DOMAIN PROTOCOL

To be read in conjunction with CoReCCT Master Protocol.

CoReCCT (Confederation of Respiratory Critical Care Trials)

The clinical and cost effectiveness of advanced airways protection device veschedulrsus conventional endotracheal tubes in Intensive care unit patients requiring mechanical ventilation: a multi-centre, pragmatic randomised clinical trial (PROTECT Airways)

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WARWICK CLINICAL TRIALS UNIT

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Data Monitoring Committee:	DMC members are fully detailed in the CoReCCT master protocol
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Randomisation:	via online randomisation system

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TRIAL SUMMARY

Master Protocol Title	CoReCCT - Confederation of Respiratory Critical Care Trials	
Trial Title	*The clinical and cost effectiveness of advanced airways protection device versus conventional endotracheal tubes in intensive care unit patients requiring mechanical ventilation: a multi-centre, pragmatic, randomised clinical trial*	
Internal ref. number (or short title)	*PROTECT Airways*	
Clinical Phase	*Phase IV*	
Trial Design	*A multi-centre, pragmatic, individually randomised, open-label, parallel group trial, and economic evaluation, to determine the clinical and cost effectiveness of an advanced airways protection device, compared with conventional endotracheal tube (with or without basic subglottic suction and standard cuff) in hospitalised patients requiring mechanical ventilation.*	
Trial Participants	*Adult (age≥18), hospitalised needing mechanical ventilation, likely to remain ventilated for at least 24 hours following randomisation*	
Planned sample size	*2194 patients*	
Planned Trial Period	*Planned Start date 1st May 2024* *63 months: 6-months set-up; 9-months internal pilot; 39-months recruitment; 6-months follow-up; 3-months data analysis, reporting and dissemination.*	
	Objectives	Outcome Measures
Primary	*To determine the clinical and cost effectiveness of an advanced airways protection device*	*Duration of mechanical ventilation as measured from time from randomisation to first successful unassisted breathing, measured in days (full definition in section 2.3)*
Secondary	*To determine the clinical and cost effectiveness of an advanced airways protection device*	• *Core clinical outcome set as per CoReCCT master protocol* *In addition to:* • *Endotracheal intubation duration in hours* • *Ventilator Associated Pneumonia (VAP)* • *Hospital Acquired Pneumonia (HAP)*

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
APACHE II	Acute Physiology And Chronic Health Evaluation II
CI	Chief Investigator
CACE	Compliers Average Causal Effect
CEACs	Cost Effectiveness Acceptability Curves
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CoReCCT	Confederation of Respiratory Critical Care Trials
COVenT	Core Outcomes in Ventilation Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
ETT	Endo Tracheal Tube
GCP	Good Clinical Practice
HAI	Hospital Acquired Infection
HES	Hospital Episode Statistics
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
ICEs	Inter Current Events
ICER	Incremental Cost Effectiveness Ratio
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention To Treat
MRC	Medical Research Council
NHS	National Health Service
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 & Public Involvement
PSS	Personal Social Services
PVC	Poly Vinyl Chloride
QoL	Quality of Life
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RUQ	Resource Use Questionnaires
R&D	Research and Development

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SHR	Sub-distribution Hazard Ratio
SOP	Standard Operating Procedure
SOFA	Sequential Organ Failure Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
VAP	Ventilator-Associated Pneumonia
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Care of the critically ill typically occurs in the intensive care unit (ICU), although it may commence elsewhere, such as the operating theatre or emergency department. If a patient cannot breathe adequately, they may be assisted by mechanical ventilation. This involves placing a tube into the trachea (endotracheal tube (ETT)), which connects to a ventilator. This system 'takes over' breathing for the patient. In the UK, over 60,000 adults receive invasive ventilation each year[1], with most of these surviving to leave hospital (66%)[2] . Mechanical ventilation is known to be associated with some clinically important unwanted effects; one is Ventilator-Associated Pneumonia (VAP). Patients who develop VAP have a protracted ICU stay and worse outcome. In addition to the personal cost and risk for each patient, there are significant healthcare costs associated with a protracted stay on ICU, with each day of care costing around £1500. [3, 4].

VAP is the most common Hospital Acquired Infection (HAI) in ICUs occurring in ~30% of mechanically ventilated patients [5-8]. This increased to 45% during the COVID-19 pandemic.[9] A new class of endotracheal tube aimed at providing advanced airway protection may significantly reduce the incidence of VAP (pneumonia occurring >48 hours after intubation)[10] and in turn the length of mechanical ventilation and stay on ICU. Consequently, reducing VAP incidence is important to patients, clinicians, and policy makers.

The National Institute for Health and Care Excellence (NICE) produced medical technologies guidance 48, (April 2020) [11], highlighting the potential for a new ETT, an advanced airway protection device, to prevent Ventilator Associated Pneumonia[11]. However, the current evidence base is not strong enough for formal NICE approval. Therefore, NICE have recommended definitive research to assess the clinical and cost effectiveness of such advanced airway devices in NHS critical care. NICE have identified the PneuX system as the only current example of an advanced airways protection system, that has the best current evidence for the potential to reduce ventilator associated pneumonia and in turn reduce length of time on a ventilator.

1.2 Research Question

In critically ill adults who require invasive mechanical ventilation (population), does the use of an advanced airways protection device (intervention) compared with the conventional endotracheal tubes (comparator) reduce the duration of mechanical ventilation (primary outcome)?

1.3 Need for a trial

The James Lind Priority Setting Partnership for intensive care identified "what is the best way to prevent, diagnose and treat hospital acquired infections" as a top-ten research priority. Infections in the critically ill can significantly impact outcomes. ICU is an expensive and scarce resource such that any reduction in stay could save money and ensure bed capacity for other patients.

Various ETT devices have been tested to reduce the possibility of secretion aspiration from the upper airway, with the hypothesis that this will reduce VAP. These include the importance of maintaining cuff pressure [1, 2], the active removal of secretions above the endotracheal tube cuff and below the vocal cords (sub-glottic suction) [3] and a cuff design that reduces microchannels formation, down which infectious material can pass into the lungs leading to pneumonia[4].

These approaches have been consolidated within new advanced airways protection device(s) as recently as April 2020 identified and reviewed by NICE[5].

In this NICE review, the clinical safety and efficacy was identified from three prospective studies[6-9] that included 341 adult ICU patients. It also highlighted a potential average saving of £738 per patient [10]. The resulting NICE Medical Technologies Guidance (MTG48) recommends a definitive clinical and cost effectiveness randomised controlled trial be performed in NHS care, and there are currently no such studies registered or planned (UK or internationally).

We conducted a new (October - November 2022) national survey of critical care clinicians (n=144) which reported that 35% of respondents intubate critically unwell patients with a standard ETT, and 65% intubate patients with a basic ETT with subglottic suction. Only 20% of respondents measure continuous cuff pressure. Venner (manufacturers of NICE recommended airways system) have confirmed this advanced airways protection device is only used in two UK hospitals. At present, no other comparable ETTs are available on the UK market at present for use in the NHS.

1.4 Ethical considerations

We will conduct the trial in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The trial and supporting documents will be submitted to the Sponsor, Research Ethics Committee and Health Research Authority for approval prior to commencing any trial activities.

In collaboration with patient and public colleagues, we will develop participant information that is succinct, relevant and user-friendly in line with Health Research Authority guidance on proportionate consent [11]. We have developed procedures in line with the Mental Capacity Act 2005 (and equivalent Scottish legislation, where possible) to enable all patients requiring tracheal intubation to participate in the study, ranging from patients undergoing elective tracheal intubation (e.g. patients undergoing surgery) where we will seek prior informed consent to those patients requiring emergency tracheal intubation where we will enrol patients initially under a deferred consent model.

Where the patient's consent was not sought prior to enrolment, we will seek this at the earliest reasonable and practical opportunity once the patient has regained capacity. Warwick Clinical Trials Unit is extremely experienced in delivering trials in unscheduled care with these consent models.

1.5 CONSORT

The trial will be reported in line with the CONSORT (*Cons*olidated *S*tandards *o*f *R*eporting *T*rials) statement (*BMJ* 2010;340:c869).

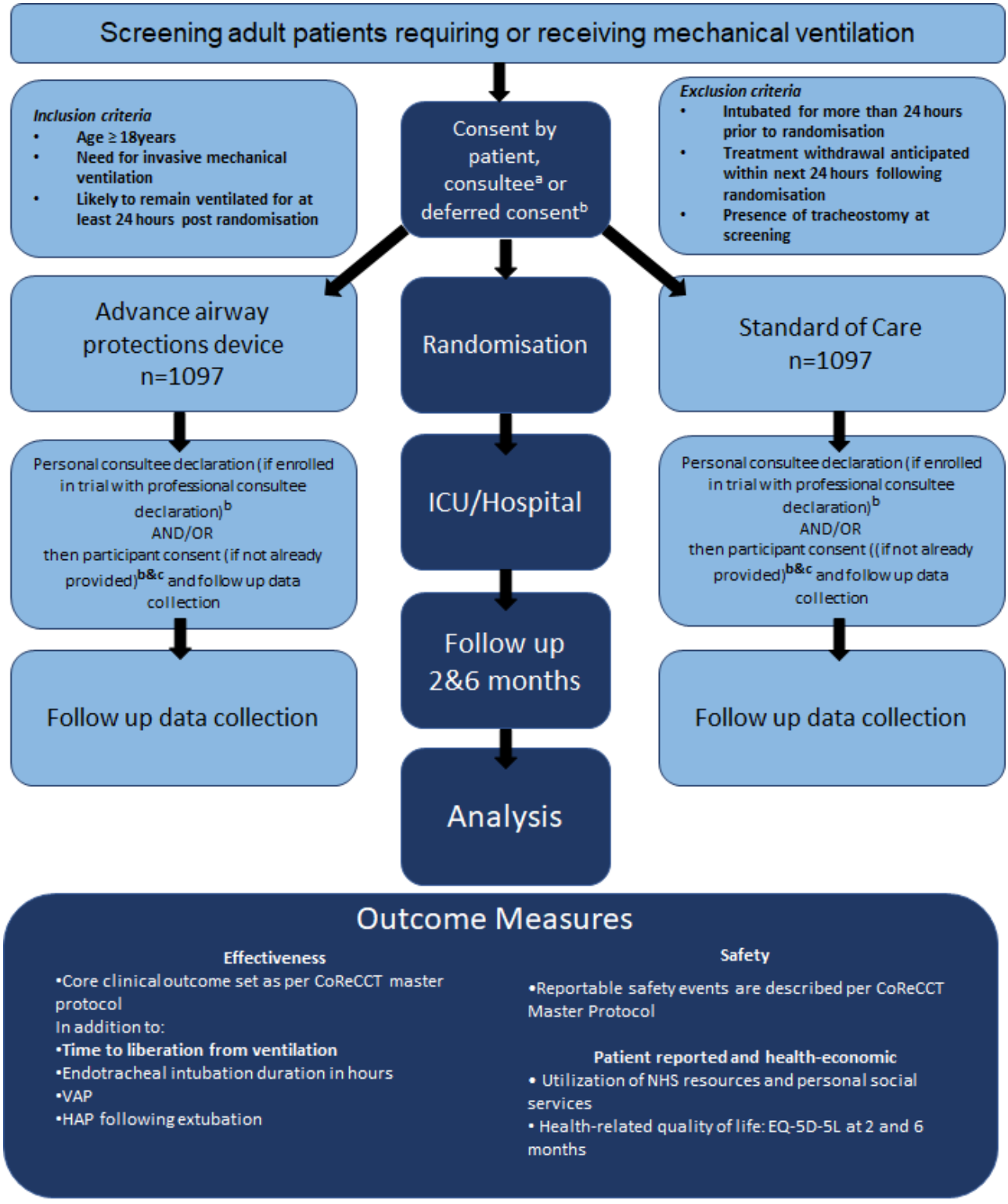
1.6 Confederation of Respiratory Critical Care Trials

PROTECT Airways sits as one of four trial domains 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

Figure 1 Trial flow diagram



[a] in Scotland referred to as welfare guardian/nearest relative
[b] not in Scotland
[c] within 30 days of randomisation

2.2 Internal pilot

The main trial will be preceded by an internal pilot study of 9 months duration. This will follow the same processes as the main trial. All patients recruited in the pilot study will be included in the final analysis and this will run seamlessly into the main trial. The pilot study will aim to take place in 32 representative sites. We aim to recruit 220 patients, representing 10% of the total study sample. The aim of the pilot study will be to audit: (a) screening data and assess reasons for exclusion of patients; (b) site and patient recruitment; (c) treatment delivery and fidelity; (d) protocol adherence; (e) unplanned cross-overs; (f) implementation of the training; (g) protocol implementation, using screening logs and case report forms (CRFs); (h) data completeness.

Table 1: Criteria for progression from pilot study to main trial

	Red	Amber	Green
RECRUITMENT			
% Threshold	<50%	50-99%	100%
Sites recruited	<16	16-31	32
Total number of patients recruited	<110	110-219	220
COMPLIANCE/ADHERENCE (of those recruited)			
% Threshold	<50%	50-79%	80-100%

Success criteria for recruitment will be (a) 100% recruitment: progress to main trial; (b) 50-99% recruitment: progress to main trial with review of screening log and protocol and explore the possibility of additional sites; (c) less than 50% recruitment: progression to main trial not anticipated.

Success criteria for protocol adherence and fidelity to the intervention: (a) 80-100% adherence: progress to main trial; (b) 50-79% adherence: progress to main trial with intensive efforts to improve adherence; (c) < 50% adherence: progression not anticipated.

These criteria will be reviewed by the Data Monitoring Committee (DMC) and the Trial Steering Committee (TSC) in association with the health technology assessment (HTA) secretariat.

2.3 Aims and objectives

Objectives:

(1) Conduct an internal pilot study to confirm the feasibility of a large-scale multicentre trial.

(2) To conduct a UK-wide multi-centre, open-label, pragmatic, individually randomised, parallel group trial and economic evaluation to determine the clinical and cost effectiveness of an advanced airways protection device versus conventional endotracheal tubes (with and without basic subglottic manual suction and standard cuff) in patients with respiratory failure requiring mechanical ventilation. The outcomes are duration of mechanical ventilation, survival, ICU, and hospital stay outcomes and health-related quality of life.

(3) Estimate, in an integrated economic evaluation, the cost-effectiveness of an advanced airways protection device versus the conventional endotracheal tubes.

Justification of outcomes

We have worked with patients, the public, researchers and clinicians to determine both our primary and secondary outcomes. This clinical effectiveness trial comprises key core outcomes from the Core Outcomes in Ventilation Trials (COVent) core outcome set and NICE guidelines for ventilation trials and NICE guidelines [5, 12, 13].

Primary effectiveness outcome

The primary variable (outcome) of interest is the duration of mechanical ventilation as measured from time from randomisation to first successful unassisted breathing, measured in days. This outcome is one of the 'COVenT' core outcomes for trials of interventions intended to modify the duration of mechanical ventilation[14]. To clarify:

- Unassisted breathing is defined as no inspiratory support or extracorporeal lung support
- Success is defined as maintaining unassisted breathing at 48 hours.
- Duration includes time receiving extracorporeal lung support, invasive mechanical ventilation and non-invasive ventilation delivering volume or pressure support ventilation.
- Duration excludes time receiving high-flow oxygen therapy and continuous positive airway pressure.
- Patients with a tracheostomy in situ may still achieve successful unassisted breathing.

Secondary outcomes - refer to CoReCCT master protocol for core clinical outcome set.

Effectiveness

- *Duration of endotracheal intubation*: time from randomisation to endotracheal extubation (in hours).
- Ventilator Associated Pneumonia (VAP): Diagnosed by treating clinician with commencement of antibiotics [16] from randomisation up to ICU discharge.
- Hospital Acquired pneumonia (HAP) following extubation- clinician diagnosis and commencement of antibiotics from randomisation up to ICU discharge.

Safety Outcome Measures

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

Adverse event rates, including device-related

Adverse event rates related to endotracheal tube intubation within 1 hour of intubation, or tube change if allocated to intervention arm:

- *Traumatic insertion, bleeding*
- *Injury to the throat or trachea*
- *Dental damage*
- *Failed intubation*
- *Aspiration during intubation*
- *Pneumothorax*
- *Obstruction or kinking of the endotracheal tube*
- *Cuff leak*
- *Unintentional extubation*

Adverse event rates related to endotracheal tube intubation after one hour of intubation, or tube change if allocated to intervention arm, up to ICU discharge:

- *Tracheal stenosis*
- *Vocal cord injury / paralysis / Arytenoid dislocation*
- *Hoarse voice / voice changes*
- *Sinusitis*
- *Laryngo-tracheal stenosis*
- *Tracheomalacia*
- *Obstructive fibrinous tracheal pseudo membrane*
- *Pressure injuries related to tube securing or pressure from tracheal tube*

- *Tracheo-oesophageal fistula*
- *C-spine and spinal cord injuries due to intubation*

Patient reported and health-economics outcomes:

- Costs associated with use of NHS & personal social services (PSS) resources arising during hospital stay and after hospital discharge; personal expenditures (out-of-pocket costs) incurred by patients after hospital discharge. (also see section Health Economic Evaluation).
- Health-related quality of life using a widely used and recommended preference-based quality of life instrument (EQ-5D-5L) collected at 2 and 6 months.

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

1. Adult (age ≥18 years)
2. Need for invasive mechanical ventilation
3. Likely to remain ventilated for at least 24 hours post randomisation

2.4.2 Exclusion criteria

1. Intubated for more than 24 hours prior to randomisation
2. Treatment withdrawal anticipated within next 24 hours post randomisation
3. Presence of tracheostomy at screening

2.5 Participant identification / Screening

Staff will identify potential participants in appropriate clinical areas, such as emergency departments, critical care units, acute wards, operating theatres. Potential processes for identifying patients include referrals, screening in clinical areas, or review of electronic health systems using appropriate queries. We will work with each participating site to support the development of strategies to optimise screening in their hospital.

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 determined 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 who need intubating, or who have been intubated within the last 24 hours prior to randomisation are eligible for the trial. 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

Training for recruitment:
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.

Training programme for delivering the intervention: To standardise the delivery of the intervention across and within sites, the Venner PneuX™ advanced airways protection device has a detailed manual and training programme[17]. The inclusion of this innovation will not change routine NHS practice, when handling patients who need assistance using a ventilator. Training will be provided to research, care teams and clinicians involved in delivery of usual airway clearance management, so that they are accustomed in delivering the intervention. Training videos, material and face-to-face training will be provided by the supplier (Qualitech Healthcare). The training programme consists of: (i) introduction to the Venner PneuX™ device (endotracheal tube and tracheal seal monitor); (ii) practical demonstration (subglottic irrigation and drainage); (iii) hands-on session; (iv) questions and answers; (iv) verification of understanding certificate; (v) training evaluation forms and training records. Online training resources will also be utilised : (i) PneuX System™ Tube Exchange [18] (ii) Irrigation with the PneuX System™ [19] (iii) Intubating with the PneuX System™ [20] Information on potential barriers during implementation and mitigating actions are detailed in online documentation [21].

Comparator
Standard care is to intubate a patient using a conventional endotracheal tube or endotracheal tube with basic subglottic suction and standard cuff (made of Polyvinyl Chloride (PVC)). These tubes have a single lumen subglottic port. Pressure within the cuff is checked every 12 hours (once per nursing shift). The subglottic port is aspirated every four hours to clear subglottic secretions, or more, if there is a high secretion load.

2.7 Informed consent

We have carefully considered the patient eligibility criteria. As described above, we made the trial eligibility criteria as broad and inclusive as possible. Ineligible groups are minimal and based on likely lack of efficacy (unlikely to be intubated longer than 24 hours), and tracheostomy formation, although there are tracheostomy versions of this system, here we view tracheostomy as a key outcome.

The trial will recruit from all hospital areas that treat patients with ventilation support likely to last 24 hours or more, and which can safely deliver the intervention. We will attempt to target patients as early as possible in their illness. This will increase the generalisability of our findings.

The consent process should be performed according to section 4.2.3 of the CoReCCT master protocol.

Once a patient who initially lacks mental capacity, regains capacity during their initial acute hospital admission or up to 30 days from randomisation, they will be informed about the trial and invited to consent to continue in the trial. There is no requirement to reaffirm consent in Scotland.

2.8 Randomisation

2.8.1 Randomisation

A bespoke online randomisation system will be developed, by the WCTU programming team. The system will be based on a computerised algorithm using the minimisation method for randomising patients. The randomisation sequence will be created, stratified by hospital site, if the patient is intubated prior to randomisation and prior enrolment into the Awake Prone trial. Patients will be randomised, in a ratio of 1:1 to the advanced airways protection device or the standard of care endotracheal tube (with or without the basic subglottic suction/standard cuff). Randomisation can happen up to 24 hours after primary intubation. **If randomised to the intervention arm, this may necessitate a tube change. The tube change should occur within 24 hours of the patient initially being intubated.**

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. Withdrawing from the trial will not affect the participant or their care in any way.

Withdrawal should be handled as per section 6.8 of the CoReCCT master protocol.

In the event that a participant is transferred to another hospital, intervention delivery will usually stop at the point of transfer, unless the receiving institution is also a recruiting centre for PROTECT airways, if this is the case then the patient can continue in the trial. The recruiting hospital will liaise with the new hospital to facilitate collection of follow-up data.
Follow-up rates will be monitored by the Trial Management Group (TMG).

2.9 Trial treatments / intervention

- Intervention: A CE-marked advanced airways protection device (Venner PneuX™)
- Comparator: standard of care, conventional endotracheal tube (with or without basic subglottic suction and standard cuff).

Both the intervention and comparator group will receive standard care for mechanically ventilated patients, 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. The treatment (comparator or intervention) will continue until:

- Successful unassisted breathing (no further requirement for mechanical ventilation)
- Trial intervention-related serious adverse event
- Death or discontinuation of active treatment

If the participant is extubated and then subsequently requires re-intubating:

1. If less than 48 hours from randomisation should be done using the intervention tube if allocated to the intervention arm.
2. If greater than 48 hours from randomisation should be done according to clinicians discretion.

Intervention

An advanced airways protection device consists of a flexible ETT with ports for subglottic suction/irrigation as well as a port to attach to an electronic system to maintain cuff pressure. The Venner PneuX™ device was recommended for testing in a large scale clinical trial by NICE in MTG48[5]. It is the only advanced airway system currently available in the NHS. Venner PneuX^{TM} device is available in various sizes. We will test this system and the findings will be generalisable to future devices with similar design features and capabilities.

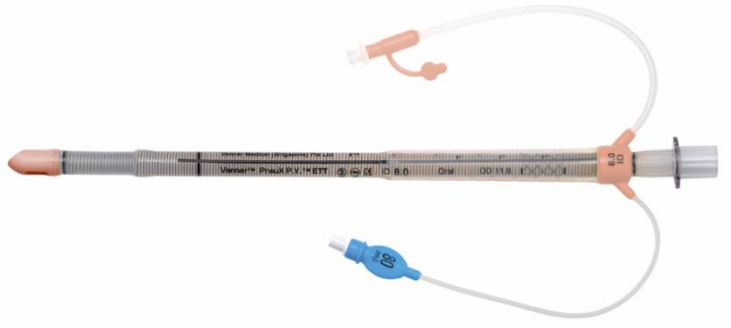


Figure 2 Venner PneuX™ device - an advance airways protection system

The Venner PneuX™ device is a flexible armoured ETT. It has a low-volume, low pressure cuff, that inflates uniformly without folds or creases. The key innovative design is the cuff which does not form microchannels and this prevents micro-aspiration during long term ventilation [18]. The endotracheal cuff and pilot balloon is connected to an electronic system that continuously maintains, monitors, and regulates the pre-set cuff pressure. It has three sub-glottic suction ports around the circumference to ensure that at least one port is patent for suctioning. Sub-glottic suction ports can facilitate irrigation and aspiration of secretions from the subglottic space.

If there is an issue with the tube that requires a tube change then unless participant safety would be compromised participants in the intervention arm should be given another advanced airways protection device (Venner PneuX™).

2.10 Design and theoretical / conceptual framework

This trial will be a multi-centre, pragmatic, individually randomised, open-label, parallel group trial with an integrated health economic evaluation. The design and theoretical framework will follow the IDEAL guidelines for conducting a clinical trial using an already CE-marked device, in line with the European Medical Device Regulation[23].

Methods for protecting against bias and contamination.

Selection bias: Treatment allocation will be concealed prior to randomisation using a bespoke randomisation system. To ensure clinicians have equipoise, we will assess the screening logs and examine reasons why patients have not been enrolled into the study.

Performance and detection bias (unblinded study): The nature of the trial intervention precludes masking of patients or care providers following randomisation. We will mitigate against potential bias in the absence of blinding, by using an objective measurable primary outcome (duration of mechanical ventilation (days)), and collecting data on intubation and readiness to extubate, and reasons why this might not occur as planned, to confirm consistency across randomised groups and assess performance bias on the part of treating clinicians. Intensive care clinical charts provide contemporaneous, hour by hour records of the patient's physiology and current treatments. Source verification (from clinical records) and hospital computer records will be used to minimise the risk of reporting bias. The main clinical and resource utilisation outcomes of this trial (e.g., ventilation status (hourly); death; level 2/3 care; adverse events, antibiotic uses) are recorded contemporaneously on patient clinical records and hospital information systems. This will enable outcomes to be verified by both site staff and the coordinating centre.
It will also not be possible to directly blind the WCTU (Warwick Clinical Trials Unit) trial team to treatment allocation, as this information will be collected on the patient clinical record forms and will be necessary to monitor and manage protocol deviations and compliance/adherence. However, the team will have some blinding regards the randomised intervention, whilst collecting the follow-up outcome data. At the pilot stages, we will assess the patient baseline characteristics at site level, to identify any outliers which may have resulted due to our inability to blind the trial. The trial statistician, who has no role in decision-making with regards the conduct of the trial, will be unblinded and this will also facilitate linkage with the DMC.

Attrition bias: Most of the outcome data will be collected during the hospital stay. It is our experience that in this patient group (ICU patients) withdrawal rates are typically <3% (see sample size section below). On the rare occasions that a patient or their legal representative chooses to withdraw from the trial we will seek their permission to retain data collected up until that point and to continue to collect the main outcome data. Our experience is that patients are normally happy to proceed on this basis. These approaches should minimize the risk of attrition bias. For this reason, we anticipate very low levels of attrition and therefore no attrition bias (e.g., withdrawal rates for ICU studies include RECOVERY-RS 1%[24]; BREATHE 0% [25]; HARP-2 0.5%[26]; REST 1.7% [27]).

Reporting bias: We will register and publish our protocol prior to the end of recruitment. In addition, we will finalise our statistical analysis plan and the health economics plan before the trial finishes the recruitment of patients. All amendments to these finalised documents will be made available to ensure transparency.

Follow-up data (at 2 and 6 months) collected from patients will be limited to a single health-related quality of life and healthcare resource use questionnaires.

Treatment fidelity: To ensure the standardisation of the delivery of the intervention across the sites, a detailed training programme will be delivered (as detailed in section 2.6). Our progression criteria for moving from the pilot to main trial includes adherence and crossover criteria. We will closely monitor and assess treatment fidelity throughout the pilot study, obtain feedback from sites and enhance any processes to ensure that the delivery of both interventions is as protocolised. In the event of evidence of non-adherence, this will be flagged to the site research team. The site research team will then investigate events through discussion with the clinical team and, where appropriate, report this as a protocol deviation. Where necessary, further training will be provided.

Crossover and non-compliance: Cross-over will be defined as those patients who move from standard care to the advanced airways system post randomisation allocation. This will be discouraged. Non-compliance will be defined when patients move from the advanced airways system to standard of care, without reaching the endpoint (as stated in section 2.3). Both crossover and noncompliance will be monitored during the pilot study and the main trial. We will work very closely with sites, especially if a site has a higher rate of non-compliance/cross-over, to assist in over-coming any challenges, through education and further training and sites with persistent high non-compliance/cross-over rates will be closed. We will also assess the impact of these using statistical methods through the Estimand framework (as detailed in the statistical analysis plan in Section 6.2.2).

2.11 Blinding

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

2.12 Co-enrolment into other trials

This is detailed in section 4.5 CoReCCT Master Protocol.

2.13 End of trial

The trial will end when all participants have completed their 6-month follow-up, or receipt of routinely collected data, including resolution of data queries and data cleaning. The trial management group and research staff will review data entered and address any data queries prior to database lock.
The trial will be stopped prematurely if:

- Mandated by the Ethics Committee.
- Following recommendations from the Data Monitoring Committee (DMC).
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 1 summarises the trial schedule of events and timing of data collection.

Table 2 Trial assessments

	Timing of assessment				
	Baseline	**Hospital stay**	**Hospital discharge**	**2 months**	**6 months**
Eligibility assessment	✓				
Deferred consent[a]/ Consent/ consultee[b] agreement	✓	✓*			
Baseline data collection	✓				
Randomisation	✓				
Intervention	✓	✓			
Critical care/ hospital stay data			✓		
Survival status		✓	✓	✓	✓
Quality of life (EQ-5D-5L) and health resource use questionnaire				✓	✓
Safety reporting		✓	✓		

[a] not in Scotland
[b] in Scotland referred to as welfare guardian/nearest relative

*- only applicable if consultee agreement/deferred consent used as basis for initial enrolment

3.2 Long term follow-up assessments

Long-term follow-up will be conducted at 2 months and 6 months following the *last* randomisation in the CoReCCT domain trials.

Follow-up questionnaires at 2 months and 6 months will capture health-related quality of life and healthcare resource use. The 6 month questionnaire will be sent out even if the 2 month questionnaire is not completed and returned. These questionnaires will usually be completed by the participant online and may be completed by postal questionnaire or over the phone. In the event that a participant is unable to complete the questionnaire (e.g.

neurological deficit), it may be completed on the participant's behalf by someone that has a good awareness of their health state (e.g. relative/ carer).
Long-term follow-up will be coordinated by WCTU. Prior to sending out follow-up questionnaires WCTU will wherever feasible liaise with the recruiting hospital to ensure that the participant has not died.

4. ADVERSE EVENT MANAGEMENT

In order to accurately assess and report SAEs relevant to PROTECT Airways, 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 PROTECT Airways Pre-Specified Complications List as given below (Table 2)

The duration of mechanical ventilation from randomisation to liberation is the primary objective of this study. Therefore, any clinically relevant intubation and mechanical ventilation related event occurring from the time of randomisation until ICU discharge will be recorded as pre-defined trial outcomes (see as listed in Safety Outcomes Section 2.2 above and SAE reporting exemptions below).

Table 3 Pre-Specified Complications List (safety outcomes)

Pre-Specified Complications List (safety outcomes)
Adverse event rates related to endotracheal tube intubation within one hour of intubation or tube change if allocated to intervention arm: - *Traumatic insertion, bleeding* - *Injury to the throat or trachea* - *Dental damage* - *Failed intubation* - *Aspiration during intubation* - *Pneumothorax* - *Obstruction or kinking of the endotracheal tube* - *Cuff leak*

- *Unintentional extubation*

Adverse event rates related to endotracheal tube intubation after one hour of intubation, or tube change if allocated to intervention arm, up to ICU discharge

- *Tracheal stenosis*
- *Vocal cord injury / paralysis / arytenoid dislocation*
- *Hoarse voice / voice changes*
- *Sinusitis*
- *Laryngo-tracheal stenosis*
- *Tracheomalacia*
- *Obstructive fibrinous tracheal pseudo membrane*
- *Pressure injuries related to tube securing or pressure from tracheal tube.*
- *Tracheo-oesophageal fistula*
- *C-spine and spinal cord injuries due to intubation*

As per the CoReCCT Safety Reporting Flowchart, if the event is present on the Pre-Specified Complications List, the event must be recorded on the appropriate CRF as an outcome and does not need to be reported as an SAE. If the event is not on the list, it must be assessed for seriousness and the remainder of the flowchart should be followed to determine next steps.

The target population for the trial is the broad group of patients that require intubation and mechanical ventilation. These patients are the sickest in the hospital and are at risk of physiological deterioration, including the need for increased organ support, and death. These events are captured as clinical outcomes.

All-cause mortality at ICU discharge, hospital discharge 2 and 6 months post randomisation will be captured as an outcome.

4.2 Expectedness Assessment

SAEs which are considered possibly related, probably related, or definitely related to the trial 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 2194 patients (1097 per arm) in total (using 90% power, 5% alpha level). Using methods based on survival analysis, the following parameters have been used for the estimation of the sample size:

- *Duration of invasive mechanical ventilation (control arm)*. Based on 133,291 admissions to 209 adult, general critical care units 1 April 2011 – 31 March 2012, the median duration of mechanical ventilation, for this trial was taken as 6 days [29].
- *Minimal clinically important difference:* In the ongoing NIHR HTA MARCH trial [30] and the BREATHE study [25], a clinically important difference of 1 day was considered to be meaningful (as defined by clinical ICU-based investigators and patient and public representatives).
- *Loss-to-follow-up:* Using the ICNARC Quarterly Quality Report Manchester Royal Infirmary, Intensive Care/High Dependency Unit (1 April 2018 to 31 March 2019) based on 2,535 patients the mortality of ventilated patients averaged at 25.6% (ICNARC, Case Mix Programme Report, 2019- obtained from ICNARC). Thus, the sample size has been inflated, to account for this loss to follow-up.
- *Withdrawal rate:* We anticipate a low rate of withdrawal of patients, as the primary outcome will be measured during the hospital stay. In our previous trials, we have consistency observed low rates of withdrawals (e.g. RECOVERY-RS 1% [24] ; BREATHE 0% [25]; HARP-2 0.5% [26]; REST 1.7% [27]). For this trial we have very conservatively assumed a withdrawal rate of 3%.
- From the above, we derive a hazard ratio of 1.2 (i.e., 6/5 days). It is anticipated that the hazards may not be constant over time (as assumed for the exponential distribution) and that the hazards are quite likely to decrease over time (as observed in the BREATHE study [31]). For this reason, the Weibull distribution may be more of an appropriate distribution, as it computes a shape parameter, *p*, which allows for non-constant hazards. Using the data from the BREATHE study [31], we derived the shape parameter, p, as 0.901. The hazard ratio is adjusted for this parameter and the sample size computed using the survival analysis methods.

We will review the sample size parameters with the DMC at the end of the pilot stage, using the observed data.

6.2 Data Analysis

6.2.1 Planned recruitment rate

The project has a total duration of 63 months: set-up (6 months); internal pilot (9 months); recruitment (39 months); final follow-up (6-months) and analysis, reporting and dissemination (3 months).
Recruitment has been modelled on ongoing critical care studies (e.g. MARCH [30] and ADAPT-sepsis [32] trials). Critical care studies typically target recruitment at 1-2 patients/ site/ month. Currently, in the ongoing MARCH trial (commenced recruitment post-pandemic), recruitment (up to April 2023) is at a rate of 1.1-1.2 patients/site/month.

Based on staggered site set-up, we will need a total of 32 sites for the pilot and 44 sites for the main trial. Our recruitment and site set-up projections are shown in Figure 2.

We are cognisant of the challenges of delivering care trials. To optimise recruitment, we will engage closely with medical and nursing research networks across anaesthesia, respiratory medicine, emergency medicine and critical care. This engagement will also help develop research capacity for the future. We also anticipate developing a network of local and regional trial champions to ensure ongoing site engagement and discussion.

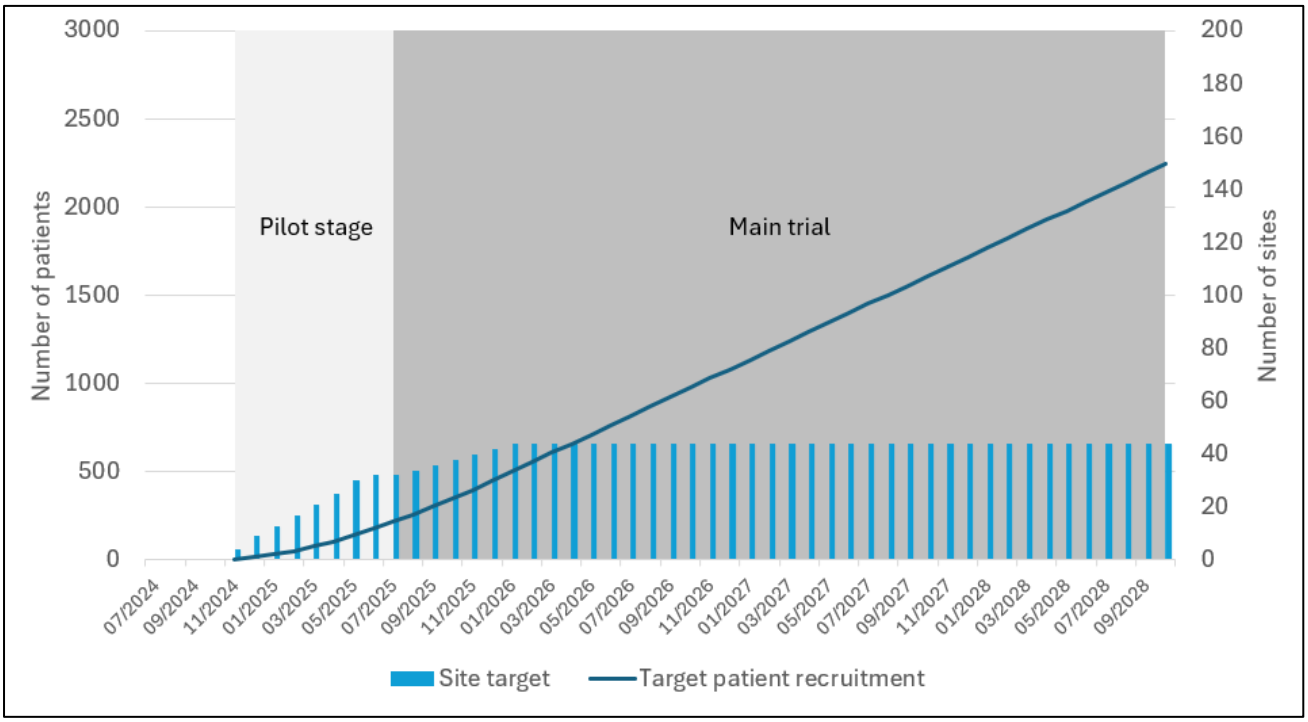


Figure 3 PROTECT Airways Site and Recruitment Projection Chart

6.2.2 Statistical analysis plan

Primary outcome analyses

The 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) [33].

Summary measure and the primary Estimand: The duration of mechanical ventilation (in days) will be summarised using median, interquartile range, mean and standard deviation. The statistical analysis for this outcome will be done using the treatment policy strategy (i.e. intention to treat). Time-to event (survival models) analysis will be used to estimate the treatment effect by summarising hazards odds ratios (and 95% confidence intervals), using both unadjusted and adjusted (for site and adjusting for e.g. age and illness severity (APACHE II)) estimates. Kaplan-Meier plots will be used to display the duration of ventilation accommodating for the censored values. Intercurrent events (ICEs) and strategies for handling ICEs: post-randomisation events that may affect the interpretation of the primary outcome will include: (a) death (ICE 1); (b) cross-over (ICE 2); (b) non-compliance (including discontinuation of treatment) (ICE 3). The ICE 1 will be analysed using a composite strategy and applying competing risk models. Fine and Gray competing risk regression will be used to assess duration of ventilation, in the presence of death[34]. Competing risk regression models address the situation when more than one mutually exclusive endpoint is possible: in this case, successful extubation or death. This analysis provides a sub-distribution hazard ratio (SHR), the magnitude of which is affected by both the time to coming off the ventilator and the probability of death. SHR assesses the association between an intervention and extubation, accounting for the existence of the alternative outcome of death. The ICE 2 and ICE 3 will be analysed using the principal stratum strategy. For the ICE 2, we will

use the inverse probability weighted analysis method to assess the treatment effect, having taken account of these events [35]. We will also assess the impact of crossovers 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 trial 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 [36]. For ICE 3, we will use compliers average causal effect (CACE) analyses [37].

Secondary outcome analysis
In general, continuous baseline and outcome data will be summarised with descriptive statistics, including n, mean, standard deviation, median, interquartile range, and n of missing data. Mixed-effects linear regression models will be used to estimate mean treatment differences (95% CI). Categorical baseline and 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.

6.2.3 Summary of baseline data and flow of patients

Baseline: Baseline data will be collected by the local research delivery team from the electronic medical records, using the time that is closest to the randomisation. These data will include (i) *demography*, admission diagnosis / cause of respiratory failure, medical history including chronic comorbidities; (ii) *entry at hospital*: date and time of hospital admission, date and time of ICU admission, receipt of antibiotics, Acute Physiology and Chronic Health Evaluation II score (APACHE II) (provided either by local participating site or national registry), determinants of the Sequential Organ Failure Assessment (SOFA) score, temperature; (iii) ventilation parameters, arterial blood gas, and clinical laboratory assessments.

6.3 Subgroup analyses

The following subgroups will be considered for this study:

- Baseline APACHE
- Baseline PF ratio
- Pre-existing chronic respiratory condition prior to randomisation
- Neurological/non-neurological injury
- ICU vs other intubation location

These subgroup analyses will be performed on the Intention to Treat (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.

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

To assess for futility, we will carry out a formalised interim analysis during the study, which will be discussed with the DMC. In planning for this interim, we propose that a futility rule be based on conditional power approach. Our primary outcome is based on the duration of ventilation, which will be assessed using survival methods. The methods for futility analyses and determining futility boundaries which account for censored observations are very limited in the literature. Assuming that there is no censoring (and for every patient, an event will be observed), we can use normal approximation methods. This assumption is reasonable in the context of this study. In consultation with the Data Monitoring Committee, we aim to plan for a futility analysis halfway through our trial (i.e., when we have 50% of our sample size). We will use the conventional conditional power boundaries at this interim point, where we will declare for futility if the conditional power is <15%[38]. Assuming our hazard ratio is 1.2 (as stated in

the sample size), this interim analysis and boundaries do not impact on the overall power of 90% for the study. This futility rule will be used as a guidance criterion by the DMC. The decision to stop will be based largely on clinical judgement of all the outcomes, as well as parameters that will drive operational futility (recruitment).

6.5 Health Economic Evaluation

An economic evaluation will be carried out to determine the costs and benefits of advanced airway protection systems compared to widely used conventional endotracheal tubes, with a view to establishing the practice that represents best use of public resources. The text below determines the approach to be followed in planning, conducting and reporting the economic evaluation. Further information can be found in the study's Health Economics Analysis Plan.

Trial perspective: In line with NICE recommendations, the base case analysis will adopt an NHS and Personal Social Services (PSS) perspective[39]. Additional analyses will adopt a wider perspective which will, in addition, explore the impact of the compared options on costs borne by patients.

Analysis of costs: Information on use of health care resources will be collected alongside the proposed trial from clinical records and through resource use questionnaires (RUQs) developed for the purposes of this study. RUQs will be completed by trial participants at two follow-up points: at 2 months (covering health care received between discharge and 2 months) and 6 months (covering health care received between 2 months and 6 months). Relevant data will include: i) costs associated with the purchase and maintenance of the compared advanced airways systems, ii) services used and care provided within the hospital setting (e.g. length of stay in ICU/wards, length of mechanical ventilation, care provided in response to VAP, other pulmonary complications and adverse events etc.), iii) costs due to use of primary care services (GP consultations, appointments with nurses, use of personal and social services) and, iv) relevant private costs incurred by the patient and their family (e.g. private consultations, out-of-pocket payments, loss of income).

Resource use data will be converted into costs using the most up-to-date unit cost values from the latest national sources at the time of analysis [40-42]. Mean per patient cost over 6 months will be calculated and reported for each trial arm. Statistical analysis will be carried out using methods that address the particularities of the distribution of cost data and account for relevant covariates [43]. Unlike existing evidence coming from non-randomised studies [44], this will provide insights into the magnitude of costs incurred in this patient group, as well as key cost drivers, through data collected from a large, randomised trial.

Analysis of outcomes: Health-related quality of life (HRQoL) will be measured using the EQ-5D-5L—a widely-used and recommended instrument—at three time points: baseline, 2 months, and 6 months. As it will not be possible for ICU patients to self-complete the baseline EQ-5D-5L questionnaire, baseline EQ-5D indices will be estimated in line with recommendations, assuming that patients are in a particular state determined with PPI input [45]. EQ-5D-5L responses at 2 and 6 months will be converted to preference-based quality of life indices (utility scores) using the UK tariff recommended at the time of analysis (and using alternative tariffs in sensitivity analyses). Quality-adjusted life years (QALYs) will be calculated using the area under the curve (AUC) method and mean per patient QALYs over 6 months will be reported for each trial arm. Sensitivity analyses will be carried out to account for the possibility that changes in HRQoL realised before the first EQ-5D-5L follow-up assessment point (2 months post randomisation) are missed. This will involve attaching HRQoL indices, identified in communication with clinicians and patient representatives, to specific periods related to health status (e.g. remaining in ICU, patient in ward, patient discharged from hospital) using data collected as part of the trial. A secondary analysis will also explore the additional outcome of VAP avoided—a relevant outcome for patients undergoing intubation [10]—on the basis of VAP incidence data collected alongside this trial.

Analysis of cost-effectiveness: The main analysis will be carried out on the basis of patient-level data obtained within the trial follow-up. Incremental analysis will be undertaken to calculate the difference in costs and the difference in

outcomes (QALYs) associated with each of the compared options. Results will be presented in the form of incremental cost-effectiveness ratios (ICER), reflecting the extra cost for an additional unit of outcome. To account for the inherent uncertainty due to sampling variation, the joint distribution of differences in cost and outcomes (QALYs) will be derived by carrying out a large number of non-parametric bootstrap simulations [46]. In line with recommendations, sensitivity analyses will be carried out to explore the impact of uncertain parameters, methods and assumptions[47].

In addition to the trial-based evaluation, decision modelling will be considered to extend the time horizon beyond the trial's follow up period, should it be found that there are differential costs and outcomes attributable to the compared options that are likely to accrue beyond the trial follow up (6 months). In this case, a decision analytic model will be built to serve as a framework for quantifying long-term costs and outcomes related to airway management and to form a basis for exploring the expected value of collecting further information [48].

Presentation of results: The main results of the economic evaluation will be expressed in terms of additional costs (or cost-savings) per QALY gained. Results of the secondary outcome of VAP avoided will also be presented in terms of additional costs per VAP avoided. Results will be depicted on a cost-effectiveness plane, will be plotted as cost-effectiveness acceptability curves (CEACs) and, where applicable, will be discussed with reference to the willingness to pay threshold (additional cost per QALY gained) specified by NICE (ref 1).

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will act as trial sponsor. The trial will be conducted in accordance with Warwick Standard Operating Procedures (SOPs).

7.2 Ethical approval

We will request ethical approval for this trial by a NHS research ethics committee, flagged for studies involving adults lacking capacity. This trial will be submitted for review via a substantial amendment on a previously submitted IRAS application for the confederation for respiratory and critical care trials (CoReCCT).

Any protocol amendments will be dealt with in accordance with Warwick SOPs.

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.

7.3 Trial Registration

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

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

The management of non-compliances will be informed by Warwick SOP 31, as detailed in the CoReCCT master protocol section 9.5. The PROTECT Airways TMG will be responsible for oversight of protocol non-compliances.

Protocol non-compliances (and actions taken to prevent recurrence) will be recorded in the case report form and the WCTU non-compliance log as per Warwick SOP 31 Handling non-compliances, research misconduct and serious breaches of GCP and/or trial protocol.

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 (NIHR156500)

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 central and remote monitoring, except where on-site monitoring is deemed to be required.

8.1 Training

Refer to section 2.5.

8.2 Visits to Sites

As per the WCTU monitoring plan, the trial manager/coordinator 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 video conference, telephone and email contact, the trial team may, where needed or requested, visit participating sites to meet with the research team, 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)

In November 2021, former patients from the Wythenshawe Hospital Intensive Care Unit were invited to discuss this trial as part of the Patient and Public Involvement and Engagement activities of the University of Manchester Academic Critical Care Research Group. The patients had all been admitted during the COVID-19 pandemic and had suffered from pneumonia, requiring invasive ventilation via a tracheal tube. Ten former patients agreed to participate in an on-line meeting, preceded by a short questionnaire. We reviewed the problems that ventilator-associated pneumonia (VAP) can cause. All patients agreed VAP was a significant complication, and the burdens and risks associated with additional antibiotic treatment, prolonged ICU stay, ventilation time and sedation can have a negative impact on the patient experience. One patient recalled being, “half sedated and on a ventilator,” as a, “living hell.” We outlined the rationale behind the PneuX tracheal tube and why we thought it was important to trial the potential of this device in reducing VAP. All our PPI group felt very strongly that efforts to reduce VAP and the associated burdens of additional treatment should be encouraged and that studying the potential of the PneuX to reduce VAP was a worthwhile endeavour. We outlined how we planned to approach patients and their families, and the consent process that we have described in this application. We explained the planned interventions, data collection and end points for the study. All of our PPI group said that they would have been happy to participate in

our trial and thought that their relatives would have agreed for them to participate if they were not able to make that decision themselves.

We will develop a trial PPI group, which will also meet the objectives of the NIHR INCLUDE initiative to progress detailed trial design and its governance. Two members of the group will join the Trial Steering Committee as full members, and regular reports will be provided to the whole group throughout the study, seeking the benefit of their experience and advice as the research proceeds. Alongside PPI co-applicants who will sit as full members of the TMG, we will convene a wider PPI panel. We will identify members through co-applicant networks, social media, and advertisements, ensuring panel members are representative of the communities that we serve across both personal characteristics (e.g. age/ ethnicity) and healthcare experiences. The panel will meet twice-yearly throughout the trial to provide advice on key aspects of trial design, delivery, and reporting, including development of patient-facing materials, the trial recruitment approach, and how we should communicate our progress and results to the communities that we serve.

We will capture, evaluate, and report the impact of PPI activity through maintaining a log of PPI activity and input throughout the project. A summary of patient and public involvement using the GRIPP2 framework [51] will be included in any final project report. In patient and clinician facing materials summarising the results, we will include a summary of how PPI members have been involved in the project.

Financial support for PPI work will be reimbursed in accordance with INVOLVE guidance.

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).[52] 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 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.

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