baseline	**Hospital stay**	**Hospital discharge**	**2 months†**	**6 months‡**
Eligibility assessment	✓				
Consent/ consultee agreement	✓				
Baseline data collection	✓				
Randomisation	✓				
Intervention	✓	✓			
Critical care/ hospital stay data			✓		
Patient consent for continued participation*		✓			
Study within a trial (SWAT)		✓			
Survival status		✓	✓	✓	✓
Quality of life (EQ-5D-5L) and health resource use questionnaire				✓	✓
Safety reporting		✓	✓		

†- For 2 month assessment, the permitted time window is 2 weeks prior to 6 weeks after. Where a participant is enrolled in Awake Prone and another CoReCCT study, the assessment will take place at 2 months following the last CoReCCT study randomisation.
‡- For 6 month assessment, the permitted time window is 2 weeks before to 6 weeks after. Where a participant is enrolled in Awake Prone and another CoReCCT study, the assessment will take place at 6 months following the last CoReCCT study randomisation.
*- only applicable if consultee agreement used as basis for initial enrolment

3.2 Long term follow-up assessments

Follow-up questionnaires at 2 months and 6 months will capture health-related quality of life and healthcare resource use. Follow up time points and management of follow up questionnaires are aligned over all CoReCCT domains and managed by WCTU. Refer to section 6 of the CoReCCT Master Protocol for further details.

3.3 Study within a trial (SWAT)

A key challenge for many non-pharmaceutical interventions in the acute hospital setting is the monitoring of adherence. Awake prone positioning trials in patients with COVID-19 have typically relied on staff collection of data for duration of awake prone positioning.

This study within a trial will explore different strategies to collect information on the completeness and acceptability of different strategies to monitor trial adherence.

Participants will be given the opportunity to opt-in to this study within a trial if they meet the following criteria:

- Randomised to the trial,
- Have mental capacity, and,
- Have access to an electronic device (phone/ tablet).

These individuals will be randomised to one of three groups: electronic diary with 1-hourly data capture, electronic diary with 6-hourly data capture, or paper diary. We will compare data completeness across arms through the data capture system and acceptability of different data strategies through a brief survey. We will also explore differences between patient-reported adherence and staff-reported adherence. Research staff views on different strategies will be collected through a survey.

We will implement the study within a trial after completion of the trial pilot phase. After completion of the pilot phase, participant information leaflets and consent forms will be updated to included information about this study within a trial. The study within a trial will not be commenced until these amendments have been approved.

This study within a trial will be registered with the registry for studies within a trial, hosted by the Northern Ireland Hub for Trials Methodology Research.

3.4 Pilot Phase

The main trial will be preceded by an internal pilot, where we will recruit 170 patients (10% of total sample).[45] The pilot will take place in 25 hospitals, representative of centres that will take part in the main trial. The internal pilot will be used to scrutinise and audit: (a) the screening logs for information on ineligible and eligible patients; (b) the recruitment and site set-up rate; (c) randomisation processes; (d) training around the implementation of the intervention; (e) adherence to the intervention, in line with the criteria below; (f) cross-over rates; (g) data completeness; (h) time from meeting eligibility criteria to randomization; (i) proportion of patients that met-defined criteria for tracheal intubation and proportion of patients that undergo tracheal intubation; and (j) acceptability of the intervention to staff

and patients. We have developed specific challenging progression criteria for items b, e, and f, as outlined in Table two. We propose that the data for all other items are closely reviewed and used to inform decisions about progression in a qualitative way. Planned recruitment rate during the pilot study is detailed below in the project timelines section.

Table 2: Trial Progression Criteria

	Red	Amber	Green
RECRUITMENT			
% Threshold	<66%	66-99%	100%
Sites recruited	<16	16-24	25
Total number of participants recruited	<112	112-169	170
Recruits/ site/ month	<0.82	0.82-1.24	≥1.25
COMPLIANCE/ADHERENCE TO INTERVNTION			
% Threshold	<70%	70-85%	85-100%
Total number of participants recruited	<119	119-144	145-170
CROSSOVER (from control to	>10%	6-10%	<5%

Success criteria for recruitment and site set-up will be (a) 100%- progress to main trial; (b) 66-99% - progress to main trial with review of screening log and protocol and explore the possibility of additional sites; and (c) less than 66% recruitment- progression to main trial not anticipated. Success criteria for protocol adherence and intervention fidelity: (a) 85-100%- progress to main trial; (b) 70-85%- progress to main trial with development of additional strategies to improve adherence; and (c) <70%- progression to main trial not anticipated. We have also set progression criteria for crossover from the control to the intervention arm.

These criteria will be reviewed by the DMC and the TSC in association with the HTA secretariat.

On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial. The pilot study results will be reported in the HTA Monograph in accordance with the CONSORT guideline for pilot studies.[46]

4. ADVERSE EVENT MANAGEMENT

In order to accurately assess and report SAEs relevant to Awake Prone, the CoReCCT Master Protocol must be read in conjunction with section 4.1 below.

Section 7 of the CoReCCT Master Protocol includes the CoReCCT Safety Reporting Flowchart and provides details on these adverse event management topics:

- Definitions of SAEs
- Assessing and reporting SAEs
- Causality Assessment of SAEs
- Expectedness Assessment of Related SAEs
- Expedited Reporting of Related and Unexpected SAEs to REC

4.1 Pre-Specified Complications

As per the CoReCCT Safety Reporting Flowchart, adverse events that 1) occur at sites between randomisation and hospital discharge and 2) are not present on the CoReCCT Exemption List, must be reviewed for their presence on the Awake Prone Pre-Specified Complications List as given below.

Pre-Specified Complications List (that occur within 5 days of randomisation)
Pressure ulcer/ skin breakdown
Dislodgement of central venous catheter
Dislodgement of arterial catheter
Dislodgement of peripheral venous catheter
Dislodgement of urinary catheter
Dislodgement of any other medical device
Nausea requiring new treatment with anti-emetics
Vomiting

As per the CoReCCT Safety Reporting Flowchart, if the event is present on the Pre-Specified Complications List and occurred within 5 days of randomisation, the event must be recorded on the appropriate CRF as an outcome and does not need to be reported on an SAE form. Pre specified complications which occur beyond 5 days of randomisation will not be recorded. If the event is not on the Pre-Specified Complications List, it must be assessed for seriousness and the remainder of the flowchart should be followed to determine next steps.

4.2 Expectedness Assessment

SAEs which are considered possibly related, probably related or definitely related to the study intervention will be assessed for expectedness by the Sponsor. This expectedness assessment may be supported by items such as, but not limited to associated domain working instructions and published literature.

5. DATA MANAGEMENT

Further details on data management are provided in sections 6 and 10 of the CoReCCT Master Protocol.

5.1 Data collection and management

Full details are listed in section 10 of the CoReCCT Master Protocol.

5.2 Data Shared with Third Parties

Full details are listed in section 12 of the CoReCCT Master Protocol.

5.3 Archiving

Full details are listed in section 13 of the CoReCCT Master Protocol.

5.4 Data access and quality assurance

Full details are listed in section 10 of the CoReCCT Master Protocol.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

We will recruit 1708 patients (854 per arm) in total (using 90% power, 5% level of significance) to detect a 6% absolute difference in tracheal intubation. The following parameters have been used for the estimation of the sample size:

Tracheal intubation for usual care. Data from a systematic review and meta-analysis of non-invasive oxygenation strategies in patients without COVID-19 and awake prone positioning in patients with COVID-19 shows an event rate for tracheal intubation in control groups was 28.1% and 29.8% respectively.[24 36] Due to differences in patient population and inclusion criteria, we anticipate a slightly lower event rate of 20% in the control arm for the primary outcome.

Effect size: The two largest randomised controlled trials of awake prone positioning in the COVID-19 population reported absolute difference of 6.37% and 7.2% between the intervention and control arms.[19 47] Based on this, we have determined a 6% absolute difference as the clinically important difference.

Withdrawal rate: We anticipate a low rate of loss to follow-up as the primary outcome will be measured during the hospital stay. In our previous trials, we have consistency observed low rates of loss to follow-up (e.g. Recovery-RS 1%;[413] BREATHE 0%[42]; HARP-2 0.5%[43]; REST 1.7%[50]). For this study we have very conservatively assumed a withdrawal rate of 4%.

The main trial will be preceded by an internal pilot, where we will recruit 170 patients (10% of total sample).[45] We will review the sample size parameters with the DMC at the end of the pilot stage. Whilst we would not plan to reduce the sample size, we will, depending on DMC advice, explore with the TMG, TSC, DMC and funder whether a sample size increase is feasible and would be supported. The sample size was calculated using R software.

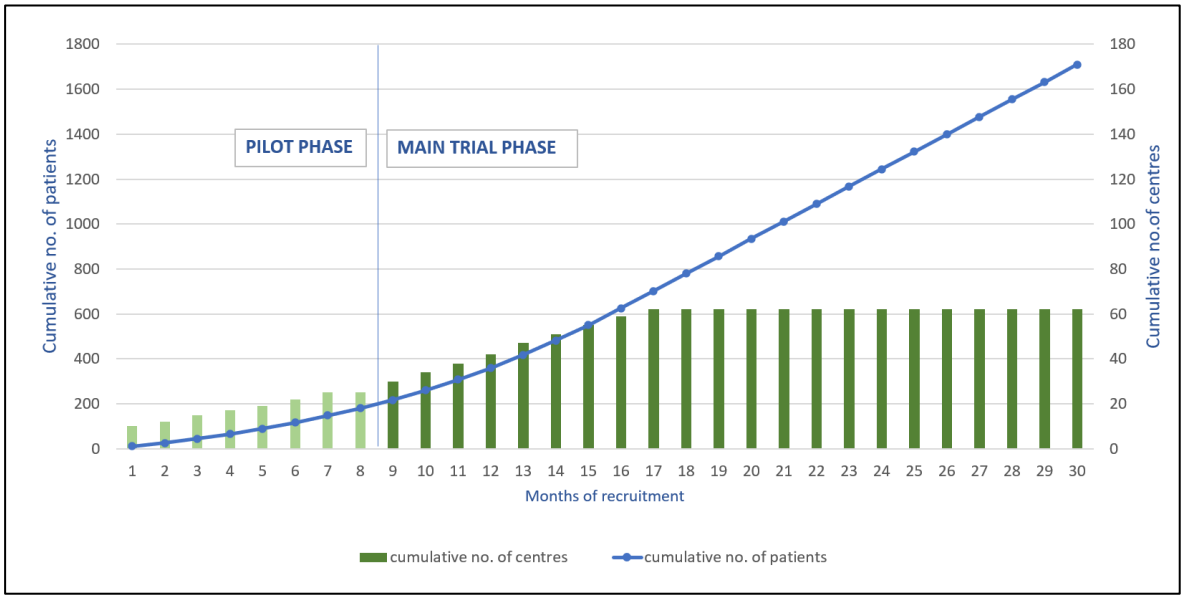
6.2 Data Analysis

6.2.1 Planned recruitment rate

Recruitment has been modelled on our survey data and ongoing critical care studies. Critical care studies typically target recruitment at 1-2 patients/ site/ month, although this trial will allow recruitment across the whole range of acute and critical care areas. In our survey, 28% respondents predicted a recruitment rate of 1-1.49 patients/ months, with 56% estimating a

recruitment rate over 1.5 patients/ site/ month of which 14% predicted a recruitment rate over 2.5 patients/ site/ month. Based on these data, we have conservatively estimated our recruitment rate to be 1.25 patients/ site/ month. Based on staggered site set-up, we will need a total of 25 sites for the pilot and 62 sites for the main trial. We anticipate opening ten sites in the first month followed by 3-5 sites/ month until all 62 required sites are open. Our recruitment and site set-up projections are shown in Figure 3.

Figure 3: Figure three- recruitment/ site set-up projections



6.2.2 Statistical analysis plan

6.2.2.1 Summary of baseline data and flow of patients

Screening log data will be collected for each site on a regular basis, and this will be scrutinised by the trial team to assess patient recruitment.

At randomisation, patient demographic data will be recorded. This will include: age, sex, body mass index, Glasgow Coma Scale score, ethnicity, respiratory rate, SpO_2, FiO_2, PaO_2, $PaCO_2$, SaO_2, blood pressure, heart rate, temperature, comorbidities, Rockwood clinical frailty score, receipt of non-invasive respiratory support (and key settings), and location of care (acute medical units, respiratory support units, emergency departments, acute medical departments, and critical care areas).

Continuous baseline data will be summarised with descriptive statistics, including number of observation (n), mean, standard deviation, median, interquartile range and number of missing data. Categorical baseline data will be summarised with frequency counts and percentages.

6.2.2.2 Primary outcome analysis

The primary outcome summaries and analyses will adopt the Estimand framework (as cited by the ICH E9 (R1) addendum on Estimand and sensitivity analyses in clinical trials).[48]

Summary measure and the primary Estimand: The proportion of patients who have tracheal intubation (from randomisation to day 30) will be summarised using number of patients (and %). The statistical analysis for this outcome will be done using the treatment policy strategy (i.e., intention to treat). The logistic regression model will be used to estimate the treatment effect by summarising odds ratios (and 95% confidence intervals), using both unadjusted and adjusted estimates. In addition to this, we will also report the unadjusted and adjusted risk difference/relative risks (and 95% confidence intervals). The model will be adjusted for the stratification variables, along with sites and any imbalance baseline variables that thought to be clinically important. A sensitivity analysis will be conducted to account for missing data, if necessary, using multiple imputation.

Intercurrent events (ICEs) and strategies for handling ICEs: post-randomisation events that may affect the interpretation of the primary outcome would include: (a) cross-over (ICE1); (b) non-adherence (including discontinuation of treatment) (ICE 2). The ICE1 and ICE 2 will be analysed using the principal stratum strategy. We will use the inverse probability weighted analysis method to assess the treatment effect, having taken account of these events.[497]

We will also assess the impact of cross-overs on the statistical power of the study: due to the contamination effect in patients who crossover from one intervention to another, there is likely to be a reduction in the study power. We will examine the loss of power, using power curves and different degrees of crossover, pivoted around the observed crossover rates, and assess this at the end of the pilot study as well as presenting these to the DMC at each 6-monthly analysis.[50]

In the event of a cross-over (patients who move from usual care to awake prone positioning) rate of over approximately 5%, we will use the inverse probability of censoring weights (IPCW) to estimate the weights for the patients in the control arm which are the inverse of the probability of not switching. Then we will fit the final outcome model to the weighted data to produce a treatment switching adjusted treatment effect.[51] Non-compliance will be defined when patients move from the awake prone positioning to usual care, without reaching the endpoint (i.e., until the point of tracheal intubation or recovery). In the presence of >5% non-compliance, we will use the compliers average causal effect analysis to carry out a sensitivity analysis to assess the effect of non-compliers on the overall treatment effect. [60]

6.2.2.3 Secondary outcome analysis

In general, the continuous baseline and secondary outcome data will be summarised with descriptive statistics, including number of observation, mean, standard deviation, median, interquartile range and number of missing data. Mixed-effects linear regression models will be used to estimate mean treatment differences (95% CI). Categorical baseline and secondary outcome data will be summarised with frequency counts and percentages and mixed-effects logistic regression models will be used to estimate the difference in binary outcomes between treatment groups, with odds ratios and 95% CIs reported. Time-to-an-event outcomes will be analysed using the Cox's proportional odds model, and data will be displayed using the Kaplan-Meier plots.

6.2.3 Subgroup analyses

The following subgroups will be considered for this study:

- Age
- Sex
- Care setting at randomisation
- SpO_2/FiO_2 ratio at baseline
- Receipt of non-invasive respiratory strategy at baseline

These subgroup analyses will be performed on the ITT strategy. The primary outcome will be used as the dependent variable and interaction with treatment and sub-group. Linear regression models will be used to assess the subgroup effect, using interaction terms. As these analyses are post-hoc analyses which are not powered for any effect size, emphasis will not be based on the statistical testing, rather than the point estimates and 99% confidence intervals.

6.2.4 Interim analysis and criteria for the premature termination of the trial

Awake prone positioning is a safe intervention with few associated complications, other than patient tolerance.[24] For this reason our early assessment, in terms of statistical monitoring, will not be focused on safety, but rather the futility of the intervention.

To assess the futility, we will carry out a formalised interim analysis during the study, which will be discussed with the DMC. In planning this interim analysis, we propose that a futility rule be based on the conditional power approach.[52] We will also devise an interim test statistic to test the treatment effect, using the O'Brien and Fleming rule.[53 54] Using this latter approach, the trial will be stopped if the value of the test statistics is negative or low, where values of the test statistic correspond to the usual care being better than the awake prone positioning intervention.[55]

On presenting this to the DMC, we will carefully consider the implication of the results of the futility analysis in the context of the whole study and in the totality of the literature. In particular, a study stopped for futility leaves the primary research question unanswered, safety data may be limited, and the confidence bounds are wider providing less precision and unreliable treatment effects, than if the study was finished as planned.

6.3 Health Economic Evaluation

The overall aim of the economic evaluation will be to conduct a within-trial cost-utility analysis comparing the costs and health impacts of the intervention with those of standard care.

The economic evaluation will adopt an NHS and Personal Social Services perspective, in line with NICE guidance.[56] Since treatment can have long-term impacts on Health-Related Quality of Life (HRQoL) and health care utilisation, the study will adopt a lifetime horizon. Any costs and utilities assumed beyond one year will be discounted at 3.5%.[56]

Costs will be analysed pre and post discharge. Pre-discharge costs will be estimated from clinical records and data obtained through linkage (e.g. Hospital Episode Statistics) on the type of ward attended, time spent on each ward, and treatment received while in hospital. Post-discharge hospital costs at 2 months and 6 months will be estimated from data obtained through linkage. Where appropriate, post-discharge NHS Community and Social care costs at 2 months and 6 months will be estimated using data from participant completed resource use questionnaires. Data from the questionnaires on resource item usage will be converted into costs using up-to-date sources of NHS and Personal Social Services reference costs.[57 58] Means, medians and 95% confidence intervals will be reported for the costs incurred by participants in each arm. Generalised linear modelling of cost data reported at 6 months will be conducted with explanatory variables, such as treatment allocation, use of tracheal intubation, duration of hospital stay, and patient characteristics. This will provide an insight into the longer-term costs incurred in this patient group and key drivers of that cost.

HRQoL will be captured using the EQ-5D-5L questionnaire administered at 2 months and 6 months.[59] Responses will be converted to health utilities using the appropriate UK tariff, as recommended by NICE, at the time of analysis. Quality-adjusted life-years (QALYs) will be calculated using the area under the curve method, and mean, median and 95% confidence intervals will be reported for each study arm. Generalised linear modelling of health utility at 6 months will be conducted with explanatory variables including treatment allocation, use of tracheal intubation, duration of hospital stays, and patient characteristics. This will provide an insight into the longer-term utilities incurred in this patient group and key drivers of that utility.

Our reference case will assume that costs and utilities reported at 6 months persist for the expected lifetime of each participant. Based on this extrapolation, mean costs and QALYs will be calculated for each arm and an incremental cost-effectiveness ratio derived for intervention compared with standard care. Probabilistic Sensitivity Analysis will be conducted by bootstrapping from participant costs and utilities to generate a cost-effectiveness acceptability curve presenting the probability that the intervention is cost-effective as a function of the willingness-to-pay for an additional QALY. All efforts will be made within the study to minimise missing data, and the impact of any such missingness will be explored via multiple imputation.[60] The dependency of conclusions on assumptions around extrapolation will be explored through scenario analyses in which no difference in incremental outcomes is assumed post 6 months, and in which the incremental difference is assumed to wane over time. Sub-group analyses will also be conducted to explore the cost-effectiveness of the intervention in sub-populations defined by subgroup identifiers mentioned above. A secondary cost-effectiveness will be presented in terms of the primary outcome, namely the incremental cost per tracheal intubation avoided.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Peer review

As part of the funding decision by the National Institute for Health and Care Research Health Technology Assessment programme (NIHR HTA), the trial underwent extensive peer-review by both the HTA board and independent individuals with clinical, methodological, and patient involvement expertise.

7.2 Trial Registration

We will prospectively register the trial with an appropriate trial registry.

7.3 Notification of serious breaches to GCP and/or trial protocol

The management of non-compliances will be informed by Warwick Standard Operating Procedure 31. The Awake Prone TMG will be responsible for oversight of protocol deviations and violations.

7.4 Trial timetable and milestones

The total planned project duration is 48 months. A summary of key trial milestones is shown as table two.

Table 3: Project Milestones

	Months	Recruitment
Set-up	1-6	-
Pilot study	7-14	170
Recruitment	15-36	1538
Follow-up	37-42	-
Analysis, reporting and dissemination	43-48	-

7.5 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or investigators, as appropriate.

7.6 Financial Support

The trial has been funded by a grant from the National Institute of Health and Care Research Health Technology Assessment programme (NIHR154796).

7.7 Ethical review

The trial has been reviewed by Wales REC 2.

8. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed by the trial team and a member of the WCTU Quality Assurance team and approved by the domain chief investigator. A risk-based proportionate approach will be outlined in the monitoring plan to facilitate remote and off-site monitoring, except where on-site monitoring is deemed to be required.

8.1 Training

Principal investigators, research team members involved in approaching patients/ consultees for agreement, and members of the WCTU team will be required to undergo GCP training. PIs will be required to provide a copy of their GCP certificate and a signed and dated CV to WCTU. Site staff listed on the delegation log should ensure their CVs and, where appropriate, evidence of GCP training is available to WCTU on request.

Training materials on trial procedures, including eligibility assessment and consent processes, will be developed by WCTU to standardise trial processes for site research staff. The training will take a modular approach, such that individuals will only need to undertake training relevant to their training role. Training may be delivered face-to-face (in-person or via video call) or through completion of the web-based training package. In-person training is required to be delivered by a member of WCTU staff or a member of the site team approved by the PI. Completion of training for individuals listed on the delegation log will be recorded in the site file.

We will also make targeted educational materials available to clinicians whose role is to deliver the intervention (i.e. support patients to turn into the prone position). These materials will provide brief information about the trial, including its rationale, design, and tips on how to support patients turn. Sites will not be expected to record completion of this training.

WCTU staff that are new to the trial will follow a thorough induction plan developed by the Trial Manager.

8.2 Visits to Sites

As per the WCTU monitoring plan, the trial manager will have regular contact with the recruiting sites to identify any problems with compliance with the protocol, training, data collection or other barriers to recruitment and progress, and to support sites with the day-to-day management of the trial. As well as regular telephone and email contact, the trial team will, where needed, visit participating sites to meet with the research team at the participating site, discuss any issues, and undertake any required monitoring.

The Trial Manager will check with each recruiting centre that all Investigator Site Files documents are up to date at least once during the trial.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

We worked closely with patients and members of the public in designing this trial, including detailed discussions with our PPI co-applicant and presentation of the proposed trial to the Clinical Research Ambassador Group at University Hospitals Birmingham NHS Foundation Trial. PPI co-applicants (Boex/ Thompson) will sit as members of the trial management group.

We will continue to embed meaningful patient and public involvement throughout the project. We will convene a PPI group of approximately 6-members with a membership that reflects the diversity of people at risk of acute hypoxaemic respiratory failure and which will also meet the objectives of the NIHR INCLUDE initiative to progress detailed study design and its governance. [35] The PPI group will meet regularly throughout the trial to provide advice and support to the trial management group.

We will identify at least two PPI members to become independent members of the Trial Steering Committee. This group will be responsible for the oversight of the trial and advising the Sponsor and Funder in accordance with the NIHR terms of reference for steering committees.

A summary of patient and public involvement using the GRIPP2 framework will be included in the final study report.[70] In all patient and clinician facing materials, we will include a summary of how PPI members have been involved in the project. We will seek PPI advice on appropriate dissemination activities to ensure outputs reach commonly marginalised groups.

10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration. The success of the trial depends on the collaboration of clinical teams from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).[61] We will prospectively register the trial with an appropriate trial registry. We will publish the trial protocol. The final trial results will be published in a high impact, open access peer reviewed journals.

We will work with the University of Warwick marketing and communication team to develop a strategy for communication with the media to enhance communication of the trial delivery and results to participants and members of the public.

We will develop a specific dissemination strategy for each of our key audiences- these strategies are likely to include:

- Clinicians- Open access publication in peer-reviewed journals, conference presentations, podcasts, and infographics.
- Policy makers- Open access publication in peer-reviewed journals, conference presentations, targeted communications to key national and international organisations.
- Patients and members of the public- lay summaries, press release, presentations at science festivals, infographics.

Co-applicant links with guideline organisations (Intensive Care Society, British Thoracic Society, European Society of Intensive Care Medicine) will support the implementation of research findings in clinical practice.

11. REFERENCES

1. Intensive Care National Audit and Research Centre. Key statistics from the Case Mix Programme- adult, general critical care units 2020 [Available from: https://www.icnarc.org/DataServices/Attachments/Download/b2d96e40-4945-eb11-912d-00505601089b accessed 1/8/22.
2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315(8):788-800. doi: 10.1001/jama.2016.0291
3. Hofhuis JGM, Schrijvers AJP, Schermer T, et al. Health-related quality of life in ICU survivors—10 years later. *Scientific Reports* 2021;11(1):15189. doi: 10.1038/s41598-021-94637-z
4. Gerth AMJ, Hatch RA, Young JD, et al. Changes in health-related quality of life after discharge from an intensive care unit: a systematic review. *Anaesthesia* 2019;74(1):100-08. doi: https://doi.org/10.1111/anae.14444
5. Kaier K, Heister T, Motschall E, et al. Impact of mechanical ventilation on the daily costs of ICU care: a systematic review and meta regression. *Epidemiol Infect* 2019;147:e314. doi: 10.1017/s0950268819001900 [published Online First: 2019/12/06]
6. Kaier K, Heister T, Wolff J, et al. Mechanical ventilation and the daily cost of ICU care. *BMC Health Services Research* 2020;20(1):267. doi: 10.1186/s12913-020-05133-5
7. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S280-s88. doi: 10.1513/AnnalsATS.201704-343OT [published Online First: 2017/10/27]
8. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respiratory Research* 2019;6(1):e000420. doi: 10.1136/bmjresp-2019-000420
9. Fan E, Sorbo LD, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine* 2017;195(9):1253-63. doi: 10.1164/rccm.201703-0548ST
10. Guérin C, Reignier J, Richard J-C, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2013;368(23):2159-68. doi: 10.1056/NEJMoa1214103
11. Guérin C, Beuret P, Constantin JM, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. *Intensive Care Med* 2018;44(1):22-37. doi: 10.1007/s00134-017-4996-5 [published Online First: 2017/12/09]
12. Qadir N, Bartz RR, Cooter ML, et al. Variation in Early Management Practices in Moderate-to-Severe ARDS in the United States: The Severe ARDS: Generating Evidence Study. *CHEST* 2021;160(4):1304-15. doi: 10.1016/j.chest.2021.05.047
13. Hochberg CH, Card ME, Seth B, et al. Factors Influencing the Implementation of Prone Positioning During the COVID-19 Pandemic: A Qualitative Study. *Ann Am Thorac Soc* 2022 doi: 10.1513/AnnalsATS.202204-349OC [published Online First: 2022/08/11]
14. Verma AA, Razak F, Munshi L, et al. Awake prone positioning and covid-19. *BMJ* 2022;379:o2888. doi: 10.1136/bmj.o2888
15. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. *J Crit Care* 2015;30(6):1390-4. doi: 10.1016/j.jcrc.2015.07.008 [published Online First: 2015/08/15]
16. Ding L, Wang L, Ma W, et al. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. *Crit Care* 2020;24(1):28. doi: 10.1186/s13054-020-2738-5 [published Online First: 2020/02/01]
17. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. *JAMA* 2020;323(22):2338-40. doi: 10.1001/jama.2020.7861
18. Caputo ND, Strayer RJ, Levitan R. Early Self-Proning in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. *Academic Emergency Medicine* 2020;27(5):375-78. doi: https://doi.org/10.1111/acem.13994
19. Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *The Lancet Respiratory Medicine* 2021;9(12):1387-95. doi: 10.1016/S2213-2600(21)00356-8
20. Grieco DL, Delle Cese L, Menga LS, et al. Physiological effects of awake prone position in acute hypoxemic respiratory failure. *Critical Care* 2023;27(1):315. doi: 10.1186/s13054-023-04600-9

21. Brunelle T, Prud'homme E, Alphonsine JE, et al. Awake prone position in COVID-19 acute respiratory failure: a randomised crossover study using electrical impedance tomography. *ERJ Open Res* 2023;9(2) doi: 10.1183/23120541.00509-2022 [published Online First: 20230327]
22. Ibarra-Estrada M, Gamero-Rodríguez MJ, García-de-Acilu M, et al. Lung ultrasound response to awake prone positioning predicts the need for intubation in patients with COVID-19 induced acute hypoxemic respiratory failure: an observational study. *Crit Care* 2022;26(1):189. doi: 10.1186/s13054-022-04064-3 [published Online First: 20220627]
23. Dos Santos Rocha A, Diaper J, Balogh AL, et al. Effect of body position on the redistribution of regional lung aeration during invasive and non-invasive ventilation of COVID-19 patients. *Sci Rep* 2022;12(1):11085. doi: 10.1038/s41598-022-15122-9 [published Online First: 20220630]
24. Weatherald J, Parhar KKS, Al Duhailib Z, et al. Efficacy of awake prone positioning in patients with covid-19 related hypoxemic respiratory failure: systematic review and meta-analysis of randomized trials. *BMJ* 2022;379:e071966. doi: 10.1136/bmj-2022-071966
25. Ibarra-Estrada M, Li J, Pavlov I, et al. Factors for success of awake prone positioning in patients with COVID-19-induced acute hypoxemic respiratory failure: analysis of a randomized controlled trial. *Critical Care* 2022;26(1):84. doi: 10.1186/s13054-022-03950-0
26. Esperatti M, Busico M, Fuentes NA, et al. Impact of exposure time in awake prone positioning on clinical outcomes of patients with COVID-19-related acute respiratory failure treated with high-flow nasal oxygen: a multicenter cohort study. *Critical Care* 2022;26(1):16. doi: 10.1186/s13054-021-03881-2
27. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19 2022 [Available from: https://www.nice.org.uk/guidance/ng191/chapter/Recommendations accessed 5th August 2022.
28. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Medicine* 2023;49(7):727-59. doi: 10.1007/s00134-023-07050-7
29. Pavlov I, Li J, Kharat A, et al. Awake prone positioning in acute hypoxaemic respiratory failure: An international expert guidance. *Journal of Critical Care* 2023;78:154401. doi: https://doi.org/10.1016/j.jcrc.2023.154401
30. Morales-Quinteros L, Schultz MJ, Serpa-Neto A, et al. Awake prone positioning in nonintubated spontaneous breathing ICU patients with acute hypoxemic respiratory failure (PRONELIFE)—protocol for a randomized clinical trial. *Trials* 2022;23(1):30. doi: 10.1186/s13063-021-05991-2
31. Kaur R, Vines DL, Mirza S, et al. Early versus late awake prone positioning in non-intubated patients with COVID-19. *Critical care (London, England)* 2021;25(1):340. doi: https://dx.doi.org/10.1186/s13054-021-03761-9
32. Danielis M, Povoli A, Mattiussi E, et al. Understanding patients' experiences of being mechanically ventilated in the Intensive Care Unit: Findings from a meta-synthesis and meta-summary. *J Clin Nurs* 2020;29(13-14):2107-24. doi: 10.1111/jocn.15259 [published Online First: 2020/04/04]
33. Tatham KC, McAuley DF, Borthwick M, et al. The National Institute for Health Research Critical Care Research Priority Setting Survey 2018. *J Intensive Care Soc* 2020;21(3):198-201. doi: 10.1177/1751143719862244 [published Online First: 2019/07/08]
34. Reay H, Arulkumaran N, Brett SJ. Priorities for Future Intensive Care Research in the UK: Results of a James Lind Alliance Priority Setting Partnership. *J Intensive Care Soc* 2014;15(4):288-96. doi: 10.1177/175114371401500405
35. Dawson S, Banister K, Biggs K, et al. Trial Forge Guidance 3: randomised trials and how to recruit and retain individuals from ethnic minority groups—practical guidance to support better practice. *Trials* 2022;23(1):672. doi: 10.1186/s13063-022-06553-w
36. Ferreyro BL, Angriman F, Munshi L, et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. *JAMA* 2020;324(1):57-67. doi: 10.1001/jama.2020.9524
37. Grieco DL, Menga LS, Cesarano M, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *JAMA* 2021;325(17):1731-43. doi: 10.1001/jama.2021.4682
38. Blackwood B, Ringrow S, Clarke M, et al. A Core Outcome Set for Critical Care Ventilation Trials. *Crit Care Med* 2019;47(10):1324-31. doi: 10.1097/ccm.0000000000003904 [published Online First: 2019/07/30]
39. Bangash MN, Hodson J, Evison F, et al. Impact of ethnicity on the accuracy of measurements of oxygen saturations: A retrospective observational cohort study. *EClinicalMedicine* 2022;48:101428. doi: 10.1016/j.eclinm.2022.101428 [published Online First: 20220506]

40. Sjoding MW, Dickson RP, Iwashyna TJ, et al. Racial Bias in Pulse Oximetry Measurement. *N Engl J Med* 2020;383(25):2477-78. doi: 10.1056/NEJMc2029240
41. Perkins GD, Ji C, Connolly BA, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. *JAMA* 2022;327(6):546-58. doi: 10.1001/jama.2022.0028
42. Perkins GD, Mistry D, Gates S, et al. Effect of Protocolized Weaning With Early Extubation to Noninvasive Ventilation vs Invasive Weaning on Time to Liberation From Mechanical Ventilation Among Patients With Respiratory Failure: The Breathe Randomized Clinical Trial. *JAMA* 2018;320(18):1881-88. doi: 10.1001/jama.2018.13763
43. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2014;371(18):1695-703. doi: 10.1056/NEJMoa1403285
44. McNamee JJ, Gillies MA, Barrett NA, et al. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial. *JAMA* 2021;326(11):1013-23. doi: 10.1001/jama.2021.13374
45. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. *J Clin Epidemiol* 2013;66(2):197-201. doi: 10.1016/j.jclinepi.2012.09.002 [published Online First: 2012/12/01]
46. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Bmj* 2016;355:i5239. doi: 10.1136/bmj.i5239 [published Online First: 2016/10/26]
47. Alhazzani W, Parhar KKS, Weatherald J, et al. Effect of Awake Prone Positioning on Endotracheal Intubation in Patients With COVID-19 and Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2022;327(21):2104-13. doi: https://dx.doi.org/10.1001/jama.2022.7993
48. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials Step 5 2020 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf accessed 20th December 2022.
49. Rimawi M, Hilsenbeck SG. Making sense of clinical trial data: is inverse probability of censoring weighted analysis the answer to crossover bias? *J Clin Oncol* 2012;30(4):453-8. doi: 10.1200/jco.2010.34.2808 [published Online First: 2012/01/05]
50. Ishak KJ, Proskorovsky I, Korytowsky B, et al. Methods for adjusting for bias due to crossover in oncology trials. *Pharmacoeconomics* 2014;32(6):533-46. doi: 10.1007/s40273-014-0145-y [published Online First: 2014/03/07]
51. Sullivan TR, Latimer NR, Gray J, et al. Adjusting for Treatment Switching in Oncology Trials: A Systematic Review and Recommendations for Reporting. *Value in Health* 2020;23(3):388-96. doi: 10.1016/j.jval.2019.10.015
52. Lachin JM. A review of methods for futility stopping based on conditional power. *Stat Med* 2005;24(18):2747-64. doi: 10.1002/sim.2151 [published Online First: 2005/09/01]
53. Penn State Eberly College of Science. 9.5 - Frequentist Methods: O'Brien-Fleming, Pocock, Haybittle-Peto 2022 [Available from: https://online.stat.psu.edu/stat509/lesson/9/9.5 accessed 20th December 2022.
54. Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. *Control Clin Trials* 1984;5(4):348-61. doi: 10.1016/s0197-2456(84)80014-8 [published Online First: 1984/12/01]
55. Chang Y, Song T, Monaco J, et al. Futility stopping in clinical trials, optimality and practical considerations. *J Biopharm Stat* 2020;30(6):1050-59. doi: 10.1080/10543406.2020.1818253 [published Online First: 2020/09/15]
56. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013: Process and Methods 2013 [Available from: https://www.nice.org.uk/process/pmg9 accessed 1st December 2023.
57. Jones K, Weatherly H, Birch S, et al. Unit Costs of Health and Social Care 2022 Manual 2022 [Available from: https://doi.org/10.22024/UniKent/01.02.100519 accessed 1st December 2023.
58. NHS England. National Cost Collection for the NHS [Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ accessed 1st December 2023.
59. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First: 20110409]
60. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8(1):3-15. doi: 10.1177/096228029900800102

61. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332. doi: 10.1136/bmj.c332