GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

NHS
Health Research Authority

VAP-X

Ventilator Aspiration with PneuX

Study Protocol

FULL TITLE: A single centre, open-label, feasibility randomised controlled trial to evaluate gastric microaspiration in critically ill patients intubated using the Venner PneuX system compared to standard of care using Pepsin biomarker.

SHORT TITLE: Ventilator Aspiration with PneuX (VAP-X)

Version 2.0 (23/06/22)

CRITICAL CARE SERVICES CARDIFF

CARDIFF
CRITICAL CARE
GOFAL CRITIGOL
CAERDYDD

Cedar
Healthcare Technology Research Centre

This protocol has regard for the HRA guidance and order of content

Administrative information

Full title of the trial	A single centre, open-label, feasibility randomised controlled trial to evaluate gastric microaspiration in critically ill patients intubated using the Venner PneuX system compared to standard of care using pepsin biomarker (VAP-X).
Short trial title / acronym	Ventilator Aspiration with PneuX (VAP-X)
Protocol version number and date	Version 2.0 (23/06/22)
Sponsor	Cardiff & Vale University Health Board
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REC reference	22/WA/0163

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Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in Good Clinical Practice guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:
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Date:
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Name (please print):
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Position:
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Chief Investigator:

Signature:
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Date:
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Name: (please print):
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Funder(s)	Internal PI account. Devices and consumables provided free of charge by manufacturer.
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List of abbreviations

AE	Adverse Event
BALF	Bronchoalveolar lavage fluid
C&V UHB	Cardiff and Vale University Health Board
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CPIS	Clinical pulmonary infection score
CRF	Case Report Form
ETT	Endotracheal tube
GCP	Good Clinical Practise
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GP	General Practitioner
HCRW	Health Care Research Wales
HME	Heat and Moisture Exchanger
HRA	Health Research Authority
HVLP	High-volume low pressure
ICU	Intensive Care Unit
IFU	Instructions For Use
ISF	Investigator Site File
LOS	Length of Stay
LVLP	Low-volume low pressure
MHRA	Medicines & Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ODP	Operating Department Practitioner
PI	Principal Investigator
PID	Patient identifiable data
PVC	Polyvinyl Chloride
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDR	Source data verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
TT	Tracheal Tube
UHW	University Hospital of Wales
VAP	Ventilator Associated Pneumonia

Trial summary

Trial Title	A single centre, open-label, feasibility randomised controlled trial to evaluate gastric microaspiration in critically ill patients intubated using the Venner PneuX system compared to standard of care using pepsin biomarker.	
Internal ref. no. (or short title)	Ventilator Aspiration with PneuX (VAP-X)	
Clinical Phase	Feasibility study on CE marked medical device	
Trial Design	A single centre, open-label, feasibility randomised controlled trial	
Trial Participants	Critically ill, hospitalised patients who require mechanical (artificial) ventilation via an orally inserted endotracheal tube.	
Planned Sample Size	25 in each group = 50 total	
Treatment duration	Length of time that the patient has the tube in place (typically 4-7 days, usually <14 days).	
Follow up duration	28 days	
Planned Trial Period	Recruitment: July 2022 – July 2023 Follow-up: Aug 2023 Analysis and reporting: Aug 2023 – Dec 2023	
Objectives		**Outcome Measures**
Main outcome measures relating to feasibility (no primary)		
Feasibility of recruitment		Ability to achieve recruitment rate of 5-6 patients per month (number screened, consented, and randomised will be logged; reasons for non-consent or withdrawal will be recorded).
Feasibility of delivering the study intervention (Venner PneuX) including device-related complications		Issues with delivering intervention will be recorded including protocol deviation and device-related complications.
Acceptability of study interventions and sampling amongst staff.		Short qualitative interviews and/or surveys will be carried out with study staff to determine acceptability of study interventions, including barriers and facilitators to delivering the study intervention.
Feasibility of pepsin sampling procedure using Peptest		Issues with pepsin sampling will be recorded (including repeated or failed pepsin sampling, problems with logistics)
Establish the rate of positive pepsin samples in both arms of the study using Peptest		Number of pepsin-positive samples
Establish the mean volume of sub-glottic aspirates using the control and intervention groups		Volume of sub-glottic secretions
Secondary outcomes		
Establish the rate of tracheobronchial colonization		Tracheobronchial colonization (no. colony forming units/ml)
Establish rates of Ventilator Associated Pneumonia (VAP)		No. patients with VAP diagnosis using CPIS scoring criteria

Assess mean time spent on the ventilator	Duration of mechanical ventilation in ICU (from time/date of intubation to time/date of extubation)
Assess both hospital and ICU length of stay (LOS)	Length of stay in ICU and length of stay in hospital
Assess in-hospital mortality rates/ All-cause mortality	Number of patients who die in hospital
Assess cuff pressure	Cuff pressures in both arms of study (measured 12 hourly)
Intervention	Venner PneuX™ Endotracheal Tube (ETT) (manufacturer by Venner Medical; distributed by Qualitech Healthcare)
Statistical Methodology and Analysis	Descriptive statistics of numerical outcome data including measurements of precision will be reported. The study is to evaluate if a larger, adequately powered randomised controlled study can be conducted to compare outcomes between groups.

Funding and support in kind

Funder	**Financial and non-financial support given**
Chief Investigator (Pathway to Portfolio grant, plus PI trading account)	Financial
Device distributor (Qualitech Healthcare Ltd)	Provision of PneuX device and consumables free of charge.

Role of trial sponsor and funder

The study sponsor is Cardiff and Vale University Health Board (C&V UHB) who will also host the study within the single site at University Hospital of Wales (Cardiff), fulfilling this role according to the principles of Good Clinical Practice (GCP). Cardiff and Vale UHB will retain all Sponsor responsibilities, but many of these responsibilities will be delegated as per study agreements and delegation logs.

Dr Matt Wise (MW) is an experienced Chief Investigator (CI) who will take overall responsibility for the study.

Dr Daniel Law (DL) is the local Principal Investigator (PI) and, together with Jade Cole (JC, an experienced Critical Care Research Nurse), will be responsible for managing the day-to-day clinical work including patient recruitment, medical history taking and study eligibility assessment, patient consent, data recording, adverse event (AE) management and recording.

Dr Judith White (JW) (Trial Manager, Cedar, Cardiff & Vale UHB) will be responsible for management of the study on a day-to-day basis including governance, documentation, data collection and monitoring, data analysis, report writing, and financial management. Dr Rhys Morris (RM) (Cedar, Cardiff & Vale UHB) will have overall responsibility for Cedar's component of the study.

If any of the study team leave, they will be replaced with a new study team member of suitable grade and experience. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, and any other publications arising from the study.

The study is funded through the CI's internal research funding account, including funds from a successful Pathway to Portfolio bid (from Health & Care Research Wales). PneuX devices will be supplied free of charge by the device distributor, Qualitech Healthcare Ltd. The study will be run independently of the device manufacturer.

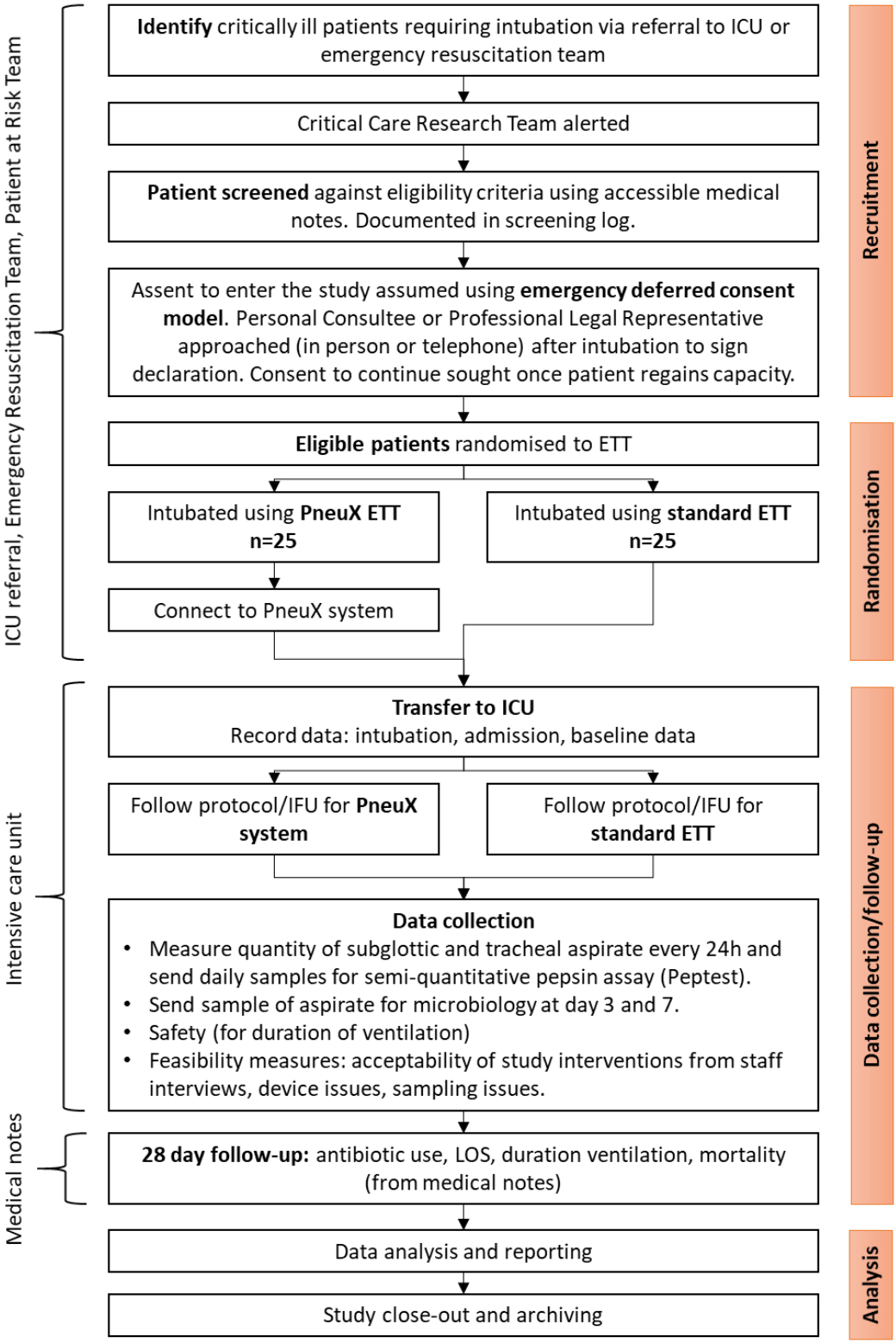
Trial Management Committees

The nature of this feasibility study and the low risk posed because this is a study of a CE marked medical device means that neither a Trial Steering Committees or Data Monitoring Committees will be appointed. A Trial Management Group (TMG) comprising the CI, PI, research nurse, and trial coordinator, will meet every 4-6 weeks to ensure all practical details of the trial are progressing and working well and everyone within the trial understands them.

Protocol contributors

The study has been designed by MW, DL, JW, JC, MB, and RM. All are employed by Cardiff and Vale UHB and work at the University Hospital of Wales, Cardiff.

Trial flow chart



ETT: endotracheal tube, ICU: intensive care unit; LOS: length of stay

1. Background

1.1. The clinical problem

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection among patients requiring intubation and mechanical ventilation in an intensive care unit (Wicky et al. 2022). It is defined as a pneumonia that develops 48 hours or more after intubation with an endotracheal or tracheostomy tube. VAP is associated with an increase in length of ventilator time, length of critical care, hospital stay, morbidity, mortality and cost (Bekaert et al. 2011; Melsen et al. 2013; Safdar et al. 2005; Nseir et al. 2005; Rello et al. 1996). However there remains no gold standard for diagnosing VAP in mechanically ventilated patients, and definite diagnosis relies upon clinical signs, symptoms, radiological and microbiological confirmation. Consequently, there is an absence of reliable epidemiological data on the incidence and mortality of VAP in the UK, but estimates for critical care environments range from 10-20%; causing an increase in hospital length of stay by an average of 4-9 days (Chastre and Fagon 2002; Morris et al. 2011). Internationally, rates of VAP also vary widely in the literature from 9.3% (Rello et al. 2002) to 20.3% in a recent meta-analysis of 6284 patient's in 24 trials (Melsen et al. 2013). In England alone, between 3,000 and 6,000 people die from VAP each year according to NHS England (NHS England, 2016).

1.2. Pathogenesis of VAP

Patients that require mechanical ventilation to help them breathe are fitted with a conventional endotracheal tube (ETT) into their mouth, or through an incision in their neck (tracheostomy). The pathogenesis of VAP is linked to the presence of the ETT in the oropharynx. This results in a loss of both the natural defence mechanisms of the cough reflex and natural anatomical barriers (i.e. the glottis and larynx); it is further compounded by the placement of foreign material within the respiratory tract (Young and Doyle 2012). As a result, oropharyngeal secretions become excessive, and combined with gastric contents refluxed into the oropharynx, causes a pool of secretions above the ETT cuff. Microfolds developing in the inelastic inflated cuff can allow the microaspiration of these bacteria-laden subglottic secretions past the cuff and into the lower respiratory tract. This is the first route of entry of bacteria into the lower respiratory tract in patients receiving mechanical ventilation, and is diagnosed in 50-75% of these patients (Nseir et al. 2011; Metheny 2006). High bacterial load combined with chemical and enzymatic injury from gastric secretions can overwhelm pulmonary defences and become a key factor in the pathogenesis of VAP (Metheny 2006). This microaspiration of contaminated secretions is *sine qua non* of VAP, and remains a limitation of the existing standard ETTs used currently. As a result, this has prompted a considerable interest in the development of an ETT that can retain adequate cuff pressure against the tracheal wall, thus preventing microaspiration (Zolfaghari and Wyncoll 2011; Metheny 2006).

1.3. Standard endotracheal tubes

Conventionally, ETTs have high-volume, low pressure (HVLP) cuffs and when inflated manually, have a diameter larger than the adult trachea which is designed to prevent tracheal mucosal injury by allowing the pressure within the cuff to be equal to the tracheal wall pressure (Young et al. 2006). Therefore, the cuff is only partially inflated and the excess material within the cuff causes material folds and channels to develop. These channels facilitate aspiration of subglottic secretions, and contribute to an increase in VAP.

The pooling of subglottic secretions requires continuous suction with standard ETTs, which can produce ischaemic injury to tracheal mucosa, and so intermittent drainage through ports in the ETT is more commonly adopted nowadays. However, these ports can become blocked by suctioned tracheal mucosa.

1.4. The Venner PneuX system

The Venner PneuX is a single use ETT intended for patients undergoing tracheal intubation during routine anaesthesia or over extended periods (not more than 30 days), and for the evacuation or drainage of secretions from the subglottic space. The system comprises three components: an ETT tube, a tracheal seal monitor, and a 2 m extension tube. The PneuX device has two unique features; a boat tip with murphy eye to aid the passage of the ETT through the larynx to the trachea to reduce the risk of airway occlusion, and an integrated bite block to resist damage from biting. In addition, the PneuX device also combines common features of ETTs designed to prevent the microaspiration of secretions; an electronic automated tracheal seal monitor to maintain the intracuff/tracheal wall seal pressure; and a low-volume, low-pressure (LVLP) cuff made from a soft silicone material. The cuff inflates automatically to a 30 cm H_20 pressure, uniformly and circumferentially, providing a continuously watertight seal between the cuff and tracheal mucosa, and thus preventing the aspiration of air and/or fluid around the ETT. This pressure reduces the mucosal injury caused by HVLP cuffs whilst preventing the formation of micro-folds. With such a tight seal, PneuX is said to be safer in allowing subglottic secretions to build up above the cuff and perform intermittent subglottic secretion drainage (Doyle 2011).

To try and circumvent the issue of subglottic port blockage, the PneuX device has three small circumferential subglottic secretion drainage and irrigation ports above the proximal end of the cuff. These ports enable intermittent subglottic drainage and irrigation to be done through the two unoccluded ports; should one of them become obstructed by suctioned tracheal mucosa. This involves the use of a cleaning fluid (usually saline) to wash out the space above the cuff and oropharyngeal space.

In a randomised controlled trial, patients using PneuX for ventilation had a lower incidence of colonization than those using standard ETT, however there was no difference in the type of bacterial colonization (Senanayake et al. 2017).

1.5. Clinical and cost-effectiveness by NICE

NICE reviewed the clinical and cost effectiveness of PneuX in 2020 (MTG48 PneuX to prevent ventilator-associated pneumonia). The clinical evidence indicated that PneuX decreases VAP incidence compared with endotracheal tubes without subglottic drainage, but does not reduce ICU length of stay or mortality. The clinical evidence comprised 3 studies including a total of 341 adults in cardiac or general intensive care. Only one of these studies was a randomised controlled trial comparing PneuX with a standard endotracheal tube (ETT) without drainage in high-risk patients (over 70 or with a left ventricular ejection from or under 50%, or both) (Gopal et al. 2015). Gopal demonstrated a significantly lower incidence of VAP in the PneuX groups than the standard care group (ETT without subglottic secretion drainage): 10.8% vs. 21% (P=0.03) with a relative risk of 0.52. There was no significant difference in length of ICU stay (PneuX: 2 days, Standard care: 1.5 days [p = 0.2]), and in-hospital mortality (PneuX survival rate: 98% Vs. 99% for standard endotracheal tube [p = 0.2].

The other studies were non-comparative and are more generalisable to people needing ventilation with a wider range of health conditions. (Smith, Khan, and Gratrix 2014; Nct, Shenfeld, and Jacob 2007; Hodd and

Young 2009; Doyle 2011). The rates of VAP were very low in these studies, however a lack of a control group and differing definitions for diagnosing VAP across the studies makes it difficult to draw any meaningful conclusions about the efficacy of PneuX in the treatment of VAP.

In a meta-analysis of 20 RCTs, including 3544 patients, subglottic secretion drainage (including devices other than PneuX) was associated with a significant reduction of VAP incidence compared with non-subglottic drainage (in four high quality trials; the relative risk was 0.54 (95% CI 0.40-0.74, p<0.00001) (Mao et al. 2016).

NICE also carried out a review of the economic evidence in 2020. The company model cost analysis (by Venner) found that PneuX was cost saving when compared to endotracheal tubes without subglottic secretion drainage. The results indicated a cost saving of £738 per patient after cardiac surgery when PneuX is used instead of an ETT without subglottic drainage. This saving was from an absolute reduction in the risk of VAP of around 10% for PneuX and the associated reduction in resource consumption based on avoided costs of around £9,000 per VAP prevented. The cost of a PneuX device was £150 vs. £5 for ETT without drainage, which is a modest cost compared to the above cost of treating VAP as cost savings for PneuX are driven by a reduction in VAP, which may cause costly increases in length of ICU stay.

1.5.1. NICE recommendations

NICE produced a series of research recommendations during its review of the PneuX device in 2020. They are as follows:

- PneuX shows promise for preventing ventilator-associated pneumonia in adults. However, there is currently not enough good-quality evidence to support the case for routine adoption in the NHS.
- Research is recommended to address uncertainties about the clinical benefits of using PneuX. This research should:
    - assess whether PneuX reduces the incidence of ventilator-associated pneumonia in all people needing ventilation
    - compare PneuX with current NHS clinical practice, that is, the use of endotracheal tubes with subglottic drainage
    - evaluate PneuX within the care bundle for ventilator-associated pneumonia prevention
    - be clear about the criteria used to diagnose ventilator-associated pneumonia in the study.

1.6. Pepsin as a biomarker of microaspiration

Several biomarkers of microaspiration have been used in the literature concerning VAPs, but it is pepsin that is the most validated as an accurate marker by several animal and human studies. Pepsin is synthesised from its inactive precursor pepsinogen, and is secreted by the chief cells in the stomach following vagal or gastrin stimulation (Garland et al. 2014). As pepsin is not normally present in the respiratory tract, its presence is a reliable marker of gastric-to-pulmonary aspiration, and as a surrogate to evaluate the efficacy of an endotracheal tube in preventing VAP (Dewavrin et al. 2014). Unlike other biomarkers of aspiration, the analysis of pepsin from tracheal secretions is rapid, easy to perform and cheap, and is therefore the biomarker of choice used in this feasibility study (Metheny 2006; Metheny et al. 2004; Bohman et al. 2018; Jaillette et al. 2013).

1.7. Pepsin analysis

To detect pepsin in the subglottic aspirate samples in this feasibility study, Peptest (RD Biomed) will be used. Peptest is a CE marked, non-invasive, single-use, *in-vitro* diagnostic medical device for detecting pepsin in saliva or sputum. The device is a lateral flow device containing two types of unique monoclonal antibodies against pepsin on a nitrocellulose membrane in a plastic case. On application of a sample, one of the antibodies tagged with a colorimetric marker becomes soluble and the second antibody is immobilised at the 'T band' line in the viewing window. Any pepsin in the sample is bound at the test line by the two antibodies, and if present at a concentration of 16 ng/ml or more, a coloured line is seen within 15 minutes, giving a qualitative result. Furthermore, the intensity of the T band is directly proportional to the pepsin quantity and can be quantified using a PepCube reader (RD Biomed). This is a portable electronic handheld lateral flow device reader using colorimetric analysis based on reflectance measurements to capture the optical density of the 'T band', giving a semi-quantitative level down to a detection limit of 25 ng/ml according to the manufacturer. There is an absence of agreed normal physiological range for pepsin levels in saliva, however published studies have used different pepsin concentrations ranging from 16 ng/ml to 25 ng/ml as a cut-off value to indicate a clinically significant concentration of pepsin in saliva – both of which are detectable by the Peptest lateral flow device.

2. Rationale

NICE have produced guidance on PneuX to prevent VAP. The committee stated that PneuX shows promise for preventing VAP in adults, however there is currently not enough good-quality clinical evidence to support the case for routine adoption in the NHS. NICE has therefore recommended that further research should be done to address several outstanding uncertainties surrounding the technology and its place in clinical practice.

We propose a full randomised controlled trial (RCT) to address the question of whether the PneuX device reduces the microaspiration of pepsin, and the impact of several secondary outcomes, including VAP rate. Before a full-scale RCT can be done, **we propose this feasibility study using 50 patients to be undertaken**. This will help to identify the intervention fidelity – the extent of which the intervention can be delivered as intended and will help to reveal any problems or obstacles related to implementation of the study. Any problems identified can then be remedied to ensure methodological rigour and scientific validity in the full-scale RCT. The feasibility study will establish the acceptability of the randomisation procedure by clinicians. Similarly, the willingness of patients to participate in the study and the appetite for clinicians to recruit participants will need to be ascertained.

2.1. Assessment and management of risk

The Venner PneuX™ Endotracheal Tube (ETT) single use device, is intended for patients undergoing tracheal intubation during routine anaesthesia or over extended periods (not more than 30 days) and for the evacuation or drainage of secretions from the subglottic space. The PneuX ETT is a Class IIa CE marked medical device. In this study the device will be used as per its intended purpose, as described in the Instructions for Use (IFU). As such the study is on a CE marked medical device used as per its intended purpose (described in the IFU). As such this trial is categorised as: Type A = No higher than the risk of standard medical care.

3. Objectives and outcome measures/endpoints

3.1. Hypothesis

This is a feasibility RCT and as such will not be testing a hypothesis.

3.2. Aims

The study aims to assess the feasibility of conducting an RCT to compare the PneuX ETT with standard care in hospitalised patients requiring mechanical ventilation. The study will investigate several feasibility measures including recruitment, delivery of the intervention (including device-related adverse events), acceptability and adherence to the intervention and sampling, use of Peptest to measure microaspiration events, rate of pepsin positive samples, volume of sub-glottic aspirate, rate of VAP, length of ICU and hospital stay, demonstrate the validity of study documentation and provide preliminary data for 50 patients. The data will inform the pilot and main phase of the study.

3.3. Main objectives

1. Feasibility of recruitment
2. Feasibility of delivering the study intervention (Venner PneuX) including device-related complications
3. Acceptability of study interventions and sampling amongst staff
4. Feasibility of pepsin sampling procedure for use in Peptest
5. Establish the rate of positive pepsin samples in both arms of the study using Peptest
6. Establish the mean volume of sub-glottic aspirates using the control and intervention groups

3.4. Secondary objectives

1. Establish the rate of tracheobronchial colonization
2. Assess antibiotic usage and duration
3. Establish rates of Ventilator Associated Pneumonia (VAP)
4. Assess mean time spent on the ventilator
5. Assess both hospital and ICU length of stay (LOS)
6. Assess in-hospital mortality rates/ All-cause mortality
7. Assess compliance with measuring and documenting cuff pressure

3.5. Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Main outcome measures relating to feasibility (no primary)		
Feasibility of recruitment	Ability to achieve recruitment rate of 5-6 patients per month (number screened, consented, and randomised will be logged; reasons for non-consent or withdrawal will be recorded)	Continuously over duration of study
Feasibility of delivering the study intervention (Venner PneuX) including device-related complications	Issues with delivering intervention will be recorded including protocol deviation and device-related complications.	Continuously over duration of study

Acceptability of study interventions and sampling amongst staff.	Short qualitative interviews and/or surveys will be carries out with study staff to determine acceptability of study interventions, including barriers and facilitators to delivering the study intervention.	Staff will be interviewed or surveyed at study end
Feasibility of pepsin sampling procedure for use in Peptest	Issues with pepsin sampling will be recorded (including repeated or failed pepsin sampling, problems with logistics)	Continuously over duration of study
Establish the rate of positive pepsin samples in both arms of the study using Peptest	Number of pepsin-positive samples	Continuously over duration of study
Establish the mean volume of sub-glottic aspirates using the control and intervention groups	Volume of sub-glottic secretions	Continuously over duration of study
Secondary outcomes		
Establish the rate of tracheobronchial colonization	Tracheobronchial colonization (no. colony forming units/ml)	Samples taken on day 3 and day 7 for cultures
Antibiotic use	Antibiotic prescribed, indication for use, number of days administered	Continuously over duration of study
Establish rates of Ventilator Associated Pneumonia (VAP)	Number of patients with VAP diagnosis. Clinical Pulmonary Infection Score (CPIS) used to predict VAP. CPIS >6 will be used to define confirmation of VAP.	Measured daily after 48 hours of intubation
Assess mean time spent on the ventilator	Days spent with mechanical ventilation in ICU (from time/date of intubation to time/date of extubation or 28 days)	Continuously over duration of study
Assess both hospital and ICU length of stay (LOS)	Length of stay in ICU and length of stay in hospital measured in days from ventilation	Continuously over duration of study
Assess in-hospital mortality rates/ All-cause mortality	Number of patients who die in hospital	Death defined up to day 28
Assess compliance with measuring and documenting cuff pressure	Documentation of cuff pressures in both arms of study. Cuff pressure in standard care will be measured every 12 hours. Assessment of intervention arm will have documentation that pressure has been maintained hourly either via the continual cuff pressure monitor or manually.	Duration that patient is intubated and mechanically ventilated

4. Trial design

This is a single centre, open-label, feasibility randomised controlled trial. Patients will be randomised in equal proportions into one of 2 arms: to be intubated using a Venner PneuX Endotracheal Tube (ETT) or using the standard tube, e.g. Covidien Taperguard. For this feasibility study, a total of 50 patients will be randomised into

two groups (25 in each). All patients will be recruited at a single site (University Hospital of Wales, part of Cardiff & Vale UHB).

This feasibility study will assess various aspects relating to the feasibility of a larger RCT which would investigate whether the PneuX ETT reduces the incidence of microaspiration events in ventilated patients. The feasibility study will aim to highlight the most appropriate outcomes to be measured in a main RCT, particularly looking at the role of Pepsin detection in subglottic-aspirate samples.

Coordination of the trial will be carried out by a trial manager from Cedar, Cardiff & Vale UHB.

4.1. Trial setting

This is a single centre trial at the University Hospital of Wales (UHW), Intensive Care Unit (ICU). UHW is a tertiary referral centre hospital and has a 1000 bed capacity. The ICU is funded for 36 adult critical care beds and accepts patients requiring level 2 and level 3 care. This selected site has the capacity to manage level three care, with a patient population who are likely to require prolonged intubation and ventilation.

The ICU has access to a specialised Critical Care Research Team who provide 24-hour care for research participants in the ICU. The team facilitate 24-hour recruitment into critical care research studies whilst also providing full time advice and management for research participants. At UHW the ICU Consultants provide 24-hour residential cover, whereby participants are under the constant care and supervision of a fully qualified Critical Care specialist consultant.

At UHW the pathways of recruitment will be via the Accident and Emergency Department, deteriorating patients from the hospital wards, or deteriorating level 2 patients within ICU.

5. Participant eligibility criteria

5.1. Inclusion criteria

- >18 years old (no upper age)
- Patient required endotracheal intubation
- Expect to remain intubated for 24 hours post randomisation

5.2. Exclusion criteria

- The person intubating the patient assesses that the patient has already aspirated.
- GCS 7 or less on presentation to hospital
- Patient is pregnant
- Patient has tracheostomy
- Patient has gastrectomy
- Patients who have been intubated prior to arrival at hospital
- Patients who are already endotracheally intubated and require a tube change.

6. Trial procedures

6.1. Recruitment

The patient population for this study are those who are experiencing critical illness requiring intubation and ventilatory support. Patients meeting these criteria will be level 2 patients that are already being cared for within the ICU or patients on the wards who are referred to the ICU team via formal referral from the medics responsible for the patients' care, the Emergency Resuscitation Team, or the Patient at Risk Team (PART). At the point that a decision to intubate the patient is made via these teams, an intubation team will be called and the patient will become eligible for screening against the study inclusion and exclusion criteria.

6.1.1. Participant identification

Identification of patients will be via intubation teams. Each intubation team called to intubate patients on the wards will include a trained airway practitioner who will intubate the patient and an Operating Department Practitioner (ODP) who will assist. Within the ICU the intubation team will consist of trained airway practitioners who will intubate the patient, with medical and nursing staff who will assist. Whilst these staff may not have received Research Good Clinical Practice (GCP) training, trained research staff will have ensured that:

- All intubation teams likely to encounter potential participants are aware of the study, its inclusion criteria and protocols
- All of the medical and nursing staff in the ICU are aware of the study, its inclusion criteria and protocols
- All relevant departments are aware of the study, its inclusion criteria and protocols, through presentations at departmental meetings
- All relevant materials to conduct the study will be available prior to the intubation. Specifically, the intubation teams will have a screening checklist, randomisation envelope, and endotracheal tubes for each arm of the study in a variety of various sizes ready.
- For patients being intubated on the wards the study materials will be transported to the patient in the emergency airway bags that the intubation team take to each intubation as standard practice. For patients in the ICU the study materials will be kept with the ‘Difficult Airway Trolley’ that is made available for all intubations.

6.1.2. Screening

The patient will be screened using the predefined study inclusion and exclusion criteria. Screening will be carried out by the airway practitioner intubating the patient, ICU medical staff who are part of the intubation team, ODP’s, or critical care research specialist nurses, who are all part of the clinical care team. Screening of participants will take place at the bedside of patients requiring intubation for critical illness. This patient population are likely of low consciousness or physiologically obtunded. Therefore, information will be gathered primarily from accessible patient medical notes along with any relevant verbal history from the doctors and nurses responsible for the patients’ clinical care.

Once the patient has been screened using the inclusion and exclusion criteria, eligibility for inclusion into the study will be confirmed by the airway practitioner intubating the patient, ICU medical staff who are part of the intubation team, ODPs, or critical care research specialist nurses. This information will be collected on a data collection document that will be kept with the Standard Operating Procedure Checklist that is used during an intubation procedure and then returned to the critical care research team. Training specific to this study will be provided to those who will be delegated the task of screening and confirming eligibility.

6.1.3. Payment

No payments will be offered to trial participants.

6.1.4. Consent

Patients who require rapid intubation due to the nature of their critical illness are likely to be of a low consciousness level or significantly physiologically obtunded and as such there will not be time to obtain informed consent from patients. Therefore, an emergency deferred consent model will be used for this study. This complies with the legal requirements for obtaining consent in patients without capacity in England and Wales (Mental Capacity Act 2005) and GCP guidelines.

The two ETTs that are being used in this study are CE marked medical devices used within their intended purpose so randomisation will occur following confirmation of eligibility for inclusion into the study. The allocated ETT will be sited. Advice will then be sought from a Personal Consultee, or if they are unavailable, a Nominated Consultee, as to what they believe the patients' wishes would be with regards to ongoing study participation.

6.1.5. Personal Consultee

A researcher from the critical care research team will seek advice from a Personal Consultee (who may be a relative, partner or friend of the participant). This should normally take place during a face-to-face meeting, however due to ongoing visiting restrictions on the ICU due to the Covid-19 pandemic, this will frequently be done via telephone. The researcher will describe the trial to the Personal Consultee and provide them with a Personal Consultee Information Sheet and Personal Consultee Declaration Form via post.

The researcher will confirm that the Personal Consultee understands what trial participation involves for the patient and answer any questions that they have. They will give the Personal Consultee sufficient time to decide as to what they believe the patients' wishes would be with regards to continuing to participate in the study. If the Personal Consultee believes that the patient would not object to participating in the study, the researcher will invite the Personal Consultee to sign the Consultee Declaration Form which they will then countersign. A copy of this signed form will be placed in the patient's medical notes, a copy given to the Personal Consultee, and a copy filed in the study site file. If the Personal Consultee is not available at site, the researcher may contact the Personal Consultee by telephone and seek verbal agreement. This verbal agreement will be recorded in the Personal Consultee Telephone Agreement Form. The Personal Consultee Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone consultation. This witness may be another member of the critical care research team or part of ICU medical or nursing staff. A copy of the signed Consultee Telephone Agreement Form should be placed in the patient's medical notes, a copy posted to the Personal Consultee (with the Personal Consultee Information Sheet) and a copy placed in the study site file. If the patient dies or does not regain capacity, the Personal Consultee Declaration will remain as the primary form of consent for the participant.

6.1.6. Approval by a Nominated Consultee

If there is no Personal Consultee, or attempts to meet with them have failed, consent to continue participation in the study will be sought from a Nominated Consultee. This will be a medically qualified doctor who may be involved in the patients' care but is not connected with the conduct of the study in any other way. The Nominated Consultee will be informed about the trial by a member of the critical care research team and given a copy of the Nominated Consultee Information Sheet. They will be asked to advise the critical care research

team as to whether they believe the patient would decline to participate in the study if they had capacity. If the Nominated Consultee decides that the patient may remain in the study the researcher will ask them to sign the Nominated Consultee Declaration Form which they will then countersign. A copy of the signed Nominated Consultee Declaration Form should be placed in the patient's medical notes, a copy given to the Nominated Consultee and a copy filed in the study site file. If a Personal Consultee is subsequently identified following the Nominated Consultee agreeing to ongoing study participation, and before the patient regains capacity, the critical care research team will attempt to approach them for a discussion regarding the patients' ongoing study participation. The process for obtaining consent from a Personal Consultee will be followed and if the Personal Consultee agrees to the patients ongoing study participation, this will become the primary form of consent for the patient. If a Personal Consultee remains unavailable, the patient dies or does not regain capacity, the Nominated Consultee Consent will remain as the primary form of consent for the participant.

6.1.7. Patient consent to continue

As per the Mental Capacity Act (2005) and GCP guidelines patients' will be regularly monitored by the critical care research team to assess when they have regained sufficient capacity to provide their consent to study participation. When the patient is ready a member of the critical care research team will discuss the study with the patient and provide them with the Patient Information Sheet. The researcher will confirm that the patient understands what trial participation involves and answer any questions that they have. Sufficient time will be given to enable them to decide if they want to participate in the study. If they are happy to continue participation on the study the researcher will invite them to sign the Patient Consent Form which they will then countersign. A copy of this signed form will be placed in the patient's medical notes, a copy given to the patient, and a copy filed in the study site file. If the participant declines on-going participation in the study, no further follow-up will take place. If the patient does not regain capacity or dies, the consent from the Personal Consultee or Nominated Consultee will remain as the primary form of consent for the participant.

6.1.8. Additional consent provisions

No data or biological specimens will be acquired, transferred or stored during the trial for use in ancillary studies.

6.2. Randomisation.

In order that randomisation does not delay immediate intubation in any way, the use of remote randomisation is dismissed.

Randomisation will be via a sealed randomised sequence envelope approach. Simple randomisation will be used and will be conducted via a computer generator. Allocation will be based on a 1:1 allocation ratio.

In order to prevent bias or tampering:

1. Envelopes will be sequentially numbered, opaque, sealed and stapled.
2. The allocation sequence will be concealed from staff who are involved in delivery of the study and from healthcare professionals involved with confirming eligibility for the study.
3. Envelopes will be prepared off-site by Cedar staff who are not involved in the design or conduct of this study.
4. The person preparing the envelope will sign the back, and a foil insert will be used to prevent transillumination.

5. To prevent subversion of the allocation sequence, the name and date of birth of the participant will be written on the envelope prior to it being opened.

Logistically, sealed envelopes will be available to intubation teams in two locations. One site within Intensive Care for all in-departmental intubations. The second attached to the ward intubation kit bag, which will attend all ward intubations. Once an envelope has been used the envelopes will be replaced by the research team in sequence until all envelopes are utilised. The box of envelopes will be held securely in a locked cupboard at the Critical Care research office.

Upon allocation the intubation team will prepare the allocated endotracheal tube as part of the standard intubation kit.

6.3. Blinding

Due to the nature of the interventional device it is not possible to blind the care providers or outcome assessors to the intervention group. The trial participants will be unconscious/sedated for the duration of the period that the PneuX device or standard ETT is in place and therefore will be unaware of their allocation. Samples sent to RD Biomed laboratory for analysis will be anonymised using individual deidentified numbers for each participant.

6.4. Baseline data

Initial data collected for patients will be used to screen patients. The majority of this information will be collected from the patient's medical notes. Additional screening criteria will be the clinical assessment performed by the airway practitioner performing the intubation or a critical care doctor. This will be recorded in the patients' medical notes and will include:

- Reason for intubation
- Size of ETT and measurement of ETT position at the teeth
- Primary diagnosis for admission to ICU
- Patient characteristics including age on admission and gender

Information regarding the intubation process will be collected. This includes amount of intubation attempts and Cormack-Lehane classification of intubation grade. This data will be used in order to present our patient population for results interpretation. The medical notes and electronic patient information databases will act as the source data for the purposes of the study.

6.5. Trial assessments

Study assessment are summarised as follows:

Task	Screening	Randomisation (day 0)	Daily (day 1-7)	Follow-up (day 28)
Assess eligibility to enter study (record reason if not eligible)	**X**			
Demographics and eligibility checklist		**X**		
Record date and time of randomisation (or reason if not randomised)		**X**		

Intubation using allocated endotracheal tube		**X**		
Admission to ICU				
Intubation details and device measurement		**X**		
ICU admission details and reason		**X**		
Quantity of aspirate and pepsin sampling for subglottic aspirate		**X**	**X (every 24h)**	
Quantity of aspirate and pepsin sampling for tracheal aspirate		**X**	**X (every 24h)**	
Send sample of aspirate for cultures			**X (Day 3 + 7)***	
Document compliance with measuring and documenting cuff pressure		**X**	**X**	
Document antibiotic use			**X**	
Document VAP			**X**	
Duration of ICU LOS				**X**
Duration of ventilation				**X**
In hospital death				**X**
Consent	**X**			
Adverse Reactions/Safety Reporting		**X**		
Protocol violations	**X**			

*Or as clinically indicated

6.5.1. Main outcomes

1) **Feasibility of recruitment** - in order to assess feasibility data will be collected on:
    a. Achieving recruitment of 50 patients
    b. Rate of recruitment via established recruitment process
2) **Feasibility of delivering the study intervention**
    a. Any issues experienced when using the study device at any point during the study will be recorded in the CRF, including device-related complications.
3) **Acceptability of study interventions and sampling amongst staff**
    a. Staff will be interviewed or surveyed to capture any issues around use of the study device or the measurement process.
4) **Feasibility of pepsin measure procedure for use in Peptest**
    a. Subglottic aspirate and tracheal aspirate for the presence of pepsin. Test performed by Peptest (RD Biomed). Subglottic aspiration is via subglottic ports on the ETT. This is performed with a 10 ml sterile clean syringe with gentle aspiration. Tracheal aspiration is defined as a noninvasive method for sampling via an endotracheal tube with a clean suction catheter. Samples will be performed by trained staff involved in the research study.
    b. Failed sampling due to insufficient sample
    c. Failed testing via Peptest due to testing error/inability to process
    d. Quantity of aspirate (mls)
5) **Establish the rate of positive pepsin tracheal aspirate samples in both arms of the study using Peptest**
    a. As above
6) **Establish the mean volume of sub-glottic aspirates using the control and intervention groups**

a. As above

6.5.2. Secondary outcomes

7) Establish the rate of tracheobronchial colonization

a. Cultures - samples will be sent for culture for the detection of tracheobronchial and subglottic secretion colonisation by Cardiff University School of Dentistry.

8) Establish rates of Ventilator Associated Pneumonia (VAP)

a. Ventilator associated pneumonias can occur after 48 hours following intubation and mechanical ventilation. Whilst VAPs have multiple definitions medically, VAP rates will be defined with a clinical pulmonary infection score (CPIS) system. CPIS scores combine clinical, radiographic, physiological, and microbiological data into a score system. A score greater than 6 is correlated to a diagnosis of a VAP.

9) Assess mean time spent on the ventilator

a. Measured in days requiring ventilatory support. An extubation will be considered successful if the patient remains free of invasive ventilatory support for 48 consecutive hours.

10) Assess both hospital and ICU length of stay (LOS)

a. Measured in days of total hospital admission following admission to critical care and the duration of the stay within critical care.

11) Assess in-hospital mortality rates/ All-cause mortality

a. Data collected from patient notes of the rates of mortality in hospital and causes of mortality

12) Assess compliance with measuring and documenting cuff pressure

a. Standard practice is to measure cuff pressures every 12 hours on the Covidien Taperguard endotracheal tube. This is recorded as per standard care on the bedside ICU chart.

b. The PneuX tube has an attached constant cuff pressure monitor. Documentation that the cuff pressure monitor is maintaining the pressure is required hourly. In the instance that the cuff pressure monitor fails, manual checks are required hourly as per guidance with the PneuX tube.

c. Rates of correct documentation will be collected

6.6. Long term follow-up assessments

Information required regarding time ventilated, hospital LOS, in hospital death will be deemed long term follow up if these events exceed the 7-day study duration. All necessary information will be collected if hospital discharge is achieved within this stated 28-day period. No data is required following discharge.

6.7. Withdrawal criteria

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

- Ineligibility (either arising during the study or if, during the study, previously unknown issues come to light which would make the participant ineligible)
- Significant protocol deviation as decided by the CI
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of consent by the patient or consultee (patients' study data up to the point of withdrawal will be kept).

Daily data collection will cease if:

- The patient has been extubated in the first 24 hours following intubation
- Planned extubation (the patient has improved, or the tube required changing for clinical reasons)
- Un-planned extubation (accidental removal of the tube)
- The patient has died with the tracheal tube still in place
- The patient has had a tracheostomy.

6.8. Storage and analysis of clinical samples

Three sample types are required for this study:

1) **Tracheal aspirate** - for the purpose of measuring the presence of pepsin in sputum.
2) **Subglottic aspirate** - for the purpose of measuring the presence of pepsin in subglottic secretions.
3) **Airway Cultures** – cultured for the detection of tracheobronchial secretion colonization.

A sample collection and transfer log will be maintained by the critical care research team, documenting the type of sample collected for each participant, date and time of collection, date, and time of storage in the critical care research laboratory, and the date, time, and destination of sample transfer to other locations.

All samples will be destroyed by the end of the study. Should the patient or consultee refuse or withdraw consent then any study samples will be destroyed.

Pepsin:

Measurement of pepsin will be via the private diagnostics company Peptest (RD Biomed Limited, UK). Peptest specialise in diagnosing medical conditions using pepsin as a biomarker. This includes gastro-oesophageal reflux and aspiration.

Peptest store samples in a citrate solution. Pepsin is stable in this solution for up to seven days. Peptest require samples to either be sent immediately via post without temperature control, or that samples be stored in a fridge (2-8°C) until posting is available. This will apply if samples are taken on the weekend, whereby samples will be stored within designated human sample refrigerators in the Critical Care Research Laboratory. Refrigerators are temperature controlled, with the temperature being continually monitored using a recognized device (Tiny Tag Data Logger). Temperatures are recorded daily and the Data Logger is downloaded weekly to ensure the temperature compliance.

Peptest process the samples by:

1. Centrifuging samples to separate sample from the citrate solution
2. Mixing with a migration buffer
3. Tested with a pepsin lateral flow device
4. Finally, via a light assay the quanitity of pepsin (ng/ml) within the sample is determined

All received Peptest samples are placed in clinical waste on completion of testing.

Contact details for Peptest manufacturer:

RD Biomed are the manufacturers of Peptest. Contact details are as follows:

Andrew Woodcock
RD Biomed Limited
Daisy building (2nd floor), Castle Hill Hospital
Cottingham, HU16 5JQ
e-mail: andrew.woodcock@technostics.com
Tel: 01482 461880

Sputum Cultures

Sputum cultures are obtained by a non-directed bronchioalveolar lavage via an inline suction device attached to the patient's endotracheal tube. Sputum cultures are a common investigation within intubated patients. For this study samples will be additionally sent on day 3 and day 7 following intubation. Sputum samples are sent direct and immediately to the Microbiology Laboratory (Cardiff University). Samples undergo a period of incubation and subsequent microscopy, identification and testing of sensitivities to antibiotics.

As samples are sent immediately to the Microbiology Laboratory no storage is required. Samples are sent in standard universal containers. Samples are destroyed as per policy via clinical waste which is sent for incineration.

6.9. End of trial

The end of the trial is defined as the end of follow-up (28 days) after recruitment of the final (50th participant).

7. Trial treatments

The two treatment arms of this study use certified medical devices (CE marked) for their intended original purpose. The Taperguard (from Covidien), the standard care arm, are endotracheal tubes for the purposes of long term ventilation within the ICU. The comparison arm is the PneuX endotracheal tube (Venner Medical) which will be used as its intended use for long term ventilation on the ICU.

7.1. Name and description of intervention

The PneuX Endotracheal Tube is a CE marked device produced by Venner. The purpose of this product is to provide invasive ventilation for patients in the ICU. The defining features of the intervention treatment are the multi-modal approach to prevent microaspiration during long term ventilation.

The PneuX internal diameter ranges from 6mm - 9mm. The tube is made from a soft silicone material. The cuff is a low-volume low-pressure cuff. Above the cuff are three subglottic ports for aspiration of subglottic secretions. The ETT has standard features including a bevel, Murphy's Eye, length markings for measuring intubation depth and markings to identify position placement at the vocal cords.

The PneuX tube is to be used with the Venner PneuX system which additionally comprises of a tracheal seal monitor and a 2m extension tube. The tracheal seal monitor is an electronic automated device which maintains constant pre-defined pressure (20 mmHg) within the cuff. The monitor contains pre-set alarms for the event of blockage, disconnection, inability to maintain cuff pressure or continual high cuff pressures. The 2m extension tube connects the PneuX ETT to the tracheal seal monitor.

Venner recommend that the ETT is used with a humidified circuit. The silicone internal lining is prone to the depositing of sputum causing blockages. This risk is reduced by having a humidified circuit. Use of a humidifier is not standard care within our ICU. However, this is considered a standard method of humidifying ventilation circuits for long term ventilation.

The ETT is packaged individually in sterile packaging as per the manufacturer. No amendments are required to this due to the non-blinded nature of this study.

7.2. Regulatory status of the device

The Venner PneuX™ Endotracheal Tube (ETT) single use device, is intended for patients undergoing tracheal intubation during routine anaesthesia or over extended periods (not more than 30 days) and for the evacuation or drainage of secretions from the subglottic space. The PneuX ETT is a Class IIa CE marked medical device. In this study the device will be used as per its intended purpose, as described in the Instructions For Use (IFU).

This study is on a CE marked medical device used as per its intended purpose (described in the IFU).

7.3. Contraindications etc

The device IFU contains no contraindications. The following warning and precautions are described:

- The Venner PneuX™ ETT/TT must only be used with the Venner PneuX TSM™ and Venner PneuX™ Extension Tube.
- An increase or decrease in cuff pressure can occur due to trans-cuff diffusion of gases. The Venner PneuX™ ETT/TT is designed to be used with the Venner PneuX TSM™ or a standard cuff manometer at least hourly to minimise these changes.
- The Venner PneuX™ ETT/TT are single use devices. Reuse may cause cross-infection, reduce product reliability and functionality.
- The Venner PneuX™ ETT/TT are not intended to be cut.
- Three-way stopcocks or other devices should not be left inserted in the pilot valve for extended periods.
- The resulting stress could crack the valve, causing the ETT/TT cuff to deflate.

7.4. Standard care (control arm)

Standard care in UHW ICU is to intubate patient using the Taperguard ETT. The Taperguard ETT is designed with a tracheal shaped cuff made of PVC. This has 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 high secretion load.

Within the ventilation circuit is a Heat and Moisture Exchanger (HME). This is sufficient in order to maintain the required humiditiy for long term ventilation, without reported incidence of deposition of secretions within the ETT.

7.5. Assessment of compliance with treatment

For the use of the PneuX Venner System, two tasks are required. Firstly the connection of the PneuX ETT to the tracheal seal monitoring for correct pressure maintenance. Secondarily, four hourly aspiration of the subglottic

port to drain subglottic secretions. Both of these will be documented for compliance. The critical care research team will check daily to ensure compliance with tasks.

In the event of the tracheal seal monitor does not effectively maintain the pressure in the cuff, the cuff pressure can be monitored with a manual cuff manometer hourly until constant pressure monitoring is re-established. This is as per the manufactory guidance.

8. Safety reporting

This study is a study of a CE marked medical device and as such it poses a low risk.

8.1. Definitions of adverse events, serious adverse events, and relatedness

Adverse Events (AEs): any untoward medical occurrence in a clinical trial participant to whom a study intervention has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease.

Serious Adverse Event (SAE): Adverse events are classified as serious or non– serious. A serious adverse event (SAE) is an adverse event which results in any of the following:

- Results in death;
- Is life-threatening, in the sense that the patient was at risk of death at the time of the event (but not if the event could have caused death if more severe);
- Requires hospitalisation (or prolongation of existing hospitalisation) defined as an unplanned admission of any length, even if precautionary for continued observation; however pre-planned hospitalisation (e.g. for an elective procedure or a pre-existing condition which has not worsened does not constitute an adverse event);
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect; or
- Is otherwise considered medically significant by the investigator

Relatedness: Whether the reporting investigator considers the adverse event to be related to any of the study procedures can be classed as follows:

- Definite
- Probable
- Possible
- Unlikely
- Not related

8.2. Identifying AEs

AEs will be identified by the critical care research team and the clinical teams caring for study participants whilst they are in hospital.

8.3. Expected AEs

The manufacturer's Instructions for Use for the PneuX device do not report any expected device-related AEs.

8.4. Recording and Reporting SAEs

All SAEs occurring from the time of randomisation until 28 days post cessation of trial treatment must be recorded on the Study SAE Form and sent to the Sponsor (via Cedar) within 24 hours of the research staff becoming aware of the event.

For each SAE, the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

A SAE which has been classified by the CI as RELATED and UNEXPECTED (see definitions above) must be reported to both the Research Ethics Committee (REC) that gave a favourable opinion of the study and C&V R&D office. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event, using the HRA report of SAE form.

Unrelated and expected SAEs do not require reporting to C&V R&D but a copy of the SAE report should be retained in the Investigator Site File for monitoring/audit.

Details of all AEs (not just those thought to be device related) will be recorded on the AEs form in the participant's Case Report Form (CRF) and in their medical notes. Subjects experiencing AEs may be withdrawn from the study at the discretion of the clinical investigator. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious. Hospitalisation for elective surgery or routine clinical procedures, which are not the result of an AE need not be considered AEs.

AEs which result in changes of the ETTs or blockages will also be recorded.

8.5. Contact details for reporting SAEs

Cedar study manager contact details for reporting SAEs:

Dr Judith White (or other delegated member of the Cedar team)
Principal Researcher (Clinical Research Lead)
Cedar, Cardiff and Vale University Health Board, Cardiff Medicentre, Heath Park, Cardiff, CF14 4UJ
Tel: 029 218 44771
E-mail: Judith.White3@wales.nhs.uk

(Monday to Friday 09:00-17:00)

Cedar study manager will then collect the SAE form from the clinical team at UHW

8.6. Reporting adverse incidents involving medical devices

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

The following will be notified by the Cedar Study Manager to the Medicines & Healthcare products Regulatory Agency (MHRA) via the Yellow Card Scheme (https://yellowcard.mhra.gov.uk/):

- AEs or SAEs considered to be related to the PneuX device
- Safety incidents (or near misses) for users of PneuX device
- Delays or interruptions to a participant's treatment due to a faulty device

The following contact details should be used to inform the device manufacturer/distributor of any device-related adverse incidents:

Nicki Dill
Managing Director
Qualitech Healthcare Ltd
16 Cordwallis Park
Maidenhead
SL6 7BU
Tel: 07917156747
n.dill@qualitechhealthcare.co.uk

Karen Gillard
Administration Manager
Qualitech Healthcare Ltd
16 Cordwallis Park
Maidenhead
SL6 7BU
Tel: 07880234188
k.gillard@qualitechhealthcare.co.uk

8.7. Urgent Safety Measures

The CI and PI may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However they must alert the Sponsor as soon as possible of any such urgent measures by contacting the C&VUHB R&D Office and CI. The CI will notify the REC of the presenting issue within 3 days of the urgent measure setting out the reasons for the urgent measure and the plan for further action.

8.8. Responsibilities

Principal Investigator (PI)

Checking for when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event was anticipated.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that

SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

3. Ensuring that SAEs and AEs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI):

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
3. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

9. Statistics and data analysis

9.1. Sample size calculation

This study is a feasibility study to assess recruitment targets and the acceptability of study procedures. As such, a sample size calculation has not been used. Instead, the sample size has been selected to assess the feasibility of recruiting 1-2 patients per week for 12 months. A conservative sample size of 50 patients has been selected. The information from this study will be used to inform further studies for a future pilot/RCT study.

9.2. Planned recruitment rate

A conservative recruitment rate of 1-2 patients per week for the during of the study has been chosen based on a review of local data. We have estimated that 50% of eligible patients would be recruited into the study.

9.3. Statistical analysis plan

The main outcome of recruitment feasibility will be reported as frequency of patients recruited during the study period. Reasons for screening or randomisation failure will be collated and presented as frequencies. Issues described by staff in relation to any study processes will be described in a narrative fashion to feed into the design of a future RCT. Dichotomous variables such as number of failed pepsin tests, incidence of VAP, number of positive pepsin tests, will be presented as frequencies (with reasons where appropriate). Continuous outcomes (volume of tracheal aspirate, volume of sub-glottic aspirate, time on ventilator, LOS) will be presented as mean or median, as appropriate following tests for normality.

No between-groups comparisons will be undertaken.

Levels of missing data are expected to be low because most outcomes are measured whilst the patient is still in hospital and easily accessible by research nurses. Where outcome data cannot be collected from patients this will be recorded with reasons. Proportions of patients with missing data will be reported in full.

10. Data management

10.1. Data handling and record keeping

The PI and critical care research team will collect all clinical data. The data will be collected in a timely manner and be extracted from and consistent with the relevant source data. Each participant will be allocated a unique Participant Study Number at trial entry, and this will be used to identify him or her on the CRF for the duration of the trial. Data will be collected from the time of trial entry until hospital discharge. Trial data will be collected from the source data using a paper case report form (CRF) and then entered onto a secure electronic database (REDCap). The electronic database will be secured by appropriate access control and password protection.

Cedar will undertake a short survey or interview with staff involved in the study to collect data on the acceptability of the study procedures and to identify barriers and facilitators.

All paper and electronic documents will be stored securely at UHW (paper) or on Cardiff & Vale UHB servers (electronic) and only accessible by the critical care research team and authorised personnel. No patient identifiable data (PID) will be transferred outside of Cardiff & Vale UHB. Paper CRFs will be kept at the study site during the study period and when completed the CRFs will be signed-off by the study PI/CI or designee. Completed and signed-off CRFs will be transferred to Cedar (in person) as each patient completes the study period. Appropriate checks will be made to enable cross validation against the original source data and ensure accurate data entry. The database will be stored on Cedar's secure server (part of Cardiff and Value UHB server) which is backed-up every 24 hours. Data queries will be raised by Cedar (Cardiff and Vale UHB). Where clarification from site staff is required for data validations or missing data, site staff will respond to data queries ensuring that amendments are made as required.

SPSS will be used for data analysis.

Cedar will undertake source data verification for 100% of CRFs. This will require Cedar to access personal identifiable data in the study recruitment and in patients' medical notes. Study participants will provide explicit consent to the use of identifiable data for the purposes of the study.

10.2. Access to Data

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

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

Cedar will perform the analyses of all study data. Procedures will be in place to enable transfer of study data as follows:

- From Critical Care Dept to Cedar (anonymous data) for the purposes of analysis of outcome data and archiving.
- From Critical Care Dept to Cedar to enable Cedar to verify CRF data against the patient medical records, requiring access to personal identifiable data

All access to personal identifiable data by the investigators will be with documented consent by the participant.

The device manufacturer will not have access to any patient identifiable data. Fully anonymised data may be made publicly available following publication of the study results.

10.3. Archiving

The TMF and Investigator Site File (ISF) containing essential documents will be kept for a minimum of 5 years after completion of study. Documents (paper and electronic) will be retained in a secure location during. Cedar will archive study documentation at the end of the study. A label stating the required retention time should be placed on the inside front cover of the medical records for study participants.

Essential documents pertaining to the study shall not be destroyed without permission from the sponsor.

10.4. Monitoring, audit & inspection

Cedar will be responsible for trial monitoring. On-site or remote monitoring visits will be conducted in accordance with the trial monitoring plan. On-site or remote monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP). The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor. Before the trial starts at a participating site, an initiation meeting will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring visits during the trial will check the accuracy of data entered into the CRF against the source documents, adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up. The PI or designee should ensure that access to all trial related documents including source documents are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan. The close out procedure at each site will commence once the final patient enrolled has completed all site follow-up required by the protocol.

11.Ethical and regulatory considerations

This study complies with the World Medical Association Declaration of Helsinki (2013) and GCP. The study will respect the rights of participating patients and ensure confidentiality of patient information. Should participants have additional questions about the trial, advice will be available from both within the research team and outside the research team in the form of websites such as the NHS website page: http://www.nhs.uk/Conditions/Clinical-trials/Pages/Takingpart.aspx .

11.1. Research Ethics Committee (REC) review & reports

Before the start of the study, approval will be sought from Health Care Research Wales (HCRW) and REC for the protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Amendments that require review by HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments to the Sponsor, in the first instance, and their National Coordinating Unit, HCRW). The HCRW Permissions Service will assess and approve the amendment.

All correspondence with the REC will be retained in the TMF/ISF.

A progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required.

The CI will notify the REC of the end of the study

If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

11.2. Peer review

The protocol has undergone scientific review by two people independent of the study and with relevant experience. Furthermore, the protocol has been reviewed by C&V UHB as part of the Sponsor Assessment Meeting.

The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied HCRW will issue HRA/HCRW approval. The study should not commence until local confirmation of capacity and capability is also received via email by the CI/ PI.

11.3. Patient and public involvement (PPI)

All patient-facing documents have been reviewed for content and readability by a PPI representative. Given the nature of this feasibility study and the patient population we have not included a PPI representative as part of the TMG. However, should a large scale RCT go ahead we intend to approach Health and Care Research Wales to identify relevant PPI representatives who will be involved in the design, conduct, and dissemination of findings.

11.4. Regulatory Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

11.5. Protocol compliance

Protocol non-compliances are departures from the approved protocol. Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported

to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

11.6. Notification of Serious Breaches to GCP and/or the protocol

In the event that a serious breach of GCP or the Protocol is suspected, this will be reported to the Sponsor immediately in accordance with C&V UHB *SOP 235 Managing Breaches of Good Clinical Practice or the Study Protocol*. The incident in question will be investigated by the Sponsor who will determine whether the breach constitutes a serious breach and report it to Cardiff and Vale UHB's research governance department. Any corrective action required will be undertaken by the CI and REC informed if required. If necessary a protocol amendment will be submitted for review.

11.7. Data protection and patient confidentiality

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The data custodian in this study is Judith White (Cedar) and the data will be held on Cedar's secure server.

Study CRFs will be kept in secure locations (locked cupboard) at the study site and at Cedar. The study database at Cedar (part of Cardiff and Vale UHB) will be accessible only by Cedar personnel directly involved in the study (password protected files on Cedar secure NHS servers).

The device manufacturer will not have access to any patient identifiable data.

11.8. Financial and other competing interests for the investigators

No financial or other competing interests are held by the CI, PI or any member of the research team. The device manufacturer will provide the device and consumables free of charge, and will provide training as required, but will not be involved in the design, conduct or reporting of the study.

11.9. Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

11.10. Amendments

It is the sponsor's responsibility to classify amendments as being non substantial or substantial. The CI will seek advice from C&V UHB R&D office prior to submission to the relevant bodies. The CI will follow Health Research Authority (HRA) processes for any amendments to the protocol or other study documents. The NHS R&D Office will need to confirm capacity and capability prior to implementation. Amendments to the protocol or other study documents will not be implemented prior to appropriate approvals being granted.

12. Dissemination policy

The study will be registered on clinicaltrials.gov.

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared. The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline. The study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion). Study results will be published in a peer-reviewed scientific journal on an 'Open Access' basis so that they are freely available to anybody with internet access. Any publication would be in a journal that is peer reviewed and included in major evidence databases such as MEDLINE. The study report will follow the journal's authorship criteria and will acknowledge the contributions made by everyone related to the study.

A lay language report of the study will be made publicly available on the Cedar website.

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