NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: MT273 PneuX

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Assessment report: PneuX

Document cover sheet

EAC team:

- **Project Lead(s) Kate Goddard, Tom Macmillan**
- **Information specialist: Tom Macmillan**
- **Clinical evidence reviewer: Kate Goddard, Tom Macmillan**
- **Economic evidence reviewer: Murali Kartha, Mark Pennington**
- **EAC sign-off: Anastasia Chalkidou**

Version number	Brief description of changes	Author/Reviewer (e.g. J. Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
1.0	First draft to NICE	K Goddard T Macmillan A Chalkidou M Pennington M Kartha	08/08/2019	08/08/2019
2.0	Second draft to NICE – comments addressed	T Macmillan	21/08/2019	21/08/2019
2.1	Second draft amended after factual check by company	K Goddard T Macmillan	28/08/2019	29/08/2019

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT273 PneuX for preventing ventilator-associated pneumonia in intensive care

External Assessment Centre report

Produced by:	**King's Technology Evaluation Centre**
Authors:	**Anastasia Chalkidou, Associate Director, KiTEC** **Kate Goddard, Health Technology Assessor, KiTEC** **Murali Kartha, Senior Health Economist, KiTEC** **Tom Macmillan, Health Technology Assessor and Information Specialist, KiTEC** **Mark Pennington, Senior Lecturer in Health Economics, KiTEC**
Correspondence to:	**Joanne Boudour, joanne.boudour@kcl.ac.uk**
Date completed:	**21/08/2019**

Contains confidential information	No
Number of attached appendices	0

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance

Declared interests of the authors

None.

Acknowledgements

"Copyright belongs to King's Technology Evaluation Centre."

Dr Peter Alexander is a Consultant in Anaesthesia and Intensive Care Medicine at the University Hospital of South Manchester NHS Foundation Trust, no conflict declared.

Dr Thomas Hellyer is a Specialist Registrar in Intensive Care Medicine, Northern Deanery, no conflict declared.

Dr Ben Messer is a Consultant Anaesthetist in Intensive Care Medicine at the Newcastle upon Tyne Hospitals NHS Foundation Trust, no conflict declared.

Dr David Ray is a Consultant in Anaesthesia and Critical Care at the Royal Infirmary of Edinburgh, NHS Lothian. He was Convenor of the Scottish Standing Committee, Association of Anaesthetists and member of UK Council, Association of Anaesthetists.

Mr Neil Smith is a Research Nurse at Hull University Teaching Hospitals NHS Trust, no conflict declared.

Dr Andrew Walder is a Consultant Anaesthetist at the Northern Devon Healthcare NHS Trust, no conflict declared.

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Instructions for EAC:

The purpose of the External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence and may include additional analysis of the submitted evidence or new clinical and/or economic evidence.

The Assessment Report is an important component of the information available to the Medical Technologies Advisory Committee (MTAC) when developing its provisional and, following consultation, final recommendations on the technology.

The template should be completed with reference to the NICE 'Medical Technologies Evaluation Programme methods guide'. The headings and prompt questions in the template provide a consistent structure for the assessment of the company's submission but the assessment, format and presentation may be adapted by the EAC to maximise the clarity of the report.

Any 'commercial in confidence' information in the submission document should be underlined and highlighted in turquoise.

Any 'academic in confidence' information in the submission document should be underlined and highlighted in yellow.

If either type of confidential information is quoted or described in the assessment report, it must be underlined and highlighted as in the original. This allows the automated removal of this information and makes subsequent editing far quicker and more reliable. It is very important to ensure removal of confidential information before public consultation. It is the assessment centre's responsibility to ensure all confidential information in the assessment report is underlined and highlighted in the appropriate colours.

All grey text in this template should be removed before submitting the final version to NICE.

Table to be removed by NICE prior to publication in the MTAC pack and on the website

Contents

ABBREVIATIONS

Term	Definition
CI	Confidence interval
EAC	External Assessment Centre
ETT	Endotracheal tube
FDA	Food and Drug Administration
ICU	Intensive care unit
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
SD	Standard deviation
TT	Tracheostomy tube
VAP	Ventilator associated pneumonia
vs	Versus

Executive Summary

The company included 6 publications in their submission (Doyle et al. 2011, Gopal et al. 2014, Hodd et al. 2009, Fletcher et al. 2009a, 2009b, and Smith et al. 2014). The EAC decided that 4 publications from 3 studies matched the scope and were therefore included in the final selection (Doyle et al. 2011, Gopal et al. 2014, Hodd et al. 2009, Smith et al. 2014). Gopal et al. (2014) was the only study retrieved that was randomised and provided a comparator group. The 2 remaining studies lacked direct comparators and were retrospective in design.

Due to the lack of high quality design studies (only 1 RCT was included), no meta-analysis was carried out. The primary outcome in the Gopal et al. (2014) RCT was the incidence of VAP in high risk patients undergoing cardiac surgery. VAP incidence was significantly lower in the PneuX groups than in the standard care group (endotracheal tubes without subglottic secretion drainage): 10.8% compared with 21%, (p=0.03), a relative risk of 0.52. There was no significant difference between the 2 groups in terms of length of ICU stay (2 days with PneuX compared with 1.5 days with standard endotracheal tube, p=0.2) and in-hospital mortality (98% survival with PneuX compared with 99% survival with standard endotracheal tube, p=0.2).

The cost analysis undertaken by the company found that PneuX is cost saving when compared to endotracheal tubes without subglottic secretion drainage. The cost of the technology is modest compared to the cost of treating VAP, which is a relatively common infection for intubated patients. Cost savings are driven by the reduction in VAP, which may cause costly increases in length of ICU stay. The sensitivity analysis undertaken by the company on the risk of VAP and the effectiveness of PneuX found that the technology was cost saving across a broad range of combinations of the two parameters. If PneuX is clinically effective it is likely to be cost saving over tubes that do not have subglottic secretion drainage. Additional analysis found that there was minimal evidence to support the superiority of PneuX over other endotracheal tubes with subglottic drainage. Selection of the most appropriate subglottic drainage technology might best be guided by

acquisition costs (including any additional equipment required) and preferences of the clinical staff. In a meta-analysis of 20 RCTs including 3544 patients (Mao et al. 2016), subglottic secretion drainage (including devices other than PneuX) was associated with 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).

The clinical evidence indicates that PneuX decreases VAP incidence compared with endotracheal tubes without subglottic drainage, but does not reduce ICU length of stay or mortality. The economic evidence suggests that PneuX is cost saving when compared to standard endotracheal tubes without subglottic secretion drainage although there are a number of uncertainties about the parameters. The EAC highlights the variation in ICU length of stay in the studies contributing these parameters (Gopal et al. 2014, Luckraz et al. 2018). In addition, there are a number of limitations to the evidence and further research is required to address these gaps. Firstly, there is no consensus definition for VAP and incidence varies widely when different definitions are used. Future research would benefit from the use of more stringent and up-to-date criteria. Secondly, it may not be possible to generalise the results from the RCT population to the wider critical care setting. Therefore, further comparative evidence is required in a study population that is more representative of an NHS ICU. Thirdly, future comparative research needs to include direct comparison of PneuX with tubes with subglottic secretion drainage. Finally, future studies should investigate, and be adequately powered for detecting the impact on hospital and ICU length of stay and/or antibiotic use as primary outcomes because these are the most clinically relevant outcomes and the main drivers of increased cost following VAP.

1 Decision problem

The company have not proposed any variation to the decision problem specified in the scope.

Table 1 Final scope

Decision problem	**Scope**
Population	Adult patients requiring ventilation in a critical care setting for at least 24 hours and up to 30 days.
Intervention	Venner PneuX™ System
Comparator(s)	Conventional endotracheal tube Conventional tracheostomy tube Any other equivalent or similar endotracheal tube aimed at VAP prevention including subglottic secretion drainage (both intermittent versus continuous suction)
Outcomes	The outcome measures to consider include: • incidence of VAP • length of ICU/ITU stay • length of hospital stay • incidence of aspiration • duration of mechanical ventilation • incidence of unplanned extubation and/or re-intubation • antibiotic usage • mortality

	• sedation usage • difficulty of placement and maintenance of tube position • device-related adverse events e.g. tracheal injury
Cost analysis	Comparator(s): • any other equivalent or similar endotracheal tube aimed at VAP prevention • conventional endotracheal tube • conventional tracheal intubation tube Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.
Subgroups	• Endotracheal tubes • Tracheostomy tubes • Specific patient groups: for example, severely immunocompromised patients burn and polytrauma patients, Prone ventilated patients, major heart surgery patients, neurological patients and transplant patients

2 Overview of the technology

The PneuX system is intended for patients undergoing tracheal intubation in the critical care setting 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 was formerly known as the Venner PneuX P.Y.– VAP Prevention System and the Lo-Trach system. The company indicates there are no functional differences between the different versions. The EAC confirmed that the differences relate to the integrated bite block, which is designed to resist damage from patient biting.

The PneuX system consists of two class IIa medical devices: the Venner PneuX endotracheal/tracheal tube and Venner PneuX tracheal seal monitor (TSM) and cuff pressure controller. The company, Venner Medical (Singapore) Pte, received a CE mark for the most recent versions of the PneuX endotracheal (ETT) and tracheostomy (TT) tubes, tracheal seal monitor and extension tubes on 19 January 2016.

The Venner PneuX system consists of 3 component parts:

- ETT/ TT – a single use, flexible, silicone tube that is reinforced with nitinol wire (MRI compatible) and is designed to conform to the patient's anatomy. The lumen is coated with non-stick lining to reduce development of bacterial bio-film. The tube has a cuff, a flange, a drain tube, an inflation tube, a reservoir and a 15 mm standard connector. The tubes are available in 3 sizes: 7.0, 8.0, 9.0mm inner diameter.
- Extension tube – a 2 meter extension tube for the PneuX tracheal seal monitor. It connects the air outlet on the PneuX tracheal seal monitor and the pilot valve of the ETT/TT.
- Tracheal seal monitor and cuff pressure controller – an electronic automated pressure controller for monitoring, maintaining and regulating the pressure within the cuff during use.

There are 3 subglottic secretion drainage and irrigation ports above the proximal end of the cuff to facilitate subglottic drainage and/or syringe irrigation of accumulated secretions via the subglottic connector. Drainage happens intermittently and is recommended every 4 hours (or more often if required), by attaching a sterile 20ml luer syringe to the subglottic connector and briefly applying vacuum until the flow of secretions has ceased. Drainage happens more frequently or continuously in comparator devices, such as the Medtronic Shiley™ Evac Endotracheal tube.

The main innovative features are the low-volume, low-pressure silicone cuff. with elastic characteristics that is designed to expand on inflation without folds or creases to ensure that a low and consistent intracuff pressure is transmitted to the tracheal wall. The seal monitor automatically controls and maintains the inflation volume and pressure within the cuff during use. An intracuff pressure of 80 cm H_2O provides a continuous tracheal wall seal pressure of approximately 30 cm H_2O (20 mm Hg) depending on the patient's anatomy and ventilation pressures. The company claims that by maintaining constant low pressure, the risk of tracheal mucosal injury is reduced. In addition, the cuff is designed to produce a tracheal seal without folds or creases which may reduce the risk of aspiration. The cuff pressure can be temporarily increased to introduce fluid into the subglottic space at a higher pressure in order to perform subglottic irrigation. Cuff pressure may also be increased in patients with abnormal tracheal anatomy or high intrathoracic pressures.

The company recommends that the PneuX tube and seal monitor are used together and not with other devices.

3 Clinical context

1. How is VAP diagnosed?

Ventilator-associated pneumonia (VAP) is a hospital-acquired lung infection that develops in a person who is on a ventilator. NICE MIB45 advises that although "there is no consensus definition, it is often defined as pneumonia that occurs in patients who have had intubation with an ETT or TT to help or control respiratory function continuously for at least 48 hours before the onset of the pneumonia (American Thoracic Society and Infectious Diseases Society of America, 2005)".

There is no gold standard for diagnosing VAP nationally or internationally. Definitions and tests used to diagnose VAP are not standardised across the NHS, although criteria may be standardised across critical care networks. Commonly used clinical signs for VAP identification include a combination of:

- Clinical assessment, for example of temperature, hypotension, worsening oxygenation/ventilation and presence of purulent tracheal secretion
- Chest imaging (x-ray and CT)
- Microbiology (such as white cell count, c-reactive protein tests)

Commonly used published definitions discussed by clinical experts are included in Table 2.

Table 2 Definitions of VAP

Definition	**Parameters**
Hospital in Europe Link for Infection Control through Surveillance (HELICS)	*Radiology:* One or, in patients with underlying cardiac or pulmonary disease, two chest x-rays or CT scans with image suggestive of pneumonia. *Clinical symptoms:* AND at least one of the following Fever >38° C OR Leucopenia (<$4x10^9$ white blood cells/L) or leucocytosis (>$12x10^9$ white blood cells/L) AND at least one of the following (or two if clinical pneumonia only = PN4 and PN5) New onset of purulent sputum ot change in character of sputum (colour, odour, quantity, consistency) Cough, dyspnoea or tachypnoea Suggestive auscultation, rhonci, wheezing Worsening gas exchange AND according to the used diagnostic method

	Microbiology: PN1 Positive quantitative culture from lower respiratory tract specimen – bronchoalveolar lavage specimen ≥10^4 colony forming units/mL PN2 Positive quantitative culture from lower respiratory tract with a threshold of 10^5 colony forming units/mL PN3 Positive culture related to no other source of infection – positive pleural fluid culture, pulmonary abcess with positive needle aspiration, positive histology, or positive exams for pneumonia with virus or particular organism PN4 Positive sputum culture or non-quantitative lower respiratory tract culture PN5 No positive microbiology
Center for Disease Control Ventilator Associated Events (VAEs) surveillance	VAEs are defined by an increase oxygen (>0.2 in FiO_2) or positive end-expiratory pressure (PEEP) (≥3 cm H_2O), after a previous stable baseline of at least 2 days. There are three definition tiers within the VAE algorithm: 1) Ventilator-Associated Condition (VAC); 2) Infection-related Ventilator-Associated Complication (IVAC); and 3) Possible VAP (PVAP).
Clinical Pulmonary Infection Score (CPIS)	A composite score is made from the following six criteria: Temperature - >36.5 and <38.4 (0); >38.5 and <38.9 (1); >39.0 or <36.5 (2) White blood cell count - >4,000 and <11,000 (0); <4,000 or >11,000 (1); <4,000 or >11,000 AND band forms >50% Tracheal secretions - None or scant (0); Non-purulent (1); Purulent (2)

	Oxygenation - >240, acute respiratory distress syndrome (ARDS*) or pulmonary contusion (0); <240 and no ARDS* (2) Chest radiograph - No infiltrate (0); Diffuse (or patchy) infiltrate (1); Localised infiltrate (2) Culture of tracheal aspirate – Little or no growth (0); Moderate growth (1); Moderate or florid growth AND pathogen consistent with Gram stain (2) Total: VAP diagnosis if score >6.
American College of Chest Physicians criteria: Chest Echography and Procalcitonin Pulmonary Infection Score (CEPPIS)	Temperature - >36.5 and <38.4 (0); >38.5 and <38.9 (1); >39.0 or <36.5 (2) Procalcitonin, ng/mL - <0.5 (0); ≥0.5 and <1 (1); ≥1 (2) Culture of tracheal aspirate – Negative (0); Positive (2) Tracheal secretion – Non-purulent (0); Purulent (2) Infiltrates on chest echograph – Negative (0); Positive (2) Oxygenation - >240, ARDS* or pulmonary contusion (0); <240 and no ARDS* (2) Total: VAP diagnosis if score >5.
CDC-NHSN (Centre for Disease Control	A pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, AND the ventilator was in place on the date of event or the day before.

National Healthcare Safety Network)	(The diagnostic algorithm for pneumonia is presented in Figure 1.)

*ARDS is defined as a PaO2/FiO2 ≤200, pulmonary artery occlusion pressure ≤18 mmHg, and acute bilateral infiltrates

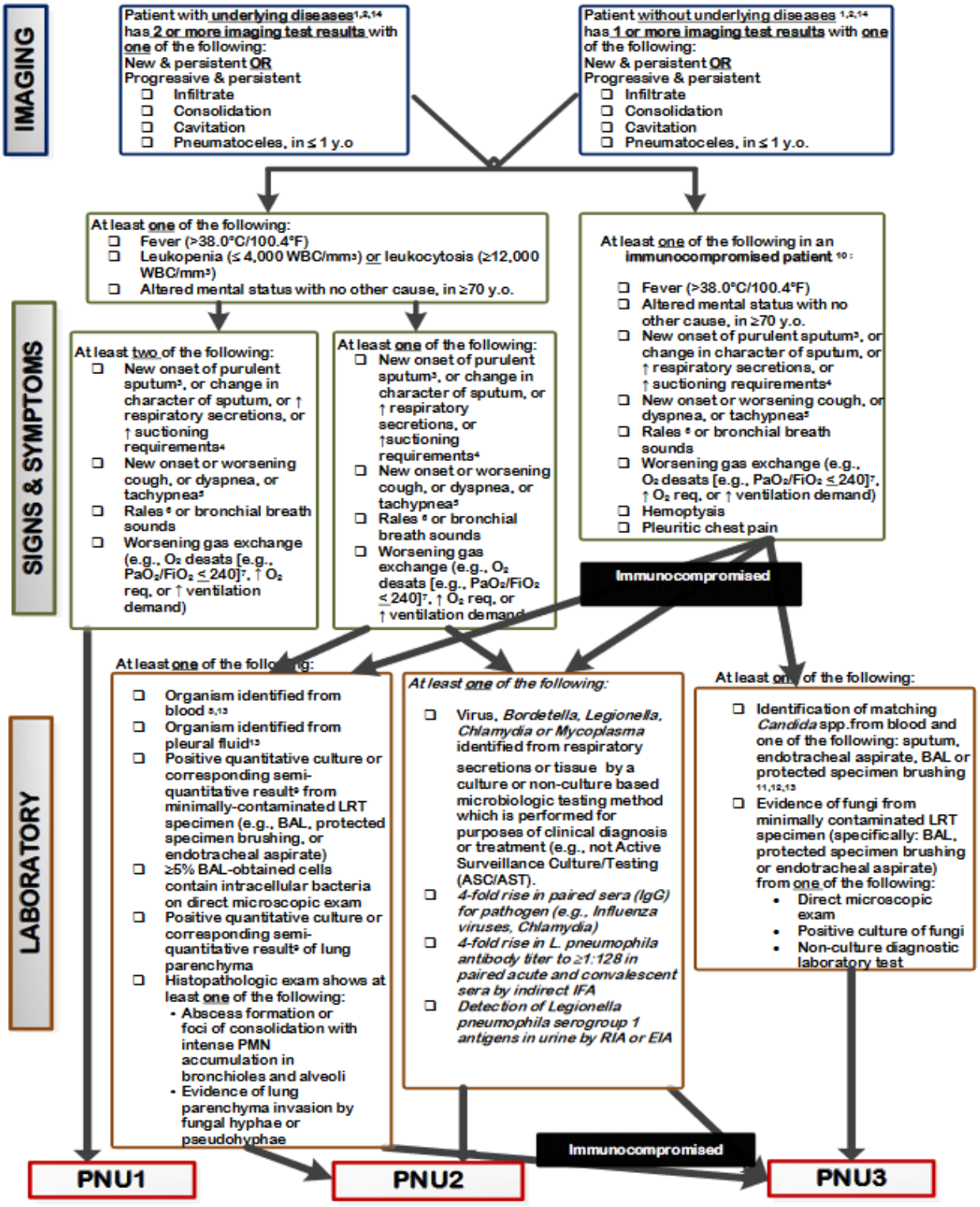


Figure 1 CDC-NHSN diagnostic algorithm for pneumonia (https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf)

The reported incidence of VAP also varies. One expert noted that there was a limited quantity of high quality evidence detailing the incidence of VAP in the UK. One study in an 18 bed, mixed medical–surgical UK ICU reported a VAP incidence of 32 incidents per 1000 ventilator days (Morris et al. 2011) – approximately 15% of the study population. VAP was identified using HELICS criteria. One UK pilot study (Shah et al. 2018) into patients with tracheostomies reported a one-day point prevalence of 20% (7/35) of VAP across 3 ICUs. The authors used a study definition to diagnose VAP (commenced on antibiotics for chest sepsis 48 hours or more after initiation of invasive ventilation). Hart et al. 2018 reported that 32 of 227 (15%) tracheostomy patients were suspected of having VAP, over 14 UK ICU sites. When HELICS criteria were applied, this reduced to 13 of 32 patients (5.7%) – the authors concluded that the HELICS definition was not fit for purpose and that a new standard should be sought. In an audit by NHS Scotland (2017) VAP rate was very low at 1.4% (119 of 8455 ICU patients).

Wallace et al. (2015) tested 4 different definitions of VAP in the same patient group (305 patients from 4 UK ICUs) and found significant variation in VAP prevalence. Using the metric of per 1000 ventilator-bed days, the outcomes ranged from 36.3 (CPIS), 22.2 (HELICS), 15.2 (CDC-NHSN 2008) to 1.1 (IVACPossible VAP).

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 patients in 24 trials (Melsen et al. 2013).

One clinical expert noted that the only established reference standard for VAP is a quantitative or semi-quantitative culture from a bronchoalveolar lavage sample at a threshold above 10^4 colony forming units per ml, but noted that this standard still has drawbacks and that, anecdotally, quantitative culture is not routinely performed in the NHS.

The CDC definition of VAP notes that chest imaging technique, interpretation, and reporting are prone to subjectivity and variability. Consequently chest imaging is inadequate for inclusion in a definition algorithm to be used for

public reporting or inter-facility comparisons. Another significant difficulty with existing VAP definitions is their reliance on specific clinical signs or symptoms, which can be subjective and may be poorly or inconsistently documented. Schurink et al. (2004) investigated the CPIS definition of VAP in 99 patients with microbiologically proved VAP-status. They found acceptable sensitivity (83%), low specificity (17%), with an AUROC curve of 0.55, while agreement between two intensivists was "poor" (kappa = 0.16).

2. How is VAP prevented/managed?

Recent ICS Guidelines for the Provision of Intensive Care Services (published June 2019 by the Faculty of Intensive Care Medicine) recommend that for critically ill patients a "ventilated patient care bundle should be in place with appropriate mechanisms for ensuring adherence". Measures for VAP prevention are currently implemented via a number of multifactorial care bundles. Experts suggested that the bundles developed by the Institute for Health Improvement (IHI) and Intensive Care Society (ICS) are the main guidelines for VAP prevention. One expert noted that although the IHI VAP bundle includes the use of chlorhexidine mouthwash safety concerns have been raised over its use. The IHI bundle has not been updated since 2012, therefore one expert suggested that the ICS bundle is the most relevant guideline for the NHS.

The ICS guideline recommends the following 4 methods for VAP prevention:

- Elevation of head of bed (30°–45°)
- Daily sedation interruption and assessment of readiness to extubate
- Use of subglottic secretion drainage
- Avoidance of scheduled ventilator circuit changes

For preventing ventilator associated complications, the IHI guideline "How-to Guide: Prevent Ventilator Associated Pneumonia": advocates:

- raised head of bed (minimises microaspiration)
- daily sedation hold and assessment of readiness to extubate (decreases length of stay)

- peptic ulcer prophylaxis (minimises complications and length of stay)
- venous thrombo-embolism prophylaxis (minimises complications and length of stay)
- oral care with chlorhexidine (minimises microaspiration - added May 2010)

Subglottic suctioning was not included in the IHI ventilator bundle as the bundle aims to address the broader set of complications associated with patient ventilation (not solely VAP), but notes that "subglottic suctioning may be a very effective therapy for reducing the incidence of VAP".

These guidelines may be adapted more locally. For example the Scottish Intestive Care Society recommends 5 elements:

1. Sedation to be reviewed and, if appropriate, stopped each day
2. All patients will be assessed for weaning and extubation each day
3. Avoid the supine position, aiming to have the patient at least 30° head up
4. Use chlorhexidine as part of daily mouth care
5. Use subglottic secretion drainage in patients likely to be ventilated for more than 48 hours.

VAP care bundles are also shared across critical care networks. The Critical Care Network in North West London adopts the 5 elements outlined in the US IHI care bundle and adds the recommendation for subglottic aspiration. The West Yorkshire Critical Care and Major Trauma Network recommends a care bundle with 8 elements:

1. Subglottic suction for people predicted to be mechanically ventilated for more than 72 hours
2. Cuff pressure maintained between 20-30 cmH_2O (optimally $25cmH_2O$)
3. Cuff pressure measurements carried out every 4-6 hours and following any significant movement of the patient
4. Daily sedation

5. Raised head of bed
6. Tubing and suction systems should only be changed if specifically indicated, such as by visible soiling, to avoid unnecessary changes (in conjunction with manufacturer's recommendations)
7. Stress ulcer prophylaxis should be used judiciously
8. Regular oral hygiene should be maintained.

Special considerations, including issues related to equality

The company states that: "Risk factors for VAP include age (incidence increases with advancing age) and chronic illnesses (including underlying chronic lung disease, cancer and diabetes), which may significantly affect activities of daily living to the point where a person can be considered to be disabled. Age and disability are protected characteristics under the Equality Act (2010)." The EAC accepted this statement but also notes a study of 1735 patients in 24 European ICUs that found increasing age was not associated with higher VAP rates (Blot et al. 2014). The EAC did not identify any further equality issues.

4 Clinical evidence selection

4.1 Evidence search strategy and study selection

The company did not submit a formal search strategy. The company submitted 6 studies. The EAC performed its own searches, details of which are found in the appendices. Studies were selected as per the PICO table in the scope. The date limits of the search were 2007 to 2019. The EAC excluded any studies published as abstracts which were subsequently published as a full-text article (e.g. Doyle et al 2011) and any studies reporting a reanalysis of a population already included in a previously published study, except where unique outcomes relevant to the scope were reported. Two reviewers performed an initial sift of 3770 records by checking titles and abstracts. Following the initial sift, 20 records remained and the full-text documents were obtained and checked for relevance. The final selection comprised 3 studies, reported in 4 publications.

.

4.2 Included and excluded studies

Table 3 Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	Information available	EAC Comments
Doyle (2011) UK	Retrospective non-comparative single-centre cohort study investigating VAP incidence in patients either initially intubated with PneuX (n=9, 17%) or electively exchanged from conventional ETT to PneuX. Funding not declared. Intervention: PneuX 🟢 Comparator: None 🔴	53 consecutive ICU patients (22 female (41.5%), mean age 67.8-yrs [s.d 15]), recruited between 2006 and 2009. 91% of patients were treated with antibiotics prior to intubation. Mean intubation time was 5.3 days (all patients at least 48 hours). VAP was defined by (i) clinical suspicion (including any clinically diagnosed pneumonia where antibiotics were started) and/or (ii) international consensus criteria. Criteria were similar to those outlined in Pugh et al. (2016) for ventilator-associated respiratory tract infection (VARTI) 🟢	VAP occurred in 1 patient (1.8%), although this was in a patient who had exchanged from PneuX to a standard ETT. VAP incidence was 0% while PneuX was in situ. 🟢	Full-text publication.	The non-comparative nature of the study limits its usefulness to the decision problem. However, the UK ICU setting means the outcome is generalisable to NHS contexts. The co-author Dr Peter Young is the inventor and a minor shareholder of PneuX.

Gopal (2014) UK	Prospective non-blinded single-centre RCT investigated VAP incidence in high-risk patients undergoing cardiac surgery (age >70-yrs and/or impaired left ventricular function, LVEF <50%). Funded by Department of Health, UK. Intervention: PneuX Comparator: Conventional ETT	240 patients were randomised 1:1 (174 male (72.5%), mean age 72.2-yrs), recruited between 2010 and 2011. There were no significant differences in preoperative characteristics of the groups (EuroSCORE, lung disease, myocardial infarction, peripheral vascular disease, impaired LVEF, diabetes, isolated CABG, or preoperative stay). Median intubation time was 15 and 13 hours in the PneuX and control groups, respectively. VAP was defined using the HELICS definition.	VAP incidence was significantly lower in the PneuX group compared to the control group (10.8% vs. 21%, p=0.03), as was VAP incidence density (52 vs. 184 VAP episodes per 1000 ventilator days, p<0.01). Binary logistic regression showed PneuX delivered a significant VAP reduction (odds ratio 0.45, p=0.03). CPB time, ICU stay, re-exploration for bleeding and survival were not significantly different between the groups.	Full-text publication.	The study is the only available comparative evidence for PneuX and shows a significant benefit for the device. However, the length of intubation is outside that of the scope (>24 hours). The patient population is specifically cardiac surgery patients at high risk of developing VAP, which limits generalisability to other populations. The lack of concealment/blinding and the single-centre nature of the study also introduce potential for bias. The decision to select high risk cardiac surgery patients was taken for pragmatic reasons. The authors considered it unfeasible to consent patients in the general ICU and therefore chose elective surgery patients. The further inclusion criteria of 'high risk' was chosen because these

					patients tend to have a higher rate of VAP. It is not clear from the reported information if the study is powered to detect a significant difference in the primary outcome. The calculated alpha of 0.01 was not met and the power calculation is not reported adequately. The EAC concludes the study is underpowered. The EAC ran further statistical calculations on the sample size needed to adequately power the Gopal RCT and found that the study is underpowered at a range of effect sizes for the alpha and beta values chosen by the authors. Briefly, at the effect size found in the RCT (odds ratio 0.45) and an alpha value of 0.05, a total sample size of 330 would be required for a study with a power (beta) of 0.8; a total sample size of 420 would be required for a power of 0.9. The

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	Information available	EAC Comments
					Gopal RCT had a total sample size of 240 patients.
Hodd (2009) UK	Retrospective non-comparative single-centre cohort study investigating extubations incidence in patients intubated with PneuX. Funding not declared. Intervention: PneuX Comparator: None	185 intubations between 2006 and 2009 (all intubated ICU patients). Mean intubation time of 5.3 days.	Self-extubation was 1.02 per 1000 intubation days.	Conference abstract	Note – this study is the same patient population as that of Doyle (2011), but is included because the self-extubation outcomes are not reported elsewhere. The non-comparative nature of the study limits its usefulness to the decision problem. However, the UK ICU setting means the outcome is generalisable to NHS contexts. The study is published as a conference abstract only so there is limited reporting of baseline demographic details.

Smith (2014) UK	Retrospective non-comparative single-centre cohort study investigating VAP incidence either initially intubated with PneuX (n=14, 29.2%) or electively exchanged from conventional ETT to PneuX. Funded by Intavent Direct. Intervention: PneuX 🟢 Comparator: None 🔴	48 ICU patients, recruited in 2010. Median intubation time was 2.47 days; 71% of patients were exchanged to PneuX from standard ETT after a mean intubation time of 13 hours 41 minutes. VAP was defined using American Thoracic Society and the Infectious Diseases Society of America (ADS/ISDA). Post hoc analysis was carried out using the CPIS guidelines, in the 24 patients who had necessary data available at 48-hours post-intubation. 🟢	Overall, VAP incidence was 6.25% (95% CI: 1.3-17%) – 3 patients in total. In primary PneuX intubation the rate was 7.14% as opposed to 5.88% in the exchange to PneuX group. Outcomes were re-analysed using the CPIS criteria, where data was available in 24 patients, of whom 5 (20.8%) had potential VAP. 2 had pre-existing pneumonia, and 2 were confirmed by the ATS/IDSA criteria. 83% (40) of extubations were planned. Of the remaining 8, 2 were accidental, 5 self-extubation and 1 removed for clinical reasons.	Full-text publication.	The non-comparative nature of the study limits its usefulness to the decision problem. However, the UK ICU setting means the outcome is generalisable to NHS contexts. The authors note that the PneuX is no longer in use in their institution. However, they have continued to use a different subglottic suctioning tracheal tube device. ("Following this study, and considering the cost, the department has not continued to use the PneuX VAP prevention system.")

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	Information available	EAC Comments

Table 4 Studies included by the company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants	Outcomes	Information available	EAC comments

Fletcher (2009a)	Retrospective non-comparative single-centre cohort study investigating VAP incidence in patients either initially intubated with PneuX (n=9, 17%) or electively exchanged from conventional ETT to PneuX. Funding not declared. Intervention: PneuX 🟢 Comparator: None 🔴	53 consecutive ICU patients (22 female (41.5%), mean age 67.8-yrs [s.d 15]). 91% of patients were treated with antibiotics prior to intubation. Mean intubation time was 5.3 days (all patients at least 48 hours). All patients completed follow-up. VAP was defined by (i) clinical suspicion and/or (ii) international consensus criteria.	VAP occurred in 1 patient (1.8%), although this was in a patient who had exchanged from PneuX to a standard ETT. VAP incidence was 0% while PneuX was in situ. 🟢	Conference abstract.	The patient population is the same as in Doyle et al (2011), which is included in Table 3 as a full-text article. This publication includes no additional outcomes relevant to the scope. 🔴
Fletcher (2009b)	See Fletcher (2009a)	See Fletcher (2009a)	See Fletcher (2009a)	See Fletcher (2009a)	See Fletcher (2009a) 🔴

Senanayake (2017)	Prospective non-blinded single-centre RCT investigated VAP incidence in high-risk patients undergoing cardiac surgery (age >70-yrs and/or impaired left ventricular function, LVEF <50%). Funded by Department of Health, UK. Intervention: PneuX Comparator: Conventional ETT	240 patients were randomised 1:1 (174 male (72.5%), mean age 72.2-yrs), recruited between 2010 and 2011. There were no significant differences in preoperative characteristics of the groups (EuroSCORE, lung disease, myocardial infarction, peripheral vascular disease, impaired LVEF, diabetes, isolated CABG, or preoperative stay). Median intubation time was 15 and 13 hours in the PneuX and control groups, respectively. VAP was defined using the HELICS definition.	Microbial analysis was available for 234 patients. There were no significant differences between the groups in types of microbial colonisation (gram-positive cocci, gram-negative cocci or bacilli). In the PneuX group VAP occurred in 9% of patients intubated for <24-hrs, and 0% of patients intubated for 24-48-hrs. In the control group the rates were 16% and 33%.	Full-text publication.	The patient population is the same as in Gopal et al (2014), which is included in Table 3 as a full-text article. This publication includes no additional outcomes relevant to the scope.

5 Clinical evidence review

5.1 Overview of methodologies of all included studies

The EAC included 3 studies in 4 publications: 1 RCT Gopal et al. (2014) and 2 non-comparative, retrospective cohort studies (Doyle et al. 2011, Smith et al. 2014). The primary outcome of Gopal et al. (2014), Doyle et al. (2011) and Smith et al. (2014) was incidence of VAP. In Hodd et al. (2009) the primary outcome was incidence of extubation – this study is the same patient population as in Doyle et al. (2011).The highest quality study was a single centre RCT (Gopal et al. 2014) comparing PneuX with conventional ETT (without a subglottic drainage function) in a high-risk cardiac surgery population (n = 240). The follow up period was 48 hours after extubation. The studies by Smith et al. (2014) and Doyle et al. (2011) observed 48 and 53 consecutive ICU patients who were initially intubated with PneuX or electively exchanged from conventional ETT to PneuX. The Hodd et al. (2009) publication focused on the incidence of extubations. The study was published as an abstract and includes the same patient population as in Doyle et al. (2011). The follow-up periods for the non-comparative studies were not reported. All 3 studies were UK based.

5.2 Critial appraisal of studies and review of company's critical appraisal

The company included 6 studies in their submission (Doyle et al. 2011, Gopal et al. 2014, Hodd et al. 2009, Fletcher et al. 2009a, 2009b, and Smith et al. 2014). The EAC decided that 4 matched the scope and were therefore included in the final selection. The EAC added no other studies to the final list. The 2 studies by Fletcher et al. (2009a, 2009b) were abstracts, and reported data from the published study by Doyle et al. (2011) and were therefore superceded. The Hodd et al. (2009) abstract included outcomes not reported elsewhere that matched the scope and was therefore also added by the EAC, despite including the same patient population as in Doyle et al. (2011). The company did not submit a critical appraisal of the studies.

The company did not provide a quantitative or qualitative synthesis and did not present conclusions on the strength of the evidence presented.

Gopal et al. (2014) was the only study retrieved that was randomised and provided a comparator group. The study used an explicit and commonly used criteria for defining VAP (the HELICS definition). However, no information was provided about how samples were acquired and processed or what micro-organisms were present for the diagnosis of VAP. In addition, VAP diagnosis may be biased by subjectivity and therefore inter-observer variability may be high (Schurink et al. 2004, Klompas et al. 2010, Tejerina et al. 2010, Klouwenberg et al. 2013). No information was provided about inter-observer agreement of VAP diagnoses. The VAP incidence in the intervention and control arms (10.8% and 21% respectively) was beyond the outer bounds of the limits of the incidences found in the literature (9.3% to 20.3%, see section 3). The study population, high-risk cardiac surgery patients[1], was atypical for the wider critical care setting. Consequently, it is unclear how generalisable results are to the typical ICU setting in the NHS (for example in non-cardiac surgery or medical patient populations). In addition, the duration of intubation was 13-15 hours, which is shorter than in the scope (>24 hours). The authors discuss that the study shows there may be benefit of subglottic suctioning drainage and irrigation when the intubation time duration is less than 24 hours. This is not consistent with most VAP definitions that require that a patient has been intubated for at least 24-48 hours. The comparator in the study was a standard ETT without subglottic drainage. ETT with subglottic drainage (such as the Portex SACETT or Medtronic Shiley™ Evac Endotracheal tubes, both of which have subglottic drainage above the cuff) are commonly used in the NHS, and subglottic drainage is recommended in the ICS ventilator care bundle. One expert noted that the efficacy of PneuX in the Gopal RCT is consistent with other ETTs that have subglottic drainage, and contended that PneuX should be compared to such tubes. In terms of study outcomes the VAP episodes did not result in any increase in ICU stay, nor mortality. Therefore the clinical significance of the VAP episodes may require further investigation. Although Gopal et al. reported that the study was adequately powered, the EAC carried out further statistical calculations and found that the study is underpowered at a range of effect sizes for the alpha

[1] Patients aged over 70 years and/or impaired left ventricular function

and beta values chosen by the authors (0.01 and 0.9), as well as for more relaxed alpha and beta values (0.05 and 0.8).

The 2 remaining studies lacked direct comparators and were retrospective in design. The study populations were 48 and 53 ICU patients with a mean intubation time of 2.5 and 5.7 days (Smith et al. 2014, and Doyle et al. 2011 and Hodd et al. 2009 respectively). These studies reported low rates of VAP and unplanned extubations, but without a comparator it is impossible to draw any meanginful conclusions on the efficacy of PneuX. The patient population in Doyle et al. (2011) included people who were initially intubated with standard ETT and were exchanged to PneuX. The EAC highlights this heterogeneity in the patient population.

5.3 Results from the evidence base

Table 5 Summarised outcomes

Study	VAP incidence	Unplanned extubation rate	Mortality	ICU length of stay
Gopal 2014	PneuX: 10.8% Standard ETT: 21%	NR	PneuX: 1.66% Standard ETT: 0.83%	PneuX: 2 days Standard ETT: 1.5 days
Doyle 2011	PneuX: 1.8%	NR	PneuX: 35.8%	NR
Smith 2014	PneuX: 6.25%	17%	NR	NR
Hodd 2009	NR	0.1% (1.02 per 1000 intubation days)	NR	NR

VAP: ventillator associated pneumonia; NR: not reported

The primary outcome in the Gopal et al. (2014) RCT was the incidence of VAP, as confirmed by the HELICS definition. VAP incidence was significantly lower in the PneuX groups than in the standard ETT group (10.8% compared with 21%, p=0.03). There was no significant difference between the 2 groups in terms of length of ICU stay (2 days with PneuX compared with 1.5 days with standard ETT, p=0.2) and in-hospital mortality (99% survival with PneuX compared with 98% survival with standard ETT, p=0.2).

The incidence of VAP in the Smith et al. (2014) and Doyle et al. (2011) studies was 6.25% (95% CI 1.3% to 17%) and 1.8% (CI unreported) respectively. Smith et al. (2014) reported a 17% incidence of unplanned extubation, of which 5 incidents (10%) were classed as self-extubations.

Hodd et al. (2009) reported 1 incidence of extubation (self-extubation), resulting in an incidence of 0.1% (1.02 unplanned extubations per 1000 intubation days).

6 Adverse events

The company reported 3 adverse event incidents, which are detailed in Appendix C. All cases are marked as 'closed'.

The EAC carried out a search of the FDA MAUDE databases and found no reported adverse events. The EAC carried out a search of the MHRA database and confirmed 1 reported incident (MHRA reference: 2018/003/021/291/019) relating to the PneuX tube being damaged by the teeth of a patient due to excessive chewing. The patient was reintubated and suffered no long-term harm.

Expert advisors did not raise any safety concerns with use of PneuX.

7 Evidence synthesis and meta-analysis

Due to the lack of high quality design studies (only 1 RCT was included), no meta-analysis has been carried out.

8 Interpretation of clinical evidence

The company has stated that that all versions of PneuX are functionally the same, so study results are generalisable between versions. All studies were UK based, which supports generalisability to the NHS population.

The population in the most important study (Gopal et al. 2014) was high-risk cardiac surgery patients. Experts suggested that the incidence of VAP in this patient group is higher than populations in a general ICU setting. In addition, the intubation time (13-15 hours) and the follow-up (48 hours) were both of short duration. Incidence of VAP in patients with shorter intubation times may be confounded by possible community acquired infections, as well as the possibility that VAP might develop later. The EAC notes that although it does not strictly fit the scope (which includes intubation time of greater than 24 hours and less than 30 days), the study has been included because it is the only relevant RCT found in the literature. The population is not representative of the general ICU population, therefore the data may not be fully generalisable to ICU populations in the NHS. The EAC tested the power of the study and found it was underpowered for its primary outcome.

The study compared PneuX with ETT without subglottic drainage. One meta-analysis (Mao et al. 2016) reported that subglottic drainage alone was associated with significant reduction of VAP incidence (in 24 trials, relative risk (RR) of 0.55 [95% CI:0.48-0.63], $p<0.0001$; and in 4 high quality RCTs RR = 0.54, [95 % CI:0.40–0.74], $p < 0.001$). In addition tubes with subglottic drainage are widely used in the NHS and is recommended as part of the ventilator care bundle in the ICS guideline. Therefore, to extrapolate the results to the NHS and adequately investigate effectiveness against standard treatment, the PneuX would also need to be compared with tubes with subglottic drainage.

The variability in VAP definition may also hinder the generalisability of results to the NHS. One expert noted that incidence of VAP may be difficult to accurately define unless current, strict criteria for diagnosis are used. In addition, they also estimated that only around half of suspected cases of VAP

are confirmed with microbiology testing. Similarly, it was stated that defining incidence of aspiration is difficult to accurately and consistently assess. As a result data related to such measures may not be accurate or meaningful which may limit the clinical evaluation of the product. It is notable that the reduction of VAP in the PneuX group did not result in a concomitant reduction in mortality or length of ICU stay. One expert commented that without a reduction in these two outcomes, a reduction in VAP is not clinically meaningful.

The EAC noted wide variation in the secondary outcomes in the studies with mortality ranging from 1.6% to 35.8% and unplanned extubations from 0.1% to 17%. This indicates a high level of heterogeneity in the studies and reinforces the view that only the RCT should be considered with any degree of certainty.

8.1 Integration into NHS

In all 3 included studies, patients were selected from ICUs. Expert opinion indicates this is the most likely setting for using PneuX in the NHS. Adoption of PneuX over other ETT/TT tubes would not require any significant changes to the current care pathway.

The company offers a comprehensive training programme at no additional cost to the hospital/trust. A “Verification of Understanding” Certification is available on completion of the training programme. Training time is estimated to take 15-30 minutes. There are no other relevant human factors to consider.

8.2 Ongoing studies

No ongoing studies were identified by the company or by the EAC (see Appendix D for details of search).

9 Economic evidence

9.1 Published economic evidence

9.1.1 Search strategy and selection

A systematic search for economic evidence was not carried out by the company. Instead, all studies known to the company that reported economic evidence relevant to the decision problem (n=2) were included in the review of economic evidence. The EAC conducted its own search (see Appendix A) to confirm no relevant papers had been missed out. Following application of cost and economic filters, the searches retrieved 395 abstracts related to economic evidence. After reviewing these abstracts, the EAC confirmed that no economic evidence additional to the two studies by the company was available for the technology.

The company selected studies based on the scope: the population included adult patients requiring ventilation in a critical care (with a length of stay of 30 days or less); the intervention included the PneuX system compared with standard ETT; outcomes included any health economics outcomes. All economic studies, such as cost-minimisation and cost-effectiveness analyses were included. The exclusion criteria included studies estimating the cost of VAP that did not use the PneuX System. The EAC reviewed the inclusion and exclusion criteria and determined that they were appropriate. The EAC also used the same inclusion and exclusion criteria. The EAC did not locate any additional relevant studies.

9.1.2 Published economic evidence review

The company identified two relevant studies (Andronis et al. 2018 & NHS Innovation Accelerator, 2017). Both the studies compared the PneuX system with standard ETTs, and were conducted in the UK. Andronis et al. (2018) used a decision analytic model to undertake a cost-utility analysis. Though no model structure was explicitly stated, the other study (NHS Innovation Accelerator 2017) estimated cost savings with PneuX system using the same decision model structure as Andronis et al.

The study by NHS Innovation Accelerator (2017) undertook a cost-minimisation analysis comparing PneuX versus standard care. The key outcome of interest was the incidence of VAP and the impact on the cost of care. Data on the incidence of VAP following intubation with PneuX and standard intubation was taken from a UK-based, single-centre RCT which reported an indicated incidence of VAP using PneuX and under standard care of 10.8% and 20.8%, respectively (Gopal et al. 2014). The study assumed an additional treatment cost of £10,000 for patients contracting VAP. This estimate was sourced through a personal communication with a National Institutes of Health Fellow. Costs for PneuX and standard intubation devices were £150 and £5, respectively. The estimated cost saving associated with PneuX was £850 per intubation. This saving resulted from the additional costs of treating VAP in the standard care group, which substantially outweighed the higher acquisition costs PneuX. Although the population for the analysis included any patient receiving mechanical ventilation in critical care, effectiveness data came from a single study (Gopal et al. 2014) conducted in a subset of the population relevant to the scope (patients undergoing cardiac surgery).

Andronis et al. (2018) undertook a cost-utility analysis comparing intubation with PneuX and standard ETTs for patients requiring mechanical ventilation after cardiac operations. The study is similar to the NHS Innovation Accelerator study with respect to the structure of the decision model and uses the same source for effectiveness data (Gopal et al. 2014). The additional cost of treating VAP in Andronis et al. (2018) was estimated from observational data collected in a UK setting. Luckraz et al. (2018) report the cost of treating VAP based on data for patients in critical care following cardiac surgery. From a cohort of over 3,000 patients, 338 patients who contracted VAP were matched to patients who had not contracted VAP using propensity score matching. The matched cohort differed from the study by Gopal et al. in that patients were younger and a minority had impaired left ventricular function. The mean treatment cost for patients who did and did not contract VAP was £15,124 and £6,295, respectively, generating an additional treatment cost associated with VAP of £8,829. The vast majority of additional

costs were attributable to increased length of stay in critical care. Andronis et al. took health state utility values for patients with and without VAP from published literature (Edwards et al. 2012; Eddleston et al. 2002).

Andronis et al. (2018) reported a cost saving of £738 per patient for the PneuX system. In the cost-utility analysis, the PneuX system dominated standard ETT. Probabilistic sensitivity analysis suggested the likelihood that PneuX was cost-effective was 96% across the entire range of values from zero to £30,000 per QALY. The EAC noted that QALY estimates were driven by ICU length of stay, the outcomes of which are very different in the Luckraz et al. and Gopal et al. studies that contributed to the analysis by Andronis et al. The results were robust to extreme values of the key parameters in one-way analysis. The analysis is unusual in reporting a cost per case of VAP averted which did not account for VAP treatment costs. However, the cost-minimisation and cost-utility analyses included VAP treatment costs and appear to have been carried out appropriately.

9.1.3 Results from the economic evidence

The company's review concludes that both the studies are relevant to the decision problem and both indicate a cost saving for the PneuX system when compared to standard ETT without subglottic secretion drainage. The EAC concurs with the company's assessment. The EAC notes that both analyses rely on the same study to estimate the effectiveness of PneuX in suppressing VAP. This study is undertaken in a subset of the patient population in the scope and patients were intubated for short periods of time (typically less than 24 hours) and has a number of methodological shortcomings. For these reasons there is considerable uncertainty regarding the generalisation of the findings from the two analyses. Nevertheless, the EAC regards the literature as relevant and robust evidence to indicate that PneuX is cost saving when compared against standard tracheal tubes (without subglottic drainage).

9.2 Company de novo cost analysis

9.2.1 Cost model structure

The population for the analysis is adult patients requiring mechanical ventilation in critical care following major heart surgery. This constitutes a subgroup of the population of patients requiring mechanical ventilation in the scope. This choice reflects the available comparative clinical effectiveness (Gopal et al. 2014) and resource use data (Luckraz et al. 2018). As noted above, there are significant differences in the patient populations in these two studies (age and left ventricular function, as well as baseline VAP rate, which was 21% in Gopal et al. and 10% in Luckraz et al).

The technology used in the model is the PneuX System and compared to standard care (i.e. conventional ETT without subglottic secretion drainage), and is aligned with the scope. The company's submission has not considered alternative ETTs that have subglottic secretion drainage.

The model is a simple decision tree (structure in Figure 2) with a time horizon of less than one year. The analysis considers a time horizon limited to the initial hospitalisation following surgery. This period is likely to capture the vast majority of any cost impacts arising from the incidence of VAP and the EAC considers this short time horizon to be appropriate, although some patients may end up in the ICU requiring ventilation without having had surgery. The model applies the same structure as the economic model reported by Andronis et al. (2018). A hypothetical cohort of 1,000 patients requiring mechanical ventilation in critical care receive intubation with PneuX or a standard ETT. Patients in both arms are at risk of contracting VAP. The model assesses the total cost of care as the cost of treatment patients with or without VAP and the acquisition costs of PneuX or standard ETT. The EAC considers the simple model structure to be adequate to capture the cost and consequences of the technology.

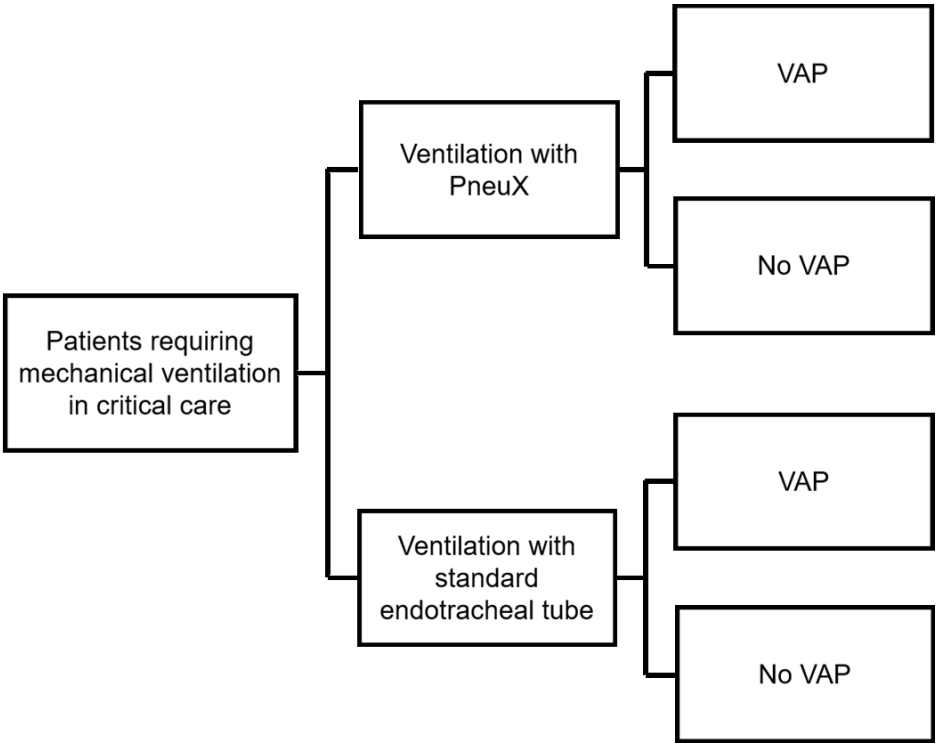


Figure 2 Economic model structure

The company's submission makes the following assumptions:

- There are no training costs associated with the implementation of PneuX
- There are no additional costs for placement of the PneuX when compared to alternative intubation (such as a bougie)
- Additional equipment required for subglottic drainage will continue to be provided free of charge
- The effectiveness of Pneux is similar across the range of severity of VAP infections
- The evidence on the effectiveness of PneuX can be generalised from cardiac patients to all patients in critical care
- The evidence on the additional cost of treating VAP can be generalised from cardiac patients to all patients in critical care
- There are no long term sequalae following treatment of VAP
- There is no additional mortality associated with VAP

- The relative reduction in VAP observed over short intubation times for the patients in Gopal et al. (2014) would be maintained over a longer period

The EAC regards these assumptions as acceptable with the exception of the generalisability of cardiac surgery patients to a wider critical care setting. Clinical experts stated that the high-risk cardiac surgery patient population in Gopal et al.'s study is not generalisable more widely. The EAC also notes caution assuming the generalisability of costs of treating VAP given the discrepancies in ICU length of stay in the studies referenced (Gopal et al. 2014, Luckraz et al. 2018). The EAC notes that an estimate of additional training costs is included in a sensitivity analysis. The EAC further notes that this estimate is generous and likely to cover the cost of additional equipment, such as a bougie, required to insert PneuX.

The company reports that the model implemented by Andronis et al. (2018), and upon which the company's submission is based, was validated by four critical care and cardiothoracic surgery clinicans.

9.2.2 Cost model parameters

The cost of treating VAP is taken from a recent UK based study which estimated the additional cost based on a large cohort of patients who contracted VAP matched to a similar cohort of patients who did not contract VAP. The EAC undertook a search of the cost of treating VAP and did not locate any other studies based in the UK. The EAC considers the study to be a robust and reliable estimate that is relevant to the NHS and the most appropriate source for this data. The EAC highlights the lack of a standardised or consensus definition for VAP and the variation in ICU length of stay in the studies contributing these parameters (Gopal et al. 2014, Luckraz et al. 2018).

9.2.3 Clinical parameters and variables

The key clinical parameters used in the model are the risk of VAP. The model uses a risk of VAP of 20.8% for standard ETT, and a risk of VAP in PneuX arm of 10.8%, as reported by Gopal et al. (2014). The EAC notes this study is

the only source for estimating the risk of VAP with PneuX and standard ETTs without drainage.

9.2.4 Resource identification, measurement and valuation

Costs attributable to VAP were sourced from Luckraz et al. (2018), who report a cohort study which estimated the cost to the NHS of treating patients in critical care following cardiac surgery who did and did not contract VAP. Costs from this study were also used in the published economic model by Andronis et al. (2018). Of 3,416 patients mechanically ventilated after cardiac surgery, 342 developed VAP. The 342 patients who developed VAP were matched with 342 patients who did not develop VAP using propensity score matching. The matching algorithm exploited a range of variables indicative of patient frailty such as creatinine, renal function and Euroscore. The matched cohort was well balanced on each variable. Costs for each patient were estimated on the basis of Healthcare Resource Group (HRG) codes in conjunction with NHS reference costs. Mean treatment costs for those who did and did not develop VAP were £15,124 and £6,295 (2013/14 GBP), respectively. The additional treatment cost associated with VAP was £8,829. This figure is driven entirely by the increased length of ICU stay for patients developing VAP compared to those who did not in this study (7.8 days (range 0-74) vs. 2.9 days (range 0-46), respectively).

The EAC considers this analysis to be a large, robust study, and the most relevant source of data on the additional cost of treating VAP in the NHS.

The use of PneuX requires staff time to attend training. The company has not included this cost in the base case analysis. The 15-30 minutes of training needed is modest, and unlikely to significantly add to the cost of PneuX when spread across the number of patient intubated over a year. The exclusion of this cost in the base case is acceptable to the EAC. The impact of including training costs is explored in sensitivity analysis.

9.2.5 Technology and comparators' costs

The PneuX system, currently used in the NHS, has a ITT-03 2017-19 Innovation and Technology Tariff of £150. The company applies this cost in the model.

The cost of a standard ETT was taken from the study by Andronis et al. (2018). In their economic model a cost of £5.00 is used, based on data from the procurement department of an NHS Trust.

The EAC finds the costs reasonable and appropriate.

9.2.6 Sensitivity analysis

The company has undertaken scenario analysis on three parameters: baseline risk of VAP (reduced from 20.8% to 10%), cost of standard ETT (reduced from £5 to £1.12) and training cost to use PneuX (assumed to be £10 per patient). Sensitivity analysis on the baseline risk of VAP was informed by a systematic review of 89 studies in a critical care setting (Safdar et al. 2005). The value of 10% represents the lower limit of the confidence interval. The EAC regards the scenario analysis examing the baseline risk of VAP to be relevant to consideration of the generalisability of findings to other populations. However, the EAC notes more recent evidence reporting VAP rates in the UK of 1.4% (NHS Scotland, 2017). The cost of a standard ETT is unlikely to influence the overall additional cost of PneuX. Nevertheless, the sensitivity analyses on the cost of the standard tube and potential training costs are relevant to determining the robustness of results to these parameters.

The company has undertaken a two-way sensitivity analysis of the baseline risk of VAP and the relative risk of VAP with PneuX. Baseline risk was varied from 0-50% and the relative risk of VAP with PneuX was varied from 0 to 1. Additional one-way sensitivity analysis of the cost of treating VAP has been undertaken. The EAC considers the sensitivity analyses to be robust and exhaustive with regard to the impact of parameter uncertainty.

The company undertook a probabilistic sensitivity analysis (PSA) to characterise the impact of uncertainty in the model parameters. Appropriate distributions were selected for model parameters; the variance of the distributions were informed from 95% confidence intervals derived from parameter sources. Training costs were not included in the PSA.

9.3 Results from the cost analysis

9.3.1 Base case results

Table 6 Summary of base case results

	Company's results		
	Technology	**Comparator**	**Cost saving per patient**
Device	£150	£5	£145
Expected cost of VAP	£956	£1,839	-£883
Total	£1,106	£1,844	**-£738**

The company's analysis indicates PneuX is associated with a saving of £738 per patient. This saving arises from an absolute reduction in the risk of VAP of around 10% (from 20.8% to 10.8%) and the estimated additional cost of treating VAP of around £9,000. As a result, PneuX generates a cost offset of around £900 which is considerably greater than the additional cost of PneuX when compared to a standard ETT. The EAC accepted the cost model submitted by the company and has not made alterations to the model.The EAC notes that there are alternative drained ETTs. The EAC has undertaken further cost analysis to consider the relative cost of using PneuX compared to an alternative ETT with subglottic secretion drainage.

9.3.2 Sensitivity analysis results

In the company's submission, PneuX remained cost saving in scenario analysis in which the baseline risk of VAP was 10%, and in which the cost of a standard ETT was reduced to £1.12 or an additional cost of £10 was assumed for PneuX for training. The assumption of lower costs for the standard ETT or additional training costs for PneuX had little impact on the results. This finding supports the assertion that the inclusion of additional equipment costs, such as a bougie, to insert PneuX is unlikely to change the conclusion that PneuX is cost saving. The cost saving with PneuX was considerably reduced when the baseline risk of VAP was reduced to 10%, but Pneux remained cost saving (Table 7).

Table 7 Company sensitivity analyses

	Mean cost per patient - PneuX (£)	Mean cost per patient – standard tube (£)	Difference in cost per patient (£)
Scenario 1 – baseline risk of VAP of 10%	£609	£888	-£279
Scenario 2 – cost for standard tube £1.12	£1,106	£1,840	-£734
Scenario 3 – training cost of £10 per patient	£1,116	£1,844	-£728

One-way sensitivity analysis of the additional cost of treating VAP indicates that PneuX is cost saving if the cost of treating VAP is as low as £4,000. The break-even point for the cost of treating VAP to offset the cost of the use of PneuX is not reported but extrapolation of plotted data indicates a value of approximately £2,000.

In the two-way analysis of the baseline risk of VAP and the relative effectiveness of PneuX, PneuX remained cost saving for most combinations of the two parameters. At 5% baseline risk of VAP, PneuX becomes cost saving at a relative risk of 0.6 or less. At a 10% baseline risk of VAP, PneuX becomes cost saving at a relative risk of 0.8 or less. At a 20% baseline risk of VAP, PneuX is cost saving at a relative risk of 0.9 and below. The EAC notes that the 95% confidence interval for relative risk in the Gopal RCT is 0.28-0.97, the higher bound of which would indicate PneuX is cost incurring with a ≤20% baseline risk of VAP.

The PSA indicates that there is a 96% likelihood that PneuX is cost-saving compared with ETTs without subglottic drainage given the uncertainty in parameters (and assuming that the structural assumptions are correct).

The EAC considers the sensitivity analysis to have exhaustively explored the impact of parameter uncertainty on the decision. This analysis indicates that the finding the PneuX is cost saving is robust to parameter uncertainty. The two-way sensitivity analyses gives confidence that inference on costs are

generalisable to other populations where it is possible that PneuX is less effective compared to standard ETTs without drainage or the baseline risk of VAP is lower.

9.3.3 Additional results

The EAC is aware that there are other ETTs with subglottic drainage available. The EAC undertook additional analysis in which an alternative ETT with subglottic secretion drainage, the Portex Blue Line (SACETT™ Suction Above Cuff ET Tube), was included as a comparator. The evidence on the effectiveness of this tube is limited. The EAC notes two relevant sources. Firstly, a meta-analysis which combined data on all ETTs with subglottic drainage and compared results with tubes without subglottic secretion drainage (Mao et al. 2016). Second, a trial of the Portex Blue Line against a standard (undrained) ETT (Jena et al. 2016). Mao et al. (2016) combined data from 20 studies and 3544 patients and reported a relative risk of VAP. Subglottic secretion suction was associated with reduction of VAP incidence in four high quality trials; the relative risk was 0.54 (95% CI 0.40-0.74, p<0.00001). The finding was robust to sensitivity analysis. The study by Jena et al. (2016) is a small trial in which 54 patients were randomised to receive intubation using the Portex Blue Line tube or a standard undrained ETT. Fifty patients (25 in each arm) were available for follow-up. The incidence of VAP was 12% in the patients intubated with the drained ETT compared to 20% in the comparator arm. The difference was not statistically significant due to the small sample size.

The EAC estimated the cost of the Portex Blue Line at £20 based on a US price of $240 for a box of 10. The EAC estimated a relative risk of VAP of 0.6 based on the data from Jena et al. (2016). The results of the cost analysis are tabulated below alongside the base case analysis submitted by the company.

Table 8 Base case analysis of PneuX versus Portex SACCET

	PneuX	**Portex Blue Line (SACETT)**	**Undrained tube**	**Cost saving PneuX vs Portex**
Device	£150	£20	£5	£130

Expected cost of VAP	£956	£1,104	£1,839	-£148
Total	£1,106	£1,124	£1,844	-£18

In the extended analysis, PneuX is cheaper than Portex Blue Line (SACETT) due to slightly increased effectiveness (RR for PneuX of 0.52 compared to 0.6 for Portex) which offsets the higher acquisition cost of PneuX.

It should be noted the the effectiveness of Portex is based on data from a very small trial. The trial results were not statistically significant, although consistent with data from the meta-analysis of the effectiveness of ETTs with subglottic drainage. It should also be noted that the above analysis did not consider the additional cost of any other equipment required to operate subglottic drainage with the Portex Blue Line. If, as seems reasonable, PneuX and Portex Blue Line are of equivalent effectiveness the difference in overall costs would be equivalent to the difference in acquisition costs minus any additional equipment costs for Portex Blue Line (per patient).

9.4 EAC Interpretation of economic evidence

The EAC did not amend the company's cost model. It did undertake additional analysis to consider the overall cost impact of an alternative ETT with subglottic secretion drainage. The company concludes that there is a high degree of certainty that PneuX is cost saving. The company notes the uncertainty arising when generalising the findings from acute coronoary patients to other patients in critical care. The company considers this to be mitigated through the sensitivity analysis which indicates that the PneuX remains cost saving at much lower risk of VAP and a much higher (less effective) relative risk of VAP with PneuX.

The company notes some limitations with trial of PneuX which provides the evidence of the effectiveness of PneuX (Gopal et al. 2014). The population in this trial was restricted to patients undergoing major heart surgery and most patients were intubated for less than 24 hours. The company also noted some limitations to the study which estimated the cost of treating VAP in the UK. Finally, the company noted the limitations of the relatively simple modelling approach which does not distinguish severity of VAP.

A strength of the company's model is the UK source of the data underpinning the analysis, which increases relevance to NHS practice.

The EAC is broadly in agreement with the company's assessment of the cost implications when comparing the PneuX system with standard ETTs without subglottic secretion drainage. The EAC views the assessment of the cost of treating VAP in the NHS to be robust and directly relevant to the scope, although length of ICU stay was significantly different between the studies contributing these parameters. The EAC considers the robustness of the findings in sensitivity analysis to be reassuring considering the small size of the studies underpinning the estimates of the cost of treating VAP or the effectiveness of PneuX. The EAC did not consider the simple structure of the model to be a limitation and did not regard a more complex evaluation considering the severity of VAP to be necessary.

The EAC notes that the cost model in the submission is almost entirely the same as that in the study by Andronis et al. (2018). Therefore the similarity of results is unsurprising. This supports the assertion that the two analyses have been implemented without errors but does not provide further reassurance from the confluence of results in the two analyses. The remaining limitation is that the effectiveness of PneuX is based on a single study with short intubation times. The publications by Andronis, Luckraz and Gopal et al. all share co-authors, which introduces the possibility that methodological biases are common to all studies.

The EAC regards the modelling approach, parameter selection and sensitivity analysis undertaken in the company's submission to be appropriate. Whilst concerns remain regarding the extent of generalisability of findings on effectiveness of PneuX from Gopal et al. (2014), the cost analysis indicates that PneuX is highly likely to be cost saving, and almost certainly cost-effective, when compared with a standard ETT without subglottic secretion drainage. The EAC supports the company's assessment that there is a fair degree of certainty that PneuX is cost saving compared with standard ETTs without drainage.

The EAC notes that there are other ETTs that are considerably cheaper. The EAC's own analysis indicates that PneuX remains cost saving when compared against an alternative tube with subglottic secretion drainage. This finding rests on the superiority of PneuX in averting VAP compared to Portex Blue Line (SACETT), based on two underpowered RCTs (Gopal et al. 2014, Jena et al. 2016). A systematic review and meta-analysis by Mao et al. (2016) considered all ETTs with drainage similar enough to pool data across 20 trials. The relative risk reported in the meta-analysis of 0.55 is in line with the Gopal and Jena RCTs (0.52 and 0.60, respectively), which indicates that any ETT with drainage is likely to be cost effective. In this scenario PneuX could not be considered superior and cost-effectiveness would be driven by the price of the tube. The finding also rests on an assumption that any additional equipment cost to operate ETTs with drainage is minimal when spread over the total number of patients benefitting. Clinical experts expressed the view that tubes with drainage are now considered standard in the NHS and are recommended in the ICS ventilator care bundle.

10 Conclusions

10.1 Conclusions on the clinical evidence

The evidence for PneuX comprises 2 non-comparative retrospective cohort studies (in 3 publications) and 1 non-blinded RCT, which is the pivotal study for this assessment report. The study (Gopal et al. 2014) indicates that the use of PneuX significantly decreases incidence of VAP in high-risk cardiac surgery patients compared with a standard ETT without subglottic drainage. The secondary endpoints (ICU length of stay and mortality) did not significantly differ between the two study cohorts.

The evidence from the non-comparative studies is more generalisable to the wider critical care setting, but the lack of a control group makes it impossible to draw any conclusions about the efficacy of PneuX. The wide range of reported values for some of the secondary outcomes, such as mortality, further decreases confidence in these studies. However, the rates of VAP and unplanned extubations are very low in these studies.

- **Does the evidence present an unbiased estimate ot the technology's treatment effect?**

The evidence based is very limited, comprising only 1 published comparative study, and the biases inherent in this study mean it is difficult to estimate the treatment effect reliably.

- **Was the treatment effect relevant to the population, intervention, comparators and outcomes in the decision problem?**

The patient population in the Gopal RCT is very specific (high-risk cardiac surgery patients) and the results may not be generalisable to the wider critical care setting. Additionally, the intubation time was shorter than that specified in the scope[2]. The comparator in this study is a standard ETT, whereas tubes with subglottic secretion drainage tubes are commonplace in the NHS and subglottic drainage is recommended as part of the ICS ventilator care bundle and therefore would be a more suitable comparator to PneuX. The study

[2] However, it has been included due to the paucity of other evidence.

showed no significant differences in length of ICU stay or mortality, outcomes the experts highlighted as being particularly clinically meaningful.

- **Is there evidence on any important subgroups?**

The available evidence does not report subgroup outcomes.

- **Are there any other important uncertainties in the clinical evidence?**

There is no standardised definition of VAP and studies have shown there is an element of subjectivity in diagnosis (see section 3). Therefore, there are inherent uncertainties in VAP research. It is important that a diagnostic method contain a high level of detail so it is replicable and reliable, although this necessarily makes it more difficult to use in clinical settings.

There is very little published evidence for PneuX (3 studies included in 4 publications[3]). The most important study has a number of weaknesses: it is underpowered for its primary endpoint (VAP incidence), it has an atypical population for an NHS ICU (high risk cardiac surgery patients), and it does not include the most NHS-relevant comparator (ETT with subglottic drainage).

10.2 Conclusions on the economic evidence

The cost analysis undertaken by the company provides relatively strong evidence that PneuX is cost saving when compared to standard ETTs without subglottic secretion drainage. The cost of the technology is modest compared to the cost of treating VAP, which is a relatively common infection for intubated patients. However, these costs are driven by the extended length of ICU stay and there is no evidence for PneuX reducing this. The two-way sensitivity analysis undertaken by the company on the risk of VAP and the effectiveness of PneuX supports this – the technology was cost saving across a broad range of combinations of the two parameters. If PneuX is effective it is highly likely to be cost saving over standard tubes that do not have subglottic secretion drainage.

[3] Not incidentally, the evidence base has not changed in the last four years – the evidence presented here is the same as that in MIB45 on PneuX, published in 2015.

Robust evidence on the effectiveness of PneuX appears to be limited to a single underpowered RCT. The evidence from that trial would suggest that PneuX is effective at reducing VAP. However, the EAC notes that incidence of VAP in the control arm of that study was high. Hence, some uncertainty remains with regard to the effectiveness of PneuX. It is possible that the difference on VAP infection rates with PneuX and standard endotracheal intubation may narrow over longer intubation times and in different patient populations. Therefore, the limitations on inference on cost impact rest on the generalisability of the data on effectiveness.

The economic evidence submitted by the company is supported by 3 studies, which contribute different elements to the cost-effectiveness model. The study by Luckraz et al. (2018) provides values for the additional costs associated with developing VAP. The RCT by Gopal et al. (2014) provides the clinical effectiveness of PneuX (versus standard ET tubes) in preventing VAP. Finally, Andronis et al. (2018) provide the cost-effectiveness analysis of PneuX, with parameters sourced from the other two studies. The company's model is very similar to that used by Andronis et al. The EAC examined the model and found that the approach chosen and the assumptions made are acceptable for this kind of technology. The model shows PneuX to be cost-saving in a broad range of scenarios tested by sensitivity analyses. However, there are a number of areas of uncertainty surrounding the economic evidence. Firstly, the results rely entirely on the Gopal RCT, which, as discussed elsewhere in this report, has a number of methodological limitations, including the fact the study is underpowered and that the baseline rate of VAP is outside the range reported elsewhere in the literature. Secondly, it is not possible to say whether the patient population in the Gopal RCT (high risk cardiac surgery patients with very short intubation times) is generalisable to a wider critical care cohort. Thirdly, the evidence for additional costs associated with VAP comes from a study (Luckraz et al. 2018) that used a different definition of VAP to the Gopal RCT[4]. Fourthly, the cost data is derived from extended length of ICU stay and

[4] Gopal et al used the HELICS criteria, while Luckraz et al used the clinical element of the HELICS criteria in combination with the CDC 2008 definition.

Pneux has not been shown to reduce this. Finally, the 3 studies that support the company's model all share a number of co-authors and while this does not directly imply they are methodolically flawed, it raises the possibility that they have biases in common.

The EAC is of the view that there is minimal evidence to support the superiority of PneuX over other ETTs with subglottic drainage. Application of any ETT with subglottic drainage is likely to generate significant cost savings from VAP averted. Selection of the most appropriate drainage technology might best be guided by acquisition costs (including any additional equipment required) and preferences of the clinical staff.

11 Summary of the combined clinical and economic sections

There is a distinct lack of evidence for PneuX, with only 1 comparative study published (the Gopal RCT). Although the primary endpoint of VAP incidence was significantly in favour of PneuX, the study has a number of methodological flaws and there is significant uncertainty about its reliability.The non-comparative evidence was generally poorly reported and did not contain enough information to add certainty to the RCT. The economic evidence shows the PneuX is almost certainly cost saving over standard ET tubes that do not have subglottic secretion drainage. The evidence is more equivocal when PneuX is compared to tubes with drainage. However, there are a number of uncertainties surrounding the economic evidence, not least that the outcomes depend on the Gopal RCT, as well as the fact that additional costs are caused by increased length of ICU stay, rather than VAP incidence itself. PneuX has not been shown to reduce length of ICU stay.

In conclusion, the incidence of VAP could be considered a surrogate endpoint for more clinically and economically meaningful outcomes, such as ICU/hospital length of stay or mortality (Luckraz et al. 2018 derived their estimate for the cost of VAP from extended length of ICU and hospital stay in those patients). The evidence shows that PneuX does not reduce ICU length of stay or mortality, which means that, irrespective of the significant reduction

of VAP found in the Gopal RCT, it is very difficult to conclude the device is clinically or cost effective.

12 Implications for research

The weak existing evidence based for PneuX needs to be expanded in a number of important areas. More evidence is required on the following points:

- Comparative evidence on a study population that is representative of an NHS ICU
- Comparison of VAP incidence in PneuX versus tubes with subglottic drainage
- Comparison of length of ICU/hospital stay as the primary outcome in PneuX versus relevant comparator
- More detailed, up-to-date and stringent criteria for defining VAP
- Comparative evidence on the effectiveness of care bundles for reducing VAP alongside PneuX or other ETTs

References

Andronis, L., R. A. Oppong, N. n. Manga, et al. (2018) "Is the Venner-PneuX Endotracheal Tube System a Cost-Effective Option for Post Cardiac Surgery Care?" The Annals of Thoracic Surgery 106(3): 757-763

Blot, S., D. Koulenti, G. Dimopoulos, et al. (2014) "Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old, and very old critically ill patients*." Crit Care Med 42(3): 601-609

Doyle, A., A. Fletcher, J. Carter, et al. (2011) "The incidence of ventilator-associated pneumonia using the PneuX System with or without elective endotracheal tube exchange: A pilot study." BMC research notes 4(92-92

Eddleston, J. M., P. White and E. Guthrie (2000) "Survival, morbidity, and quality of life after discharge from intensive care." Crit Care Med 28(7): 2293-2299

Edwards, S. J., S. Wordsworth and M. J. Clarke (2012) "Treating pneumonia in critical care in the United Kingdom following failure of initial antibiotic: a cost-utility analysis comparing meropenem with piperacillin/tazobactam." Eur J Health Econ 13(2): 181-192

Fletcher, A. (2009) "Lotrach tracheal tube airway symptom surveillance following critical care." A251

Fletcher, A., J. Carter, M. Blunt, et al. (2009) "Incidence of ventilator-associated pneumonia in patients undergoing elective tube exchange to LoTrach endotracheal tubes." Critical Care 1)(S122

Gopal, S., H. Luckraz, R. Giri, et al. (2014) "Significant reduction in ventilator-associated pneumonia with the Venner-PneuX System in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia study†." European Journal of Cardio-Thoracic Surgery 47(3): e92-e96

Hart, R., M. S., M. S., et al. (2018) "Influence of tracheostomies, sub-glottic suction endotracheal tubes and routine chlorhexidine on the rate of suspected ventilator-associated pneumonia in Scottish intensive care units." Intensive Care Medicine Experimental 6(Supplement 2): 0075

Hodd, J., A. Doyle, M. Irvine, et al. (2009) "Preventing unplanned extubation with the Pneux P.Y. System (LoTrach) - An engineered solution." Critical Care Medicine 37 (12 SUPPL.)(A192

Klein Klouwenberg, P. M., D. S. Ong, L. D. Bos, et al. (2013) "Interobserver agreement of Centers for Disease Control and Prevention criteria for classifying infections in critically ill patients." Crit Care Med 41(10): 2373-2378

Klompas, M. (2010) "Interobserver variability in ventilator-associated pneumonia surveillance." American Journal of Infection Control 38(3): 237-239

Luckraz, H., N. Manga, E. L. Senanayake, et al. (2018) "Cost of treating ventilator-associated pneumonia post cardiac surgery in the National Health Service: Results from a propensity-matched cohort study." Journal of the Intensive Care Society 19(2): 94-100

Mao, Z., L. Gao, G. Wang, et al. (2016) "Subglottic secretion suction for preventing ventilator-associated pneumonia: an updated meta-analysis and trial sequential analysis." Critical Care (London, England) 20(1): 353

Melsen, W. G., M. M. Rovers, R. H. Groenwold, et al. (2013) "Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies." Lancet Infect Dis 13(8): 665-671

Morris, A. C., A. W. Hay, D. G. Swann, et al. (2011) "Reducing ventilator-associated pneumonia in intensive care: impact of implementing a care bundle." Crit Care Med 39(10): 2218-2224

NHS Scotland (2017) “Audit of Critical Care in Scotland 2017 Reporting on 2016” (https://www.sicsag.scot.nhs.uk/docs/2017/2017-08-08-SICSAG-Report.pdf?24) Accessed 07-Aug-2019

Pugh, R., W. Harrison, S. Harris, et al. (2016) "Is HELICS the Right Way? Lack of Chest Radiography Limits Ventilator-Associated Pneumonia Surveillance in Wales." Frontiers in Microbiology 7(1271-1271

Rello, J., D. A. Ollendorf, G. Oster, et al. (2002) "Epidemiology and outcomes of ventilator-associated pneumonia in a large US database." Chest 122(6): 2115-2121

Safdar N, Dezfulian C, Collard HR, et al. (2005) Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 33(10): 2184-93.

Schurink, C. A. M., C. A. V. Nieuwenhoven, J. A. Jacobs, et al. (2004) "Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability." Intensive Care Medicine 30(2): 217-224

Senanayake, E. L., R. Giri, S. Gopal, et al. (2017) "Incidence of endotracheal tube colonization with the use of PneuX endotracheal tubes in patients following cardiac surgery." Journal of Hospital Infection 95(1): 81-86

Shah, N., H. J., Z. P., et al. (2018) "A point prevalence study of ventilator associated pneumonia (VAP) across four London ICUs." Intensive Care Medicine Experimental 6(Supplement 2): 0176

Smith, N., F. Khan and A. Gratrix (2014) "A Retrospective Review of Patients Managed with the Pneux PY™ VAP Prevention System." Journal of the Intensive Care Society 15(2): 99-103

Tejerina, E., A. Esteban, P. Fernández-Segoviano, et al. (2010) "Accuracy of clinical definitions of ventilator-associated pneumonia: Comparison with autopsy findings." Journal of Critical Care 25(1): 62-68

Wallace, F. A., P. D. G. Alexander, C. Spencer, et al. (2015) "A comparison of ventilator-associated pneumonia rates determined by different scoring systems in four intensive care units in the North West of England." Anaesthesia 70(11): 1274-1280

YHEC (2017) “NHS Innovation AcceleratorEconomic Impact Evaluation Case Study:PneuX™” (https://nhsaccelerator.com/wp-

content/uploads/2017/10/PneuX-Economic-Case-Study-YHEC-August-2017.pdf) Accessed 06-Aug-2019.

Appendices

- Appendix A: search strategies and PRISMA diagram
- Appendix B: methodological appraisal of included and excluded studies
- Appendix C: adverse events
- Appendix D: ongoing studies
- Appendix E: economic evidence

Appendix A

Total number of records retrieved: 5475

Total following de-duplication: 3770

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to July 03, 2019
- Search date: 5th July 2019

1	pneux*.af.	7
2	(Iotrac? or Io-trac? or Io trac?).mp,in.	5
3	qualitech*.af.	1
4	venner-pneux*.af.	2
5	or/1-4	12
6	Pneumonia, Ventilator-Associated/	3192
7	Intubation/ or Intubation, Intratracheal/ or exp Airway Management/	114862
8	6 and 7	1014
9	((vap or pneumonia or ((ICU or ITU) adj2 (length of stay or duration)) or aspiration) adj5 (intubat* or extubat* or tracheal tube* or endotracheal tube* or tracheostomy tube*)).tw.	1126
10	5 or 8 or 9	2029
11	limit 10 to yr="2007 -Current"	1566

- Embase 1974 to 2019 Week 26
- Search date: 5th July 2019

1	pneux*.af.	18
2	(lotrac? or lo-trac? or lo trac?).mp,in,mv,my,dm,dv.	13
3	qualitech*.af.	6
4	venner-pneux*.af.	3
5	or/1-4	32
6	ventilator associated pneumonia/	9716
7	exp assisted ventilation/	153859
8	6 and 7	1446
9	((vap or pneumonia or ((ICU or ITU) adj2 (length of stay or duration)) or aspiration) adj5 (intubat* or extubat* or tracheal tube* or endotracheal tube* or tracheostomy tube*)).tw.	1984
10	5 or 8 or 9	3282
11	limit 10 to yr="2007 -Current"	2680

- Cochrane (CDSR and CENTRAL)
- Search date: 5th July 2019

ID	Search	Hits
#1	pneux*	6
#2	(lotrach or lo-trach or lo trach) or (lotrack or lo-track or "lo track")	5
#3	qualitech*	1
#4	venner-pneux*	3
#5	{OR #1-#4}	13
#6	[mh "Pneumonia, Ventilator-Associated"]	357
#7	[mh Intubation] or [mh "Intubation, Intratracheal"] or [mh "Airway Management"]	10194
#8	#6 and #7	125
#9	((vap or pneumonia or ((ICU or ITU) NEAR/2 ("length of stay" or duration)) or aspiration) NEAR/5 (intubat* or extubat* or "tracheal tube*" or "endotracheal tube*" or "tracheostomy tube*"))	490
#10	#5 or #8 or #9 with Cochrane Library publication date from Jan 2007 to present	456

- Web of Science

- Search date: 8th July 2019

# 7	759	#6 OR #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019
# 6	748	TS=((vap or pneumonia or ((ICU or ITU) NEAR/2 ("length of stay" or duration)) or aspiration) NEAR/5 (intubat* or extubat* or "tracheal tube*" or "endotracheal tube*" or "tracheostomy tube*")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019
# 5	16	#4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019
# 4	3	TS=(venner-pneux*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019
# 3	1	TS=(qualitech*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019
# 2	6	TS=((lotrach or lo-trach or lo trach) or (lotrack or lo-track or "lo track")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019
# 1	11	TS=(pneux*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2019

- Grey literature sources
- Search date: 8th July 2019

SOURCE	TERMS	RESULTS
https://caod.oriprobe.com	PneuX	0
https://ntrl.ntis.gov/NTRL/	PneuX	
https://webarchive.nationalarchives.gov.uk	PneuX	107
http://www.opendoar.org	PneuX	0
https://patents.google.com	("pneux") language:ENGLISH	3

- ClinicalTrials.gov
- Search date: 8th July 2019

TERMS	RESULTS
pneux OR lotrach OR lo-trach OR lotrack OR lo-track OR qualitech OR venner-pneux OR "lo trach" OR "lo track"	0

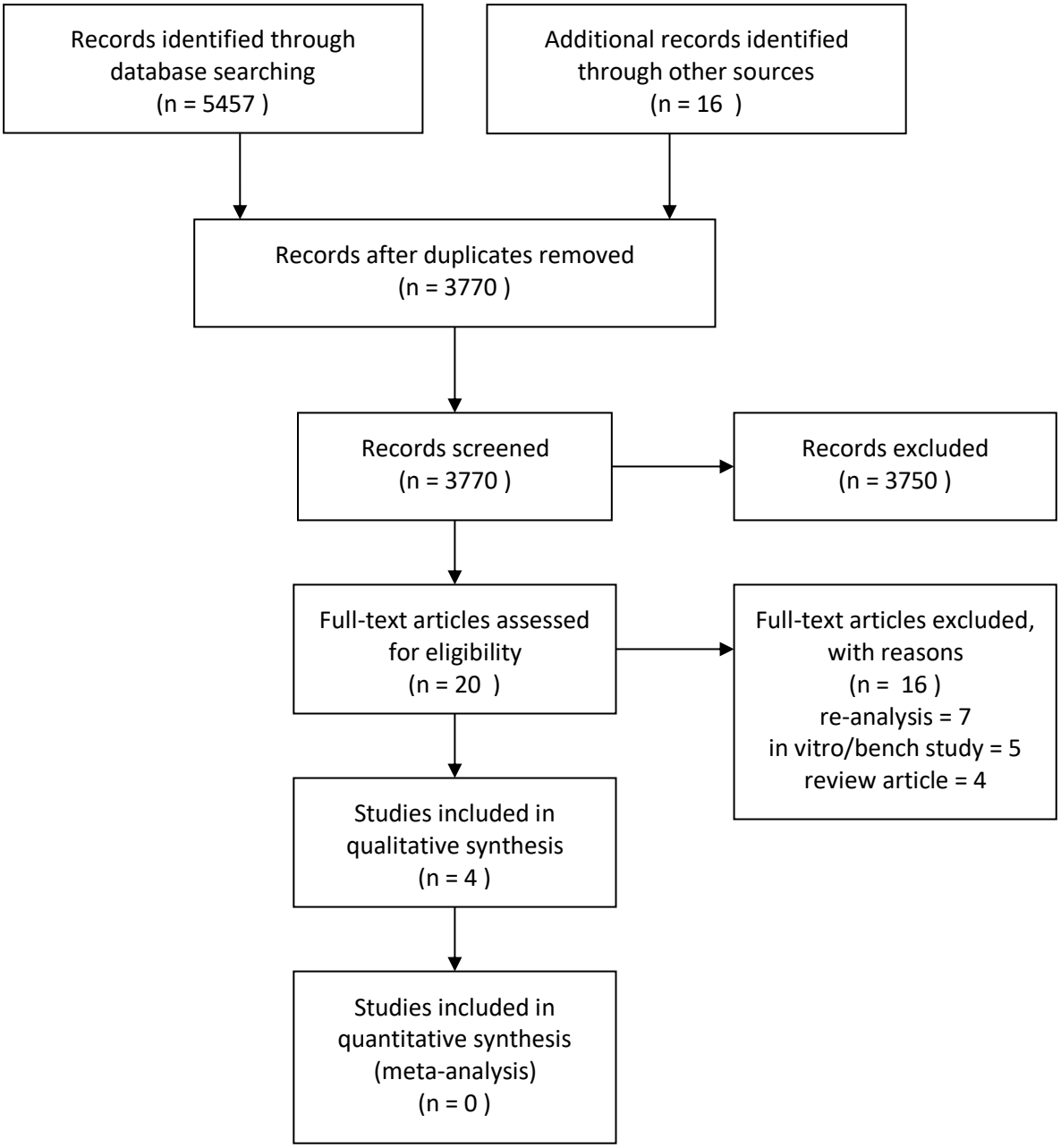
- WHO ICTRP
- Search date: 8th July 2019

TERMS	RESULTS
pneux OR lotrach OR lo-trach OR lotrack OR lo-track OR qualitech OR venner-pneux OR "lo trach" OR "lo track"	1

- PROSPERO
- Search date: 8th July 2019

Line	**Search for**	**Hits**
#1	pneux	0
#2	lo-trach	0
#3	qualitech	0
#4	venner-pneux	0

PRISMA 2009 Flow Diagram



Appendix B

Table 9 Methodologies of company and EAC included studies

Study and type	population	intervention	comparator	outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Doyle (2011) Retrospective non-comparative single-centre cohort study	UK NHS ICU, 53 consecutive patients (22 female (41.5%), mean age 67.8-yrs [s.d 15]).	PneuX, mean intubation time of 5.3 days.	N/A	VAP	PneuX ETT	Company included EAC included
Gopal (2014) Prospective non-blinded single-centre RCT	UK NHS cardiac ICU, high-risk patients undergoing cardiac surgery (age >70-yrs and/or impaired left ventricular function, LVEF <50%).	Pneux, mean intubation time of 15 hours	Conventional endotracheal tube	(Primary) VAP (Secondary) CPB time, ICU stay, re-exploration and survival.	PneuX ETT	Company included EAC included
Hodd (2009) Retrospective non-comparative single-centre cohort study	UK NHS ICU, 185 intubations between 2006 and 2009 (all intubated ICU patients).	PneuX, mean intubation time of 5.3 days.	N/A	Self-extubation	PneuX ETT	Company included EAC included

Smith (2014) Retrospective non-comparative single-centre cohort study	UK NHS ICU, 48 ICU patients, recruited in 2010	PneuX, median intubation time was 59.3-hours; 71% of patients were exchanged to PneuX from standard endotracheal tube after a mean intubation time of 13 hours 41 minutes.	N/A	VAP Unplanned extubations	PneuX ETT	Company included EAC included
Fletcher (2009a) Retrospective non-comparative single-centre cohort study	UK NHS ICU, 53 consecutive patients (22 female (41.5%), mean age 67.8-yrs [s.d 15]).	PneuX, mean intubation time of 5.3 days.	N/A	VAP	PneuX ETT	Company included EAC excluded The patient population is the same as in Doyle et al (2011) and this publication included no additional outcomes relevant to the scope.
Fletcher (2009b) Retrospective non-comparative single-centre cohort study	UK NHS ICU, 53 consecutive patients (22 female (41.5%), mean age 67.8-yrs [s.d 15]).	PneuX, mean intubation time of 5.3 days.	N/A	VAP	PneuX ETT	Company included EAC excluded The patient population is the same as in Doyle et al (2011) and this publication included no additional outcomes relevant to the scope.

Senanayake (2017) Prospective non-blinded single-centre RCT	UK NHS cardiac ICU, high-risk patients undergoing cardiac surgery (age >70-yrs and/or impaired left ventricular function, LVEF <50%).	Pneux, mean intubation time of 15 hours	Conventional endotracheal tube	Microbial analysis	PneuX ETT	Company included EAC excluded The study is a re-analysis of Gopal (2014) and the new outcomes are not relevant to the scope.

Table 10 Summary of the strengths and weaknesses of the trial incorporating internal and external validity

Gopal (2014)		
	Strengths	**Weaknesses**
Study design	Prospective RCT, with well matched baseline characteristics	Primary endpoint of VAP does not necessarily reflect clinical significance in this patient group. It does not appear to be a surrogate outcome for increased length of stay or mortality.
Patient selection	The patient population is a homogeneous, indicating strong internal validity.	The inclusion of only high-risk cardiac surgery patients limits the generalisability of this study. This patient group is not necessarily reflective of the wider population who are eligible to use PneuX.
Randomisation	The randomisation protocol was effective, as indicated by the well-matched baseline characteristics between the groups.	-
Blinding	-	The study was not blinded which increases the risk of performance bias.
Patient attrition	There were no drop outs during this study.	The short intubation time means that the likelihood (or opportunity) for dropouts was very limited.

Reporting of outcomes	Primary endpoint (VAP) is defined using international criteria (HELICS)	The short intubation time may have excluded potential cases of VAP (increasing the possibility of detection bias) and the follow-up of patients was also very short, which may have excluded other relevant outcomes. The HELICS criteria has a number of different sections and these are not reported individually.
Statistical analysis	-	The power calculation is incorrectly reported and the EAC calculates that the study is underpowered at the effect size reported. It is also underpowered had the input data reflected both NIHR trial specifications and the outcomes found in the study itself.
Study company	The study was funded by the Department of Health, UK, which reduces the likelihood of publication bias.	-

Table 11 Methodological quality of RCT

Study identification Gopal (2014)					
Checklist completed by: TM					
		Circle or highlight one option for each question:			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors	**Yes**	~~No~~	~~Unclear~~	
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	~~Yes~~	~~No~~	**Unclear**	**The groups were well matched following randomisation so this was unecessary.**
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	**Yes**	~~No~~	~~Unclear~~	
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			

Likely direction of effect: **N/A**					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	**Yes**	~~No~~	~~Unclear~~	
B2	Participants receiving care were kept 'blind' to treatment allocation	~~Yes~~	**No**	~~Unclear~~	
B3	Individuals administering care were kept 'blind' to treatment allocation	~~Yes~~	**No**	~~Unclear~~	
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	**Unclear/unknown risk**	~~High risk of bias~~			
Likely direction of effect: **Unknown, if any**					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	**Yes**	~~No~~	~~Unclear~~	
C2	a. How many participants did not complete treatment in each group? **0 in both groups**				
	b. The groups were comparable for treatment completion	**Yes**	~~No~~	~~Unclear~~	
C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data	**Yes**	~~No~~	~~Unclear~~	
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	~~Unclear/unknown risk~~	~~High risk of bias~~			
Likely direction of effect: **N/A**					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	~~Yes~~	**No**	~~Unclear~~	**Follow-up was very short and could have excluded certain incidences of the primary outcome.**

D2	The study used a precise definition of outcome	**Yes**	~~No~~	~~Unclear~~	**The definition was not fully reported but the international criteria were used.**
D3	A valid and reliable method was used to determine the outcome	**Yes**	~~No~~	~~Unclear~~	**Definition of the primary endpoint (VAP) does not have a reliable gold standard.**
D4	Investigators were kept 'blind' to participants' exposure to the intervention	~~Yes~~	**No**	~~Unclear~~	
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	~~Yes~~	**No**	~~Unclear~~	
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
~~Low risk of bias~~	**Unclear/unknown risk**	~~High risk of bias~~			
Likely direction of effect: **It is possible that VAP was overdiagnosed which could have biased the trial in favour of the intervention.**					

Table 12 Methodological quality of observational studies

Study	Doyle (2011)	Hodd (2009)	Smith (2014)
Is the study based on a representative sample selected from a relevant population?	Yes	Yes	Yes
Are criteria for inclusion explicit?	Yes	No	Yes
Did all individuals enter the study at a similar point in their disease progression?	Unknown	Unknown	Unknown

Was follow up long enough for important events to occur?	Yes	Yes	Unclear
Were outcomes assessed using objective criteria or was blinding used?	Unknown	Unknown	Yes
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	N/A	N/A	N/A

Appendix C

The company reported the following adverse events:

MHRA Reported Adverse Events:

Great Western Hospital - Date of Event - 17.01.18. Ref. 2018/001/024/601/003 and 2018/003/021/291/019 - Closed. NB. Allocated two different reference numbers on initial log.

NB. Field Safety Notice - issued by Manufacturer, distributed and signed acknowledgement from all accounts received.

Stepping Hill Hospital - Date of Event - 26.01.18. Ref. 2018/001/029/601/006 - Closed.

York District Hospital – Date of Event – 12.07.18. Ref. 2018/006/028/401/013 – Closed.

The EAC ran an additional search of the FDA-MAUDE website but found no other records of reported adverse events.

Appendix D

The EAC did not identify any ongoing studies from its searches of ClinicalTrials.gov, WHO ICTRP or PROSPERO (see Appendix A).

Appendix E

The EAC did not run an additional search for economic evidence. The results of the clinicial evidence searches (see Appendix A) were filtered in EndNote X7.8, using terms “econo*” and “cost*”. There were 395 results, which were sifted for relevance by two independent health economists.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

PneuX for preventing ventilator-associated pneumonia

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem from scope

1 The technology

The PneuX system is an endotracheal/tracheostomy tube (ETT) designed to prevent ventilator-associated pneumonia (VAP) by minimising the risk of pulmonary aspiration and micro-aspiration during mechanical ventilation. The PneuX system consists of 3 component parts: PneuX ETT, PneuX tracheal seal monitor, and a 2 m extension tube. The PneuX system is not compatible with other ETTs. Both the PneuX ETT and the extension tube are supplied sterile and for single use.

The PneuX ETT has a low-volume, low-pressure cuff made from a soft silicone material. The PneuX tracheal seal monitor is an electronic automatic pressure controller which controls and maintains the safe inflation volume and pressure within the cuff during use. PneuX has 3 subglottic secretion drainage and irrigation ports above the proximal end of the cuff to ensure that the tube functions properly even if one of the ports is blocked. The small size of the subglottic ports is intended to prevent damage to the tracheal mucosa.

The PneuX system was formerly known as the 'Venner PneuX P.Y. VAP Prevention System and the Lo-Trach system', there are no functional differences between the 2 versions.

2 Proposed use of the technology

2.1 Disease or condition

The PneuX system is intended for use people in critical care who need mechanical ventilation. The PneuX system can be used with tracheal intubation during routine anaesthesia. It is placed by anaesthetists and can be maintained by critical care nurses.

VAP is a hospital-acquired infection. Although there is no consensus definition, it is often defined as a pneumonia that occurs in patients who have had continuous intubation with an ETT for at least 24 hours before the onset of the infection. The presence of a tracheal tube interferes with the normal protective reflexes of the upper airway, such as coughing. This can result in

impaired clearance of secretions and micro-organisms leading to the rapid colonisation of the oropharyngeal secretions with aerobic Gram-negative bacteria. These contaminated secretions gather above the cuff of the tracheal tube and slowly leak down into the airway, leading to the entry of very small amounts of contaminated material into the respiratory tract (micro-aspiration). There are no standard criteria to diagnose VAP; a diagnosis is usually based on a combination of clinical signs and symptoms and confirmed with chest X-rays and microbiological testing.

2.2 Patient group

Around 100,000 patients are admitted for ventilation to UK critical care units each year and 10–20% of these will go on to develop VAP (NHS England). Between 3,000 and 6,000 people die from VAP every year (NHS England). Risk factors for the development of VAP include the duration of mechanical ventilation, the need for reintubation, the use of intracuff pressure of less than 20 cmH_2O, older age, lying flat and the presence of comorbidities.

2.3 Current management

VAP prevention strategies vary considerably in current practice. In 2008, the Working Party on Hospital-Acquired Pneumonia produced evidence-based guidance on prevention, diagnosis and treatment of hospital-aquired pneumonia (including VAP). The guidance states that measures should be taken to prevent VAP by reducing the risk of pulmonary aspiration using subglottic secretion drainage; by correctly positioning the ETT; and by ensuring a correct cuff pressure to avoid aspiration but prevent tracheal damage.

Bundles of care to prevent VAP have also been recommended in more recent guidelines published by the Scottish Intensive Care society/Health Protection Scotland and the Intensive care Society. The Intensive Care Society identifies 4 key elements to be addressed together to minimise the risk of VAP: elevation of head of bed (30º-45º), daily sedation interruption and assessment

of readiness to extubate, use of subglottic secretion drainage and avoidance of scheduled ventilator circuit changes.

NICE has produced medtech innovation briefings on the PneuX endotracheal tube system and the TaperGuard Evac oral tracheal tube (now the Shiley Evac oral tracheal tube with TaperGuard cuff).

2.4 Proposed management with new technology

PneuX is intended to be used instead of standard ETT (tubes with no subglottic drainage, subglottic drainage access with a high-pressure cuff or a tube with a non-continuous cuff-pressure monitor) in people who are expected to need ventilation for 24 hours or longer.

3 Company claimed benefits and the decision problem

The decision problem is described in the scope here (link to Appendix E).

4 The evidence

4.1 Summary of evidence of clinical benefit

The company submission presented 6 studies, comprising 2 prospective non-blinded randomised controlled trials (Gopal 2014 and Senanayake 2017) and 4 retrospective, non-comparative cohort studies (Doyle 2011, Hodd 2009, Smith 2014, Fletcher 2009). The EAC excluded 2 of these studies and identified no further studies. The final selection comprised of 3 studies reported in 4 publications.

Table 1 Study selection

Study	Type of publication	Type of study	Comment
Studies included by both EAC and company			
4 publications included by both	3 full-text publications, 1 conference abstract	1 prospective non-blinded randomised controlled trial, 3 retrospective,	Gopal 2014, Smith 2014, Doyle 2011 and Hodd 2009.

		non-comparative cohort studies.	
Studies in submission excluded by EAC			
3 publications from 2 studies excluded by EAC	1 full-text publication, 2 conference abstracts	1 prospective non-blinded randomised controlled trial, 1 retrospective, non-comparative cohort study.	Senanayake 2017 – the patient population is the same as in Gopal 2014, this publication includes no additional relevant outcomes. Fletcher 2009 a and b – the patient population is the same as in Doyle 2011, this publication includes no additional relevant outcomes.

The evidence considered for PneuX comprises 2 non-comparative retrospective cohort studies (in 3 publications) and 1 non-blinded RCT. Gopal et al. 2014, Doyle et al. 2011 and Smith et al. 2014 reported incidence of VAP and Hodd et al. 2009 reported extubation rate (which was also reported as a secondary outcome in Smith et al. 2014). Only Gopal et al. 2014 compared PneuX to standard ETT.

The patient population included in Gopal et al. 2014 was specific, high-risk cardiac surgery patients, and the EAC confirmed with the clinical experts that the incidence of VAP in this patient group is higher than populations in a general ICU setting. In addition, the intubation time (13–15 hours) and the follow-up (48 hours) were both of short duration. This was shorter than the intubation time specified in the scope (longer than 24 hours), this was chosen because most VAP definitions state that the patient should have been intubated for at least 24–48 hours. The EAC noted that although it does not strictly fit the scope, the study has been included because it is the only relevant RCT found in the literature. The comparator used in the study was standard ETT without subglottic drainage, the EAC and clinical experts noted that tubes with subglottic secretion drainage tubes are commonplace in the NHS and subglottic drainage is recommended as part of the ICS ventilator care bundle and therefore would be a more suitable comparator to PneuX. The study found no significant differences in length of ICU stay or mortality, between the intervention and comparator groups. One clinical expert

commented that without a reduction in these two outcomes, a reduction in VAP is not clinically meaningful. The results of this study showed a significant decrease in VAP for PneuX compared with standard ETT but was underpowered for this outcome.

Due to the patient populations, the evidence from the non-comparative studies is more generalisable to the wider critical care setting but the lack of a control group makes it difficult to draw any conclusions about the efficacy of PneuX. There was also wide variation in the secondary outcomes measured in these studies (e.g. mortality 1.6–35.8% and unplanned extubations 0.1–17%), suggesting a high level of heterogeneity. However, the rates of VAP and unplanned extubations are very low in these studies.

There is no standardised definition of VAP and studies have shown there is an element of subjectivity in diagnosis (see table 2 of the assessment report), and this may hinder the generalisability of the results to the NHS. One clinical expert noted that incidence of VAP may be difficult to accurately define unless current, strict criteria for diagnosis are used. In addition, they also estimated that only around half of suspected cases of VAP are confirmed with microbiology testing. Similarly, it was stated that defining incidence of aspiration is difficult to accurately and consistently assess. As a result data related to such measures may not be accurate or meaningful which may limit the clinical evaluation of the product. The studies used different definitions of VAP, did not examine inter-observer variability, and did not provide information on how samples were acquired and processed or what micro-organisms were present for the diagnosis of VAP.

Table 2 Selected studies

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Funding	Comments
Doyle et al. 2011, retrospective, non-comparative, single centre cohort study. Full-text publication	53 consecutive patients (41.5% female mean age 67.8 years, SD 15) recruited between 2006 and 2009. UK	Intervention: PneuX Comparator: none n=9 (17%) were initially intubated with PneuX, the rest electively exchanged from conventional ETT to PneuX. 91% of patients were treated with antibiotics prior to intubation.	VAP was defined by (i) clinical suspicion (including any clinically diagnosed pneumonia where antibiotics were started) and/or (ii) international consensus criteria. Mean intubation time was 5.3 days (all patients at least 48 hours).	VAP occurred in 1 patient (1.8%), although this was in a patient who had exchanged from PneuX to a standard ETT. VAP incidence was 0% while PneuX was in situ.	No funding declared. One of the authors is the inventor and a minor shareholder of PneuX.	The non-comparative nature of the study limits its usefulness to the decision problem. However, the UK ICU setting means the outcome is generalisable to NHS contexts.
Gopal et al. 2014, prospective non-blinded single-centre RCT. Full-text publication	240 high-risk patients undergoing cardiac surgery (72.5% male, mean age 72.2 years) were randomised 1:1, recruited	Intervention: PneuX Comparator: conventional ETT There were no significant differences in preoperative	VAP was defined using the HELICS definition. Median intubation time was 15 and 13 hours in the PneuX and	VAP incidence was significantly lower in the PneuX group compared to the control group (10.8% vs. 21%, p=0.03), as was VAP incidence	Funded by Department of Health, UK.	This study is the only available comparative evidence for PneuX. However, the length of intubation is outside that of the scope (>24 hours). The patient

	between 2010 and 2011.	characteristics of the groups	control groups, respectively.	density (52 vs. 184 VAP episodes per 1000 ventilator days, p<0.01). Binary logistic regression showed PneuX delivered a significant VAP reduction (odds ratio 0.45, p=0.03). CPB time, ICU stay, re-exploration for bleeding and survival were not significantly different between the groups.		population is specifically cardiac surgery patients at high risk of developing VAP, which limits generalisability to other populations. The lack of concealment/blinding and the single-centre nature of the study also introduce potential for bias. It is not clear from the reported information if the study is powered to detect a significant difference in the primary outcome. The calculated alpha of 0.01 was not met and the power calculation is not reported adequately. The EAC concluded that the study is underpowered.
Hodd et al. 2009, retrospective non-comparative	53 consecutive patients (41.5% female mean	Intervention: PneuX	Extubation rates were recorded for all intubated	Self-extubation was 1.02 per	No funding declared.	The non-comparative nature of the study limits its

single-centre cohort study. Conference abstract.	age 67.8 years, SD 15) recruited between 2006 and 2009. UK Note – this study is the same patient population as that of Doyle (2011), but is included because the self-extubation outcomes are not reported elsewhere.	Comparator: none The study is published as a conference abstract only so there is limited reporting of baseline demographic details.	ICU patients (185 intubations) between 2006 and 2009. Mean intubation time was 5.3 days.	1000 intubation days.		usefulness to the decision problem. However, the UK ICU setting means the outcome is generalisable to NHS contexts.
Smith et al. 2014, Retrospective non-comparative single-centre cohort study. Full-text publication.	48 ICU patients (56% male mean age 57.5 years, SD 18.7), recruited in 2010.	Intervention: PneuX Comparator: none 71% of patients were exchanged to PneuX from standard ETT after a mean intubation time of 13 hours 41 minutes.	VAP was defined using American Thoracic Society and the Infectious Diseases Society of America (ADS/ISDA). Post hoc analysis was carried out using the CPIS guidelines, in the 24 patients who	Overall, VAP incidence was 6.25% (95% CI: 1.3-17%), 3 patients in total. In the primary PneuX intubation group the rate was 7.14% as opposed to 5.88% in the exchange to PneuX group. Outcomes were re-analysed	Company funded (Intavent Direct).	The non-comparative nature of the study limits its usefulness to the decision problem. However, the UK ICU setting means the outcome is generalisable to NHS contexts. The authors note that the PneuX is no longer in use in their institution. However, they have continued

			had necessary data available at 48-hours post-intubation. Median intubation time was 2.47 days.	using the CPIS criteria, where data was available in 24 patients, of whom 5 (20.8%) had potential VAP. 2 had pre-existing pneumonia, and 2 were confirmed by the ATS/IDSA criteria. 83% (40) of extubations were planned. Of the remaining 8, 2 were accidental, 5 self-extubation and 1 removed for clinical reasons.		to use a different subglottic suctioning tracheal tube device and stated that the cost of PneuX prevented them from continuing to use it.

4.2 Summary of economic evidence

The company identified two relevant studies, Andronis et al. 2018 and NHS Innovation Accelerator, 2017. The EAC agreed with the inclusion of these 2 studies and carried out a systematic literature search but did not identify any additional relevant studies. Both the studies compared the PneuX system with standard ETTs and were conducted in the UK.

De novo analysis

The company submitted a simple decision tree (see figure 2 of the assessment report) based on the model published in Andronis et al. (2018). The population modelled is adult patients requiring mechanical ventilation in critical care following major heart surgery. This constitutes a subgroup of the population of patients requiring mechanical ventilation in the scope, the EAC note that there is considerable uncertainty regarding the generalisability of results from this population. This choice reflects the available comparative clinical effectiveness (Gopal et al. 2014) and resource use data (Luckraz et al. 2018).

The model compares the PneuX System to conventional ETT without subglottic secretion drainage. The model has a time horizon of less than one year which is intended to capture the initial hospitalisation period following surgery. The EAC considered this short time horizon to be appropriate as it is likely to capture any cost impacts arising from the incidence of VAP. The model includes a hypothetical cohort of 1,000 patients requiring mechanical ventilation in critical care who receive intubation with PneuX or standard ETT, with both arms at risk of contracting VAP. The model assesses the total cost of care as the cost of treatment patients with or without VAP and the acquisition costs of PneuX or standard ETT.

The company model makes the following assumptions:

- There are no training costs associated with the implementation of PneuX

- There are no additional costs for placement of the PneuX when compared to alternative intubation (such as a bougie)
- Additional equipment required for subglottic drainage will continue to be provided free of charge
- The effectiveness of PneuX for preventing VAP is similar in all patients
- The evidence on the effectiveness of PneuX can be generalised from cardiac patients to all patients in critical care
- The evidence on the additional cost of treating VAP can be generalised from cardiac patients to all patients in critical care
- There are no long term sequalae following treatment of VAP
- There is no additional mortality associated with VAP
- The relative reduction in VAP observed over short intubation times for the patients in Gopal et al. (2014) would be maintained over a longer period

The EAC considers the simple model structure to be adequate to capture the cost and consequences of the technology and did not make any changes to the model. It regarded all assumptions as acceptable except for the generalisability of cardiac surgery patients to a wider critical care setting. The EAC also advised caution in assuming the generalisability of costs for treating VAP given the discrepancies in ICU length of stay in the studies referenced (Gopal et al. 2014, Luckraz et al. 2018).

Model parameters

The cost of treating VAP is taken from a recent UK based study which estimated the additional cost based on a large cohort of patients who contracted VAP matched to a similar cohort of patients who did not contract VAP. The EAC undertook a search of the cost of treating VAP and did not locate any other studies based in the UK. The EAC considers the study to be a robust and reliable estimate that is relevant to the NHS and the most appropriate source for this data.

The key clinical parameter used in the model is the risk of VAP, in the PneuX arm this is 10.8% and 20.8% in the standard ETT arm, these values are sourced from Gopal et al. (2014). The EAC noted that this is the only study available that compares the risk of VAP with PneuX and standard ETT without subglottic drainage, however it does include an atypical patient population and short intubation times.

Costs and resource use

Costs attributable to VAP were sourced from Luckraz et al. (2018), who report a cohort study which estimated the cost to the NHS of treating patients in critical care following cardiac surgery who did and did not contract VAP. Costs from this study were also used in the published economic model by Andronis et al. (2018). Costs for each patient were estimated based on Healthcare Resource Group (HRG) codes in conjunction with NHS reference costs. Mean treatment costs for those who did and did not develop VAP were £15,124 and £6,295 (2013/14 GBP), respectively. The additional treatment cost associated with VAP was £8,829. This figure is driven entirely by the increased length of ICU stay for patients developing VAP compared to those who did not in this study (7.8 days (range 0-74) vs. 2.9 days (range 0-46), respectively). The EAC stated that this analysis is a large, robust study, and the most relevant source of data on the additional cost of treating VAP in the NHS.

The use of PneuX requires staff time to attend training and this cost was not included in the base case analysis. The EAC noted that the 15–30 minutes of training needed is modest, and unlikely to significantly add to the cost of PneuX when spread across the number of patients intubated over a year. The impact of including training costs is explored in a sensitivity analysis.

The PneuX system, currently used in the NHS, has an Innovation and Technology Tariff (ITT-03 2017-19) of £150. The company applies this cost in the model. The cost of a standard ETT (£5.00) was taken from the study by Andronis et al. (2018). The EAC noted the costs are reasonable and appropriate.

Results

The company base case indicates PneuX is associated with a saving of £738 per patient (see table 3). This saving arises from an absolute reduction in the risk of VAP of around 10% (from 20.8% to 10.8%) and the estimated additional cost of treating VAP of around £9,000. As a result, PneuX generates a cost offset of around £900 which is considerably greater than the additional cost of PneuX when compared to a standard ETT. The EAC accepted the company's base case and made no changes.

Table 3 Base case results

	PneuX	Standard ETT	Cost saving per patient
Technology cost	£150	£5	£145
Expected cost of treating VAP	£956	£1,839	-£883
Total cost per patient	£1,106	£1,844	**-£738**

The EAC noted that there are alternative drained ETTs and did an additional cost analysis to consider the costs of using PneuX compared to an alternative ETT with subglottic secretion drainage, Portex Blue Line (SACCET). Despite a lower technology cost for Portex Blue Line (£20 vs. £150), PneuX remains slightly cost saving by £18 due to lower cost of treating VAP. The cost of treating VAP was lower for PneuX because the relative risk of VAP was lower, 0.52 for PneuX compared to 0.6 for Portex Blue Line. The relative risk of VAP for Portex Blue Line was taken from 1 study, done in 54 patients, which compared the device with undrained ETT. The EAC noted the data for the relative risk of VAP for Portex Blue Line came from a very small trial. The results of this trial were not statistically significant, although were consistent with data from a large meta-analysis of the effectiveness of ETTs with subglottic drainage and was the only trial available that compared an ETT with subglottic drainage to an ETT with no drainage.

Table 4 Base case results for PneuX vs. Portex Blue Line (SACCET)

	PneuX	Portex Blue Line (SACETT)	Cost saving per patient
Technology cost	£150	£20	£130
Expected cost of VAP	£956	£1,104	-£148

Total cost per patient	£1,106	£1,124	**-£18**

The company did scenario analyses on 3 parameters (see table 5): baseline risk of VAP (reduced from 20.8% to 10%), cost of standard ETT (reduced from £5 to £1.12) and training cost to use PneuX (assumed to be £10 per patient). The company also reported a one-way sensitivity analysis of the cost of treating VAP, a two-way sensitivity analysis of the baseline risk of VAP (0–50%) and the relative risk of VAP with PneuX (0–1), and a probabilistic sensitivity analysis (PSA) to characterise the impact of uncertainty in the model parameters. The EAC noted that the sensitivity analyses are robust and exhaustive in exploring uncertainties in the model.

PneuX remained cost saving in all 3 scenario analyses. The one-way sensitivity analysis of the additional cost of treating VAP indicates that PneuX is cost saving when cost of treating VAP is as low as £4,000. The EAC extrapolated these data and estimate that the break-even point for the cost of treating VAP is approximately £2,000. In the two-way analysis of the baseline risk of VAP and the relative effectiveness of PneuX, PneuX remained cost saving for most combinations of the two parameters. The PSA indicates that there is a 96% likelihood that PneuX is cost saving compared with standard ETT. The EAC noted that the sensitivity analyses confirm the cost savings for PneuX compared with standard ETT are robust to parameter uncertainty.

Table 5 Sensitivity analysis results

	Mean cost per patient: PneuX	**Mean cost per patient: standard ETT**	**Difference in cost per patient**
Scenario 1: baseline risk of VAP of 10% (20% in base case)	£609	£888	-£279
Scenario 2: cost for standard tube	£1,106	£1,840	-£734

£1.12 (£5.00 in base case)			
Scenario 3: training cost of £10 per patient (£0 in base case)	£1,116	£1,844	-£728

5 Ongoing research

The company and the EAC are not aware of any ongoing research on PneuX.

6 Issues for consideration by the Committee

Clinical evidence

The evidence available for PneuX is limited and includes only 1 comparative trial (Gopal et al. 2014). This study included a very specific patient population of high-risk cardiac surgery patients and so may not be generalisable to the wider NHS population. The other 2 studies recruited patients who were more representative of the general NHS ICU population, however these studies are of lower quality due to their non-comparative design and wide range of secondary outcome results. All studies were conducted in the NHS.

The Gopal et al. (2014) trial is the pivotal study of the assessment and it showed a significant reduction in VAP for PneuX in comparison with standard ETT. In addition to recruiting an atypical patient population, the study included patients who had been intubated for less than 24 hours, which is less than the minimum time for VAP to develop in most definitions of VAP. The study was also underpowered for its primary outcome. The secondary endpoints of the study, ICU length of stay and mortality, did not differ between the PneuX and standard ETT groups. These issues question the clinical relevance of the results for a population in NHS clinical practice .

There is no standardised definition of VAP and there is an element of subjectivity in diagnosis. The studies included in the assessment used different definitions of VAP, did not examine inter-observer variability, and did not provide information on how samples were acquired and processed or what micro-organisms were present for the diagnosis of VAP.

Bundles of care are implemented to reduce VAP in NHS trusts. If PneuX is used as part of bundle of VAP prevention methods, it may not be clear which intervention is causing the reduction. Baseline infection rates for VAP will also vary by centre.

Cost evidence

Clinical experts advised that ETTs with subglottic drainage are now standard NHS practice and that standard ETTs are rarely used. The EAC compared the cost of using PneuX with a cheaper ETT with subglottic drainage. The results showed that PneuX was very slightly cost saving due to reduced risk of VAP.

The key clinical parameter that drives the cost savings of the model is the risk of VAP. For both arms of the model this is sourced from the Gopal et al. (2014) trial, the limitations of which are discussed in the previous section. Due to a lower risk of VAP in the PneuX arm the cost of VAP treatment is lower. It is important to note that most costs for VAP come from longer ICU stays, in Gopal et al. (2014) there was no significant difference in ICU stay between PneuX and standard ETT.

7 Authors

Kimberley Carter, health technology assessment analyst

Lizzy Latimer, health technology assessment adviser

NICE Medical Technologies Evaluation Programme

September 2019

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Goddard K, Macmillan T et al., MT273 PneuX for preventing ventilator-associated pneumonia in intensive care, August 2019

B Submissions from the following sponsors:

- Qualitech Healthcare Limited

C Related NICE guidance

- Pneumonia in adults: diagnosis and management. NICE clinical guideline 191 (2014). Available from www.nice.org.uk/guidance/CG191
- Healthcare-associated infections: prevention and control. NICE public health guidance 36 (2011). Available from www.nice.org.uk/guidance/PH36

D References

- Please see EAC assessment report for full list of references.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Peter D G Alexander
Consultant in Anaesthesia and Intensive Care Medicine, University Hospital of South Manchester NHS Foundation Trust.

Dr Shameer Gopal
Consultant in Anaesthesia and Intensive Care Medicine, The Royal Wolverhampton NHS Trust.

Dr Thomas Hellyer
Specialist Registrar in Intensive Care Medicine, Northern Deanery.

Dr Petr Martinovsky
Consultant Cardiothoracic Anaesthetist, Blackpool Teaching Hospitals.

Dr Ben Messer
Consultant Anaesthetist in Intensive Care Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust.

Prof Gary Mills
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Foundation Trust and University of Sheffield.

Dr David Ray
Consultant in Anaesthesia and Critical Care, Royal Infirmary of Edinburgh, NHS Lothian.

Dr Murali Shyamsundar
Clinical Senior Lecturer and Consultant in Intensive Care Medicine, Queen's University Belfast.

Mr Neil Smith

Research Nurse, Hull University Teaching Hospitals NHS Trust.

Dr Andrew Walder

Consultant Anaesthetist, Northern Devon Healthcare NHS Trust

Please see the clinical expert statements included in the pack for full details.

Appendix C: Comments from patient organisations

The following patient organisations were contacted, and no response was received.

- Critical Care Patient Liaison Committee (CritPaL)
- ICU Steps
- British Lung Foundation

Appendix D: Decision problem from scope

	Scope issued by NICE
Population	Adult patients requiring ventilation in a critical care setting for at least 24 hours and up to 30 days.
Intervention	PneuX system
Comparator(s)	conventional endotracheal tube conventional tracheostomy tube any other equivalent or similar endotracheal tube aimed at VAP prevention including subglottic secretion drainage (both intermittent versus continuous suction)
Outcomes	The outcome measures to consider include: incidence of VAP length of ICU/ITU stay length of hospital stay incidence of aspiration duration of mechanical ventilation incidence of unplanned extubation and/or re-intubation antibiotic usage mortality sedation usage difficulty of placement and maintenance of tube position device-related adverse events e.g. tracheal injury
Cost analysis	Comparator(s): • any other equivalent or similar endotracheal tube aimed at VAP prevention • conventional endotracheal tube • conventional tracheostomy tube • Early versus late onset of VAP Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.
Subgroups to be considered	Endotracheal tubes Tracheostomy tubes Specific patient groups: for example, severely immunocompromised patients burns and polytrauma patients, Prone ventilated patients, major heart surgery patients, neurological patients and transplant patients
Special considerations, including those	Risk factors for VAP include age (incidence increases with advancing age) and chronic illnesses (including underlying chronic lung disease, cancer and diabetes), which may significantly affect activities of daily

related to equality	living to the point where a person can be considered to be disabled. Age and disability are protected characteristics under the Equality Act (2010).	
Special considerations, specifically related to equality issues	None	
	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

SCOPE

The PneuX system for preventing ventilator-associated pneumonia in patients in intensive care

1 Technology

The PneuX system is designed to prevent ventilator-associated pneumonia (VAP) by minimising the risk of pulmonary aspiration and micro-aspiration during mechanical ventilation, which is expected to last more than 24 hours but no more than 30 days. The PneuX system consists of 3 component parts:

- PneuX endotracheal/tracheostomy tube – a flexible silicone tube with a low-volume, low-pressure (LVLP) cuff, fixation block, winged tube holder, integrated bite block, a flange, a drain tube, an inflation tube, a reservoir, sub-glottic line leading to 3 sub-glottic ports, inflation line, non-stick lining and boat-tip with murphy eye and a 15 mm standard connector. The tube is compatible with magnetic resonance imaging (MRI) and is available in 4 sizes: 6.0, 7.0, 8.0 or 9.0 mm inner diameter.

- The PneuX tracheal seal monitor – an electronic automated cuff pressure controller (formerly known as Venner PneuX TSM Cuff Pressure controller)

- Extension tube – a 2-metre extension tube for the PneuX tracheal seal monitor. It connects the air outlet on the PneuX tracheal seal monitor and the pilot valve of the PneuX endotracheal/tracheostomy tube.

The PneuX endotracheal/tracheostomy tube has a low-volume, low-pressure cuff made from a soft silicone material. The PneuX tracheal seal monitor is an electronic automatic pressure controller which controls and maintains the safe

inflation volume and pressure within the cuff during use. PneuX has 3 subglottic secretion drainage and irrigation ports above the proximal end of the cuff to ensure that the tube functions properly even if one of the ports is blocked. The small size of the subglottic ports is intended to prevent damage to the tracheal mucosa.

The manufacturer recommends that the PneuX endotracheal/tracheostomy tube and the PneuX tracheal seal monitor are used together, and so neither should be used with other devices. The PneuX system is not compatible with other endotracheal/tracheostomy tubes. Both the PneuX endotracheal /tracheostomy tube and the extension tube are supplied sterile and for single use. The PneuX system was formerly known as the Venner PneuX P.Y. - VAP Prevention System and the Lo-Trach system

1.1 Description of the technology

1.2 Regulatory status

The PneuX system received a CE mark in January 2006 for adult critical care patients who require intubation (primary or tube-exchange) and mechanical ventilation. The system has a class III device (the endotracheal/tracheal tube) and a class IIb device (the PneuX tracheal seal monitor, previously known as Venner tracheal seal monitor).

1.3 Claimed benefits

The benefits to patients claimed by the company are that the technology:

- Reduces the incidence of ventilator-associated pneumonia
- Facilitates the application of evidence-based VAP Preventative Measures
- Prevents/reduces aspiration
- Reduces complications
- Improves management
- Reduces mortality, since ventilator-associated pneumonia is consistently associated with an increased in mortality
- Increases life expectancy for all patients treated in the Intensive Care Unit

The benefits to the healthcare system claimed by the sponsor are that the technology:

- Reduces overall costs of care
- Reduces overall hospital length of stay for patients in critical care on mechanical ventilation
- Increases patient turnover/productivity due to change in practice

1.4 Relevant diseases and conditions

The PneuX system is intended for use in intensive or critical care patients requiring mechanical ventilation where the duration of intubation is expected to be more than 24 hours but not more than 30 days. The PneuX system is also compatible with tracheal intubation during routine anaesthesia. It is placed by anaesthetists and can be maintained by critical care nurses.

Ventilator-associated pneumonia (VAP) is a hospital-acquired infection. Although there is no consensus definition, it is often defined as a pneumonia that occurs in patients who have had continuous intubation with an endotracheal or tracheostomy tube for at least 48 hours before the onset of the infection (American Thoracic Society and Infectious Diseases Society of America, 2005). The presence of a tracheal tube interferes with the normal protective reflexes of the upper airway, such as coughing. This can result in impaired clearance of secretions and micro-organisms leading to the rapid colonisation of the oropharyngeal secretions with aerobic Gram-negative bacteria. These contaminated secretions gather above the cuff of the tracheal tube and slowly leak down into the airway, leading to the unintentional entry of very small amounts of contaminated material into the respiratory tract (micro-aspiration). This is thought to be the main cause of VAP (Gunasekera et al. 2016). There are no standard criteria to diagnose VAP; a diagnosis is usually based on a combination of clinical signs and symptoms and confirmed with chest X-rays and microbiological testing (American Thoracic Society and Infectious Diseases Society of America, 2005).

Around 100,000 patients are admitted for ventilation to UK critical care units each year and 10-20% of these will go on to develop VAP (NHS England). Between 3,000 and 6,000 people die from VAP every year (NHS England). It is acknowledged that the latest incidence of VAP is somewhat uncertain but that this will be considered in the assessment of the evidence.

Risk factors for the development of VAP include the duration of mechanical ventilation, the need for reintubation, the use of intracuff pressure of less than 20 cmH_2O, older age, lying flat and the presence of comorbidities (Timsit et al. 2017). The risk for patients is highest during the early part of an ICU stay when it is estimated to be 3% per day during days 1–5 of ventilation, 2% per day during days 5–10 of ventilation and 1% per day thereafter (Masterton, 2008).

Various strategies have been developed to reduce the risk of ICU patients developing VAP, including advances in endotracheal tube technology. These developments include features for continuous subglottic drainage and ensuring adequate pressure of the endotracheal-tube cuff is maintained to prevent leakage of colonised subglottic secretions into the lower airway (Fernandez et al. 2012).

1.5 Current management

VAP prevention strategies vary considerably in current practice. In 2008, the Working Party on Hospital-Acquired Pneumonia of the British Society for Antimicrobial Chemotherapy produced evidence-based guidance (Masterton et al. 2008). The scope of the guidance excluded oral antiseptic treatments, management of severely immunocompromised patients, children under 16 years old and people with cystic fibrosis. The guidance states that measures should be taken to prevent VAP by reducing the risk of pulmonary aspiration using subglottic secretion drainage; by correctly positioning the endotracheal tube (ETT); and by ensuring a correct cuff pressure to avoid aspiration but prevent tracheal damage.

Bundles of care to prevent ventilator-associated pneumonia (VAP) have also been recommended in more recent guidelines published by the Scottish

Intensive Care society/Health Protection Scotland and the Intensive care Society. The Intensive Care Society identifies 4 key elements to be addressed together to minimise the risk of VAP: elevation of head of bed (30°-45°), daily sedation interruption and assessment of readiness to extubate, use of subglottic secretion drainage and avoidance of scheduled ventilator circuit changes.

NICE has produced medtech innovation briefings on the PneuX endotracheal tube system and the TaperGuard Evac oral tracheal tube (now the Shiley Evac oral tracheal tube with TaperGuard cuff).

2 Statement of the decision problem

	Scope issued by NICE
Population	Adult patients requiring ventilation in a critical care setting for at least 24 hours and up to 30 days.
Intervention	PneuX system
Comparator(s)	• conventional endotracheal tube • conventional tracheostomy tube • any other equivalent or similar endotracheal tube aimed at VAP prevention including subglottic secretion drainage (both intermittent versus continuous suction)
Outcomes	The outcome measures to consider include: • incidence of VAP • length of ICU/ITU stay • length of hospital stay • incidence of aspiration • duration of mechanical ventilation • incidence of unplanned extubation and/or re-intubation • antibiotic usage • mortality • sedation usage • difficulty of placement and maintenance of tube position • device-related adverse events e.g. tracheal injury
Cost analysis	Comparator(s): • any other equivalent or similar endotracheal tube aimed at VAP prevention • conventional endotracheal tube • conventional tracheostomy tube • Early versus late onset of VAP Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.

	Sensitivity analysis will be undertaken to address uncertainties in the model parameters.	
Subgroups to be considered	Endotracheal tubes Tracheostomy tubes Specific patient groups: for example, severely immunocompromised patients burns and polytrauma patients, Prone ventilated patients, major heart surgery patients, neurological patients and transplant patients	
Special considerations, including those related to equality	Risk factors for VAP include age (incidence increases with advancing age) and chronic illnesses (including underlying chronic lung disease, cancer and diabetes), which may significantly affect activities of daily living to the point where a person can be considered to be disabled. Age and disability are protected characteristics under the Equality Act (2010).	
Special considerations, specifically related to equality issues	None	
	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No

3 Related NICE guidance

Published

- Pneumonia in adults: diagnosis and management. NICE clinical guideline 191 (2014). Available from www.nice.org.uk/guidance/CG191
- Healthcare-associated infections: prevention and control. NICE public health guidance 36 (2011). Available from www.nice.org.uk/guidance/PH36

4 External organisations

4.1 Professional organisations

The following societies have been alerted to the availability of the scope for comment:

- British Association of Critical Care Nurses
- Royal College of Anaesthetists
- Royal College of Nursing

- Society for Cardiothoracic Surgery of Great Britain and Ireland
- The British Thoracic Society
- The Faculty of Intensive Care Medicine

4.2 Patient organisations

At the selection stage, NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the scope for comment:

- British Lung Foundation
- Critical Care Patient Liaison Committee (CritPaL)
- ICU Steps

NICE National Institute for Health and Care Excellence

Adoption scoping report: MTG 273 PneuX for preventing ventilator-associated pneumonia in intensive care

Summary

Adoption levers

- Includes an electronic automatic cuff pressure monitor
- May prevent ventilator-associated pneumonia (VAP)
- May reduce duration on mechanical ventilation
- Offers subglottic drainage access to support suction and irrigation, allowing wash out of the airway above the cuff

Adoption barriers

- Cost of the technology
- Perceived poor quality of evidence to support its use on ICU
- Current VAP rates reported to be low
- Technologies with similar benefits available at a lower cost
- Difficult to identify long term ventilated patients. Not perceived to be cost effective in short term ventilated patients.
- Delay in adoption due to procurement and training
- A bougie is required to intubate

1. Introduction

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt PneuX into routine NHS use.

The technology described in this report is the PneuX tube system which includes an endotracheal tube, tracheostomy tube, tracheal seal monitor and extension tube.

2. Contributors

Adoption information was gathered from the manufacturer and 7 NHS staff, 2 of whom are currently using the technology on a trial basis and 5 who are experienced users of endotracheal and tracheostomy tubes:

- 1 consultant in cardiothoracic anaesthesia and intensive care (used both tubes on 4 patients in the past 3 months).
- 1 consultant in intensive care and anaesthetics
- 1 consultant paediatric anaesthetist
- 1 consultant respiratory physician and intensivist (critical care)
- 1 intensive care consultant (used the endotracheal tube and tracheal seal monitor on 2 patients in the past month).
- 2 consultants in anaesthesia and critical care medicine (1 currently waiting to start training)

For clarity this report will refer to current triallers, non-users and contributors (where comments have been made by triallers and non-users alike).

3. Use of PneuX in practice

The company states there are 16 NHS hospitals in various stages of adopting PneuX in May 2019. The company business model is that it loans 1 monitor to 24 tubes purchased. The 2 triallers are funding the technology through the Innovation and Technology Tariff until March 2020.

Endotracheal tube

Endotracheal tubes are usually inserted in theatre or in the emergency department and kept in situ when the patient is moved to ICU. Contributors explained they would use a basic tube unless the patient would benefit from added features from other tubes or they might require long term ventilation. This is because these patients may benefit from tubes with added features, such as a subglottic port to minimise tracheal injury. This is perceived to be a cost effective approach.

At one trial site PneuX tubes are kept on ICU and are therefore not easily accessible to the emergency department. When a patient arrives on ICU after a standard endotracheal tube has been inserted in the emergency department reintubation with a PneuX tube is generally not recommended due to the risk of patient injury such as hypoxia.

At 1 trial site only consultants or consultant guided procedures have been authorised. This is because the PneuX endotracheal tube requires a bougie for intubation. Contributors have said using a bougie requires clinical experience as it can increase the risk of injury to a patient.

Once an endotracheal tube is in place an ICU nurse maintains the tube and monitor. The tube is usually held in place with a tape or a fastener as they can sometimes migrate.

There are either wet (heated humidified) or dry breathing circuits used with ventilators. At 1 trial site they routinely use a dry breathing circuit and were not aware PneuX requires a wet (heated humidified) breathing circuit. The trial site have therefore had to start using a saline nebuliser with the PneuX equipment to overcome this issue. The trialler said the additional equipment could be an adoption barrier for organisations using dry breathing circuits.

Contributors explained choosing the appropriate endotracheal tube for a patient can be challenging. They are required to consider the presenting clinical condition, forecast duration of mechanical ventilation and whether the patient would eventually require a tracheostomy tube.

Tracheostomy tube

If long term ventilation is required the endotracheal tube may be replaced with a tracheostomy tube. Contributors report this may be considered after 7 days, depending on the patient's clinical condition.

4. Reported benefits

The potential benefits of adopting PneuX, as reported to the adoption team by the healthcare professionals either using the technology or with expertise in this area are that it:

- Includes an electronic automatic cuff pressure monitor
- May prevent ventilator-associated pneumonia (VAP)
- May reduce patient duration on mechanical ventilation

- Offers subglottic drainage access to supports suction and irrigation, allowing wash out of the airway above the cuff

5. Insights from the NHS

Patient selection

Both triallers said they use PneuX on patients requiring ventilation for more than 48 hours due to the perceived cost effectiveness compared to a basic tube. All contributors agreed it can be difficult to identify long term ventilated patients when they are first intubated in the emergency department or theatre.

Clinician confidence

All non-users were not convinced with the available evidence on preventing VAP and reducing duration on mechanical ventilation.

Some contributors said research data from coronary care units (CCU) would not be applicable to ICU due to the high turnover rates in CCU. All agreed the evidence available for the benefits of the technology is of limited quality and would benefit from further research including impact on mortality and length of stay on ICU.

Clinician preference

Two non-users said their current tubes and ventilators offer some of the benefits of PneuX at a lower cost and reported that the need for additional training, existing low VAP rates and lack of evidence would prevent them adopting the technology.

Contributors agreed that the continuous cuff pressure monitor was a benefit as it does not rely on a nurse to manually check and maintain the cuff pressure. They all commented that the subglottic secretion drainage and irrigation feature is beneficial.

One non-user said the wire reinforced tube could be useful but not all contributors agreed as it prevents the tube being cut to size. One contributor said the soft bevel tip was useful as it can prevent injury when intubating. All contributors mentioned that whilst these features are not individually unique to PneuX the technology novelly combines them all into one system.

All contributors reported that because the tube is flexible it requires intubating with a bougie and this may increase the risk of trauma to the patient. Some contributors reported that they prefer familiar and simple tubes that don't require a bougie especially with complex patients.

One non-user said the PneuX reinforced and thicker tube may be difficult to intubate particularly in head and neck trauma patients.

Tracheostomy tube

One trialler does not use the PneuX tracheostomy tube as it does not have an inner tube or cannula which can be removed and cleaned easily. This feature is considered advantageous as it prevent risks of blocking with mucus and infection.

The PneuX tracheostomy tube currently does not have an introducer kit. The second trialler reported that they failed one tube placement for a new tracheostomy due to the lack of the introducer kit. They had to use a tube from another company which comes with an introducer kit. The same trialler has successfully replaced an existing tracheostomy with the PneuX system on another patient as they did not require the introducer kit.

Procurement

The company states that procurement of PneuX can take up to 8 months. This is because, as a relatively new company, they are unlikely to be on trusts' preferred supplier list and therefore require indemnity and product insurance checks which can delay adoption.

Resource impact

All contributors agreed the cost of the technology was a barrier. Some non-users said a separate introducer kit would be required for the placement of a tracheostomy and a bougie is required for intubation. Both would be an added cost in addition to the PneuX system.

Training

The 2 trial users said no specific training was required for clinician's experienced in intubation. A company representative discussed the technology for 15 to 30 minutes in a regular consultant's meeting.

The company offers videos and a cascade training model for ICU nurses on how to maintain the PneuX tubes and monitor. This takes between 15 minutes to 1 hour. One trialler explained 4 ICU nurses were trained together and it took 4 months at their site. This is because back fill is required for ICU nurses to be released for training. The second trialler confirmed 80 ICU nurses required training at their unit and this delayed adoption.

The company said some trusts require more than 90% of ICU nurses to have training before a new technology is introduced and this can be up to 200 members of staff.

Patient safety

One non-user was concerned that the continuous pressure from PneuX may cause trachea injury whereas another contributor said it may prevent trachea injury from occurring as it maintains cuff pressure.

Some contributors said endotracheal tubes can migrate. As the PneuX tube can't be cut to size there were concerns it may slip into the lung. The company has recently added winged tube holders to the PneuX endotracheal tubes to prevent this occurring.

Three contributors said their existing ventilators have an integrated cuff pressure controller and therefore PneuX is not compatible. These contributors agreed another monitor on a well-equipped ICU may be a hindrance due to space and that this would be a barrier to adoption.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT273 PneuX for preventing ventilator-associated pneumonia in intensive care

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Qualitech Healthcare Limited
Submission date	26th June 2019
Regulatory documents attached	CE Certificate Instructions for Use – Venner PneuX™ ETT/TT Instructions for Use – Venner PneuX TSM™ Cuff Pressure Controller and Venner PneuX™ Extension Tube
Contains confidential information	No

Contents

1 Decision problem

	Scope issued by NICE
Population	Adult patients requiring ventilation in a critical care setting for at least 24 hours and up to 30 days.
Intervention	Venner PneuX™ System
Comparator(s)	Conventional endotracheal tube Conventional tracheostomy tube Any other equivalent or similar endotracheal tube aimed at VAP prevention including subglottic secretion drainage (both intermittent versus continuous suction)
Outcomes	The outcome measures to consider include: • incidence of VAP • length of ICU/ITU stay • length of hospital stay • incidence of aspiration • duration of mechanical ventilation • incidence of unplanned extubation and/or re-intubation • antibiotic usage • mortality • sedation usage • difficulty of placement and maintenance of tube position • device-related adverse events e.g. tracheal injury
Cost analysis	Comparator(s): • any other equivalent or similar endotracheal tube aimed at VAP prevention • conventional endotracheal tube • conventional tracheal intubation tube Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.
Subgroups to be considered	Endotracheal tubes Tracheostomy tubes Specific patient groups: for example, severely immunocompromised patients burn and polytrauma patients, Prone ventilated patients, major heart surgery patients, neurological patients and transplant patients
Special considerations, including issues related to equality	Risk factors for VAP include age (incidence increases with advancing age) and chronic illnesses (including underlying chronic lung disease, cancer and diabetes), which may significantly affect activities of daily living to the point where a person can be considered to be disabled. Age and disability are protected characteristics under the Equality Act (2010).

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	Venner PneuX™ System (Formerly Venner™ PneuX P.Y.™ VAP Prevention System and LoTrach™)
Approved name	Venner PneuX™ System
CE mark class and date of authorisation	Class IIA No. 501847– 03.01.06.

Version(s)	**Launched**	**Features**
Venner PneuX™ System Refer part - Venner PneuX™ETT	April 2019	The Venner PneuX™ System addresses multiple-known risk factors associated with intubation systems in current standard use and its design features have been proven in practice to prevent leakage and aspiration of secretions by the patient. The Venner PneuX™ Endotracheal (ETT)and Tracheostomy Tube (TT) are of a flexible silicone/nitinol wire (MRI Compatible) construction which conforms to the anatomy, yet with strength against kinking. The endotracheal/tracheostomy tubes have a low-volume, low-pressure cuff (which forms a no-fold seal), and a non-stick lining which prevents the build-up of biological adhesions. The Venner PneuX™ ETT/TT has a fixation block/winged tube holder for optimal tube securement and the Venner PneuX™ ETT an integrated bite block to resist damage from patient biting. The system facilitates subglottic irrigation and subglottic drainage, with a total of 3 subglottic ports. The Venner PneuX™ ETT/TT work in conjunction with the Venner PneuX™ Extension Tube, which attaches to the pilot balloon valve of the Venner PneuX™ ETT/TT and the Venner PneuX TSM™ Cuff Pressure Controller, which then maintains a constant cuff/tracheal wall seal pressure, preventing aspiration.
Venner PneuX™ System Refer part – Venner	June 2016	The Venner PneuX™ System addresses multiple-known risk factors associated with intubation systems in current standard use and its design features have been proven in practice to prevent leakage and aspiration of secretions by the patient. The Venner PneuX™ Endotracheal (ETT)and Tracheostomy Tube (TT) are of a flexible silicone/nitinol wire (MRI Compatible) construction which conforms to the anatomy, yet with strength against kinking. The endotracheal/tracheostomy tubes have a

PneuX™ ETT		low-volume, low-pressure cuff (which forms a no-fold seal), and a non-stick lining which prevents the build-up of biological adhesions. The Venner PneuX™ ETT has a tapered sleeve and integrated bite block to resist damage from patient biting. The Venner PneuX™ TT has a fixation block/winged tube holder. The system facilitates subglottic irrigation and subglottic drainage, with a total of 3 subglottic ports. The Venner PneuX™ ETT/TT work in conjunction with the Venner PneuX™ Extension Tube, which attaches to the pilot balloon valve of the Venner PneuX™ ETT/TT and the Venner PneuX TSM™ Cuff Pressure Controller, which then maintains a constant cuff/tracheal wall seal pressure, preventing aspiration.
Venner™ PneuX P.Y.™ VAP Prevention System	April 2010	As current version. However, with fixation block/winged tube holder (single).
LoTrach™ System	April 2007	As current version, However, with fixation block/winged tube holder (single).
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Reduces the incidence of Ventilator-Associated Pneumonia	Gopal S, et al. Significant reduction in ventilator-associated pneumonia with the Venner-PneuX system in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia Study. European Journal of Cardio-Thoracic Surgery. Advance Access December 26th, 2014. 1 – 5	This study assessed whether the Venner-PneuX endotracheal tube (ET) system, which has sub-glottic suction as well as irrigation ports and continuous cuff-pressure monitoring, is associated with a reduction in ventilator-associated pneumonia (VAP) when compared with the standard ET in high-risk patients undergoing cardiac surgery.
	Smith N, et al. A retrospective review of patients managed with the Venner PneuX P.Y. VAP Prevention System. 2014. Journal of Intensive Case Medicine Vol 15, No. 2	Ventilator-associated pneumonia (VAP) is common-place in intensive care and has implications for patients' morbidity and mortality in hospital. A range of interventions exists to prevent the development of VAP - To review of the impact of Venner PneuX P.Y. Prevention System on the incidence of VAP and its effects on local practice.
	Fletcher A, et al. Incidence of VAP in patients undergoing elective tube exchange.	The objective was to study a cohort of general ICU patients electively re-intubated with the Lo-Trach

	Crit Care 2009;13(Suppl 1) P295	tracheal tube (tube exchange) to determine safety and audit post procedural ventilator-associated pneumonia (VAP).
	Fletcher A, et al. The Lo-Trach™ tracheal tube – airway symptom surveillance following critical care. Crit Care 2009;13(Suppl 1) P295	The objective was to study a cohort of general intensive care patients treated with the LoTrach tracheal tube and cuff pressure controller for symptomatic or post-mortem laryngo-tracheal pathology.
Facilitates the application of evidence based VAP Preventative Measures	Fletcher A, Ruffell A, et al. The Lo-Trach™ System: it's role in the prevention of ventilator-associated pneumonia. 2008. British Association of Critical Care Nurses, Nursing in Critical Care. Vol. 13, No.5.	The objective was to discuss the development of the LoTrach™ system in light of current evidence around of the prevention of ventilator-associated pneumonia (VAP) and its practical application in the intensive care setting.
	National Resource for Infection Control (NRIC) 2011 High Impact Intervention – Care bundle to reduce ventilator-associated pneumonia (Use of subglottic drainage)	The aim of the care bundle, as set out in this high impact intervention, is to ensure appropriate and high-quality patient care.
Prevention/reduction of aspiration	Mariyalselvam M, et al. Endotracheal tubes and fluid aspiration: an *in vitro* evaluation of new cuff technologies.	This study is to compare the performance of seven subglottic secretion drainage endotracheal tubes

	BMC Anaesthesiology 2017; 17:36	against a non-subglottic secretion drainage endotracheal tube in preventing aspiration beyond an inflated cuff.
	Mariyaselvam M, et al. An *in vitro* microbiological study comparing eight endotracheal tubes and their ability to prevent micro aspiration. Intensive Care Medicine Experimental 2015, 3 (Suppl.1): A382	To compare properties of the new design endotracheal tubes against the Venner PneuX™ ETT and their ability to prevent leakage of a microbial contaminated solution.
	Itagaki T, et al. Comparison of the ability of five endotracheal cuffs to prevent leakage: A bench evaluation. MGH (Massachusetts General Hospital) Poster Presentation – American Association of Respiratory Care (AARC). Dec 2014	To compare the ability of endotracheal tube cuffs to prevent leakage.
	Young P, et al. Evaluation of a new design of tracheal cuff to prevent leakage of fluid to the lungs. 1998 British Journal of Anaesthesia 80:796-799	To evaluate a new design of tracheal tube cuff compared with two types of high-volume, low-pressure (HVLP) cuffed tracheal tubes for leakage of fluid from the subglottic space into the trachea.
	Young P, et al. The pressure limited tracheal tube cuff: prevention of	To demonstrate that the pressure-limited

	aspiration of oro-pharyngeal fluid to the lungs. Anaesthesia 1999; 54:559-563	cuffed tracheal tube, in combination with a constant-pressure inflation device, prevents leakage of fluid into the lungs that occurs with high-volume, low-pressure cuffs in the critically ill, intubated patient.
	Young P, et al. The prevention of pulmonary aspiration with control of tracheal wall pressure using a silicone cuff. Anaesthesia and Intensive Care 2000; 28:660-6	To assess the ability of a silicone endotracheal tube cuff to prevent pulmonary aspiration.
	Young P, et al. A low-volume, low-pressure tracheal cuff reduces pulmonary aspiration. 2006. Crit Care Med Vol 34, No.3	Leakage of fluid from the subglottic space to the lungs occurs along the longitudinal folds within the wall of an inflated, high-volume, low-pressure (HVLP) cuff. To demonstrate the low-volume, low-pressure (LVLP) cuff does not have these folds yet allows for convenient and reliable control of tracheal wall pressure. Pulmonary aspiration during anaesthesia has been linked with post-operative pneumonia and during critical illness causes ventilator-associated pneumonia.

	Young P, et al. Inflation of a pressure-limited cuff inside a model trachea. Med Eng Phys 2003; 25:465-73	To assess theory of elastic behavioural characteristics of inflated tracheal tube cuffs.
I	Young P, et al. Leakage of fluid past the tracheal tube cuff in a bench top model. BJA 1997; 78:557-562	To assess range of HVLP cuffed tracheal tubes for leakage of fluid above the cuff to the model trachea below.
	Metheny N A, et al. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. Crit Care Med 2006;34(4):1007-1015	To describe the frequency of pepsin-positive tracheal secretions (a proxy for the aspiration of gastric contents), outcomes associated with aspiration (including a positive Clinical Pulmonary Infection Score (a proxy for pneumonia) and use of hospital resources, and risk factors associated with aspiration and pneumonia in a population of critically ill tube-fed patients.
Increased life expectancy for all patients treated in the Intensive Care Unit	Young P, et al. Comparison of LoTrach™ and Portex Soft Seal Cuff: tracheal wall pressure and fluid leakage in a bench top study and clinical study. Crit Care 2007. 11(Suppl 2): P215	To demonstrate two methods of measuring tracheal wall pressure (*in vitro* and patients)
	Young P. A tracheal tube for critical care. 2007.	To summarise how the LoTrach™ tube has been designed to

	The Journal of the Intensive Care Society. Vol. 8, No.1	address five important risk factors - cuff leakage, cuff pressure maintenance, drainage of subglottic space, prevent tube movement and minimise biofilm formation and tube occlusion.
Increase in quality-adjusted life years	Dick A, et al. A decade of investment in infection prevention: A cost effectiveness analysis. 2015. American Journal of Infection Control. 43. 4 – 9	To examine the cost effectiveness of hospital's on-going investments in Hospital Acquired Infection (HAI) prevention in Intensive Care Units.
	Dick A, et al. A decade of investment in infection prevention: A cost effectiveness analysis. 2015. American Journal of Infection Control. 43.4 – 9.	To examine the cost effectiveness of hospital's on-going investments in Hospital Acquired Infection (HAI) prevention in Intensive Care Units.
	Andronis K, et al. Is the Venner-PneuX endotracheal a cost-effective option for post cardiac surgery care? 2018. Ann Thorac Surg; 106:757-63	To evaluate the costs and benefits of Venner PneuX™ System to determine whether replacing standard endotracheal tubes with Venner PneuX™ System is a cost-effective option for intensive care units.
Enter text.	Enter text.	Enter text.
System benefits		

Overall patient benefit	Fletcher A, Ruffell A, et al. The LoTrach™ system: its role in the prevention of ventilator-associated pneumonia. 2008. British Association of Critical Care Nurses, Nursing in Critical Care. Vol 13, No. 5	The objective was to discuss the development of the LoTrach™ system in light of current evidence around of the prevention of ventilator-associated pneumonia (VAP) and its practical application in the intensive care setting.
	Ruffell A, et. al. Ventilator-associated pneumonia: prevention is better than cure. British Association of Critical Care Nurses, Nursing in Critical Care. 2008. Vol. 13, No. 1	The aim of this paper is to critically review the available literature and identify current evidence based nursing and medical interventions to support practitioners in preventing VAP in their patients.
	Senanayake E L, Giri R, Gopal S, Nevill A, Luckraz H. Incidence of endotracheal tube colonization with the use of PneuX endotracheal tubes in patients following cardiac surgery. J Hosp Infect. 2017 Jan;95(1):81-86. doi: 10.1016/j.jhin.2016.09.007. Epub 2016 Sep 16	The Venner PneuX™ ETT has been shown to halve ventilator-associated pneumonia in high risk patients undergoing cardiac surgery. This is a secondary analysis of bacterial colonisation in relation to ventilator-associated pneumonia between the Venner PneuX™ ETT and standard endotracheal tubes.

	Masterton R G, et al. Guidelines on the diagnosis, prevention and treatment of VAP in the UK. 2008. Journal of Antimicrobial Chemotherapy 2008 62:5-34	Evidence-based guidelines produced after a systematic literature review of a range of issues involving prevention, diagnosis and treatment of hospital-acquired pneumonia (HAP).
	Nseir S, et al. Variations in endotracheal cuff pressure. Eur J Anaesth. 2009; 3:229-34	To assess variations (under and over-inflations) pressures in endotracheal tube cuffs
	Doyle A, et al. The pressure exerted on the tracheal wall by two endotracheal tube cuffs: A prospective, observational bench-top, clinical and radiological study BMC Anaes 2010; 10:21	To estimate the pressure exerted on the tracheal wall by the LVLP cuff and conventional cuffs.
	Safdar N, et al. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 2005;33(10):2184-2193	To perform a systematic review to determine the incidence of VAP and its attributable mortality rate, length of stay, and costs.
	Vincent J L, et al. The prevalence of nosocomial infection in Intensive Care Units in	To determine the prevalence of intensive care unit (ICU)-acquired infections and the risk

	Europe: Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. 1995. JAMA. August 23/30. Vol. 274 No.8 Muscedere J, et al. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis. Crit Care Med 2011. Vol. 39, No. 8 Evans L, et al. The efficacy of subglottic secretion drainage. July 2007.	factors for these infections, identify the predominant infecting organisms, and evaluate the relationship between ICU-acquired infection and mortality. To conduct a systematic review and meta-analysis following published new evidence on subglottic secretion drainage as a preventative measure for ventilator-associated pneumonia. To examine intermittent subglottic secretion drainage quantifying leakage past the cuff in a benchtop model.
Enter text.	Enter text.	Enter text.
Cost benefits		
Cost-effective option for post cardiac surgery care	Andronis L, et al. Is the Venner-PneuX endotracheal tube system a cost-effective option for post cardiac surgery care ? Ann Thorac Surg 2018; 106:757-63)	To evaluate the costs and benefits of the Venner PneuX™ System to determine whether replacing standard endotracheal tubes with Venner PneuX™ System is a cost-effective option for intensive care units.

Costs of treating ventilator-associated pneumonia post cardiac surgery in the National Health Service	Luckraz H, Manga N, Senanayake EL, Abdelaziz M, Gopal S, Charman SC, Giri R, Oppong R, Andronis L. Cost of treating ventilator-associated pneumonia post cardiac surgery in the National Health Service: Results from a propensity-matched cohort study. J Intensive Care Soc. 2018May;19(2):94-100. doi: 10.1177/1751143717740804. Epub 2017 Nov 9	To assess the costs of managing ventilator-associated pneumonia in a cardiac intensive care unit in the National Health Service in the United Kingdom.
Cost effectiveness in prevention of VAP	York Health Economics Consortium (YHEC) NHS Innovation Accelerator Economic Impact Evaluation Case Study: PneuX™ February 2018	To provide a cost-benefit analysis of the Venner PneuX™ System, based on information and evidence available at the time.
	Wyncoll D. Number needed to treat and cost effectiveness in prevention of VAP. Critical Care 2012, 16:430	An analysis to help clinicians make the important economic decisions of whether to adopt a new VAP Prevention device or procedure.
	Dick A, et al. A decade of investment in infection prevention: A cost effectiveness analysis. 2015. American Journal of Infection Control. 43. 4 – 9	To examine the cost effectiveness of hospital's on-going investments in Hospital Acquired infection (HAI) prevention in Intensive Care Units.

	Gentile MA et al. Are specialized endotracheal tubes and Heat-and-Moisture Exchangers cost effective in preventing Ventilator-Associated Pneumonia? Respiratory Care 2010;55(2):184-196 Christianne A., et al. Oral decontamination is cost-saving in the prevention of ventilator-associated pneumonia in intensive care units. Crit Care Med 2004. Vol. 32, No. 1	To assess evidence of cost-effectiveness and benefits of current Ventilator-Associated Pneumonia (VAP) prevention methods. To assess the incremental cost effectiveness of a preventative measure for VAP – oral decontamination.
Enter text.	Enter text.	Enter text.
Sustainability benefits		
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The Venner PneuX™ System addresses multiple-known risk factors associated with intubation systems in current standard use and its design features have been proven in practice to prevent leakage and aspiration of secretions.

It is designed to prevent pulmonary aspiration, the leading cause of ventilator-associated pneumonia (VAP), the most common nosocomial infection in critically ill patients (13) and is indicated for use in adult critical care patients requiring intubation (primary or tube/exchange) and mechanical ventilation.

The technology comprises of the Venner PneuX™ ETT/TT, a specially designed, sterile, single use endotracheal/tracheostomy tube and works in conjunction with the Venner PneuX™ Extension Tube and Venner PneuX TSM™ Cuff Pressure Controller, as a complete system.

The Venner PneuX™ ETT 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 Venner PneuX™ TT is intended for patients undergoing tracheal intubation during extended periods (not more than 30 days) of intensive or critical care to facilitate ventilation and for the evacuation or drainage of secretions from the subglottic space.

The Venner PneuX™ ETT/TT are made of a flexible silicone/nitinol construction (MRI Compatible), designed for atraumatic insertion, which conforms to the anatomy, yet with strength against kinking and occlusion, whilst minimising damage to the airway. It is designed to prevent injuries to the palate, arytenoids and trachea, which are often associated with more rigid tubes (7). The depth markings indicate the distance to the distal tip of the tube and a printed black line aids orientation of the tube.

The Venner PneuX™ ETT/TT has a low-volume, low-pressure (LVLP) silicone cuff, with elastic characteristics that expands on inflation without folds or creases. Folds are present in every inflated standard endotracheal tube cuff made of polyvinyl chloride (PVC) or polyurethane chloride (PUC) and these can act as a pathway for liquids to travel to the lungs (1,2,3,4,5), as well as limiting their ability to mould to the size and the shape of the trachea.

The Venner PneuX™ ETT/TT cuff ensures that a low and consistent intracuff pressure is transmitted to the tracheal wall. It has been shown not to cause overpressure on the tracheal wall, therefore minimising the risk of mucosal injury associated with high pressure cuffs. An intracuff pressure of 80 cmH2O provides a calculated tracheal wall seal pressure of approximately 30 cmH2O (20 mmHg), depending on the patient's anatomy and ventilation pressures.

The Venner PneuX™ Endotracheal Tube has been shown in comparative bench studies to prevent pulmonary aspiration (leakage past the cuff) across the entire tracheal diameter range compared to standard tubes and maintains the seal in spite of either vertical or rotational movement of the tube, (1,4,13).

The silicone boat tip with murphy eye allows for atraumatic passage through the vocal cords and minimises forces when intubation is performed and is designed to lie straight and not push forwards into the tracheal wall (9). The silicone tip, with its hemispherical bevel design, exerts forces 7-10 times lower than a PVC tube, in vitro, (7) and reduces the risk of airway occlusion.

The Venner PneuX™ ETT/TT has a non-stick lining, which prevents the build-up of biological adhesions. Standard endotracheal tubes develop a biofilm load soon after placement which is out of reach of the body's natural defences, resistant to antibiotic therapy and acts as a constant source of reinfection. Bronchoscopes and suction catheters can normally pass without the need for additional lubrication, thereby reducing the forces on the delicate laryngeal structures (10).

The Venner PneuX™ ETT/TT has a fixation block/lock nut/winged tube holder for optimal tube securement and has opening(s) on each end for a head/neck strap to pass through. The fixation block with integrated bite block fixes the position of the tube, prevents unnecessary movement during use and resists damage from patient biting. There are lateral grooves around the inside of the fixation block which resists slippage and allows for securement. The lock nut enables correct fixation of the fixation block through loosening or tightening.

The Venner PneuX™ TT has an obturator which fits in the airway tube and guides placement. Its tip is designed to aid the passage through the surgical opening of a tracheostomy stoma and has a hole which allows a guidewire to pass through, if clinically required.

The Venner PneuX TSM™ Cuff Pressure Controller is designed for the monitoring, maintenance and regulation of the pressure within the cuffs of the Venner PneuX™ ETT/TT and maintains a constant cuff/tracheal wall seal pressure of 30cm H_2O, thus preventing aspiration (12).

The Venner PneuX™ System also facilitates subglottic irrigation (12-hourly or every shift change) and subglottic drainage (every 4 hours or more often if required), with a total of three subglottic ports, thereby directly influencing two steps in the pathogenesis of VAP. This maintains the cleanliness of the subglottis, larynx, pharynx and oral cavity and by having three ports around the circumference of the tube, ensures that at least one is always patent. Tubes with single subglottic drainage ports frequently fail (48% incidence), (9) and this failure is associated with an increase incidence of VAP (10). A single port may also cause mucosal damage (11) and become blocked.

The Venner PneuX™ Extension tube is a 2-metre, single use tube, used to connect the Venner Pneux™ ETT/TT to the Venner PneuX TSM™ Cuff Pressure Controller. One end of the extension tube is a uniquely designed luer lock connector for attachment to the connector outlet on the Venner PneuX TSM™ Cuff Pressure Controller and the other end is a luer slip connector which has a protective sleeve impeding connection to luer lock devices for attachment to the pilot balloon valve of the Venner PneuX™ ETT/TT. The luer lock connector incorporates several features – a twist-to-connect one-way valve to prevent accidental disconnection with the Venner PneuX TSM™ Cuff Pressure Controller, free coupling rotation to avoid the potential of tube kinking, and turning latch clicks when connected to prevent damage from over torqueing.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Economic/Environmental -

Our manufacturer, as a responsible company strives to consider the environmental impacts of what they develop from conceptualisation to commercialisation, conforming to ISO13485.

They ensure compliance to all applicable environmental, health and safety rules and regulations for the materials, product packaging that is used and implement clinical and industrial validation tests to achieve a product design that offers shared value and which is sustainable throughout its life cycle.

Social/Stakeholder Engagement -

We are committed to all our stakeholders, just as they are to our business. We invest a significant amount of time and resources in continued education, such as clinical training programmes and operational skills upgrade to attract and develop our internal stakeholders to grow with the business.

We also actively participate in medical conferences and clinical exchanges, as part of our responsibility in nurturing the next generation of medical professionals and contribute to the advancement of medical practice for the benefit of humanity.

Economic -

We review our production capabilities to the supply/demand of our global markets and make adaptations from the business dynamics. e.g. A Group decision for a manufacturing site transfer offered production economies and reduced operational risks for the company where few manufacturers were maintained, for a more stringent control process. This enabled production to be streamlined and offered greater quality assurance.

Ethical/Business Model and Culture -

Each stakeholder has an ethical responsibility towards the organisation and to promote such a culture that we adopt an open communication throughout, where management sets the tone. Ethics play an important role in our organisational strategy and decision-making process. We promote open discussion within the organisation and encourage problems to be handled openly and swiftly.

Eco-efficiency –

Achieved by the delivery of competitively priced goods, traceability and services that satisfy hospital/patient needs and bring quality of life, whilst progressively reducing ecological impacts and resource intensity throughout the product lifecycle.

Product Stewardship –

Focused around creating environmentally friendly manufacturing and industrial processes and products, utilising a sustainability-based approach to the product lifecycle and supply chain from design stage, and device designs that take into account the total lifecycle of these products. Mainly minimising the amount of non-renewable materials consumed and considering alternative hybrid reusable/disposable approaches for the new design of PneuX™ devices.

Reduced operational risks –

Providing visibility into Operations. Operations Risk Management is being utilised to establish risk-related business processes, manage change, monitor risk analytics and leverage the effectiveness of process.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

SEE ATTACHED WORD DOCUMENT – CLINICAL PATHWAY

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

Training Implementation Programme

Qualitech Healthcare is committed to the provision of clinical programmes and formalised training for the life of its products, ensuring optimum clinical benefit of the device, together with its safe, effective and appropriate use.

Our customer training and education provides the knowledge, understanding and support essential to gain the necessary expertise in the use of Venner PneuX™ System. This would be at no additional cost to the Hospital/Trust.

Literature Support Material Packs, which include Department Information Flyers, Product Literature, Quick Start Guides, Instruction for Use Manuals, Clinical Reviews, References, Abstracts, will be readily available together with "Verification of Understanding" Certification, on completion of comprehensive training.

Methods of Training

The use of "Train the Trainer" process would facilitate a more rapid expansion of the Training Programme -
Regional/Hospital Seminars
Webinars
On-site training
NAMDET (National Association of Medical Device Educators and Trainers)

Training Programme

The Training Programme consists of -
Introduction
The Principles of Ventilator-Associated Pneumonia (VAP)
The Venner PneuX™ System Overview - Venner PneuX™ Endotracheal Tube/Tracheostomy Tube and Venner PneuX TSM™ Cuff Pressure Controller
Practical Demonstration - Subglottic Drainage and Subglottic Irrigation
Hands-on Session
Clinical Support Material
Questions and
Verification of Understanding Certificate
Training Evaluation Forms will be available, together with appropriate Training Records and Attendance Certificates.

ADOPTION/IMPLEMENTATION

To ensure successful adoption, Qualitech Healthcare would work with the Hospital/Trust by identifying and liaising with all key personnel and decision makers, to instigate and implement the effective introduction of the use of the Venner PneuX™ system, as a new clinical practice, as well as fulfilling all Hospital/Trust requirements for the evaluation of new equipment. A dedicated "Team" would be formed to consolidate the implementation programme. All clinical references, papers, abstracts, and supporting data would be readily available.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		38
Number of studies identified as being relevant to the decision problem.		5
Of the relevant studies identified:	Number of published studies (included in table 1).	5
	Number of abstracts (included in table 2).	0
	Number of ongoing studies (included in table 3).	0

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Author/Company	Gopal S, et al. Significant reduction in ventilator-associated pneumonia with the Venner-PneuX system in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia Study. European Journal of Cardio-Thoracic Surgery. Advance Access December 26th, 2014. 1 – 5	Single-institution, prospective, randomized control trial	High-risk patients undergoing cardiac surgery	Endotracheal tube intubation for patients requiring mechanical ventilation	Standard endotracheal tube	The Venner-PneuX VAP Prevention System is associated with a significant reduction in VAP. This can potentially lead to significant cost reductions and should be implemented as part of the VAP reduction bundle
Author/Company	Smith N, et al. A retrospective review of patients managed with the Venner PneuX P.Y. VAP Prevention System. 2014. Journal of Intensive Case Medicine Vol 15, No. 2	Retrospective Review	Adult Critical Care	Endotracheal tube intubation for patients requiring mechanical ventilation	Standard endotracheal tube	Use of the Venner™ PneuX P.Y.VAP Prevention System facilitated lower VAP rates.

Author/Company	Fletcher A, et al. Incidence of VAP in patients undergoing elective tube exchange. Crit Care 2009;13(Suppl 1) P295	Single institution, sequential study	Adult Critical Care	Endotracheal tube intubation for patients requiring mechanical ventilation	Standard endotracheal tube	There were no complications associated with elective tube exchange and no subsequent cases of VAP in this cohort of patients who were re-intubated with the LoTrach tube. Elective tracheal tube exchange can be safely performed in General ICU patients
Author/Company	Fletcher A, et al. The Lo-Trach™ tracheal tube – airway symptom surveillance following critical care. Crit Care 2009;13(Suppl 1) P295	Single institution, sequential study	Adult Critical Care	Endotracheal tube intubation for patients requiring mechanical ventilation	Standard endotracheal tube	There were no cases of clinically apparent laryngotracheal injury in this cohort of patients with the LoTrach system and care plan.
Author/Company	Senanayake E L, Giri R, Gopal S, Nevill A, Luckraz H. Incidence of endotracheal tube colonization with the use of PneuX endotracheal	Single-institution, prospective, randomised, controlled trial	High risk patients undergoing cardiac surgery	Endotracheal tube intubation for patients requiring mechanical ventilation	Standard endotracheal tube	Colonisation of the ETT does not seem to play an important role in early onset VAP. There is a tendency for

	tubes in patients following cardiac surgery. J Hosp Infect. 2017 Jan;95(1):81-86. doi: 10.1016/j.jhin.2016.09.007. Epub 2016 Sep 16					reduced colonisation in the PneuX ETT with longer intubation times. This may have an impact on reducing the incidence of late-onset VAP.

Table 2 Summary of all relevant abstracts

None provided

Table 3 Summary of all relevant ongoing or unpublished studies

None provided

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Gopal S, et al. Significant reduction in ventilator-associated pneumonia with the Venner-PneuX system in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia Study. European Journal of Cardio-	Results: There were no significant differences in the patients' demographics. The mean (SD) ages for the two groups were 72.4 (8.2) and 72.1 (7.4) years (*P*=0.6), respectively. The mean EuroSCORE was 6.39 (2.2) for Group A and 6.48 (2.6) for Group B (*P*=0.9). The median intubation times were 14.7 (7.3, 2927.2) h and 13 (2.5, 528.7) h, respectively. VAP incidence was significantly lower in the Venner-PneuX ET group, being 10.8% when compared with 21% in the standard ET group (*P*=003). There was no significant difference between the two groups in terms of intensive care unit	Supports claimed benefits of the technology.

Thoracic Surgery. Advance Access December 26th, 2014. 1 – 5	stay (*P*=0.2) and in-hospital mortality (*P*=0.2). A binary logistic regression analysis (type of ET tube, age, LVEF, history of lung disease, smoking history, surgical procedure, EuroSCORE, cardiopulmonary bypass time, blood transfusion, intubation duration among others) confirmed that the Venner-PneuX ET tubes was associated with significant VAP reduction (Odds ratio 0.45, *P*=003)	
Smith N, et al. A retrospective review of patients managed with the Venner PneuX P.Y. VAP Prevention System. 2014. Journal of Intensive Case Medicine Vol 15, No. 2	Conclusion: Use of the Venner™ PneuX facilitated lower VAP rates.	Supports claimed benefits of the technology.
	Text	Text
Fletcher A, et al. Incidence of VAP in patients undergoing elective tube exchange. Crit Care 2009;13(Suppl 1) P295	Results: Forty-four patients (83%) patient underwent elective tube exchange. No complications were associated with the procedure. There were no episodes of VAP while the Lo-Trach was in situ. On an intention to treat basis there was a 1.8% VAP rate because one patient who required emergency reintubation following elective extubation received a conventional tube and developed a VAP 2 days later. No other patients had antimicrobials begun for chest infections.	Supports claimed benefits of the technology.
Fletcher A, et al. The Lo-Trach™ tracheal tube – airway symptom surveillance following critical care. Crit Care 2009;13(Suppl 1) P295	Results: There were a total of 306 days of intubation with a mean of 5.3 days (range 1 – 18 days). 83% of patients underwent a tube-exchange (using a bougie), the remaining were primary LoTrach intubations on the ICU. No evidence of tracheal injury was noted at post-mortem. No patients complained of upper airway	Supports claimed benefits of the technology.

	symptomatology and there were no referrals to local or regional ENT services.	
Senanayake E L, Giri R, Gopal S, Nevill A, Luckraz H. Incidence of endotracheal tube colonization with the use of PneuX endotracheal tubes in patients following cardiac surgery. J Hosp Infect. 2017 Jan;95(1):81-86. doi: 10.1016/j.jhin.2016.09.007. Epub 2016 Sep 16	Conclusion: Colonisation of the ETT does not seem to play an important role in early onset VAP. There is a tendency for reduced colonisation in the PneuX ETT with longer intubation times. This may have an impact on reducing the incidence of late-onset VAP.	Supports claimed benefits of the technology.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Gopal S, et al. Significant reduction in ventilator-associated pneumonia with the Venner-PneuX system in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia Study. European Journal of Cardio-Thoracic Surgery. Advance Access December 26th, 2014. 1 – 5	
How are the findings relevant to the decision problem?	The LoVap study has confirmed that VAP (or VAC) is a common post-operative problem in cardiac patients even when the intubation duration is short and that the Venner-PneuX VAP prevention system significantly reduces the incidence of developing VAP in patients at high risk.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes – overall patient and cost benefits, reduction in the incidence of VAP, facilitates the application of evidence based VAP preventative measures, prevents/reduces aspiration and increase in quality-adjusted life years.
Will any information from this study be used in the economic model?	Yes.
What are the limitations of this evidence?	Patient numbers.
How was the study funded?	Department of Health.

Smith N, et al. A retrospective review of patients managed with the Venner PneuX P.Y. VAP Prevention System. 2014. Journal of Intensive Case Medicine Vol 15, No. 2	
How are the findings relevant to the decision problem?	Use of the Venner™ PneuX P.Y.™ System facilitated lower VAP rates.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes – Overall patient benefit. Reduction in the incidence of VAP.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Patient numbers and lack of control group.

Smith N, et al. A retrospective review of patients managed with the Venner PneuX P.Y. VAP Prevention System. 2014. Journal of Intensive Case Medicine Vol 15, No. 2	
How was the study funded?	The Venner™ PneuX P.Y.™ Systems were provided by Intavent Direct Limited.

Fletcher A, et al. Incidence of VAP in patients undergoing elective tube exchange. Crit Care 2009;13(Suppl 1) P295	
How are the findings relevant to the decision problem?	This study showed that there were no episodes of VAP while the Lo-Trach was in situ and there were no complications associated with the procedure.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes – Overall patient benefit, reduction in the incidence of VAP, prevents/reduces aspiration, facilitates the application of evidence based VAP preventative measures.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Patient numbers.
How was the study funded?	By Hospital Trust.

Fletcher A, et al. The Lo-Trach™ tracheal tube – airway symptom surveillance following critical care. Crit Care 2009;13(Suppl 1) P295	
How are the findings relevant to the decision problem?	There were no cases of clinically apparent laryngotracheal injury in this cohort of patients with the LoTrach system and care plan.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes – Overall patient benefit.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Patient numbers.
How was the study funded?	By Hospital Trust.

Senanayake E L, Giri R, Gopal S, Nevill A, Luckraz H. Incidence of endotracheal tube colonization with the use of PneuX endotracheal tubes in patients following cardiac surgery. J Hosp Infect. 2017 Jan;95(1):81-86. doi: 10.1016/j.jhin.2016.09.007. Epub 2016 Sep 16	
How are the findings relevant to the decision problem?	Demonstrates an impact on reducing late-onset VAP.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes – reduction in the incidence of VAP.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Patient numbers
How was the study funded?	Department of Health

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

MHRA Reported Adverse Events:

Great Western Hospital - Date of Event - 17.01.18. Ref. 2018/001/024/601/003 and 2018/003/021/291/019 - Closed. NB. Allocated two different reference numbers on initial log.

NB. Field Safety Notice - issued by Manufacturer, distributed and signed acknowledgement from all accounts received.

Stepping Hill Hospital - Date of Event - 26.01.18. Ref. 2018/001/029/601/006 - Closed.

York District Hospital – Date of Event – 12.07.18. Ref. 2018/006/028/401/013 – Closed.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

None reported.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Report all relevant results, including diagrams if appropriate.

Enter text.

Explain the main findings and conclusions drawn from the evidence synthesis.

Enter text.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Currently, Qualitech Healthcare are unable to provide enough comparable quantitative evidence in the form of evidence synthesis and meta-analyses.	Enter text.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The main clinical evidence considers incidence of VAP, length of ICU/ITU stay, length of hospital stay, incidence of aspiration, duration of mechanical ventilation, incidence of unplanned extubation and/or re-intubation, antibiotic usage, mortality, sedation usage, difficulty of placement and maintenance of tube position. device-related adverse events e.g. tracheal injury, alongside significant cost saving. In relation to adverse incident at the Great Western Hospital - Date of Event - 17.01.18. Ref. 2018/001/024/601/003 and 2018/003/021/291/019 (Closed). Patient bit down and through the endotracheal tube. Venner Medical Singapore acted upon this event and manufactured the Venner PneuX™ ETT/TT with fixation block/lock nut/winged tube holder for optimal tube securement and has opening(s)

on each end for a head/neck strap to pass through (April 2019). The fixation block with integrated bite block fixes the position of the tube, prevents unnecessary movement during use and resists damage from patient biting. There are lateral grooves around the inside of the fixation block which resists slippage and allows for securement. The lock nut enables correct fixation of the fixation block through loosening or tightening.
Training - This was provided by the company prior to the clinical trial. This is essential to effective implementation of the system.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The integration of knowledge and experience leads to improved patient outcomes and safer, more efficient and effective patient care.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The only difference is detailed in, Gopal S., et al. 2014. Significant reduction in ventilator-associated pneumonia with the Venner-PneuX system in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia Study. European Journal of Cardio-Thoracic Surgery. Advance Access December 26th, 2014. 1 – 5, these patients were high risk cardiac cases.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

Adult patients requiring mechanical ventilation in a critical care setting for at least 24 hours and up to 30 days duration.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

Strengths:

100,000 ventilating patients entering the Critical Care setting per annum, all at risk of developing Ventilator-Associated Pneumonia (VAP)
Reduces the incidence of Ventilator-Associated Pneumonia (VAP)
Prevention/reduction of aspiration.
Facilitates the application of evidence based VAP Preventative Measures.
Cost-effective option for post cardiac surgery care.
Costs of treating ventilator-associated pneumonia post cardiac surgery in the National Health Service.

Limitations:

No agreed criteria for defining Ventilator-Associated Pneumonia.
Challenges with training

9 References

Please include all references below using NICE's standard referencing style.

Section 2 - Description of technology

1. Young P, et al. A low-volume, low-pressure tracheal tube cuff reduces pulmonary aspiration. Crit Care Med 2006 Vol.34, No. 3

2. Young P, et al. Prevention of tracheal aspiration using the pressure-limited tracheal tube cuff. 2009. Anaes Vol.54 Issue 6, Pages 559-563

3. Young P, et al. Evaluation of a new design of tracheal tube cuff to prevent leakage of fluid to the lungs. BJA 1998;**80:**796-799

4. Mariyalselvam M, et al. An in *vitro* study comparing eight endotracheal tubes and their ability to prevent micro-aspiration. Eur Soc Int Care Med 2015. Int Care Med Exp. Vol 3. Suppl S1:A382

5. Seegobin RD, et al. Aspiration beyond endotracheal cuffs. Can Anaes Soc J 1986; 33:273-9

6. Greer JR, et al. A comparison of tracheal tube tip designs on the passage of an endotracheal tube during oral fibreoptic intubation. Anaesthesiology 2001;**94**(5):729-731

7. Joo HS, et al. PVC tracheal tubes exert forces and pressure 7-10 times higher than silicone or armoured tubes – an *in vitro* study. Can J Anaesth 2002;**49**(9):986-989

8. Steen JA, et al. Tracheal tube forces on the posterior larynx: index of laryngeal loading. Crit Care Med 1982;**10**(3):186-189

9. Dragoumanis CK, et al. Investigating the failure to aspirate subglottic secretions with the Evac endotracheal tube. Anaes Analg 2007;**105**(4):1083-1085

10. Rello J, et al. Pneumonia in intubated patients: Role of respiratory airway care. Am J Respir Crit Care Med 1996;**154**(1):111-115

11. Berra L, et al. Evaluation of continuous aspiration of subglottic secretions in an in *vivo* study. Minerva Anaesthsio. 2003 May;**69**(5):342-7

12. Nseir S, et al. Continuous control of tracheal cuff pressure and micro aspiration of gastric contents in critically ill patients. Am J Crit Care Med 2011; 184:1041-7

13. Mariyalselvam M. et al. Endotracheal tubes and fluid aspiration: an *in vitro* evaluation of new cuff technologies. BMC Anaesthesiology 2017;**17:36**

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	26th June 2019
Date span of search:	April 2007 to 26th June 2019
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
All studies relevant to the technology have been correlated since April 2007 to date. All clinical studies listed in Table 1 were conducted independently therefore, search strategies were undertaken by the individual Trust or Governing Body i.e. Department of Health. This information has not been shared with Qualitech Healthcare Ltd.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

None given

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	26th June 2019
Date span of search:	April 2007 – 26th June 2019.
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
It has not been necessary to conduct a search as Qualitech Healthcare Limited, as a distributor, has appropriate Adverse Event reporting procedures in place, directly with the Hospital/Trust, the Manufacturer (Venner Medical (Singapore) Pte Limited), our Authorised Representative (Advena Limited) and the Medicine and Healthcare Products Regulatory Agency (MHRA).	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT273 PneuX for preventing ventilator-associated pneumonia in intensive care

Company evidence submission

Part 2: Economic evidence

Company name	Qualitech Healthcare Limited
Submission date	17th July 2019
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		N/A – studies identified were those known to Qualitech Healthcare Limited
Number of studies identified as being relevant to the decision problem.		2
Of the relevant studies identified:	Number of published studies.	2 (1 study published in an academic journal and 1 case study published by the NHS Innovation Accelerator)
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Author/company	Andronis et al, 2018, UK	Patients requiring mechanical ventilation after major cardiac surgery. NHS critical care setting	Venner-PneuX endotracheal system; standard endotracheal tube	• PneuX system, £150 • Standard endotracheal tube, £5 • Mean NHS treatment cost post-cardiac surgery (with VAP), £15,124 • Mean NHS treatment cost post-cardiac surgery (without VAP), £6,295	PneuX is associated with an expected cost saving per patient of £738 PneuX is dominant (i.e. more effective and less costly) compared with a standard endotracheal tube	Deterministic sensitivity analysis (DSA) suggested that PneuX is less costly and more effective than a standard endotracheal tube for all alternative values of uncertain parameters. Probabilistic sensitivity analysis (PSA) indicated a 96% probability of PneuX being cost-effective at willingness to pay values up to £30,000 per QALY. Threshold analysis indicated cost savings associated with PneuX if the absolute reduction in risk of VAP is over 0.02 (base case value: 0.1). Conclusion: Intubation with PneuX is less costly and more effective than standard care
Author/company	NHS Innovation Accelerator (NIA), 2017, UK	Patients intubated in the intensive care ward of an NHS District General Hospital	Venner-PneuX endotracheal system; standard care	• Intubation using Pneux, £156 • Standard intubation, £6.36 • Cost of treating VAP per episode, £10,000	PneuX is cost saving compared with standard care. The estimated total net savings for a hospital performing 300 episodes of intubation per year were £255,108. Return on investment (ROI): 668%	No sensitivity analyses performed. Conclusion: PneuX is strongly cost saving compared with standard care and is likely to give a strongly positive ROI from an NHS perspective

2 Details of relevant studies

Andronis 2018	
What are main differences in resource use and clinical outcomes between the technologies?	Use of PneuX was associated with reduced risk of VAP compared with standard intubation (11% versus 21%, taken from Gopal et al, 2014). This in turn resulted in reduced resource use because VAP is associated with increased length of stay in critical care (cost of treatment with/without VAP taken from Luckraz et al, 2018). Use of PneuX was also associated with an increase in quality-adjusted life years (QALYs) due to reduced stay in critical care.
How are the findings relevant to the decision problem?	The study estimates cost-effectiveness of PneuX, with the setting, intervention, comparator, outcomes and perspective fully aligned with the decision problem. The patient population represents a subgroup of interest (major heart surgery patients).
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes - reduces overall costs of care; reduces overall hospital length of stay for patients in critical care on mechanical ventilation.
Will any information from this study be used in the economic model?	Yes – the structure of the economic model presented in Section 3 is based on that of the model reported in this study. Data from secondary sources used in the study were also used to populate some model input parameters.
What cost analysis was done in the study? Please explain the results.	An expected cost saving of £738 per patient was calculated. This saving resulted from the additional costs of treating VAP in the standard intubation group, which substantially outweighed the higher acquisition costs in the PneuX group. The results of DSA indicated that the direction of these results did not change for any alternative parameter values. Cost-effectiveness analysis comparing the change in costs and the change in QALYs associated with PneuX indicated that PneuX was dominant. This is because use of PneuX was less costly and resulted in better health-related quality of life (measured in QALYs) compared with standard intubation.
What are the limitations of this evidence?	• The evidence was generated in a subset of the patient population only (major heart surgery patients). • The effectiveness data used in the model are taken from a study in which the median duration of intubation was 13-15 hours, which is below the 24-hour minimum period specified in the decision problem.
How was the study funded?	Three of the study authors received an educational grant from Qualitech Healthcare Limited. The company had no involvement in any aspect of the study, including data collection, analysis and interpretation of results.

NHS Innovation Accelerator (NIA) 2017	
What are main differences in resource use and clinical outcomes between the technologies?	Use of PneuX was associated with reduced risk of VAP compared with standard intubation (11% vs 21%, taken from Gopal et al, 2014). This in turn resulted in a reduction in costs (a cost for treating VAP of £10,000 per episode was used).
How are the findings relevant to the decision problem?	The study estimates cost savings associated with PneuX, with the patient population, setting, intervention, comparator, outcomes and perspective fully aligned with the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes - cost-effectiveness in prevention of VAP; reduces overall costs of care.
Will any information from this study be used in the economic model?	No, although the economic model presented in Section 3 uses some of the same sources as the study (namely Gopal et al, 2014).
What cost analysis was done in the study? Please explain the results.	Net costs associated with use of PnueX versus standard care were calculated for a hypothetical District General Hospital with 10 critical care beds, where 300 intubations were performed every year. The estimated cost saving associated with PneuX was £255,108 (£850 per intubation). This saving resulted from the additional costs of treating VAP in the standard care group, which substantially outweighed the higher acquisition costs in the PneuX group.
What are the limitations of this evidence?	• No sensitivity analyses were conducted. • The cost of an episode of VAP came from an NIA fellow and so is less reliable than an estimate from a more robust source (e.g. a published costing study). • Although the population for the analysis included any patient receiving mechanical ventilation in critical care, effectiveness data came from a study conducted in a subset of the population only (major heart surgery patients).
How was the study funded?	NIA programme.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

In line with the available comparative clinical effectiveness (Gopal et al, 2014) and resource use data (Luckraz et al, 2018), the model base case considers adult patients requiring mechanical ventilation in critical care following major heart surgery. This is a subgroup of the wider population of patients requiring mechanical ventilation who are eligible for PneuX. Sensitivity analysis in the model aims to consider this broader population, using published clinical and economic evidence where possible. In particular, a range of alternative values for the baseline risk of VAP, which may differ between patient groups, is explored.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Intervention: Venner-PneuX System Comparator: standard care (i.e. conventional endotracheal tube) This is fully aligned with the scope.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

The model has a simple decision tree structure, based on the economic model reported by Andronis et al (2018). A hypothetical cohort of 1,000 patients requiring mechanical ventilation in critical care can receive either PneuX or a standard endotracheal tube. After intubation, patients in both arms can either go on to contract VAP or have no VAP.

This is aligned with the clinical care pathway presented in Part 1 Section 3 of the submission, where any adult patient in critical care who requires mechanical ventilation is eligible for PneuX. Patients who contract VAP often require prolonged inpatient stay and additional interventions and, therefore, patients with and without VAP follow separate branches of the decision tree. As described in Part 1 Section 6 of the submission, no adverse events have been noted in the clinical evidence for PneuX and, therefore, no adverse events were included in the model. Adverse events from MHRA are reported, but as this database provides no denominator any risk of adverse events could not be estimated.

Table 2 Assumptions in the model

Assumption	Justification	Source
Mortality not included (although evidence suggests VAP results in increased mortality)	Simplifying assumption. Reductions in mortality resulting from use of PneuX could increase costs in the long term but would also bring substantial patient benefits. The published economic model by Andronis et al (2018), on which this model is based, did not include mortality.	Safdar et al, 2005 Andronis et al, 2018
Cases of VAP not stratified by severity	Simplifying assumption. This is aligned with the published economic model and the available clinical evidence, where rates of differing severities of VAP and the impact of PneuX on severity of VAP are not reported.	Andronis et al, 2018 Gopal et al, 2014
No cost applied for staff time to undertake training	Training for nursing staff is provided free of charge by Qualitech Healthcare Limited. Training in the use of the system only takes 15-30 minutes and can then be used to treat all patients coming through the critical care unit. A previous NIA analysis of PneuX estimated that around 300 patients would be intubated per year in a typical critical care unit with 10 beds. If 30 minutes of training are needed, this equates to 6 seconds of each individual staff member's time per patient per year. Therefore, it seems likely that the per patient cost of staff time for training would be negligible. This assumption is explored in scenario analyses.	Reported by trainers at Qualitech Healthcare Limited NHS Innovation Accelerator (NIA), 2017

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Baseline risk of VAP	Gopal et al, 2014	20.8% (25/120)	Not reported. Standard error calculated for use in PSA: 3.7%	Applied as the risk of VAP in standard care (i.e. when a standard endotracheal tube is used)
Relative risk (RR) of VAP with PneuX	Gopal et al, 2014	0.52	Not reported. 95% confidence interval (CI) calculated for use in PSA: 0.28-0.97	Applied to the baseline risk of VAP to calculate the risk of VAP in the PneuX arm (10.8%)

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

No outcomes were extrapolated beyond the study follow-up period.

Table 4 Other parameters in the model

Parameter	Description	Justification	Source
Time horizon	<1 year (including intubation time plus any additional time required for VAP to be treated)	To capture the duration of intubation and also includes any additional time required for the patient to recover from VAP after mechanical ventilation has ceased.	Gopal et al, 2014
Perspective (NHS/PSS)	NHS	As specified in the final scope	NICE, 2019
Sources of unit costs	• Device distributor (cost of PneuX) • Published economic model (cost of standard endotracheal tube) • Published costing study (additional cost of treating VAP)	• Current price agreed with NHS England. • Secondary source is an NHS Trust procurement department. Used in the published economic model and validated by clinical experts as part of that study. The cost falls in the middle of the range reported in the NICE MedTech Innovation Briefing for PneuX (MIB45). The minimum and maximum costs in this range (£1.12-£11.60) are explored in scenario analyses. • Study in an NHS critical care setting with high patient numbers. The study population represents a subgroup of the population of interest.	• ITT-03 2017-19 Innovation and Technology Tariff • Andronis et al, 2018 & NICE, 2015 • Luckraz et al, 2018

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

No transition matrix was used in the model and no data were transformed.

The patient population in the RCT used to populate the clinical inputs (Gopal et al, 2014) and the costing study used as the source for the additional cost of treating VAP (Luckraz et al, 2018) represents patients requiring mechanical ventilation following major heart surgery, which is a subgroup of the patient population in the final scope for this evaluation (NICE, 2019). It is possible that these data may not be representative of the broader population requiring mechanical ventilation in a critical care setting.

The baseline risk of VAP in particular may differ depending on the reason the patient is in critical care, the severity of their condition and the length of intubation. Therefore, alternative values for the baseline risk were explored in sensitivity and scenario analyses, using data from the published literature.

The cost of treating VAP is not likely to differ substantially between cardiac surgery patients and general critical care patients because the management of VAP is consistent across these groups (Luckraz et al, 2018). However, the cost of VAP itself is already uncertain, with Luckraz et al, 2018 reporting a 95% CI of £6,937 to £11,189. For these reasons, the cost is varied widely in sensitivity analyses.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

£150 per patient.

This is the price agreed with NHS England under the ITT-03 2017-19 Innovation and Technology Tariff.

If the list price is not used in the model, provide the price used and a justification for the difference.

N/A

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

There is no NHS reference cost or national tariff specific to VAP. Costs for pneumonia are given, but these are likely to differ substantially because patients with VAP will always be in a critical care unit, where costs are higher than in other hospital settings. NHS reference costs for stays in critical care range from £1,136 per day for 1 organ supported (the minimum if a patient is mechanically ventilated) to £2,075 for 6 or more organs supported.

The PneuX system, which is currently used in the NHS, is costed at £150 under the ITT-03 2017-19 Innovation and Technology Tariff.

The cost of a standard endotracheal tube used by Andronis et al (2018) in their economic model is £5.00. This figure was retrieved from the procurement department of an NHS Trust. The NICE MedTech Innovation Briefing for PneuX (MIB45) reports costs between £3.25 and £11.60 for tubes with subglottic suction and £1.12 and £1.35 for tubes without subglottic suction. The cost of £5.00 reported by Andronis et al (2018) is used in the model base case, with the minimum value from MIB45 explored in scenario analyses.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

Luckraz et al (2018) report a cohort study that estimated the cost to the NHS of treating patients in critical care following cardiac surgery. Costs from this study were used in the published economic model by Andronis et al (2018). The cohort comprised 3,416 patients mechanically ventilated after cardiac surgery, of whom 342 developed VAP. Costs were estimated on the basis of Healthcare Resource Group (HRG) codes, using resource use data from the hospital's database and unit costs from NHS reference costs. The mean treatment cost was £15,124 for those who developed VAP and £6,295 for those who did not. This gave an additional treatment cost associated with VAP of £8,829, the vast majority of which was attributable to increased length of stay in critical care. Bootstrapping techniques were used to estimate a 95% CI around this value, which was £6,937 to £11,189. Although the mean costs of treatment were calculated using reference costs data from 2013/14, the additional cost of treating VAP was not inflated in the current model. The cost, which represents a difference, could have changed with inflation if both the cost of treating patients with VAP and the cost of treating patients without VAP grew. However, the value is already uncertain, and a wide range of alternative values is explored in sensitivity analysis. Although the study only considered cardiac surgery patients, rather than general critical care patients, it is likely that the costs reported are generalisable to the

treatment of VAP in the wider critical care population. This is because the management of VAP is consistent regardless of the patient's condition (Luckraz et al, 2018).

No other studies were identified that used resource use data from the UK NHS to estimate the cost of VAP. Wyncoll and Camporota (2012) assume a hypothetical cost of £10,000, which was based partly on costs reported in a previous study conducted in the USA. The authors adjusted the US figure to account for the fact that healthcare costs are generally lower in the UK. However, the value is fairly arbitrary and less robust than the cost reported by Luckraz et al (2018) and so was not used in the model base case. The value was explored in sensitivity analyses.

Studies in the USA have estimated costs associated with VAP of $21,163 (Dick et al, 2015), $39,828 (Kollef et al, 2012) and $10,019 (Safdar et al, 2005). However, these are unlikely to be representative of costs in the UK NHS due to substantial differences in the healthcare system and resource use.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Training of critical care nursing staff is required before PneuX is implemented. This training is provided free of charge by Qualitech Healthcare Limited. There is likely to be a small cost to the NHS associated with the staff time required to attend this training. However, given that only 15-30 minutes of training are needed, and this can then be used to treat all patients coming through the critical care unit, the per patient cost would be negligible. This is explored in scenario analyses, where a conservative assumption is made that the cost of staff time for training is £10 per patient.

Aside from this, no resources are needed above those routinely used with standard endotracheal tubes. There are no maintenance or calibration requirements for the PneuX system and the monitor is serviced at two-year intervals by the manufacturer at no additional cost.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

Use of PneuX changes patient outcomes by decreasing the proportion of patients who develop VAP (Gopal et al, 2014). Therefore, it is anticipated that fewer resources will be required after implementing the technology because fewer cases of VAP will be treated.

There is an increased risk of mortality associated with VAP (Safdar et al, 2005), meaning that mortality rates are likely to decrease after implementing PneuX. This could increase healthcare resource use in the long term because patients who would otherwise have died are likely to consume healthcare in the future. However, a decrease in mortality would be highly beneficial in terms of patient outcomes.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Patients who develop VAP typically remain in critical care for longer (Luckraz et al, 2018) so it is expected that a decrease in the rate of VAP will increase patient turnover, meaning that more patients can be treated in the critical care unit over a given period. This is a beneficial system outcome that is unlikely to affect resource use.

Table 5 Resource use costs

	Technology costs	Comparator 1 costs	Difference in resource use costs (technology vs comparator 1)
Cost of resource use to implement technology	£0 (£10 in scenario analysis)	£0	£0 (£10 in scenario analysis)
Cost of resource use associated with patient outcomes	£0	£0	£0
Cost of resource use associated with system outcomes	£0	£0	£0
Total costs	£0 (£10 in scenario analysis)	£0	£0 (£10 in scenario analysis)

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

As noted in Part 1 Section 6 of the submission, no adverse events have been noted in the clinical evidence for PneuX. Therefore, no adverse event costs were included in the model.

Table 6 Adverse events and costs in the model

Adverse event	Items	Cost	Source
N/A	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
N/A	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

None.

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

No

Total costs

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per treatment/patient over lifetime of device	£150	ITT-03 2017-19 Innovation and Technology Tariff
Consumables per year (if applicable) and over lifetime of device	£0	N/A
Maintenance cost per year and over lifetime of device	£0	N/A
Training cost over lifetime of device	£0 (assumption of £10 per patient used in scenario analysis)	Assumption
Other costs per year and over lifetime of device	£0	N/A
Total cost per treatment/patient over lifetime of device	£150 (£160 in training cost scenario)	N/A

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per treatment/patient over lifetime of device	£5 (£1.12 used in scenario analysis)	Andronis et al, 2018 (NICE MIB45 for scenario analysis)
Consumables per year (if applicable) and over lifetime of device	£0	N/A
Maintenance cost per year and over lifetime of device	£0	N/A
Training cost over lifetime of device	£0	N/A
Other costs per year and over lifetime of device	£0	N/A
Total cost per treatment/patient over lifetime of device	£5 (£1.12 in scenario analysis)	N/A

Results

Table 9 Base-case results

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator 1*
Device cost (per treatment)	£150	£5	£145
Cost of VAP (per treatment)	£956	£1,839	-£883
Total	£1,106	£1,844	-£738

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

As identified in Part 1 Section 1 of the submission, the population eligible for PneuX is any adult requiring mechanical ventilation in a critical care setting. The clinical evidence used in the model base case (Gopal et al, 2014) was generated in a subset of this population, adults requiring mechanical ventilation in critical care following major heart surgery (this is a subgroup of interest to the evaluation – see Part 1 Section 1). Additionally, most of these patients were intubated for <24 hours, which is outside of the 24-hour to 30-day period outlined in the decision problem. For this reason, scenario analyses were performed where a lower baseline risk of VAP was applied (10%), using data from published studies that considered all intubated patients in a critical care setting, rather than just cardiac surgery patients, as well as those who were intubated for >24 hours. The results of this scenario analysis indicate the likely cost impact of PneuX if the baseline risk of VAP was lower in a general critical care setting.

The comparator used in the model is a conventional endotracheal tube (see Part 1 Section 1 of the submission). A range of costs for conventional endotracheal tubes are presented in the literature, with the cost varying partially dependent on whether the tube has subglottic suction (MIB45; NICE, 2015). For this reason, 2 scenario analyses were performed in which the impact of using the lowest reported cost (£1.12 for a tube without subglottic suction) on model results was explored. Use of the highest cost (£11.60 for a tube with subglottic suction) would result in higher cost savings associated with PneuX and so this is not presented as a separate scenario.

As identified in Part 1 Section 3 of the submission, staff training in the use of the system is required before PneuX can be implemented. This training is provided free of charge by Qualitech Healthcare Limited. However, there would be an opportunity cost associated with the staff time required to attend this training. An assumption is used in the base case analysis that there is no cost associated with training because at a per patient level the cost of nursing staff time is likely to be negligible (see Table 2). However, a scenario analysis was performed in which a large training cost was applied (£10 per patient) to determine how this might affect the cost impact of PneuX. This scenario represents a conservative estimate because the costs associated with training are likely to be less than £10 per patient in reality.

Describe the differences between the base case and each scenario analysis.

1. **Baseline risk of VAP = 10%.** This is lower than in the base case, where the baseline risk is 20.8%. All other inputs are the same as in the base case.
2. **Cost of standard endotracheal tube = £1.12**. This is lower than in the base case, where the cost is £5. All other inputs are the same as in the base case.
3. **Cost of training per patient = £10.00**. This is higher than in the base case, where no cost is applied. All other inputs are the same as in the base case.

Describe how the scenario analyses were included in the cost analysis.

Scenarios 1 and 2 used input parameters already included in the model base case. Therefore, including these in the cost analysis simply involved updating the base case values and generating model results. Scenario 3 involved an additional cost not included in the base case. Therefore, a 'training cost' parameter was incorporated into the PneuX arm of the model, with a value of £10 applied.

Describe the evidence that justifies including any scenario analyses.

1. **Baseline risk of VAP = 10%.** Safdar et al. (2005) report a systematic review in which data from 89 studies of VAP in a critical care setting (representing over 50,000 patients) were pooled. In the majority of studies, patients were intubated for >48 hours. The authors present a range of values for the risk of VAP, of which the lower limit is 10%. Chastre & Fagon (2002) also pool values from a series of international studies conducted in critical care settings and report a range of 8-28% for the baseline risk of VAP. In the case of both papers, it is worth noting that the studies cited were conducted at least 15 years ago (and, in some cases, considerably longer ago) and so may not be generalisable to the NHS today. Data from the USA between 2005 and 2013 demonstrate a 10% risk of VAP (Metersky et al, 2016). It is unclear how generalisable US data are to the UK NHS, with another US study reporting a much lower risk of VAP and appearing to use different diagnostic criteria (Kollef et al, 2012).
2. **Cost of standard endotracheal tube = £1.12**. Lowest cost reported in MIB45 (NICE, 2015) for an endotracheal tube without subglottic suction.
3. **Cost of training per patient = £10.00**. Based on an assumption because no published evidence on the cost of staff time required for training is available. This is a conservative assumption because the cost associated with training is likely to be much smaller in reality.

Table 10 Scenario analyses results

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in cost per patient (£) *
Scenario 1 – lower baseline risk of VAP (total costs)	£609	£888	-£279
Scenario 2 – lowest cost for standard tube (total costs)	£1,106	£1,840	-£734
Scenario 3 – training cost included (total costs)	£1,116	£1,844	-£728
* Negative values indicate a cost saving.			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Uncertainty in the model input parameters was assessed through PSA and DSA. PSA involved varying uncertain parameters using 95% CIs sourced from the published literature. PSA was run for 1000 iterations. DSA included one-way sensitivity analyses around the cost of VAP and the cost associated with training, as well as two-way sensitivity analysis around the baseline risk of VAP and the RR with PneuX.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Variable	Justification	Values	Source
Baseline risk of VAP	Key variable driving the cost savings associated with PneuX. There is some uncertainty around this value, especially because the clinical data were generated in a subgroup of the population of interest.	DSA: 0-50% PSA: 13.6-28.1% (95% CI)	Assumption Gopal et al, 2018 (95% CI calculated from patient numbers)
RR of VAP with PneuX	Key variable driving the cost savings associated with PneuX. There is uncertainty around the base case value, as shown by the calculated 95% CI.	DSA: 0-1 PSA: 0.28-0.97 (95% CI)	Assumption Gopal et al, 2018 (95% CI calculated from patient numbers)
Additional cost of treating VAP	Key variable driving the cost savings associated with PneuX. There is uncertainty around this variable, as shown by the 95% CI reported in the literature.	DSA: £4,000-£40,000 PSA: £6,937-£11,189 (95% CI)	Assumption Luckraz et al, 2018 (95% CI reported in the paper)
Cost of training	There is uncertainty as to the per patient cost of staff time needed for training in the use of PneuX. This will depend on the number and seniority of staff that need to be trained and the number of patients they would treat in the remainder of their working life.	DSA: £0-40 (Not varied in PSA because a value of £0 is used in the base case)	Assumption

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All parameters listed in Table 3 were varied in sensitivity analyses.

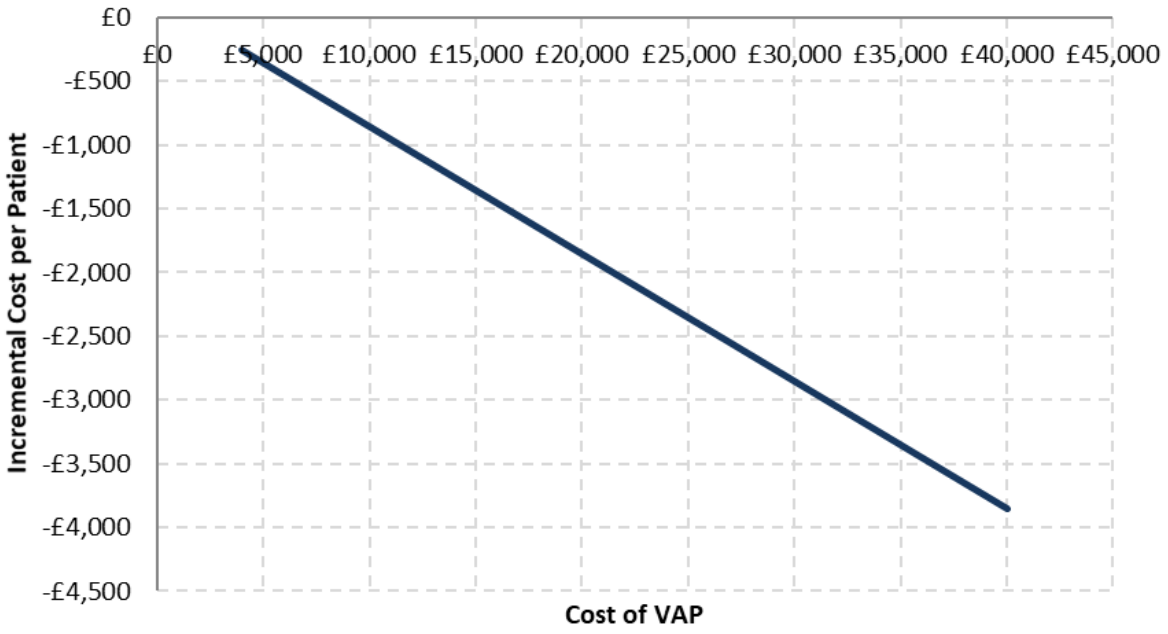
Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

Two-way sensitivity analysis of baseline risk of VAP and RR with PneuX:

Baseline risk / RR with PneuX	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
0%	£145	£145	£145	£145	£145	£145	£145	£145	£145	£145	£145
5%	-£296	-£252	-£208	-£164	-£120	-£76	-£32	£13	£57	£101	£145
10%	-£738	-£650	-£561	-£473	-£385	-£296	-£208	-£120	-£32	£57	£145
15%	-£1,179	-£1,047	-£914	-£782	-£650	-£517	-£385	-£252	-£120	£13	£145
20%	-£1,621	-£1,444	-£1,268	-£1,091	-£914	-£738	-£561	-£385	-£208	-£32	£145
25%	-£2,062	-£1,842	-£1,621	-£1,400	-£1,179	-£959	-£738	-£517	-£296	-£76	£145
30%	-£2,504	-£2,239	-£1,974	-£1,709	-£1,444	-£1,179	-£914	-£650	-£385	-£120	£145
35%	-£2,945	-£2,636	-£2,327	-£2,018	-£1,709	-£1,400	-£1,091	-£782	-£473	-£164	£145
40%	-£3,387	-£3,033	-£2,680	-£2,327	-£1,974	-£1,621	-£1,268	-£914	-£561	-£208	£145
45%	-£3,828	-£3,431	-£3,033	-£2,636	-£2,239	-£1,842	-£1,444	-£1,047	-£650	-£252	£145
50%	-£4,270	-£3,828	-£3,387	-£2,945	-£2,504	-£2,062	-£1,621	-£1,179	-£738	-£296	£145

One-way sensitivity analysis of additional cost of treating VAP:



One-way sensitivity analysis of cost of staff training:

PSA: PneuX is cost saving in 95.8% of iterations.

Mean cost (per patient) of all iterations	PneuX System	Standard Care	Incremental
Total costs	£1,177	£1,877	-£700

Distribution of iterations	Incremental cost
Minimum value	-£1,954
Lower quartile	-£941
Median	-£697
Upper quartile	-£476
Maximum value	£1,112

What were the main findings of each of the sensitivity analyses?

Two-way sensitivity analysis of baseline risk of VAP and RR with PneuX:
The finding that PneuX is cost saving is relatively robust to changes in the baseline risk of VAP and RR with PneuX. As expected, PneuX is not estimated to be cost saving when the baseline risk of VAP is 0%, nor when the RR with PneuX is 1.

- If the RR of VAP with PneuX is ≥0.6 (base case value = 0.52), cost savings are predicted when the baseline risk of VAP is ≥5%.
- If the RR with PneuX is ≥0.7, cost savings are predicted when the baseline risk of VAP is ≥10%.
- If the RR with PneuX is 0.9, cost savings are predicted when the baseline risk is ≥20% (base case value = 20.8%).

These results attempt to mitigate uncertainty resulting from the fact that clinical data used to populate the model came from a single trial with relatively small patient numbers (n=120 in each arm) (Gopal et al, 2014).

One-way sensitivity analysis of additional cost of treating VAP:
Increasing the cost of VAP increases the predicted cost savings associated with PneuX. Even at a cost of £4,000, which is less than half of the base case value, cost savings of £255 per patient are estimated. At a cost of £10,000, the value used in the previous economic analyses by the NIA (2017) and Wyncoll and Camporota (2012), cost savings of £855 are predicted. As we would expect, this result is greater than the cost saving in the base case analysis.

One-way sensitivity analysis of cost of staff training:
The finding that PneuX is cost saving is relatively insensitive to changes in the cost of staff training. This is line with the results of scenario 3, in which applying a training cost of £10 per patient had little effect on the incremental costs. Even at a cost of £40 per patient, which is very high considering that the duration of training is minimal and trained staff will treat many patients, cost savings of around £700 are predicted. Therefore, even if very extensive staff training were required, it is likely that PneuX would be cost saving.

PSA:
The results of PSA indicate that the finding that PneuX is cost saving has a high degree of certainty. PneuX was predicted to be cost saving in 96% of iterations, with a mean estimated cost saving of £700 (median=£697). This is slightly lower than, but comparable to, the base case result.

What are the main sources of uncertainty about the model's conclusions?

There are few sources of uncertainty in the model results.

The main source of uncertainty is the generalisability of evidence generated in the heart surgery subgroup of patients to the broader critical care population. However, this was tested thoroughly in sensitivity and scenario analyses. If in reality the baseline risk of VAP was low, for example less than 10% (which is half of the base case value) and the RR with Pneux was higher than 0.8 (i.e. the reduction in the risk of VAP associated with PneuX was minimal), PneuX may not result in cost savings. If the additional cost of treating VAP was lower than in the base case analysis, the cost savings associated with PneuX could be reduced.

Miscellaneous results

Include any other relevant results here.

None.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

The model structure and inputs were aligned with the model presented by Andronis et al (2018) and the cost saving in the base case results (£738) is equal to the cost saving reported in that paper. The finding that PneuX is cost saving is also supported by the results of the NIA (2017) analysis, which predicted cost savings of £850 per patient per intubation. The estimated cost saving in the NIA paper was higher than in the current analysis primarily because the cost of VAP used was higher (£10,000 in the NIA analysis versus £8,829 in the current analysis). Quality assurance involved a cell-by-cell check of all calculations in the Excel model and pressure testing of the results. This was conducted by a separate health economist to the one who developed the model.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

The model developed for this evaluation was not directly validated by any clinicians. However, the results of the model by Andronis et al (2018), upon which the current model is based, were validated by several of the paper's authors, who are clinicians specialising in cardiac surgery, critical care and anaesthesiology: • E. Senanayake – cardiothoracic surgery • S. Gopal – critical care • R. Giri – cardiothoracic anaesthesiology • H. Luckraz – cardiothoracic surgery Further details of the author's qualifications and affiliations can be found in the published paper.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The results of this model provide further evidence for the conclusion reached in published studies (namely the NIA analysis published in 2017), which is that use of PneuX for mechanical ventilation of adult patients in a critical care setting is likely to result in substantial cost savings to the NHS.

These cost savings can be attributed to the reduced number of cases of VAP and, therefore, reduced costs of treating VAP when PneuX is implemented. Secondary sources of cost data suggest that treating patients with VAP is more expensive than treating those without VAP due primarily to an increased length of stay in critical care while the patient is recovering (Luckraz et al, 2018).

Despite uncertainty in individual input parameters, the results of sensitivity and scenario analyses suggest a high degree of certainty around this finding. Even if the baseline risk of VAP were markedly lower or PneuX was much less effective at preventing VAP than the evidence suggests, the system is still likely to be cost saving. Similarly, if the additional cost of treating VAP was much lower in reality (which would reduce the benefit of PneuX because prevented cases of VAP would be worth less to the NHS) or PneuX was associated with a much higher training cost than predicted, the system is still likely to save costs in the NHS.

Briefly discuss the relevance of the evidence base to the scope.

The evidence base is partially relevant to the scope. The study by Gopal et al (2014), which is the best available source of clinical evidence for PneuX, only considered a subgroup of the patient population outlined in the scope. In addition, the duration of intubation for the majority of patients in the study was outside of the 24-hour to 30-day period specified in the scope. It is possible that the baseline risk of VAP and the RR with PneuX would vary in other subgroups eligible for PneuX (e.g. severely immunocompromised patients or burns patients) or in the critical care population more generally.

Similarly, evidence around the additional cost of treating VAP was only identified in a subgroup of the patient population outlined in the scope (the same subgroup as in the clinical evidence – major heart surgery patients). However, it is unlikely that this cost would vary substantially between patient groups because management of VAP in the NHS is consistent regardless of the patient's condition (Luckraz et al, 2018).

Overall, the evidence base is most relevant to the subgroup of patients requiring mechanical ventilation following major heart surgery, which is a subgroup of interest in the scope. However, it is likely that the conclusion of the model is also generalisable to the wider critical care setting.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

The results are consistent with the published literature. The predicted cost saving in the base case analysis is identical to that presented by Andronis et al (2018) because the model used the same structure and input parameters. The results of PSA are similar to those reported by Andronis et al, who found a 96% likelihood that PneuX is cost-effective at willingness-to-pay thresholds up to £30,000. It is worth noting that Andronis et al assess cost-utility (i.e. the ratio of the cost impact to the impact on patients' health-related quality of life), while the current analysis only considers cost impact.

The direction of results matches that in the NIA (2017) analysis, although the predicted cost saving in the current model is slightly smaller. This is largely due to the fact that a higher cost of VAP (£10,000) was used in the NIA analysis. This cost of VAP was tested as part of two-way sensitivity analyses in the current model and increased the predicted cost saving. The model results likely represent a more accurate estimate of the cost saving to the NHS than those presented in the NIA analysis because more reliable data were used to inform the additional cost of VAP. The current analysis did not consider return on investment (ROI) to the NHS but, based on the NIA results, it is likely that the ROI would be strongly positive.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The cost analysis was undertaken in line with the scope as far as possible. As discussed above, due to the availability of evidence, most inputs in the base case analysis were taken from studies in a subgroup of the patient population eligible for PneuX. However, it seems likely that these data are at least partially generalisable to other patient groups who could use PneuX. Furthermore, the impact of uncertainty in these data was tested thoroughly in sensitivity and scenario analyses, using wide ranges of alternative values.

Previous published economic evaluations of PneuX present the same limitations in relation to the patient population because they used the same clinical effectiveness data (Andronis et al, 2018; NIA, 2017).

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths:

- High degree of certainty in results. Results of PSA predicted a 96% likelihood that PneuX would be cost saving.
- Model populated with data generated in the UK NHS from an RCT, which is more likely to be reliable than data from a non-randomised study.
- Model followed a structure and used inputs previously validated by clinicians and the peer-review process of an academic journal (Andronis et al, 2018).
- Extensive sensitivity and scenario analyses were undertaken to assess the impact of uncertainty and variability on the results of the model. The conclusions of the model are robust to fairly wide variations in input parameters.

Limitations:

- Simplified model that did not include mortality or stratify VAP by severity.
- Data used in the base case analysis were generated in a subgroup of the patient population eligible for PneuX (major heart surgery patients).
- Effectiveness data used in the base case analysis came from a study with relatively low patient numbers (n=120 in each arm; Gopal et al, 2014).
- Cost of staff training associated PneuX is unknown, although it is likely to be negligible.

Detail any further analyses that could be done to improve the reliability of the results.

Further analyses could include mortality and severity of VAP in economic modelling. However, this would likely be limited by the availability of clinical data at present. Although estimates of the impact of VAP on mortality have been reported (Safdar et al, 2005), the relative effect of PneuX on mortality is currently unknown. However, because PneuX reduces the risk of VAP, it would still have a positive effect on mortality even if the mortality rate was consistent for VAP contracted when the patient is treated with PneuX versus in standard care. If mortality were included in the economic analysis, use of PneuX may increase costs in the long term due to future healthcare requirements of patients who would otherwise have died after contracting VAP. However, there would be substantial patient benefit.

Similarly, the effect of PneuX on severity of VAP is currently unknown. It is possible that use of PneuX could lead to less severe cases of VAP where the infection is contracted despite the use of the system. This would likely lead to higher cost savings than those predicted in the current analysis because patients with less severe VAP would require shorter critical care stays to recover and, therefore, incur fewer costs. No evidence was identified that described costs and/or resource use associated with VAP stratified by severity.

In the future, further analyses could be performed using clinical data generated in the wider population of patients in critical care eligible for PneuX. This would be dependent on these data becoming available from randomised studies.

5 References

Please include all references below using NICE's standard referencing style.

Andronis L, Oppong RA, Manga N, et al. (2018) Is the Venner-PneuX Endotracheal Tube System a Cost-Effective Option for Post Cardiac Surgery Care? Ann Thorac Surg 106(3): 757-763. 10.1016/j.athoracsur.2018.03.058.

Dick AW, Perencevich EN, Pogorzelska-Maziarz M, et al. (2015) A decade of investment in infection prevention: a cost-effectiveness analysis. American journal of infection control 43(1): 4-9. 10.1016/j.ajic.2014.07.014.

Gopal S, Luckraz H, Giri R, et al. (2015) Significant reduction in ventilator-associated pneumonia with the Venner-PneuX System in high-risk patients undergoing cardiac surgery: the Low Ventilator-Associated-Pneumonia study. Eur J Cardiothorac Surg 47(3): e92-6. 10.1093/ejcts/ezu483.

Kollef MH, Hamilton CW and Ernst FR (2012) Economic Impact of Ventilator-Associated Pneumonia in a Large Matched Cohort. Infection Control & Hospital Epidemiology 33(3): 250-256. 10.1086/664049.

Luckraz H, Manga N, Senanayake EL, et al. (2018) Cost of treating ventilator-associated pneumonia post cardiac surgery in the National Health Service: Results from a propensity-matched cohort study. J Intensive Care Soc 19(2): 94-100. 10.1177/1751143717740804.

Metersky ML, Wang Y, Klompas M, et al. (2016) Trend in Ventilator-Associated Pneumonia Rates Between 2005 and 2013Trend in Ventilator-Associated Pneumonia Rates, 2005-2013Letters. JAMA 316(22): 2427-2429. 10.1001/jama.2016.16226 %J JAMA.

National Institute for Health and Care Excellence (2015) PneuX for preventing ventilator-associated pneumonia in intensive care (MIB). [online] Available from: https://www.nice.org.uk/advice/mib45/chapter/Technology-overview [accessed 10th July 2019].

National Institute for Health and Care Excellence (2019) Scope: The PneuX system for preventing ventilator-associated pneumonia in patients in intensive care. [online] Available from: https://www.nice.org.uk/guidance/gid-mt528/documents/final-scope].

NHS Innovation Accelerator (2017) Economic Impact Evaluation Case Study: PneuX. [online] Available from: https://nhsaccelerator.com/wp-content/uploads/2017/10/PneuX-Economic-Case-Study-YHEC-August-2017.pdf.

Safdar N, Dezfulian C, Collard HR, et al. (2005) Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 33(10): 2184-93.

Wyncoll D and Camporota L (2012) Number needed to treat and cost-effectiveness in the prevention of ventilator-associated pneumonia. Critical care (London, England) 16(3): 430-430. 10.1186/cc11346.

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	N/A
Date span of search:	N/A
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
A systematic search for economic evidence was not carried out. Instead, all studies known to Qualitech Healthcare Limited that reported economic evidence relevant to the decision problem (n=2) were included in the review of economic evidence.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
N/A	
Inclusion and exclusion criteria:	
Inclusion criteria: • Studies including adult patients requiring mechanical ventilation in a critical care setting (with a length of stay of 30 days or less) • Studies using the PneuX system • Studies reporting economic outcomes, including cost savings, incremental cost-effectiveness ratios etc. Exclusion criteria: • Studies estimating the cost of VAP that did not use the PneuX System	
Data abstraction strategy:	
N/A	

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

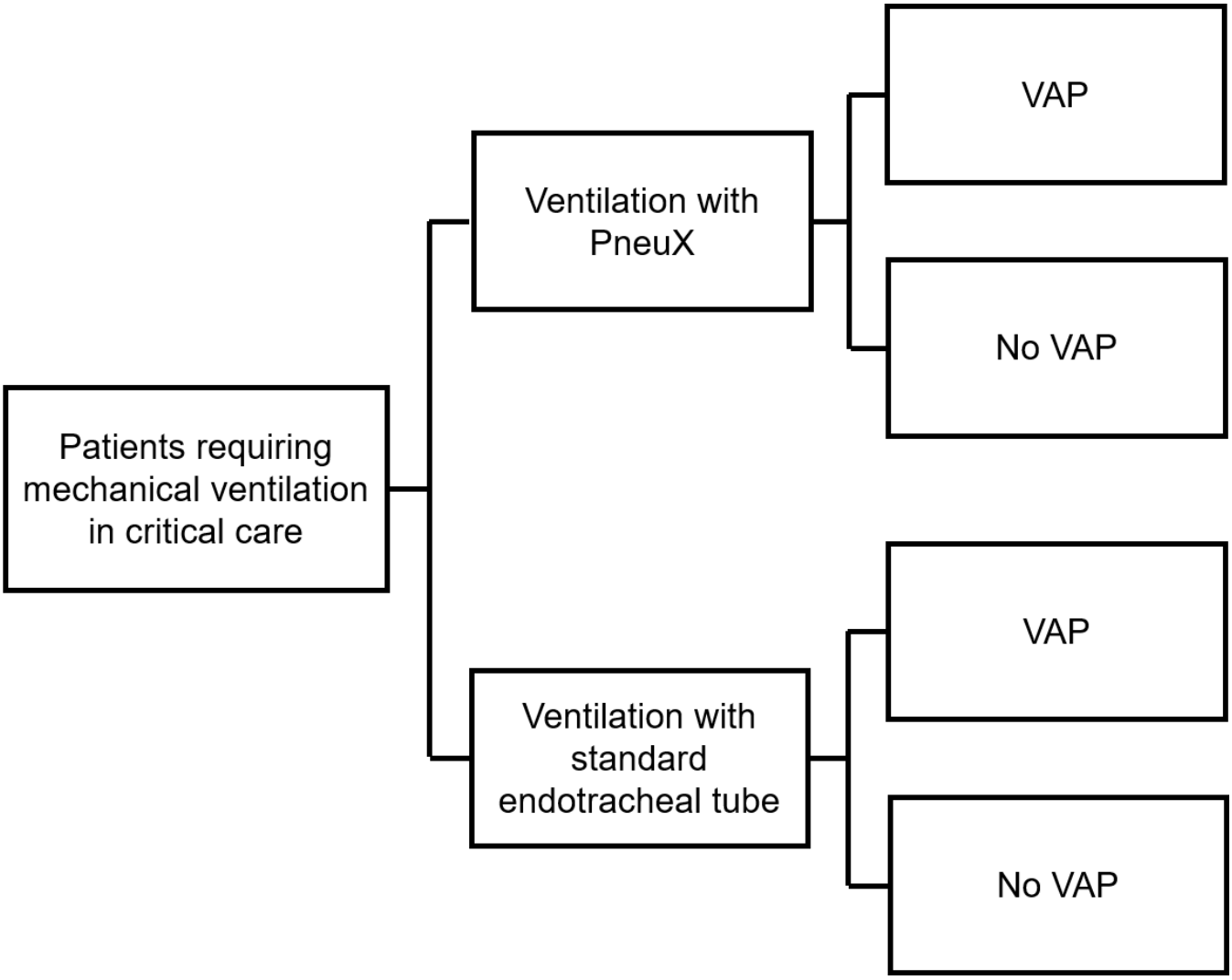
N/A - no formal search was undertaken

Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



NICE National Institute for Health and Care Excellence

Medical technologies guidance

Collated expert questionnaires

Technology name & indication: PneuX for preventing ventilator-associated pneumonia in intensive care

Experts & declarations of interest (DOI)

Expert #1	Andrew Walder, Consultant ICU and Anaesthesia, North Devon District Hospital
	DOI: NONE
Expert #2	Ben Messer, Consultant, Newcastle-upon-Tyne Hospitals NHS Foundation Trust
	DOI: NONE
Expert #3	Neil Smith, Senior Research Nurse, Hull University Teaching Hospitals NHS Trust
	DOI: NONE
Expert #4	Thomas Hellyer, NIHR Clinical Lecturer Intensive Care Medicine, Newcastle University
	DOI: NONE
Expert #5	Murali Shyamsundar, Clinical Senior Lecturer/Consultant in Intensive Care Medicine, Queen's University Belfast
	DOI: NONE
Expert #6	Dr David Ray, Consultant in Anaesthesia & Critical Care, Royal Infirmary of Edinburgh, NHS Lothian
	DOI: Yes, Convenor of the Scottish Standing Committee, Association of Anaesthetists and member of UK Council, Association of Anaesthetists
Expert #7	Professor Gary H Mills, Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Foundation Trust and University of Sheffield
	DOI: NONE

Expert #8	Peter D G Alexander, Consultant In Anaesthesia and Intensive Care Medicine, Manchester University NHS Foundation Trust
	DOI: (NONE)
Expert #9	Dr Petr Martinovsky, Consultant Cardiothoracic Anaesthetist, Lancashire Cardiac Centre, Blackpool Teaching Hospitals
	DOI: (NONE)
Expert #10	Dr Shameer Gopal, Consultant in Anaesthesia and Intensive Care Medicine, The Royal Wolverhampton NHS Trust
	DOI: (NONE)

How NICE uses this information: the advice and views given in these questionnaires are used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on a technology. It may be passed to third parties associated with NICE work in accordance with the Data Protection Act 2018 and data sharing guidance issued by the Information Commissioner's Office. Expert advice and views represent an individual's opinion and not that of their employer, professional society or a consensus view (unless indicated). Consent has been sought from each expert to publish their views on the NICE website.

For more information about how NICE processes data please see our privacy notice.

1. **Please describe your level of experience with the technology, for example: Are you familiar with the technology? Have you used it? Are you currently using it? Have you been involved in any research or development on this technology? Do you know how widely used this technology is in the NHS?**

Expert #1	We have been using the PneuX ET tube for several years and have found them very useful
Expert #2	I have been a consultant in ICM for 8 years. I have not used the PneuX system but our ICU has used ETT/Tracheostomy with Subglottic suction (SGS) ports for at least 3 years and I was instrumental in the introduction to our ICU of Hamilton Ventilators which utilise “Intellicuff” which regulates tracheal tube cuff pressures. I am not involved in any research on this technology.
Expert #3	I led a study to assess the impact of the PnueX system of VAP locally and had regular usage over the period it was in use I was also the de facto trainer for the device whilst it was in use after being trained by the company I currently do not use the device. https://journals.sagepub.com/doi/abs/10.1177/175114371401500203 Historical low usage pre 2018 around 3 sites. However, usage within the NHS may have improved as a result of the NHS England Innovation & Technology Payment scheme 2018/19, which reimbursed Trust for PneuX usage.
Expert #4	I am familiar with much of the evidence base for subglottic secretion drainage (SSD) endotracheal tubes and in particular familiar with the evidence for the PneuX tube. Subglottic secretion drainage tubes are commonly used in ICU but I have no personal experience of using the PneuX tube. The main features of this tube over other ETT with subglottic suction ports are the cuff pressure monitor and multiple suction ports that reduce the chance of the suction port becoming blocked.

	I am not aware of any data on how widely this ETT is used in the NHS. However, the PneuX tube has been supported by Innovate UK funding that has allowed it to be used in some UK ICUs.
Expert #5	No. I have not used this specific technology I have not been involved in its development Its use is not widespread within the NHS
Expert #6	Limited familiarity with subglottic drainage tubes, no experience with PneuX system. Not currently using subglottic drainage in my ICU but will be introducing this shortly for patients expected to be ventilated longer than 48 hours. Not involved in any research or development on this technology. Not sure how prevalent subglottic drainage is in +UK ICU practice but suspect it will vary throughout the four home nations.
Expert #7	Yes, familiar Yes No No Commonly used
Expert #8	I am familiar with the technology. I have handled the device but not used it in a patient. I have colleagues who have evaluated it but the device is not in routine clinical practice at our site.

	I have not been involved in the development of the product but have published in the area of diagnosis of ventilator associated pneumonia. I have also undertaken a technology review of similar device for NICE in 2017. I am aware that there has been an initiative (NHS Innovation Accelerator) via the Academic Health Science Networks to promote the tubes use. Adoption in some regions has apparently been high but, to my knowledge, use in the Northwest remains low.
Expert #9	I am familiar with the PneuX system. I trialled the system in early 2017 and used it since, we are using the system currently in selected patients. I haven't been involved in any research or development but I gave repeatedly a feedback to the company representatives, the feedback seem to have been reflected in the newer and improved design that we are currently using. I don't know how widely used this technology is in the NHS.
Expert #10	I was the Chief Investigator on the only RCT to assess the efficacy of this system to reduce Ventilator Associated Pneumonia (VAP) in high risk cardiac surgical patients. We have just started using this tube on our Intensive Care Unit. Regrettably even though we were the unit to provide the evidence on the efficacy of this tube to prevent VAP we were not able to introduce its use routinely on the unit due to cost. At present we are using the tube on the National Tariff as it is currently cost neutral to us. My understanding is that those few units that are using the tube currently are doing so under the Tariff.

2. Has the technology been superseded or replaced?

Expert #1	no
Expert #2	No but the data published so far have compared PneuX to standard ETT *not* SGS ETT.
Expert #3	No

Expert #4	The ability to maintain a constant ETT cuff pressure is also provided by other technologies. For example Hamilton Ventilators use the Intellicuff that monitors and maintains cuff pressure.
Expert #5	No
Expert #6	Not to my knowledge
Expert #7	No, but should be considered as one of a number of examples of endotracheal tube or tracheal tube that are designed with supraglottic suction and maintenance of cuff pressure in mind to potentially reduce ventilator associated pneumonia.
Expert #8	Not in this form to my knowledge but there are similar devices with elements of this product within them. Prices for these have fallen considerably in recent years.
Expert #9	Not to the high complex standard of the PneuX system.
Expert #10	I am not aware any new research comparing the PneuX to other endotracheal tube systems.

Current management

3. How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?

Expert #1	It is a novel concept and design. Its impact on VAP is not entirely certain
Expert #2	The SGS port is not innovative. Other systems do not specifically encourage irrigation but this would remain possible. The Cuff pressure monitoring is widespread both manually (which is a national recommendation) and in any unit which uses Hamilton Ventilators. Therefore, in our unit which uses SGS ETT and Hamilton Ventilators, this technology would add very little.
Expert #3	It is the only product I am currently aware of that incorporates a number of different evidence based interventions, (cuff maintenance, subglottic suction) into a single device
Expert #4	I do not believe that this is a major innovation over standard care. I base this on the view that SSD ETT should be standard of care and so I think that the PneuX tube is a variation on the concept of SSD ETTs.
Expert #5	Endotracheal tubes with subglottic suction is not innovative. Continuous cuff pressure monitoring is also available. So this is a variation.
Expert #6	It is a variation – subglottic drainage is recommended as standard practice by some organisations, automatic cuff pressure regulation is more novel and the combination of subglottic drainage and automatic cuff pressure control is more innovative.
Expert #7	Standard care consists of low pressure high volume cuffed entrotracheal tubes or tracheostomies. This type of technology: supraglottic suction and maintenance of cuff pressure technology provides an important reduction in ventilator associated pneumonia. This group of products with subglottic suction and maintenance of suitable cuff pressure are an important step forward and an important design development. PneuX is one example of this type of technology. It is important to look across all the different types and see them in the context of a plan of management designed using several techniques to reduce ventilator associated pneumonia.
Expert #8	This brings together several technologies into one package.

Expert #9	It is a novel concept incorporating a full spectrum of novel designs.
Expert #10	I am of the opinion that the PneuX is a novel concept as it is the only system that has been shown to prevent subglottic secretions leaking past the endotracheal tube cuff and it is the only system currently in use that allows continuous monitoring of endotracheal tube cuff pressure.

4. Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?

Expert #1	No other tube combines the benefits of subglottic suction, more secure balloon and soft non-damaging construction material.
Expert #2	Hamilton Ventilators. Multiple other companies make SGS ETT/Tracheostomy. The main difference is the lack of automated cuff pressure monitoring in standard SGS ETT.
Expert #3	Not as a combined device, there are individual products that provide the individual components. Such as Pressure Easy (Smiths) for endotracheal cuff inflation maintenance (however, in this case insufflation is semi-automatic) in addition most manufacturers now have endotracheal (and tracheostomy) tubes that enable subglottic suction.
Expert #4	There are a number of other SSD ETT that are considerably cheaper than the PneuX tube. Cheaper types of SSD ETT cost approx. £7-12. If the ICU also has a ventilator such as the Hamilton that monitors cuff pressure, its hard to see what the additional cost of the PneuX will offer.
Expert #5	Cost seems to be a significantly different with this product being more expensive.
Expert #6	Not with the combination of subglottic drainage and automatic cuff pressure control. Other tracheal tubes and tracheostomy tubes with subglottic drainage exist – some of these are listed in the medtech innovation briefing on the PneuX system.
Expert #7	There are a number of manufacturers with similar concepts ie supraglottic suction, maintenance of cuff pressure.

	Supraglottic suction and maintenance of cuff pressure is provided by several different tubes with the aim of reducing secretions passing from the oropharynx into the airway. This has been achieved with different shapes on cuff: spheroid, cylindrical or tapered. These can be made from different materials: PVC, PU and silicone. Most are high volume low pressure cuffs, sometimes used with lubricant that helps reduce leakage through folds in the cuff. The PneuX is a low volume, silicone, high elasticity cuff, with a much higher targeted intracuff pressure (IP) of 80 cm H2O. The others have a targeted IP of 25 cm H2O. The PneuX is said to produce a wall pressure of 25 cmH2O ie comparable to the others. A bench study looked at the performance of 4 HVLP-cuffed endotracheal tubes (ETTs). The aim was to see if PneuX with its spheroid high pressure cuff, which is also low volume performed as well- because conventional thought might suggest it would require a high pressure to provide a good seal. The tubes compared were: Hi-Lo (polyvinyl chloride [PVC]), Microcuff (polyurethane [PU]), SealGuard (PU + tapered), and TaperGuard (PVC + tapered), and the PneuX with its dedicated tracheal seal monitor. (Respiratory Care Jan 2017, 62 (1)102-111 Chenelle CT et al.) This found the PneuX cuff s produced an average wall pressure of 27.4 cm H2O. The seal monitor on average calculated 33.4 cmH2O. PneuX showed no leakage across 8 hrs and leakage volumes were lower with PU and PneuX rather than PVC cuffs. For HVLP cuffs the leak as reduced by PU and PEEP and eliminated by lubrication. Therefore PneuX appeared to perform well in this bench situation in preventing leaks and did maintain a suitable tracheal wall pressure.
Expert #8	There are microcuff tubes, cuff pressure monitors and tubes with subglottic suction ports. The PneuX tube combines these things together.
Expert #9	Automated cuff inflation - I am aware of other automated cuff inflation systems but they can't function efficiently in my opinion unless coupled with the novel and superior design of the PneuX endotracheal tube. Subglottic suction – I am aware and I use other endotracheal tubes with subglottic suction ports but the design of the ports, the design of the cuff , the material of the cuff and the design of the tube are inferior or insufficient compared to the PneuX tube.
Expert #10	I am not aware of any other endotracheal tube system that is able to measure cuff pressure continuously. I am not aware of any other endotracheal tube system that has been clinically tested to maintain a complete seal around the endotracheal tube cuff and thus prevent aspiration of subglottic secretions pass the cuff.

Potential patient benefits

5. What do you consider to be the potential benefits to patients from using this technology?

Expert #1	Reducing VAP and reducing damage to tracheal mucosa
Expert #2	Reduction in VAP is debatable because the trials have compared PneuX to ETT/Tracheostomy without SGS ports.
Expert #3	A reduction/delay in VAP incidence and the consequence of its associated sequelae, like antibiotic usage increase hospital and ICU stay. Improved oral hygiene
Expert #4	The potential benefit is the prevention of VAP and so potentially the reduction in length of mechanical ventilation, length of ICU stay and fewer antibiotics. Whether this is beyond that can be achieved by other ETT is uncertain.
Expert #5	Reduction of VAP is a potential benefit but the supportive evidence more important outcomes such as mortality, duration of ventilation, ICU and hosp LOS is conflicting.
Expert #6	Reduction in incidence of VAP, possibly fewer complications related to ventilation longer than 48 hours, possibly reduced length of stay in ICU
Expert #7	The wider concept of supraglottic suction, cuff inflation pressure maintenance and good cuff seal design does reduce ventilator associated pneumonia risk. PneuX performs well in bench tests functionally when compared to the designs that have been produced to achieve these aims. However, the whole concept is part of a care package which includes sedation holds and maintaining a sitting up position in bed.
Expert #8	Reduction of ventilator associated pneumonia is the purported benefit. Potential for cost savings and reduction in morbidity and mortality have yet to be shown in the general ICU population. There are some publications within cardio-thoracic critical care.
Expert #9	Prevention of aspirational pneumonia resulting in lower mortality and morbidity after surgery or ICU admission, shortening the length of hospital stay and reducing the need for antibiotic cover due to pneumonia.

Expert #10	A significant reduction in VAP.

6. Are there any groups of people who would particularly benefit from this technology?

Expert #1	Intubated and ventilated intensive care patients
Expert #2	No.
Expert #3	Patients at high risk of developing VAP; those expected to ventilator for extended period of time. Neurosurgical and trauma patients in particular.
Expert #4	Ventilated patients on Cardiac ICU (See below).
Expert #5	Patients with reduced cough such as spinal injury patients or patients who are likely to be deeply sedated such as traumatic brain injury and severe ARDS could benefit.
Expert #6	Patients who require to ventilated via a tracheal tube or tracheostomy for longer than 48 hours.
Expert #7	This is designed for ventilation of patients on the intensive care unit. These are patients who are at risk of ventilator associated pneumonia
Expert #8	Critically ill patients receiving invasive ventilation. Some evidence in cardiothoracic surgery.
Expert #9	Patients who remain intubated and ventilated for a longer period of time, over 6 or 12 or 24 hours.
Expert #10	Any patient who is ventilated on an ICU will benefit from this tube by having a reduced risk of developing a VAP.

7. Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?

Expert #1	It could lead to reduced VAP, less contamination of the airway and less tracheal wall damage, each of which could reduce length of intensive care and hospital stay

Expert #2	No. The only RCT compared PneuX to non-SGS ETT rather than SGS ETT which would be *essential* to properly evaluate the technology as SGS ETT is now a standard of care nationally. Especially when it is born in mind that SGS ETT have been shown to half VAP rates. Even in the RCT, there was no difference in ICU length of stay. Intubation times were very short and VAP rates surprisingly high in both groups.
Expert #3	The clinical pathway is unlikely to change, patient outcomes in terms of length of stay could potentially be shortened.
Expert #4	As in answer to Q5, if the PneuX tube offers more protection against VAP than other SSD tubes, then yes, it could alter the care pathway for patients. But any additional benefits are unproven.
Expert #5	Unlikely especially with availability of other endotracheal tubes with subglottic suction capabilities
Expert #6	If complications related to VAP were reduced, outcome may be better but there are many other factors which need to be considered before use of the PneuX system could be linked to improved patient outcome and survival.
Expert #7	Reducing ventilator associated pneumonia, which is a cause of increased mortality and morbidity on the ICU, has the potential to lead to better clinical outcomes, reduced time on the ventilator and
Expert #8	There is potential but VAP is notoriously difficult to measure and its impact to attributable mortality remains, in my view, in question.
Expert #9	This technology has a potential to improve clinical outcomes in major operations, a potential to improve outcomes of intensive care cases requiring invasive ventilation support.
Expert #10	Yes. As per the results of our study this tube has the potential to reduce the incidence of VAP in ventilated patients on an ICU and thereby reduce morbidity, cost and potentially LOS.

Potential system impact

8. What do you consider to be the potential benefits to the health or care system from using this technology?

Expert #1	As above
Expert #2	None.
Expert #3	Reduction in patient stay, enabling the potential freeing critical care patient bed days. Reduction of antibiotic usage.
Expert #4	No foreseen harms.
Expert #5	The evidence currently for this specific system is uncertain
Expert #6	Shorter stay in ICU for some patients, potentially lower costs associated with treatment from a lower incidence of VAP
Expert #7	It is likely that used as part of an overall approach to reduce VAP that this type of technology will reduce VAP and so impact on costs, patient stay and mortality.
Expert #8	Potential for reduced costs and antimicrobial usage.
Expert #9	Improving outcomes, better treatment, preventing hospital acquired pneumonias, reduced use of antibiotics, saving costs on treating pneumonias
Expert #10	Cost reduction

9. Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	Less, if the hoped for reduction in VAP actually occurs
Expert #2	Given the lack of data showing a reduction in length of stay, I do not think this will significantly reduce costs.

Expert #3	When preventing VAP, overall the PneuX system is likely to cost organisations less
Expert #4	This is very important to consider for the PneuX tube as it is considerably more expensive that other SSD tubes. There are insufficient data at present to answer this question for two reasons: 1. UK RCT and cost effectiveness data comes from a single cardiac ICU and the RCT (although appropriately powered) is relatively small size. The patient population in cardiac ICU is very different from general ICUs. The duration of mechanical ventilation is very short, patients are admitted after elective surgery (vs medical or surgical emergencies), and chlorhexidine mouthwash is advocated (it no longer is in general ICU). Therefore conclusions of benefit from UK evidence cannot be extrapolated to general ICU population. 2. UK data has compared PneuX tube to a standard ETT not an alternative SSD ETT. Therefore cost effectiveness data does not draw conclusion of PneuX vs cheaper SSD (which are now more widespread), which could derive the same benefit. If PneuX is not superior to other SSD ETT, it could be considerably more expensive for NHS.
Expert #5	The technology will cost significantly more
Expert #6	This is difficult to answer – it all comes down to the true incidence of VAP. The 10-20% incidence quoted in the draft scope is hard to believe – modern ICU use of ventilator-bundles of care (with or without subglottic drainage) has reduced the incidence of VAP to around 2% (of which about 50% is confirmed on microbiology testing). It may be difficult to reduce this rate much and this would result in increased cost of using the system but with far less cost benefit in reducing VAP, and possible related complications.
Expert #7	York examined potential cost benefits. This assumes that this would reduce VAP in the clinical situation and if so on balance the use of this type of technology is likely to reduce costs. It should be seen as part of the package of techniques to reduce VAP
Expert #8	This is more expensive than either standard tubes or than sub-glottic tubes.
Expert #9	I guess less or about the same.
Expert #10	Overall the technology will reduce NHS costs by reducing the incidence of VAP.

10. What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?

Expert #1	It requires slightly more nursing time to perform th subglottic suction procedure.

Expert #2	The PneuX system is very expensive (20 times a SGS ETT). No other resource impact though there would be a training impact.
Expert #3	Other than a small (approx. 15 minute) impact on nursing time per shift, I would expect no impact on existing resources,
Expert #4	Training would be needed for this system but no additional staff would be needed.
Expert #5	Need for new equipment
Expert #6	Potentially shorter ICU length of stay and associated treatment cost savings but see my response in section 9 above.
Expert #7	It would not affect staff numbers, dealing with an individual patient. However, it could reduce complications and length of stay and so enable more patients annually to be cared for with a similar amount of resource
Expert #8	Yes - the tubes and associated equipment are expensive (though this was offset by NHS Innovation and Technology Tariff until March 2019) If it was proven to reduce time on a ventilator than this may impact on staff utilisation and bed availability. Evidence in the general ICU population for this benefit is limited, may reduce VAP but doesn't produce outcome benefit. Combination technology (PneuX not tested in large RCT, to my knowledge)
Expert #9	Less bed days spent in High Dependency Unit or Critical Care and less days spent in hospital (by preventing pneumonias), freeing the staff and resources that would otherwise be needed to treat patients with ventilator associated pneumonias.
Expert #10	By reducing the incidence of VAP it has the potential to reduce length of ICU stay. This in turn could potentially free up more ICU beds thereby increasing ICU bed capacity.

11. Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?

Expert #1	Specific training in subglottic suction and use of the pressure monitoring box are needed
Expert #2	Standard training with new technology.

Expert #3	To maximise its effectiveness further training for all critical care nursing staff would be required
Expert #4	No
Expert #5	Training for intubation technique, training of staff for the device management
Expert #6	No, but familiarity with using the automatic cuff pressure regulator will be key to ensure the potential benefit from this system is maximised. Additional training may be necessary to ensure clinical staff are familiar with the technology.
Expert #7	All staff would need to be taught to use the system and set the equipment and monitor its correct functioning. It is also important to not confuse the pressure monitoring or suction points for any other sort of line.
Expert #8	Reported different technique for insertion of tube. Maybe a modification to existing practice.
Expert #9	No changes to facilities or infrastructure needed. Standard training on how to use the cuff insufflation device as per manual needed and delivered the usual way according to the staff training policy.
Expert #10	Yes, nursing and medical staff need to be trained to use the cuff pressure monitor. This is not extremely arduous or time consuming.

12. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	no
Expert #2	One study showed a high level of extubations. This would require further exploration.
Expert #3	No
Expert #4	No
Expert #5	None but higher rate of unplanned extubations raise concern
Expert #6	Not to my knowledge
Expert #7	No

Expert #8	Local issue noted but not thought to be directly attributable to tube.
Expert #9	Not aware
Expert #10	No

General advice

13. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	Practice at effectivelt securing the tube is definitely needed, but is simple
Expert #2	This would have nothing to offer a unit which already uses SGS ETT and Hamilton Vantilators for reasons outlined above. In the RCT the VAP rate was halved by use of PneuX but this was against standard non-SGS ETT and SGS alone has been shown to halve VAP rates without the need for this very expensive technology.
Expert #3	Positive clinical outcomes with the device are highly reliant of staff performing the necessary ongoing management required. Simple insertion of the device will not give the desired outcomes; adherence to the package of care associated with it is key.
Expert #4	My main concerns with the evidence for the PneuX tube are in answer to Q9. There is considerable evidence to support SSD from a number of meta-analyses. However the issue with PneuX is its considerable cost and whether it offers anything in addition of other cheaper SSD tubes.
Expert #5	The main trial quoted, Gopal et al, is in a specific sub-group and the comparator is a standard ET tube and not another equivalent device with sub-glottic suction. The VAP rate is quite high in this publication considering the elective surgical nature of this speciality. The quoted cost of VAP is also from USA and cannot to directly translated to NHS.
Expert #6	I cannot make any comment here
Expert #7	PneuX tracheostomy tube did have an adjustable flange, which could slip. It is important to ensure that this does not happen. The PneuX tube is relatively flexible and as such can be more difficult to insert than some of the competitors, especially if the airway is difficult

Expert #8	My experience is limited. Reported issues from colleagues during trials both with insertion and ongoing nursing care.
Expert #9	There is an inherent resistance among some clinicians to adopt and use new or different material partially due to the lack of knowledge or lack of willingness to change or improve.
Expert #10	Despite doing the original study and showing a significant benefit to patients I was not able to introduce this tube on my ICU because of the significant cost difference between a standard endotracheal tube and the cost of the PneuX system. The only reason that we have been able to introduce the tube on the ICU recently is because it is currently under the National Tariff and is thus cost neutral to my department.

Other considerations

14. Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?

Expert #1	About 10% of the ICU population are ventilated for 5 days or more and this group are at significant risk of VAP
Expert #2	All patients intubated for more than 24 hours could in theory have this ETT the same as any standard SGS ETT.
Expert #3	80-90% of intubated patients UK wide
Expert #4	According to ICNARC there were 69,606 patients mechanically ventilated in 2012. It is unlikely that all of these patients would have a SSD tube. ICUs often use SSD in patients who are anticipated to be ventilated for more than 24-48hrs.
Expert #5	Might be considered for neurosurgical or high spinal injury patients. Use of this technology in all critical care patients can't be supported with the limited quality of evidence provided and the high cost of the device.
Expert #6	In my experience around 40% of patients admitted to my ICU are ventilated for longer than 48 hours. Around 1300 patients are ventilated each year in my unit. This percentage may be different in other ICUs, particularly if they provide specialist care for patients who may be expected to undergo longer periods of ventilation, such as those with head injury.
Expert #7	Most patients ventilated invasively on ICU, which is about 70-80% of the ICU population would benefit from this type of technology. In particular all those likely to remain ventilated for over 48hours

Expert #8	Accurate data regarding true VAP rate in our organisation is limited as it is dependent upon the method of measurement. Our range is between 1 and 30 per 1000 ventilator bed days. Our unit has around 2500 ventilator bed days per year. This would then equate to 2.5 to 75 VAP events per year.
Expert #9	I am not able to answer this question on a national level unfortunately, I haven't got the data.
Expert #10	I do not know this figure but any patient who is expected to be ventilated on an ICU for more than 48 hours would benefit from the tube.

15. Would this technology replace or be an addition to the current standard of care?

Expert #1	Replace previous ET tube
Expert #2	Neither-see above.
Expert #3	This technology would replace the current standard of care.
Expert #4	Replace.
Expert #5	No
Expert #6	Replace, but not used routinely for all patients.
Expert #7	It would do the same job, so would largely replace it.
Expert #8	Our current standard of care uses sub-glottic suction tubes and 'nurse controlled' bedside ET cuff pressures.
Expert #9	This technology would replace and improve the current standard of care in the target group of patients.
Expert #10	Replace standard care.

16. Are there any issues with the usability or practical aspects of the technology?

Expert #1	Securing tube
Expert #2	No.
Expert #3	Locally ad hoc observations were noted about difficulties performing endotracheal suction, due to the length of the ETT.
Expert #4	It would require a period of training and familiarisation.
Expert #5	No
Expert #6	None to my knowledge
Expert #7	See answer to 13
Expert #8	Identifying which patients would benefit most from PneuX a priori is a challenge. It is difficult to establish which patients are likely to be ventilated for in excess of 48 hours. The use of these tubes would have to be extended beyond the ICU (eg in ED) which may mean tubes are 'wasted' in inappropriate patients or the potential need for tube changes (this practice has previously deemed to be an unacceptable risk in our hospital).
Expert #9	I am not aware of any.
Expert #10	No

17. Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?

Expert #1	no
Expert #2	See above. Probably no role at all but certainly no role in units using Hamilton ventilators.
Expert #3	Cost implications have affected my ability for the ongoing use of the device and I expect this experience is common nationwide

Expert #4	Clinician acceptability. I believe it might be difficult to convince clinicians that an ETT costing £150 is worth the expense in their budgets.
Expert #5	Lack of evidence
Expert #6	No
Expert #7	No, but again we should consider all types of similar technologies
Expert #8	Experience in the northwest would seem to be non-adoption
Expert #9	If the system was not backed by the NIA then the upfront cost of the system would prevent its use in the NHS as it would be difficult to compile a successful business case.
Expert #10	Cost. A standard endotracheal tube costs approx. £3 whereas a PneuX tube costs £75.

18. Are you aware of any further evidence for the technology that is not included in this briefing?

Expert #1	no
Expert #2	No.
Expert #3	No
Expert #4	As above.
Expert #5	There is a further study Ann Thorac Surg. 2018 Sep;106(3):757-763. doi: 10.1016/j.athoracsur.2018.03.058. Epub 2018 Apr 27. Is the Venner-PneuX Endotracheal Tube System a Cost-Effective Option for Post Cardiac Surgery Care? This is only a model and also compares it with standard ET tube.
Expert #6	No

Expert #7	See my entries above
Expert #8	No
Expert #9	No
Expert #10	No

19. Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.

Expert #1	no
Expert #2	No.
Expert #3	No
Expert #4	No.
Expert #5	No
Expert #6	No
Expert #7	Muscedere et al 2011 39:1985-91 Crit Care Med showed support of reduction in VAP by subglottic suction Wang F J Trauma Acute Care Surg 2012 72: 1276-1285 Damas P. Crit Care Med 2015, 43: 22-30
Expert #8	No
Expert #9	No

Expert #10	No

20. Is there any research that you feel would be needed to address uncertainties in the evidence base?

Expert #1	A more definitive study of VAP reduction would be helpful
Expert #2	If this is shown to be better than standard SGS ETT in terms of VAP and length of stay, with a cost benefit, we would trial them.
Expert #3	I still believe there is a requirement for a large multicentre trial in a general Critical Care population which incorporated some health economic analysis. This more generalizable data with associated cost implications might convenience sceptical clinicians of the PnueX system's utility.
Expert #4	The work that has been done for PneuX is good but as described is not generalizable to the wider ICU population. Further work needs to be done on epidemiology of VAP in UK, cost of VAP and trial of PneuX in general ICU patients. I would be keen to liaise with NICE if you feel that future research should be commissioned. In Newcastle we have carried out multi-centre VAP research. Unfortunately our data isn't relevant to this review (diagnostics). We have established a UK network of ICUs that would participate in future work.
Expert #5	The current evidence in support of this technology is limited to a single centre study and other small studies. There is limited to no evidence currently to recommend the introduction of this technology especially considering the high cost and concern of a high rate of self extubation. We need an adequately powered multi-centre trial that compares this technology initially with a standard ET tube and then against other cheaper similar alternatives.
Expert #6	No, but please see my comments about the difficulty in identifying the true incidence of VAP and incidence of aspiration.
Expert #7	More large scale proof of the broad technique would be helpful. A comparison of one tube against another clinically would probably require very large numbers and be difficult
Expert #8	Yes. We need a true RCT in the general ICU population to prove an advantage over existing technologies.
Expert #9	More research and evidence in this area is always welcome.
Expert #10	My original study was done on a cardiac surgical population. It has not been done in a general ICU population, although one would expect the impact to have been greater in a general ICU population.

National Institute for Health and Care Excellence

External Assessment Centre correspondence

PneuX

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Clinical evidence submission	**Initial questions sent to company - 04.07.19** 1. No search strategy has been provided. In section 4 it is stated that 38 studies were identified in a systematic search. Please would you provide us some more detail about how these studies were found? 2. Is there any functional difference between the 2016 and 2019 versions of the system? a. For the 2019 Venner PneuX™ ETT/TT it is stated that there is the addition of a fixation block/winged tube holder for optimal tube securement. Is this the only addition to the 2016 version? b. Older versions are presumably similar to the newest version? 3. Please would you confirm which version of the PneuX system the CE certificate provided is for? 4. One of the references cannot be located. Please provide the correct citation (*Fletcher A, et al. The Lo-Trach™ tracheal tube – airway symptom surveillance following critical care. Crit Care 2009;13(Suppl 1) P295*) 5. What are the differences in the expected patient population between the ETT ("routine anaesthesia"?) and the TT?	**Responses in minutes of company teleconference from 11.07.19 (Appendix 1).** **E-mail from comapny dated 12.07.19** Further to yesterday's Meeting, I can confirm that I have spoken with Dr Gopal this morning and he is more than happy to speak with anyone from the KiTEC Team. Dr Gopal is available for the rest of today. However, he is then on annual leave and out of the country until Monday 29th July 2019. His contact telephone number (which he is happy for me to pass on to you) is 07751-777171. Dr Gopal is on the Critical Care Unit today, which does not always have the best mobile signal, so he has asked if anyone calls and does not get through, if they would like to leave a message he will call back as soon as possible. Dr Gopal has also asked me to advise that he has received the email dated 9th July 2019, and will reply as soon as possible. However, he did not receive any emails prior to that date and believes they may well have not got through the Trust's server. **E-mail from company dated 12.07.19** Further to yesterday's Meeting, please see attached documents, as discussed. Re. Question 2. Please see attached Declarations of Conformance. Please note, the address of our EU Authorised Representative (Advena) has changed. Re. Question 4. Please see attached Abstract as discussed, A251. The additional reference we would also like to provide is:

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
	6. The 'Critical Care Pathway' flowchart provided needs further explanation. What are the sources of this pathway protocol? 7. For adverse events, was a search of FDA-MAUDE carried out? Was a search of MHRA carried out? 8. In section 7 it is stated that there is not enough comparative evidence to provide a meta-analysis, but why is there no qualitative review?	Doyle et al. The incidence of ventilator-associated pneumonia using the PneuX System with or without elective endotracheal tube exchange: A pilot study. BMC Research Notes 2011, **4**:92. Re. Question 6. The references/sources for the Critical Care Pathway (also attached) are as follows: A. MIB45 – Management of critically ill patients requiring mechanical ventilation. B. Standard Operating Procedure (General and Cardiac Samples – previously submitted) C. NHS England/NHS Improvement Technical Guidance Notes – Published 20th June 2019. D. National Resource for Infection Control (NRIC) 2011. High Impact Intervention – Evidence based VAP Preventative Measures (Citation previously submitted) E. Fletcher et al. The Lo-Trach™ System: it's role in the prevention of ventilator-associated pneumonia. 2008. British Association of Critical Care Nurses, Nursing in Critical Care. Vol. 13, No.5 – Evidence based VAP Preventative Measures (Citation previously submitted). F. Doyle et al. The incidence of ventilator-associated pneumonia using the PneuX System with or without elective endotracheal tube exchange: A pilot study. BMC Research Notes 2011, **4**:92. G. Scottish ICS Audit Group. 2008. VAP Prevention Bundle – Guide for Implementation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Assessment report, section 3.	**Questions to expert advisers – 09.07.19** 1. How would you define/diagnose VAP in practice - how standardised is this? 2. Which type of endotracheal/tracheostomy tube system is most commonly used in intensive care in clinical practice? Does it typically have subglottic drainage access? 3. What are the main relevant guidelines for preventing VAP? For example the Intensive Care Society care bundle for VAP prevention. 4. Are the protocols for preventing VAP in intensive care standardised across the UK? 5. What are the most likely populations in which PneuX might be used? Are there certain populations that are atypical for risk of VAP e.g. cardiac surgery patients? 6. Is there a difference in risk of VAP between endotracheal and tracheostomy tubes? 7. What do you see as the main innovation/benefit of PneuX vs standard comparators (if any)? 8. Do you predict any challenges with its use? E.g. predicting if someone is going to be intubated for <30 days (as per PneuX indication).	**Response from Dr Ben Messer – 11.07.19** 1. How would you define/diagnose VAP in practice - how standardised is this? There are many commonly used definitions of VAP. They are not standardised. One is the CPIS. Another can be seen in this paper: To cite: Hellyer TP, Conway Morris A, McAuley DF, et al. Thorax Published Online First: doi:10.1136/ thoraxjnl-2014-205766 2. Which type of endotracheal/tracheostomy tube system is most commonly used in intensive care in clinical practice? Does it typically have subglottic drainage access? Most intensive care units that I know and in my region use subglottic suction tubes. I cannot speak for other regions. I do not know what make other units use. In my Trust we use Trachoe tracheostomy tubes and Portex (blue line Sackett) endotracheal tubes. 3. What are the main relevant guidelines for preventing VAP? For example the Intensive Care Society care bundle for VAP prevention. The ICS guidance is the main guideline. However, GPICS guidance is currently out for consultation from the ICS and is very likely to include VAP prevention. 4. Are the protocols for preventing VAP in intensive care standardised across the UK? They are not completely standardised over my region so I doubt whether they are standardised nationwide. See also answer to Q3 above. 5. What are the most likely populations in which PneuX might be used? I do not think that this technology has an overall role or a role in a specific patient population (as per my responses to the initial questionnaire). The incidence of VAP has been shown to be almost halved in a meta-analysis by subglottic tubes and this new technology would need to be studied against these tubes rather than standard non-subglottic suction tubes. Are there certain populations that are atypical for risk of VAP e.g. cardiac surgery patients? Trauma patients are particularly high risk. In general, the longer a patient is intubated, the higher

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		the risk of VAP. Deep sedation and paralysis probably also increase the risk of VAP. 6. Is there a difference in risk of VAP between endotracheal and tracheostomy tubes? No difference due to the tube per se but a reduction in tracheostomy ventilated patients due to the reduction in requirement for deep sedation. 7. What do you see as the main innovation/benefit of PneuX vs standard comparators (if any)? I do not see a benefit. 8. Do you predict any challenges with its use? E.g. predicting if someone is going to be intubated for <30 days (as per PneuX indication). The challenge will be gathering robust data to show that there is a VAP reduction, length of stay reduction and mortality benefit when compared against a standard subglottic suction tube rather than the main data which compare the use of PneuX with non-subglottic suction tubes. **Response from Dr Peter Alexander – 12.07.19** 1. How would you define/diagnose VAP in practice - how standardised is this? This is the crux of the issue as how it is measured substantially effects the rate (https://onlinelibrary.wiley.com/doi/full/10.1111/anae.13211). Multiple definitions are available and there is no universally applied criteria across the NHS. CDC (ventilator associated events surveillance - https://www.cdc.gov/nhsn/PDFs/pscManual/10-VAE_FINAL.pdf) and HELICS definitions are used. However, in my experience, without automated data collection the CDC definitions are difficult to audit and the HELICS definition requires chest radiography which is often absent (https://www.frontiersin.org/articles/10.3389/fmicb.2016.01271/full). 2. Which type of endotracheal/tracheostomy tube system is most commonly used in intensive care in clinical practice? Does it typically have subglottic drainage access?

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		On our unit, the placement of subglottic suction tubes for both endotracheal and tracheostomy tubes would be regarded as standard, though this is not the case from a recent audit in Scotland 35 out of 227. (https://journals.sagepub.com/doi/full/10.1177/1751143719854984) 3. What are the main relevant guidelines for preventing VAP? For example the Intensive Care Society care bundle for VAP prevention. ICS - https://journals.sagepub.com/doi/full/10.1177/1751143716644461 European Society Management guidelines - https://erj.ersjournals.com/content/50/3/1700582?ijkey=99acde7873969b9823565734fd2187b63e200d97&keytype2=tf_ipsecsha 4. Are the protocols for preventing VAP in intensive care standardised across the UK? Standardised across critical care networks 5. What are the most likely populations in which PneuX might be used? Are there certain populations that are atypical for risk of VAP e.g. cardiac surgery patients? Standard general ICU patients would be typical however due to cost and complexity of device it would be better to exclude short term use patients, often difficult a priori. Subsets would be cardiac and the long term ventilated patients e.g. spinal cord injured patients 6. Is there a difference in risk of VAP between endotracheal and tracheostomy tubes? Yes, though these are actually different patients so should not be compared directly. Patients with tracheostomies have generally failed or are inappropriate (e.g. brain injury, head and neck surgery) for primary extubation. These patinets would often have longer lengths of stay and more co-morbidities.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		7. What do you see as the main innovation/benefit of PneuX vs standard comparators (if any)? I am not convinced that there is an advantage over standard sub-glottic suction tubes with intermittent cuff pressure monitoring 8. Do you predict any challenges with its use? E.g. predicting if someone is going to be intubated for <30 days (as per PneuX indication). Yes, this is an issue for a complex and expensive to manufacture device. The cost of standard sub-glottic tubes is now very small and therefore placement in all patients is feasible. I would not advocate tube changing once a standard tube has been placed as there have been local reports of serious adverse events following this.
Assessment report, section 3.		**Response from Dr Tom Hellyer – 12.07.19** 1. *How would you define/diagnose VAP in practice - how standardised is this?* Definitions and tests used to diagnose VAP are variable. This is largely due to a lack of gold standard for VAP. Clinical signs that are used include fever, hypotension, worsening oxygenation/ventilation and presence of purulent tracheal secretions. Tests that are used include white cell count, c-reactive protein and radiological findings (chest x-ray and CT). There are diagnostic criteria including the clinical pulmonary infection score (CPIS), American College of Chest Physicians criteria, European centre for disease control criteria and the Centers for disease Control and Prevention criteria (USA). However, no criteria have performed well against microbiology or histological

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		criteria. The only established reference standard for VAP is a quantitative or semi-quantitative culture from a bronchoalveolar lavage sample at a threshold above 10^4 colony forming units per ml, but this is far from a perfect standard. Anecdotally, quantitative culture is not routinely performed in the NHS. Despite the range of clinical signs and investigations that are used to diagnose VAP, there is no standardised approach that is routinely used in clinical practice. 2. *Which type of endotracheal/tracheostomy tube system is most commonly used in intensive care in clinical practice? Does it typically have subglottic drainage access?* There is variation in practice around the UK (Baldwin, Gray and Chequers, 2014). In my practice in the North East, endotracheal tubes with subglottic drainage (SSD ETT) ports are most commonly used (Portex tubes). 3. *What are the main relevant guidelines for preventing VAP? For example the Intensive Care Society care bundle for VAP prevention.* The main bundle for VAP prevention was the Institute for Health Improvement (IHI) VAP bundle. However, this bundle and the previous NICE bundle included chlorhexidine mouthwash. Subsequently safety concerns have been raised over chlorhexidine mouthwash. NICE has withdrawn its recommendation and the Intensive care society VAP bundle does not include chlorhexidine. The IHI bundle has not been updated since 2012. Therefore the ICS bundle is the most relevant guideline. 4. *Are the protocols for preventing VAP in intensive care standardised across the UK?* Protocols are not standardised across the UK. The change regarding oral chlorhexidine is likely to of led to further inconsistency. 5. *What are the most likely populations in which PneuX might be used? Are there certain populations that are atypical for risk of VAP e.g. cardiac surgery patients?* General ICU patients are the likely population. Despite the main body of evidence for PneuX coming from cardiac ICU patients, I would suspect that this would not be the

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		main population. Cardiac patients are often intubated for a short period of time post-operatively and in my experience often without a SSD ETT. Neurosurgical patients are a group who are particularly recognised as being at risk of developing VAP. In a non-cardiac ICU the challenge will be to show that the PneuX is better than another SSD ETT, which hasn't been evaluated clinically. 6. *Is there a difference in risk of VAP between endotracheal and tracheostomy tubes?* There is no difference in risk of VAP between tracheostomy and endotracheal tube. 7. *What do you see as the main innovation/benefit of PneuX vs standard comparators (if any)?* Whether there are any additional benefits of PneuX is over other SSD ETT is unknown. The company report several innovations (such as atraumatic tips and cuff shape) but it is not clear that these are important additional features. One important feature is the device that monitors cuff pressure. This is potentially valuable but in my hospital, this is achieved via the ventilator (Hamilton). 8. *Do you predict any challenges with its use? E.g. predicting if someone is going to be intubated for <30 days (as per PneuX indication).* There would need to be training in its use, but I would imagine that would be easily done. I think there would be reluctance to use it based on its cost. While PneuX say that it can't be used for more than 30 days, I don't think that would be a barrier as it is unlikely that many patients have the same tube for 30 days. Within this time it is likely that a tracheostomy has been performed and the tube changed. When SSD ETT were first introduced in my hospital there was a period of trying to identify patients who were likely to be intubated for more than 72 hours and using the tubes in those patients (to cut cost). However this meant that uptake was difficult (ie. changing the tube from the emergency department may not be safe later on). Now the subglottic tubes are available in the emergency department, so that all emergencies are intubated first time with a SSD ETT. Given the significantly higher cost of the PneuX tubes, I would anticipate a reluctance to use them in all patients initially and so I would expect the same problems that were experienced when SSD ETT were introduced.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Assessment report, section 3.		**Response from Dr David Ray – 12.07.19** **9. How would you define/diagnose VAP in practice - how standardised is this?** There seems to be no consistently agreed gold standard for this. VAP is usually pneumonia which develops within 48-72 hours of the patient being intubated. Most clinicians would agree that VAP can be diagnosed with the following: • New or progressive infiltrates on chest X-ray • Change in composition of tracheal secretions • Signs of systemic infection (fever, altered white blood cell count) • Detection of a causative organism A genuine gold standard is identification using brochoscopic alveolar lavage samples - $>10^5$ colony-forming units/ml (cfu/ml) provides positive semi-quantitative values; $>10^4$ cfu/ml is an accepted diagnostic threshold ($>10^3$ cfu/ml if it is protected specimen brushings rather than lavage fluid) **10. Which type of endotracheal/tracheostomy tube system is most commonly used in intensive care in clinical practice? Does it typically have subglottic drainage access?** There is not one particular type of system used most commonly – standard endotracheal tubes and tracheostomy tubes, or those with capacity for subglottic drainage are used throughout ICUs but varyingly throughout the UK. These types of tubes are made by a variety of different manufacturers. **11. What are the main relevant guidelines for preventing VAP? For example the Intensive Care Society care bundle for VAP prevention.** The ICS bundle is the main international one (Scottish Intensive Care Society guidelines which preceded the ICS one is used in Scotland – but it has been

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		modified to remove daily oral chlorhexidine wash and is now very similar to the ICS guideline) **12. Are the protocols for preventing VAP in intensive care standardised across the UK?** I suspect that rigid protocols are not in place but there are VAP-prevention bundles of interventions which may be more commonly used. It is highly likely that the principles of such bundles are agreed widely throughout the UK but their interpretation and delivery may well be different between different ICUs. **13. What are the most likely populations in which PneuX might be used? Are there certain populations that are atypical for risk of VAP e.g. cardiac surgery patients?** It is difficult to answer this directly – PneuX may have additional benefit for patients who receive ventilation longer than 4 days but it can often be difficult to predict at initial presentation which particular patients will require longer duration of ventilation. Independent risk factors for development of VAP include male sex, trauma admissions and intermediate underlying disease severity. **14. Is there a difference in risk of VAP between endotracheal and tracheostomy tubes?** Not to my knowledge – I would think any difference is unlikely given the proposed genesis of VAP being biofilm generation on the plastic which will be common to both endotracheal tubes and tracheostomy tubes. . **15. What do you see as the main innovation/benefit of PneuX vs standard comparators (if any)?**

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		The combination of automated cuff pressure management and subglottic drainage is novel and this combination may offer enhanced improvement over each component part. **16. Do you predict any challenges with its use? E.g. predicting if someone is going to be intubated for <30 days (as per PneuX indication).** Yes – predicting at initial presentation may well be challenging (both for identifying patients who might require ventilation > 4 days and also < 30 days). However this is no different for planning use of other tracheal tubes with subglottic drainage.
Assessment report, section 3.		**Response from Mr Neil Smith – 14.07.19** 1. How would you define/diagnose VAP in practice - how standardised is this? a. Taking a pragmatic perspective in day to day practice, personally I would define a VAP as "The development of a (suspected) new respiratory infection, 48 hours after intubation, with purulent secretions and deterioration in oxygenation and or radiographic status". 2. Which type of endotracheal/tracheostomy tube system is most commonly used in intensive care in clinical practice? Does it typically have subglottic drainage access? a. A wide variety of endotracheal and tracheostomy tubes are used in clinical practice, most manufacturers have a version of their products that facilitates subglottic drainage. Key manufacturers include Smith's Medical, Mallinckrodt, Coviden. 3. What are the main relevant guidelines for preventing VAP? For example the Intensive Care Society care bundle for VAP prevention.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		a. The ICS care bundle builds on previous recommendations from Department of Health "High Impact Intervention (HII) 5 and the Institute for Healthcare Improvement (IHI). However, all these guidelines advocate similar practices and the ICS 2015 guidelines has simply included the elements which are currently based on recent robust evidence. 4. Are the protocols for preventing VAP in intensive care standardised across the UK? a. The key elements of the bundles are standard across most critical care units. However, adherence to each element is variable due to a variety of factors such as workload conflict, lack of oversight and educational shortcomings. 5. What are the most likely populations in which PneuX might be used? Are there certain populations that are atypical for risk of VAP e.g. cardiac surgery patients? a. Patients with greater risk for longer term use of either endotracheal or tracheostomy tube would be the most appropriate population to use the PneuX system. These include neurosurgical trauma or neuromuscular conditions (Guillian-Barre, Myasthenic crisis). An atypical group that may benefit, are patients with soiled airways, for example complex Maxilliofacial surgeries or injuries. 6. Is there a difference in risk of VAP between endotracheal and tracheostomy tubes? a. There is limited evidence comparing the two groups. However, with Tracheostomy patients the VAP risk increases due to longer periods of an airway device remaining in situ. Most tracheostomy patients will have also already had an endotracheal tube for a number of days prior to being replaced by a tracheostomy, predisposing them to the risk of VAP. The tracheostomy procedure itself may also precipitate micro aspiration and subsequent VAP. In some scenarios the risk to

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		tracheostomy patients may be mitigated by patients subsequently being more alert and having improved cough reflexes. 7. What do you see as the main innovation/benefit of PneuX vs standard comparators (if any)? a. Its ability to automatically and dynamically control cuff pressures. This closed loop process undoubtably reduces the risk of micro aspiration compared to a nurse checking hourly or less frequently. 8. Do you predict any challenges with its use? E.g. predicting if someone is going to be intubated for <30 days (as per PneuX indication). **a.** Ensuring bedside compliance in delivering all interventions associated with the PneuX system (subglottic suction, retrograde irrigation, cuff measure maintenance) will prove challenging and potentially impact on patient related outcomes. Evidence from sites with significantly reduced/low VAP rates shows good compliance and high levels of experience with its use. This is no different than the challenges associated with adhering to the VAP care bundles.
Assessment report, section 3.		**Response from Dr Andrew Walder – 15.07.19** 1. We use the CDC definition of VAP 2. 2.we use plain portex ET tubes 3. 3.ICS VAP prevention bundle 4. The ICS standards are mostly used 5. Patients ventilated for more han 2 days 6. Tracheostomy patients are usually more awake which reduces their VAP risk but the difference is not due to the tubes per se 7. No real comparator to PneuX. Subglottic suction is an innovation **8.** Teaching staff protocols for its use. Effectively securing the tubes

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Assessment report, section 3.	**Question sent to expert advisers – 25.07.19** Are you aware of any studies or references that investigate the incidence of VAP in a typical UK ICU?	**Response from Tom Hellyer – 25.07.19** Two references from the Edinburgh group – Conway Morris et al. – 2009 - Evaluation of the effect of diagnostic methodology on the reported incidence of ventilator-associated pneumonia – Thorax 2009 Conway Morris et al. – 2011 – Reducing ventilator-associated pneumonia in intensive care: Impact of implementing a care bundle – Critical Care Medicine. Tom Craven, an ICU doc in Edinburgh, may of collected VAP data for his PhD. Don't know if he collected incidence data or if its published. His email is: Thomas.Craven@ed.ac.uk, if you wanted to drop him an email. But I think the attached references will have what you need. **Response from Neil Smith – 29.07.19** In my experience there is a limited quantity of high quality evidence detailing the incidence of VAP in the UK. I've enclosed citations for two contemporary papers which might be of use for you. However, these are rather limited in both in their geographical location and specific VAP incidence (tracheostomies). Hopefully these are of some use? Shah N., Hadley J., Zolfaghari P., Hinds C. - A point prevalence study of ventilator associated pneumonia (VAP) across four London ICUs - Intensive Care Medicine Experimental 2018 Hart R., MacLean S., McNeill S., Hornsby J., Ramsay S. - Influence of tracheostomies, sub-glottic suction endotracheal tubes and routine chlorhexidine on the rate of

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		suspected ventilator-associated pneumonia in Scottish intensive care units - Intensive Care Medicine Experimental 2018 **Response from Dr David Ray – 07.08.19** Sorry but I know of no such studies – the rate of VAP is very variable between ICUs (even in UK) and so it is difficult to state what the expected incidence would be averaged over a whole country (or group of countries). There are some studies from North America and Australasia but these do not really compare with UK and even they show considerable variance between different ICUs. **Response from Dr Ben Messer – 07.08.19** Sorry for the late reply but this is a recent UK survey. Some of the references from the Hellyer paper might be helpful too. Browne E, Hellyer TP, Baudouin SV et al. – A national survey of the diagnosis and management of suspected ventilator-associated pneumonia – BMJ Open Respiratory Research 2014. Hellyer TP, et al. – Diagnostic accuracy of pulmonary host inflammatory mediators in the exclusion of ventilator-associated pneumonia – BMJ Thorax 2014.
Assessment report, section 9	**Questions sent to company – 29.07.19** Here are KiTEC's questions on the economic submission: • The submission has assumed that the only cost of PneuX is the cost of the tube. Are there any other costs?	**Response from company – 29.07.19** I can confirm the following: Question 1 - There are no other costs. Question 2 - The Venner PneuX™ System has been designed to be used with the Venner PneuX™ ETT/TT and Venner PneuX™ Extension Tube in conjunction with the Venner

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
	• Specifically is PneuX compatible with standard ventilator equipment? • Is any other equipment (a bougie?) required to insert the tube?' **Further question to company – 29.07.19** Can you just confirm that the Venner PneuX TSM™ Cuff Pressure Controller is included in the £150 cost of the PneuX tube? I presume the bougie isn't, but is that a standard requirement for insertion of any endotracheal tube? **Further questions to company – 30.07.19** Can I just check if the loan of the seal monitor is the intended sale strategy for the forseeable future? Or is this likely to change? With regard to the bougie. I believe that all the PneuX tubes and some but not all standard tubes are reinforced and hence would require the bougie? Is this a disposable or a non-disposable item? So you know roughly what the cost of a bougie is?	PneuX TSM™ Cuff Pressure Controller, as a complete system. It should not be used with any other tubes or monitors and is compatible with standard ventilator equipment. Question 3 – Yes, a bougie/introducer/fiberscope is required for insertion due to the flexible nature of the tube, as required with other armoured tubes. **Response from company – 30.07.19** The tracheal seal monitor is on loan to the Trust and is included in the £150.00 per patient use. There are several different types of bougie's on the market (each user having their own preference) therefore Qualitech Healthcare does not provide its own device. A bougie forms part of the intubating airway kit and is required when using a reinforced ETT. It isn't routinely required when using a standard ETT. **Response from company– 30.07.19** This strategy will remain the same for the foreseeable future. Your understanding of bougie use is correct. Generally all bougies are disposable. The cost of intubating bougie's depends on type and volume – estimated cost £5.00 - £15.00 per unit. Also, please note, some users prefer to use a stylet, these range from – estimated cost £2.00 - £5.00 per unit.

Appendix 1

Minutes from teleconference with company and NICE – 11.07.19

PneuX sponsor TC_Minutes_11.07.19

Appendix 2

Documents received from company by e-mail on 12.07.19.


A251 _20190712_0001.pdf


Critical Care Pathway MT273 Pne


TFVMSG-F11-1-DoC TSM issue7.0.pdf


TFVMSG-F11-2-DoC Extension tube issu


TFVMSG-F12-DoC ETT issue14.0.pdf


TFVMSG-F13-DoC TT issue14.0.pdf

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT273 PneuX for preventing ventilator-associated pneumonia in intensive care

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from King's Technology Evaluation Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **27th August 2019** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

[Date submitted to company: 21 August 2019]

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Current Trademarks	Venner PneuX™ ETT/TT Venner PneuX TSM™ Cuff Pressure Controller Venner PneuX™ Extension Tube	Accuracy	

Issue 2 Page 14 – Paragraph 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The Venner PneuX™ System does not currently include a sterile introducer set.	Remove text	Accuracy	

Issue 3 Page 14 – Paragraph 3 Bullet 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
“reinforced with nitinol wire (MRI compatible)”	To provide additional clinical information “reinforced with nitinol wire (MRI compatible) and conforms to the patient’s anatomy”.	Accuracy and understanding	

Issue 4 Page 14 – Paragraph 3 Bullet 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The Venner PneuX™ ETT is not currently available in Size 6.0 mm ID	Remove text	Accuracy	

Issue 5 Page 14 – Paragraph 3 Bullet 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Requires additional detail	Amend to “pilot valve of the Venner PneuX™ ETT/TT”.	Understanding and completeness	

Issue 6 Page 14 – Paragraph 3 Bullet 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
“for maintaining the pressure of the tube cuff during use”	Amend to “for the monitoring, maintenance and regulation of the pressure within the cuff during use”.	Accuracy and understanding	

Issue 7 Page 14 – Paragraph 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"to allow the tube to function properly if a port is blocked"	Amend to "facilitates subglottic drainage of accumulated secretions and/or syringe irrigation via the subglottic connector, thereby directly influencing two steps in the pathogenesis of VAP".	Accuracy and understanding	

Issue 8 Page 14 – Paragraph 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Drainage happens intermittently, every 6 hours"	Subglottic secretion drainage should be intermittent and not continuous and is recommended every 4 hours (or more often if required), by attaching a sterile 20ml luer syringe to the subglottic connector and briefly applying vacuum until the flow of secretions has ceased.	Accuracy and understanding	

Issue 9 Page 14 – Paragraph 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Requires additional detail – "low pressure"	Amend to "low-volume, low-pressure silicone cuff, with elastic characteristics that expands on inflation without folds or creases and ensures	Accuracy and understanding	

	that a low and consistent intracuff pressure is transmitted to the tracheal wall. The Venner PneuX™ ETT/TT has been shown in comparative bench studies to prevent pulmonary aspiration (leakage past the cuff) across the entire tracheal diameter range compared to standard endotracheal tubes and maintains the seal in spite of either vertical or rotational movement of the tube. (References previously provided in Company Evidence Submission.		

Issue 10 Page 14 – Paragraph 5 (First sentence)

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Requires additional detail – "continuous cuff pressure seal monitor"	Amend to "The Venner PneuX TSM™ Cuff Pressure Controller is designed for the monitoring, maintenance and regulation of the pressure within the cuff of the Venner PneuX™ ETT/TT and maintains a constant cuff/tracheal seal pressure of 30 cm H2O; thus preventing aspiration (Reference previously supplied in Company Evidence Submission).	Accuracy and understanding	

Issue 11 Page 14 – Paragraph 5 (Second Sentence)

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"the seal automatically controls and maintains the inflation volume	Remove text as explained in Issue 10 proposed amendment above.	Accuracy	

and pressure within the cuff during use".			

Issue 12 Page 14 – Paragraph 5 (Third Sentence)

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"the cuff is maintained at a continuous specific pressure (20-30 cm H2O"	Amend to "An intracuff pressure of 80 cm H2O provides a calculated tracheal wall seal pressure of approximately 30 cm H2O (20 mm Hg), depending on the patient's anatomy and ventilation pressures".	Accuracy and understanding	

Issue 13 Page 15 – First line

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"few or no creases"	Amend to "without folds or creases" (See explanation in Issue 9)	Accuracy and understanding	

Issue 14 Page 42 – Last line

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"standard (non-drained) intubation"	Amend to "standard tracheal tubes (without subglottic drainage facility)".	To provide a clearer definition	

Issue 15 Page 47 – 9.2.6.

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"sensitivty"	"sensitivity"	Typo	

Issue 16 Page 52 – Paragraph 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"grainage"	"drainage"	Typo	

Issue 17 Page 13 – Cost Analysis Bullet 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"conventional tracheal intubation tube"	Is this intended to describe "a conventional tracheostomy tube"?	Accuracy	

Issue 18 Page 14 – Paragraph 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"Class III device (endotracheal/tracheal tube)"	Amend to "Class IIa (Venner PneuX™ ETT/TT)	Accuracy	

NICE National Institute for Health and Care Excellence

Issue 19 Page 14 – Paragraph 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
“Class IIb (PneuX tracheal seal monitor)	Amend to “Class IIa (Venner PneuX TSM™ Cuff Pressure Controller)	Accuracy	