



STUDY PROTOCOL

Evaluation of awake prone positioning effectiveness in moderate to severe COVID-19 [version 1; peer review: awaiting peer review]

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Abstract

Evidence mainly from high income countries suggests that lying in the prone position may be beneficial in patients with COVID-19 even if they are not receiving invasive ventilation. Studies indicate that increased duration of prone position may be associated with improved outcomes, but achieving this requires additional staff time and resources. Our study aims to support prolonged (≥ 8 hours/day) awake prone positioning in patients with moderate to severe COVID-19 disease in Vietnam. We use a specialist team to support prone positioning of patients and wearable devices to assist monitoring vital signs and prone position and an electronic data registry to capture routine clinical data.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

awake prone, COVID-19, LMIC, wearables

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Introduction

Placing patients with respiratory failure in the prone position is associated with benefits in respiratory mechanics and blood oxygenation¹. In mechanically ventilated patients with acute respiratory distress syndrome (ARDS), prone positioning is associated with improved survival². The huge burden of respiratory failure resulting from COVID-19 has stimulated interest in understanding prone position in those receiving no or lesser degrees of respiratory support – often termed ‘awake prone position’ (APP).

To date, several randomised controlled trials of APP in COVID-19 have been performed. Since this protocol was written, 10 of these have been included in a meta-analysis³. The trials included varied in size (median 60 participants); location (8/10 exclusively high income countries) and inclusion criteria (room air, supplemental oxygen, non-invasive ventilation). Almost all participants were recruited in the early phase of the pandemic in unvaccinated populations. Overall the meta-analysis concluded APP was beneficial, and APP has been incorporated into many guidelines for treatment of COVID-19 in many countries, including low- and middle-income countries (LMICs). Similar to the effect observed in mechanically ventilated patients with ARDS, success of APP was noted in patient groups with the longest duration of prone positioning as well as those in ICU environments^{3–5}. Relationship with disease severity is less clear, although the largest study (Ehrmann *et al*’s) recruited only those with HFNC⁴. A further nonrandomized controlled trial of 500 patients admitted to 2 centres in North America has since been published indicating no substantial difference of APP at 5 days with a suggestion of possible harm at 14 and 28 days⁶.

Much of the interest in APP for moderate to severe COVID-19 disease, is related to its perceived low-cost and simplicity of implementation. In reality, even in high income countries, effective implementation is challenging, especially when carried out under pandemic caseloads. In one randomized controlled trial in the USA, where trained admitting teams instructed patients in the APP protocol, only 37% of patients in the intervention group actually attempted to lie prone⁷. In only a few of the reported trials were patients supervised (and if necessary helped) into the prone position. In resource-limited settings, where there are already restricted numbers of healthcare staff, this additional workload is a significant demand on the healthcare service, and likely requires additional staffing, increasing the overall cost to the healthcare system. The only two trials of APP from LMICs were both carried in ICU settings where there are likely to be significantly more staff on hand: in India, investigators succeeded in 43% of the intervention group spending ≥ 6 hours/day prone⁸, and in Mexico median 8.6 hours a day⁴. These issues of lack of staff and limited duration were cited as reasons for lack of efficacy of the recently published multicentre COVID-PRONE study and an accompanying editorial emphasised that future trials need to focus on optimal means of sustaining APP⁹. With widespread vaccination, many patients requiring respiratory support for COVID-19 are more likely to be elderly, frail and

with significant comorbidity. The feasibility of these patients achieving prolonged periods in the prone position without significant help is unknown.

For these reasons, we are conducting this randomized controlled trial of APP in COVID-19 in Vietnam. Importantly it employs a dedicated team and wearable technologies to monitor patients and accurately quantify changes in vital signs and patient position, thus attempting to ensure maximum durations of APP, but also utilize new technologies for monitoring which may ultimately reduce staff time performing these tasks. Data capture uses a combination of special case report form but also utilizes an already functioning electronic data registry where routine clinical information is recorded by a dedicated data-entry team¹⁰. Whilst this trial was designed at the height of the Delta wave pandemic in Vietnam, the situation has evolved to currently Omicron variant and widespread vaccination coverage. As a result, unlike most other preceding studies of APP, this trial will enrol a different patient population.

Protocol

Evaluation of awake prone positioning effectiveness in moderate to severe COVID-19

06NV OxTREC 39-21 Protocol EN V3.2 11NOV21

Background and scientific rationale

Supplemental oxygen is recommended to maintain oxygen saturations in those with COVID-19 associated acute respiratory failure. Many patients require escalation of therapy, from simple low-flow systems to higher flow methods, non-invasive ventilation or endotracheal intubation and invasive mechanical ventilation¹¹. Escalation of therapy necessitates increased utilization of healthcare resources such as oxygen, equipment and skilled staff. Whilst already in short supply in resource-limited countries, these are even further limited in the current pandemic situation¹¹.

In patients with severe acute respiratory distress syndrome (ARDS) receiving mechanical ventilation, prone position has been shown to increase survival and respiratory outcomes¹. Notably the PROSEVA trial, where patients with severe ARDS ($\text{PaO}_2:\text{FiO}_2$ ratio <150 mmHg) placed prone for a median 17 hours a day resulted in a reduced risk of death at 28 and 90 days compared to supine position (hazard ratio of death 0.42; 95%CI 0.26–0.66)². Furthermore, patients placed in the prone position had shorter duration of ventilation and more successful extubation events than those in the supine position.

Prone positioning has a variety of effects that may have beneficial effects on pulmonary and cardiovascular physiology and ventilation/perfusion matching. These include reducing pulmonary compression by abdominal or mediastinal organs; reducing antero-posterior pulmonary pressure gradients and localized hyperinflation; improving right heart function and reducing dead space. Improved oxygenation and carbon dioxide clearance may allow reduction in FiO_2 or ventilator settings, reducing iatrogenic pulmonary and systemic injury¹.

Currently many guidelines recommend prone position in patients with severe COVID-19 ARDS requiring mechanical ventilation¹². However, placing a patient in a prone position is a complicated process and, in severely ill patients, requires a team of trained operators and considerable time. In resource-stretched units, providing these safely is challenging. Furthermore, prone positioning may be associated with increase in events such as pressure sores, nerve compression injury or accidental displacement of lines or endotracheal tubes¹³. Evidence suggests that prone position may increase the work of breathing, thus although oxygenation improves, this benefit may be offset by fatigue¹⁴.

Prone positioning may be easier to achieve in awake, self-ventilating patients. Data from observational studies has indicated that prone positioning in such patients ('awake prone positioning') is associated with improved oxygenation, reduced intubation and mortality in a Low and Middle Income Country (LMIC) setting¹⁵. A Delphi consensus of 39 experts from 20 countries reported >90% agreed that awake self-proning could improve oxygenation in COVID-19 acute respiratory failure¹⁶. However only 54% agreed, based on their own experience, that the procedure may reduce the need for mechanical ventilation.

A recent 'meta trial' combining data from five randomized controlled trials compared prone positioning with supine position in 1126 patients receiving oxygen via high flow nasal canulae (HFNC) for COVID-19 pneumonia. Treatment failure, defined as intubation or death, occurred in 40% of 564 patients assigned to awake prone positioning and 46% of 557 patients assigned to standard care (relative risk 0.86 (95% confidence interval 0.75, 0.98). The study showed a reduction in requirement for intubation in those treated with prone position (hazard ratio 0.75, 95% confidence interval 0.62, 0.91) and a non-significant reduction in mortality (hazard ratio 0.87, 95% confidence interval 0.68, 1.11)⁴. Whilst the majority of studies and participants were from high-income countries, approximately 400 enrolled patients were from Mexico. Of note in this study, patients in the prone group achieved a median 5 hours a day in the prone position. Evidence from patients with ARDS receiving mechanical ventilation indicates that longer periods in the prone position are more beneficial². An observational study of patients receiving supplemental oxygen by mask for COVID-19 respiratory failure in Brazil reported a relative risk of mechanical ventilation of approximately 0.4 in those treated with prolonged periods of prone position of approximately 12 hours duration daily¹⁵. Therefore it is possible that longer periods of prone positioning are associated with better outcomes.

In summary, there are convincing data supporting the use of prone position in reducing mortality and ventilation time in patients with ARDS receiving mechanical ventilation. Data also support the use of awake prone position to improve oxygenation in patients with COVID-19 related acute respiratory failure, and randomized control trial data suggest this is may also prevent intubation. However, it is unclear whether patients on lower degrees of respiratory support (eg oxygen via facemask or nasal canulae) also benefit, nor whether data

from well-resourced healthcare environments apply in LMICs such as Vietnam, particularly under pandemic situations when considerable resources are required to help patients maintain prone positioning.

Objectives and purpose

Primary objective

To determine whether prone positioning of hospitalized Vietnamese patients with moderate to severe COVID-19 for \geq eight hours a day reduces the need for escalation of respiratory therapy compared to standard care.

Secondary objectives

1. To determine whether prone positioning with a protocol aiming for \geq eight hours a day results in reduced intubation rates, improved mortality and shorter duration of hospital stay compared to standard care.
2. To compare changes in FiO_2 , SpO_2 , respiratory rate and heart rate that occur during prone position of hospitalized Vietnamese patients with moderate to severe COVID-19.
3. To determine whether prone positioning for \geq 8 hours a day is associated with reduced oxygen utilization compared to standard care.
4. To determine safety of prone positioning.

Study design and endpoints

Study design

Pragmatic open label randomised controlled trial

Study population

All adult patients (\geq 18 years old) presenting to the study sites due to probable or proven COVID-19 pneumonia, subject to the inclusion and exclusion criteria.

Inclusion criteria

- Probable or confirmed COVID-19 infection according to WHO criteria (see [Extended data 2](#))
- Moderate or severe COVID-19 respiratory infection according to Vietnamese guidelines (see [Extended data 3](#))
- Requirement for supplemental oxygen therapy

Exclusion criteria

- Invasive mechanical ventilation, or non-invasive ventilation (NIV) with CPAP or BiPAP or imminent need for these
- Contraindications to prone position (see [Extended data 5](#))
- Pregnancy
- Severe obesity (BMI >35),
- Altered level of consciousness (GCS <13)
- Attending doctor judged prone position to be unsuitable for the patient for any reason

- Patients in whom there is a decision that care will not be escalated
- Failure to have informed consent

Intervention

Standard care: will consist of routine clinical care, including any advice to lie in prone position as routinely recommended by participating sites. To reduce bias, the study team will make visits at a similar schedule to those to patients in the intervention group, however these visits will be confined to general advice and measurement of vital signs. Patients will receive written advice more general in nature about COVID-19 disease.

Intervention. A special intervention team will visit patients' rooms aiming for patients to maintain the prone position for at least 8 hours a day. The team will give written and verbal advice and if necessary aid patients' positioning themselves in the prone position. The exact duration of prone sessions will be determined according to ward schedules to take account of nursing procedures, meal times and mitigation strategies (see Extended data). Other methods to encourage the maintenance of prone position includes phone calls to patients, carers or education of carers.

Compliance with the intervention will be evaluated by observation (manual and using in-room cameras) at fixed time intervals. In a subgroup of 100 patients accelerometer/gyrometer devices will be used to measure movement and position (this will be expanded to all patients if equipment is available).

Study endpoints

Primary endpoint

Escalation of respiratory therapy within 28 days of randomization, defined as any of the following:

- Escalation to next level respiratory support (with lowest level nasal canulae or face mask, escalating through HFNC to NIV or mechanical ventilation).
- Intubation

Secondary endpoints

- Requirement for intubation and mechanical ventilation within 28 days of randomization
- 28-day all-cause mortality
- Duration of hospital stay
- SpO₂ /respiratory rate/ heart rate/ FiO₂ – before and at end of period of prone positioning every day
- ROX index (ratio of SpO₂: FiO₂ to respiratory rate) before and at end of period of prone positioning every day
- Supplemental oxygen free days
- Ventilator free days
- Time to escalation of respiratory therapy
- Time to intubation

- Adverse events
- Oxygen consumption (estimated from flow rate and ventilation method)
- Duration of prone position

Additional endpoints, measured in this group of patients but reported separately, include acceptability from patients' perspectives and hospital direct medical costs.

Sample size

Our sample size is based on local data showing a current treatment failure rate of approximately 52%, a relative risk of treatment failure estimated at 0.8 for the intervention, corresponding to an absolute risk reduction from 52% to 40%. To detect this reduction with 80% power at the two-sided 5% significance level, 300 patients are required in each arm, giving a total sample size of 600 allowing for exclusions, loss to follow up and withdrawals. (also see [Extended data 4](#))

Participant withdrawal of participation

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- An adverse event which requires discontinuation or inability to continue to comply with trial procedures
- Withdrawal of Consent

Handling of participant withdrawal or termination

If a patient or the representative, who has given consent on their behalf, chooses to discontinue trial treatment, they should be followed up (providing they are willing) and encouraged to follow the study procedures in lieu of withdrawing from the trial. If they do not wish to remain on trial follow-up, however, their decision will be respected and the patient will be withdrawn from the trial completely. This will be recorded on the OUTCOME CRF. The reason for the patient withdrawing should be ascertained wherever possible. If a participant withdraws from the trial, they may agree that the medical data collected during their previous consented participation in the trial will be kept and used in analysis, or if they do not consent to this, all data will be excluded from analysis.

Participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial. Participants who stop trial follow-up early will not be replaced, as the total sample size includes adjustment for losses to follow-up.

Study procedures

Informed consent

Informed consent to enter into the trial and be randomized must be obtained from all participants. If the patient lacks capacity

to give consent due to the severity of their medical condition (eg acute respiratory failure), then consent may be obtained from a relative acting as the patient's legally designated representative or -if a suitable relative is not available after reasonable efforts to locate one – an independent doctor. Further consent will then be sought from the patient if they recover sufficiently.

Individuals trained and responsible for taking consent will be documented on the trial's Delegation Log (with signatures). This should be, if appropriate, after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed, including for the screening assessment.

It must be made completely and unambiguously clear that the participant (or their relative) is free to refuse to participate in or withdraw from all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their subsequent treatment. This will be stated explicitly in the participant information sheet. If consent was provided by a relative, the participant should be consulted and consent recorded if and when they have the capacity to do so.

Copies of consent forms must be kept in the investigator site file and a copy given to the participant or family. Considering the nature of the diseases, the study patient may be treated in an isolated area, where no paper document is allowed to be moved out of the infectious area. The study will consider applying electronic ICF capture on tablet or any other appropriate method for obtaining valid ICF.

Randomization

Patients will be randomly allocated 1:1 to either standard care or intervention, stratified according to study ward. A stratified, computer-generated randomization list will be created using block randomization with variable block length and incorporated into secure internet accessible randomization software. Once a consented patient develops eligibility criteria, or an eligible patient is consented, the initials and date of birth of the patient will be entered into the software by study staff. Based on the randomization list, the software will produce the treatment allocation, which will be displayed and recorded in the study database. All entries and outputs of the software will be auditable.

Clinical monitoring

Study staff will make regular visits to all patients in the study, to carry out study procedures, assess compliance with prone positioning and, if necessary, record vital sign data (see Extended data). Additionally, we will use in-room cameras and wearable accelerometer / gyrometer devices to verify prone positioning of participants. Using these methods, we aim to evaluate compliance with prone position hourly for eight hours a day.

We aim to monitor all patients in this study using continuous vital sign monitors to measure vital signs hourly. For patients with appropriate monitoring in situ, continuous vital sign waveform data will be recorded. For others, intermittent vital sign

summary data will be recorded with a frequency at least of routine clinical monitoring schedules.

Supplemental oxygen flow rates and method of delivery will be recorded daily to allow calculation of oxygen utilization.

Acceptability of the intervention from patient perspective will be evaluated whenever patient is recovery and available for telephone call using a Likert scale to assess comfort and acceptability (see [Extended data 10](#)).

Procedures for assessing safety

An independent data safety and monitoring committee (DSMB) will oversee the safety of the trial participants. For details on the DSMB and schedule of assessment see later section.

Study staff will perform daily monitoring for safety events. It is recognised that this study involves seriously ill patients in whom disease progression and adverse events are common. In view of this monitoring will particularly focus on adverse events related to the study intervention and serious adverse events as detailed below.

Adverse events

An adverse event (AE) is defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. The severity of all AEs in this trial should be graded in line with the toxicity gradings in Toxicity grading and management (CTCAE).

Adverse events will be graded for severity:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

When an AE occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition below.

A Serious Adverse Event (SAE), is any AE that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolonged or existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Consists of a congenital anomaly or birth defect, or

Causality. The investigator must assess the causality of all serious events or reactions in relation to the trial therapy (prone positioning) using the definitions below.

Relationship	Description	SAE Type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship. There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

Adverse events related to the intervention include¹³:

1. Pressure sore
2. Line displacement
3. Severe oxygen desaturation
4. Facial oedema
5. Arrhythmia
6. Hypotension
7. Peripheral nerve injuries
8. Barotrauma
9. Hospital-acquired pneumonia
10. Vomiting

Expectedness. If an adverse event is not expected with COVID-19 disease or with prone positioning, then it is unexpected.

Expected serious adverse events in this population include:

1. Hypotension or shock
2. Worsening respiratory failure
3. Acute renal failure
4. Myocardial failure
5. Acute liver injury

6. Rhabdomyolysis
7. Multi-organ failure
8. Venous thromboembolism or bleeding disorder
9. Electrolyte imbalance or blood test abnormality
10. Secondary infection
11. Weakness and ICU-associated weakness
12. Cardiac arrhythmia or arrest

Reporting of adverse events

Serious adverse events definitely related to the intervention and unexpected serious adverse events will be reported to OUCRU CTU within 24 hours after the investigatory/ study team become aware of the event. Investigators should notify the OUCRU CTU of these predefined SAEs occurring from the time of randomization until the participant finishes their follow-up. CTU will perform an initial check of the report, request any additional information. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports. All SAE information must be recorded on an SAE form and sent or emailed, to CTU. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and sent to CTU.

The OUCRU CTU is undertaking the duties of trial sponsor with regard to safety reporting and is responsible for the reporting to the regulatory authorities and the research ethics committees, as appropriate.

The SAEs will be reported as soon as possible to the site ethics committee (EC). An initial written report of those resulting in death, or that are life threatening, has to be reported urgently within seven working days of the study team becoming aware of the SAE. Others must be reported within 15 working days of the study team becoming aware of the SAE. Additional medical information of the SAE's development must be reported in an additional report until the trial subject recovers or stabilises without further changes expected. The format and content of the initial report should follow the relevant Ethics Committee report template and include all information available at the time of reporting.

All specified SAEs will be reported to OxTREC in the annual review form and to the DSMB in accordance to the DSMB charter.

Study halting rules

An independent DSMB will oversee the trial. Serious adverse events will be reported to the DSMB within 10 days of occurrence and followed-up until resolution. The DSMB will perform a safety analysis after the first 60 patients have completed 28-day follow-up or died. Stopping for harm will be considered if a safety issue emerges which is sufficiently large, in

the judgement of the DSMB, to suggest that continued exposure of patients to the intervention is unethical. The DSMB will be able to mandate additional safety analyses at any time-point they deem fit and will determine the schedule for further analyses throughout the trial.

At the interim analyses, the DSMB will receive a report including summaries of mortality, serious adverse events, by treatment arm. The report will be prepared by the DSMB statistician and distributed to all DSMB members for review. Based on these data, the committee will make recommendations on the continuation, cessation or amendment of the study. The study statistician will aid in setting-up the code for generating the interim analysis summaries.

As the dissemination of preliminary summary data could influence the further conduct of the trial and introduce bias, access to interim data and results will be confidential and strictly limited to the involved independent statistician and the monitoring board and results (except for the recommendation) will not be communicated to the outside and/or clinical investigators involved in the trial.

Further reviews will be at the discretion of the DSMB. All DSMB reports, replies or decisions will be sent to the responsible Research Ethical Committees.

Statistical considerations

Statistical and analytical plans

Study analysis and presentation of results will be according to an *a priori* defined statistical analysis plan which will be completed before database locking and based on the considerations below.

The primary analysis population for all analysis is the full analysis population containing all randomized patients. Patients will be analysed according to their randomized arm (intention-to-treat). Analyses for the primary endpoint will be repeated on the per protocol population which excludes the following patients: patients not receiving the randomized intervention and other major violations of inclusion/exclusion criteria or study procedures.

The primary outcome measure, will be summarized as x/n (%) in each group and compared between the groups based on a logistic regression model with the intervention as the main covariate. Time-to-event analysis will be performed using a cause-specific hazards model. Differences between intervention groups will be tested using Gray's log-rank test.

Potential heterogeneity of the treatment effect will be assessed based on appropriate interaction (likelihood ratio) tests and the following pre-defined sub-grouping variables in separate models:

- Pre-existing medical conditions
- Duration of prone position

For other secondary outcome, all analyses will be performed for the comparison of intervention vs. standard care. For continuous outcomes such as vital signs (SpO₂ /respiratory rate/ heart rate/ FiO₂), supplemental oxygen free days, etc., interventions will be compared using linear regression, but we will add a quadratic term if it gives the model a better fit. For dichotomous outcomes such as requirement for intubation and mechanical ventilation within 28 days of randomization, we will compute the number of patients who developed or did not develop the outcomes of interest and we fit a logistic regression. Time-to-event analysis will be performed using a cause-specific hazards model. Differences between intervention groups will be tested using Gray's log-rank test. For all time-to-event analysis patients that withdrew will be censored at the time of withdrawal. Mortality will be visualised in each arm using Kaplan-Meier curves and modelled using Cox regression.

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 notes (including electronic health record), laboratory and pharmacy records, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

Direct access to participant records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should be verifiable from source documents:

- all signed consent forms
- dates of assessments including dates specimens were taken and processed in the laboratory
- eligibility and baseline values for all participants
- all clinical endpoints
- all serious/severe adverse events
- routine participant clinical and laboratory data

Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data will be entered a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

Trial records retention

CRFs, clinical notes and administrative documentation will be kept in a secure location and held for 15 years after the end of the trial. Clinical information will not be released without written permission, except as necessary for monitoring, auditing and inspection purposes. During this period, all data should be accessible to the competent authorities with suitable notice. Electronic data will be kept for at least 20 years at the OUCRU CTU.

Protocol violations

A protocol deviation is any non-compliance with the clinical trial protocol or GCP requirements. If such a deviation results in an impact on patient safety or scientific integrity it becomes a protocol violation. The non-compliance may be either on the part of the participant, the investigator, or the study site staff. Whenever violations occur, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigators to use continuous vigilance to identify and report protocol deviations and violations. All deviations and violations must be documented in source documents and reported to the OUCRU CTU within 2 days of being identified. In addition, protocol violations must be reported to the relevant ethics committees.

Publication and data sharing policy

All publications are to be approved by the trial steering committee before submission for publication. Any publication arising before all patients have completed follow-up (not by randomized groups) will also be approved by the DSMB in order to ensure that the primary objective of the trial (the randomized comparison) is not compromised.

In line with Wellcome Trust policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will be published in a Plan-S compliant manner. All publications will acknowledge the trial's funding sources.

In line with research transparency and greater access to data from trials OUCRU's clinical trials are registered at ClinicalTrials.gov and a data sharing policy is in place. This policy

is based on a controlled access approach with a restriction on data release that would compromise an ongoing trial or study.

Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Quality assurance and quality control

Risk assessment

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of ICH GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

The safety profile of prone position is well-known and acceptable, given the potential benefits. The trial will be recruiting sick participants, but site investigators have considerable experience with this population. This will minimise the risks to the participants and the trial. A detailed risk assessment will be conducted prior to starting the trial.

Central monitoring at OUCRU CTU

A site initiation visit will be conducted for each study site by staff from the OUCRU CTU. All essential site staff must be in attendance. On site monitoring will also be regularly conducted by the site monitors. The frequency, type and intensity of routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan which will also detail the procedures for review and sign-off. The monitoring will adhere to the principles of ICH GCP and the Monitoring Plan.

The monitors will require access to all participant medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

Regulatory and ethical considerations

All regulatory requirements will be met by the co-sponsors or their delegated authorities.

Compliance

The trial end is 28 days after the last participant is randomized (end of follow-up for the last randomized participant).

The trial complies with the principles of the Declaration of Helsinki (2008) and will be conducted in compliance with the approved protocol and the principles of Good Clinical Practice (GCP).

All sites will comply with the above. An agreement will be in place between the site and the OUCRU CTU, setting out respective roles and responsibilities.

The site will inform the CTU as soon as they are aware of a possible serious breach of compliance. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree the safety or physical or mental integrity of the subjects in the trial, or the scientific value of the trial

Ethical conduct of the study

Ethical considerations

All participants will receive the best available treatment of COVID-19, following local and national guidelines. They will benefit from the frequent and careful follow-up of their condition throughout the treatment of their disease and for up to 28 days from randomization.

The risks and benefits of participation will be communicated in two ways. First, all potential participants or their family members will be given a participant information sheet clearly listing the risks and benefits of the trial. Second, all potential participants (or their families) will be able to discuss participation with their consulting doctor who will be able to address questions not covered or arising from the participant information sheet.

The trial protocol will seek ethical approval to include incapacitated, comatose adults in the trial as we consider many of these adults will have the most severe disease and therefore represents the group that might stand most to gain from the intervention.

Participants' confidentiality will be maintained throughout the trial. Data submitted to OUCRU CTU and samples sent to central testing facilities will be identified only by the trial number and participant initials.

Ethical approvals

The trial will be approved by the Oxford Tropical Research and local Ethics Committee.

Any further amendments will be submitted and approved by the relevant ethics committee.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without

giving a reason and without prejudicing his/her further treatment.

Confidentiality

The investigator must assure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. Participants will be assigned a trial identification number and this will be used on CRFs; participants will not be identified by their name. The investigator will keep securely a participant trial register showing identification numbers, surnames and date of birth. This unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used, in order to maintain confidentiality.

Expenses

Treatment and hospital costs from enrolment to discharge from hospital for all actively enrolled participants will be covered by the State Budget.

The study will not cover the cost of treating pre-existing diseases or those unrelated to study participation or the diagnosis and/or treatment of COVID-19.

Oversight and trial committees

Trial management group (TMG)

A Trial Management Group (TMG) will be formed to conduct the day-to-day management of the trial at the OUCRU CTU. This will include the Chief Investigator, Trial Statistician, Clinical Project Manager, Trial Manager and Data Manager. The group will meet at least once per month, although may meet more or less often as required. The group will discuss issues related to the progress of the trial at the site and to ensure that the trial is running well. The full details can be found in the TMG Charter.

Trial steering committee (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus other members. The role of the TSC is to provide overall supervision for the trial and provide advice. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

Data management and safety board (DSMB)

An independent DSMB will oversee the safety of the trial. The DSMB will be the only group which sees the confidential, accumulating data for the trial separately by randomized group. A DSMB Charter will be drawn up that describes the membership of the DSMB, relationships with other committees, terms of reference, decision-making processes, and the approximate timing and frequency of interim analyses (with a description of stopping rules and/or guidelines). In addition, an interim analysis plan will be written which details all statistical tables that will be provided to the DSMB.

Insurance

The conduct of this study is sponsored by the University of Oxford. The University has a specialist insurance policy in place: - Newline Underwriting Management Ltd, at Lloyd's of London – which would operate in the event of any participant suffering harm as a result of their involvement in the research.

Discussion

Whilst significant progress has been made towards understanding the role of APP in moderate to severe COVID-19, the evolving pandemic means that our study can make unique contributions to further our understanding of the value of this intervention, particularly in limited-resource settings.

Although the majority of cases of COVID-19 are currently in LMICs¹⁷, almost all the evidence for interventions comes from higher income settings. Evidence of APP efficacy in LMICs principally comes from Ehrmann *et al*'s study which included 430 patients from Mexico recruited before January 2021⁴. Our study, however, captures data from a largely vaccinated population in a country with a significantly lower per-capita healthcare expenditure (180 USD compared to 540 USD in Mexico¹⁸). Observation from initial recruitment is that our study will enrol many patients with immunosuppression, including HIV. Previous studies carried out early in the pandemic mainly describe unvaccinated populations and comorbidities related to cardiovascular and pulmonary disease. Understanding the role of APP in the current context however is particularly important for LMICs where HIV remains common, as do other practices such as long-term unrestricted steroid use in the community.

At present, daily cases of COVID-19 in Ho Chi Minh City are lower than when our study was conceived, and consequently we expect a slower recruitment rate¹⁹. This offers several advantages. Firstly, with improved availability of monitoring equipment and staff: patient ratios, we believe that we will be able to collect higher quality routine data with less missing data. Secondly, even though we have a specific team to deliver the intervention, they will be able to do this more carefully and thoroughly ensuring high compliance and accurate recording of any adverse events.

We believe our study is important in that we are employing a special team to deliver the proning intervention. This addresses the issue of low compliance noted in previous studies and postulated as a reason for failure of APP in many^{9,20,21}. Assessing compliance has been further complicated by considerable heterogeneity of methods used to record prone position duration in preceding studies. Some studies have used self-reported methods, whilst some others have not described methods clearly (or at all)^{20,22,23}. Our study design enables us

to accurately quantify the duration of prone position using a combination of regular study-team evaluated observations and continuous monitoring with wearable gyrometry devices.

The use of wearable devices in this study is also a new innovation for resource-limited settings. In addition to gyrometry, our use of wearable vital sign monitoring devices alleviates problems associated with equipment availability, enabling continuous monitoring and as well as remote monitoring for either routine clinical purposes or study-related observations. The formal finalized statistical analysis plan will be published before trial analysis, however we will also be able to carry out exploratory analysis using data from wearable devices. Whilst previously tested in routine ICU care²⁴, this study will provide proof-of-principal data on utility for high-consequence infectious diseases in limited-resource settings.

Ethics approvals

The trial has been approved by the Scientific and Ethics Committee of the Hospital for Tropical Diseases, Ho Chi Minh City (4178/QD-BVBND) and the Oxford Tropical Research Ethics Committee (OxTrec) (39-21)

Clinical Trial Registration

The trial is registered at ClinicalTrials.gov NCT05083130

Data (and software) availability

These will be available in a timely manner according to Wellcome Trust policy (see protocol)

Reporting guidelines

The trial will be reported according to CONSORT guidelines. The protocol is reported according to SPIRIT (see Spirit Checklist Page 32)

Author contributions

NTT, PKNO,TTDV,NLNT, VTL, TDK, NHP, DDH, GG, GT, EK, RG and CLT were involved in overall study design. NTP, NTN, LTTK, LHBT, LTML, DPT, DTD, PTK, NTPT, VTH, NNT, CTCV, TMD, AB, LDVK, DC, HBH were involved in methodology and data collection. NTT, LVT, CLT, GT, AB, GT, NTP, NTN provided supervision and resources. CLT, GG, DDH, LVT, DTH, LMY produced the first draft manuscript. All authors reviewed the final version.

Acknowledgments

We thank the Data Monitoring and Safety Board: Professor Sir Nicholas White, Professor Mavuto Mukaka, Dr Bui Hanh Duyen and Dr Duncan Wyncoll; independent members of the Trial Steering Committee: David Paterson, Mo Yin, Vu Quoc Dat

Extended data

Extended data 1: Major trials of Prone Position in ARDS

Major Trials of Prone Ventilation in ARDS

Variable	Gattinoni et al ¹⁰	Guérin et al ⁸	Mancebo et al ²	Taccone et al ¹¹	Guérin et al ⁹ (PROSEVA)
Prone group mortality, %	50.7 (ICU mortality)	32.4 (28 d)	43 (ICU mortality)	31 (28 d)	16 (28 d)
Control group mortality, %	48 (ICU mortality)	31.5 (28 d)	58 (ICU mortality)	32.8 (28 d)	32.8 (28 d)
RR of mortality (prone/control)	1.05 (<i>P</i> = .65)	1.02 (<i>P</i> = .77)	0.74 (<i>P</i> = .12)	0.97 (<i>P</i> = .72)	0.48 (<i>P</i> < .001)
Patients, No.	304	802	142	342	466
Targeted disease	ALI ^a and ARDS ^a	Respiratory failure with Pao ₂ /Fio ₂ < 300 mm Hg	ARDS ^a	ARDS ^a	ARDS^a with Pao₂/Fio₂ < 150 mm Hg
Pao ₂ /Fio ₂ at enrollment, mm Hg	128	153	139	113	100
Enrollment early in disease course?	No	No	Yes, < 2 d of intubation	Yes, < 3 d	Yes, < 1.5 d
SAPS II	40	46	43	41	46
V _T delivered, mL/kg	10.3	7.9	8.5	8	6.1
Patients paralyzed, %	Not reported	21	45	Not reported	87
Mean increase in Pao ₂ /Fio ₂ on prone positioning, mm Hg	19	18	32 ^b	44	59
Average time prone, hr/d	7	8	17	18	17
Average days prone	10	4	10	8.4	4
Significant reduction in ventilator days? ^c	No	No	No	No	Yes
Difficulty enrolling?	Yes	No	Yes	No	No
Crossover (supine to prone), %	8	21	8	12	7

Bold text indicates the most extreme value across all five trials. ALI = acute lung injury; PROSEVA = Prone Severe ARDS Patients; RR = relative risk; SAPS II = Simplified Acute Physiology Score II; V_T = tidal volume.

^aALI and ARDS were defined according to the American-European Consensus Conference definition of ARDS.⁶⁴

^bThis value was estimated based on graphic data presented in the text.

^cNot all trials reported ventilator days or ICU length of stay; absence of reporting was taken to imply no significant difference.

Extended data 2: WHO COVID-19 Case Definitions

WHO COVID-19: Case Definitions

Updated in Public health surveillance for COVID-19, published 16 December 2020

World Health Organization

Case Definitions

Suspected case of SARS-CoV-2 infection

A A person who meets the clinical **AND** epidemiological criteria:

Clinical Criteria:

- Acute onset of fever **AND** cough; OR
- Acute onset of **ANY THREE OR MORE** of the following signs or symptoms: Fever, cough, general weakness/fatigue¹, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting¹, diarrhoea, altered mental status.

AND

Epidemiological Criteria:

- Residing or working in an **area with high risk of transmission of virus**: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime within the 14 days prior to symptom onset; or
- Residing or travel to an **area with community transmission** anytime within the 14 days prior to symptom onset; or
- Working in **any health care setting**, including within health facilities or within the community; any time within the 14 days prior to symptom onset.

B A patient with **severe acute respiratory illness**: (SARI: acute respiratory infection with history of fever or measured fever of ≥ 38 °C; and cough; with onset within the last 10 days; and requires hospitalization).

C Asymptomatic person not meeting epidemiologic criteria with a **positive SARS-CoV-2 Antigen-RDT**²

¹ Signs separated with slash (/) are to be counted as one sign.

² NAAT is required for confirmation, see [Diagnostic testing for SARS-CoV-2](#)

See [Antigen detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays](#)

Probable case of SARS-CoV-2 infection

A A patient who meets clinical criteria above **AND** is a **contact of a probable or confirmed case**, or linked to a **COVID-19 cluster**³

B A **suspect case with chest imaging** showing findings suggestive of COVID-19 disease⁴

C A person with recent onset of **anosmia** (loss of smell) or **ageusia** (loss of taste) in the absence of any other identified cause.

D **Death**, not otherwise explained, in an adult with **respiratory distress** preceding death **AND** was a **contact of a probable or confirmed case** or linked to a **COVID-19 cluster**³

Confirmed case of SARS-CoV-2 infection

A A person with a positive **Nucleic Acid Amplification Test (NAAT)**

B A person with a **positive SARS-CoV-2 Antigen-RDT** **AND** meeting either the **probable case definition** or **suspect criteria A OR B**

C An **asymptomatic person with a positive SARS-CoV-2 Antigen-RDT** who is a **contact of a probable or confirmed case**

³ A group of symptomatic individuals linked by time, geographic location and common exposures, containing at least **one NAAT-confirmed case** or at least **two epidemiologically linked, symptomatic** (meeting clinical criteria of Suspect case definition A or B) persons with **positive Ag-RDTs** (based on ≥97% specificity of test and desired >99.9% probability of at least one positive result being a true positive)

⁴ Typical chest imaging findings suggestive of COVID-19 include the following:

- Chest radiography**: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution
- Chest CT**: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution
- Lung ultrasound**: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms.

Note: Clinical and public health judgment should be used to determine the need for further investigation in patients who do not strictly meet the clinical or epidemiological criteria. Surveillance case definitions should not be used as the sole basis for guiding clinical management.

Extended data 3: Vietnamese guideline of diagnosis and treatment COVID-19, Vietnamese Ministry of Health 06OCT21

Clinical severity level

Moderate:

Clinical: signs of pneumonia with dyspnoea, respiratory rate 20 – 25 breaths/minute, crackle rales, no signs of severe respiratory failure, SpO₂ 94–96% on room air, conscious. Fast or slow pulse rate, tachycardia, normal blood pressure.

Severe:

Clinical: signs of pneumonia and accompanied by one of the following: respiratory rate > 25 breaths/minute, severe dyspnoea, accessory respiratory muscle, SpO₂ < 94% on room air, tachycardia or bradycardia, normal or high blood pressure, irritable or exhausted, tired.

Extended data 4: Sample size considerations

Table showing sample size estimation and other studies upon which this was based

Study	Power	Proportion group 1	Proportion group2	Effect size (Cohen's d)	n1	n2	N
1	0.8	0.52	0.40	0.24	273	273	546
2	0.8	0.52	0.42	0.21	356	356	712
3	0.8	0.46	0.40	0.12	1090	1090	2180
4	0.8	0.82	0.32	1.06	14	14	28

Study 1 & 2 show estimated sample size with different estimated effect size.

Study 3 – effect size from study of shorter duration of prone-position in patients with HFNC⁴

Study 4 – effect size from observational study of LMIC patients receiving oxygen therapy¹⁵.

Extended data 5: Contra-indications to prone position

Spinal instability

Risk of spinal instability

Unstable fractures

Anterior burns and open wounds

Shock (persistent mean arterial pressure < 65 mmHg)

Raised intracranial pressure >30 mmHg

Sternotomy or tracheal surgery (excluding tracheostomy) within 2 weeks

Anterior chest tube with air leak

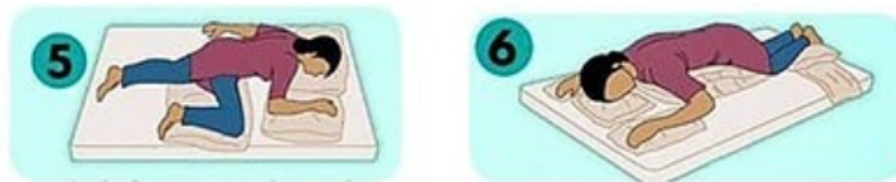
Major abdominal surgery

Recent pacemaker insertion

Extended data 6: Mitigation for prone positioning adverse events

Peripheral nerve injury & patient discomfort	One upper limb adducted by head Upper limbs along side body Lower limb with hip and knee semi-flexed Keep all joints in neutral position Avoid neck hyper extension Avoid extension of shoulder Avoid arm abduction > 70 Pillows under chest/pelvis Alternate face rotation Repositioning every 2 hours
Turning	Pre-manoevre check list
Vomiting/haemoptysis	Pillows under chest and pelvis Face rotation
Eye injuries/ Facial oedema	Face rotation Repositioning 2 hourly
Desaturation/ hemodynamic instability while positioning	Pre-manoevre check list Vital sign monitoring
Displacement of lines whilst turning	Pre-manoevre check list Discontinue non-essential infusions and monitoring

Extended data 7: Example of information to be given to patients about positioning

Extended data 8: Estimation of FiO₂ from oxygen flow

Method	O ₂ flow (l/min)	Estimated FiO ₂ (%)
Nasal Cannula (not HFNC)	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

reproduced from the ESICM guidelines on respiratory care 2019

Extended data 9: Proposed plan of prone positioning daily schedule

Intervention group

	Position	Duration	Proposed methods
After breakfast	Prone	2 hours	In-person visit, vital sign measurement. Help with positioning, verbal and written advice
	Prone	2 hours	Compliance check with camera check, vital sign measurement
Lunch	Semi-recumbent position	1 hour	
Afternoon	Prone	Prone positioning 4 hours	In-person visit, vital sign measurement, help with positioning, verbal and written advice
	Prone		Compliance check with camera check, vital sign measurement
Dinner	Semi-recumbent or sitting	1 hour	
Evening	No guidance	4-6 hours	Written reminders,
Night time	Encourage prone position	8 hours	Verbal encouragement, printed material

Standard care group

	Position	Duration	Proposed methods
After breakfast	No guidance	2 hours	In-person visit, vital sign measurement.
	No guidance	2 hours	Compliance check with camera check, vital sign measurement
Lunch	No guidance	1 hour	
Afternoon	No guidance	Prone positioning 4 hours	In-person visit, vital sign measurement.
	No guidance		Compliance check with camera check, vital sign measurement
Dinner	No guidance	1 hour	
Evening	No guidance	4-6 hours	
No guidance	No guidance	8 hours	

Extended data 10: Patient acceptability questionnaire

On a scale of 1-10, how did you find lying in the prone position [1 extremely uncomfortable – 10 comfortable]

1 --- 2 --- 3 --- 4 --- 5 --- 6 --- 7 --- 8 --- 9 --- 10

On a scale of 1- 10, how did you find getting into the prone position [1 extremely difficult, needed a lot of help – 10 very easy, could do this unaided]

1 --- 2 --- 3 --- 4 --- 5 --- 6 --- 7 --- 8 --- 9 --- 10

On a scale of 1-10, how did you find comfortable did you find the monitoring equipment [1 extremely uncomfortable – 10 comfortable]

1 --- 2 --- 3 --- 4 --- 5 --- 6 --- 7 --- 8 --- 9 --- 10

On balance, whilst you were receiving oxygen which position do you prefer to lie in for most of the day time

1. Prone position
2. Supine position
3. Side position
4. Sitting up
5. No preference

On balance, whilst you were receiving oxygen which position do you prefer to lie in for most of the night time

1. Prone position
2. Supine position
3. Side position
4. Sitting up
5. No preference



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Manuscript
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8,19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Section/item	ItemNo	Description	Page
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, Extended data
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9,10,11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9, Extended data
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10,11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Section/item	ItemNo	Description	Page
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11, Extended data
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10,16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16

Section/item	ItemNo	Description	Page
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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