Innovative ventilation technologies in adults and children: an evidence synthesis to inform clinical practice and future research priorities

Study protocol
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Co-chief investigators: Dr Keith Couper and Dr Yen-Fu Chen

Study co-applicants: Mr Peter Auguste, Mrs Rachel Court, Dr Adel Elfeky, Dr Daniel Gallacher, Prof Amy Grove, Prof Danny McAuley, Prof Gavin Perkins, Dr Barney Scholefield, Dr Marion Thompson, Dr Joyce Yeung

Contact: Dr Keith Couper
Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK.
Email: k.couper@warwick.ac.uk

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Scientific Abstract

BACKGROUND
Each year in the UK, over 60,000 adults and 10,000 children receive invasive mechanical ventilation on an intensive care unit. Over recent years, many innovative ventilation technologies have been developed with an associated rapid increase in volume of research. There is a need for comprehensive evidence synthesis to identify strategies where there is adequate evidence of clinical effectiveness to support their use in clinical practice, and which should be prioritised by researchers and funders for further research.

RESEARCH QUESTION
What is the current evidence informing use of specific innovative ventilation technologies at different stages of the ventilation care pathway in adults and children, and to what extent are they clinically and cost-effective?

AIM
To conduct a comprehensive evidence synthesis to map current evidence underpinning innovative ventilation technologies across adults and children, and to appraise evidence on clinical and cost-effectiveness of promising technologies prioritised by key stakeholders.

METHODS
We plan to undertake an evidence synthesis, comprising a scoping review and multiple systematic reviews.

Work package one: We will conduct a scoping review according to the latest methodological guidance proposed by the Joanna Briggs Institute to summarise the volume and nature of evidence underpinning innovative technologies. We will identify and summarise all relevant evidence in a written summary, supported by evidence maps. Our population, concept, context (PCC) framework for the scoping review is:
Population: patients requiring invasive ventilation or at risk of requiring invasive ventilation.
Concept: innovative ventilation strategy, defined as an approach to ventilation that is not recommended by current clinical guidelines due to uncertainty of evidence or not yet addressed due to its novelty. It can cover ventilation techniques, patient positioning concepts, and digital technologies to optimise ventilation.
Context: evidence related to clinical effectiveness and cost-effectiveness potentially applicable to UK settings.

We will then undertake a collaborative prioritisation exercise with key stakeholders using the findings of the scoping review to identify key research gaps that should be addressed through an evidence synthesis.

Work package two: We will evaluate the clinical and cost-effectiveness of four innovative technologies via systematic review. Where appropriate, we will undertake a meta-analysis to provide a pooled estimate of the treatment effect for each comparison. We will also consider the use of more advanced techniques such as network meta-analysis to inform comparative effectiveness and trial sequential analysis to help gauge the need for further evidence.

Expert reference group: We will convene an expert reference group to i) support identification of innovative ventilation technologies, ii) prioritise technologies for evaluation in systematic reviews, and iii) support dissemination.

ANTICIPATED IMPACT AND DISSEMINATION
This evidence synthesis will provide new knowledge, and best practice recommendations on innovative ventilation strategies. We will publish lay and professional summaries using written and infographic forms. We will engage the public and wider community at national engagement events and via social media. We will disseminate findings to clinicians and research funders through peer-reviewed publications, conference presentations and professional societies. We will engage policy makers through our membership of key organisations.

Background

Each year in the UK, over 60,000 adults and 10,000 children receive invasive ventilation on an intensive care unit (ICU).(1, 2) Invasive ventilation is a life-saving intervention, but it comes at substantial individual and societal cost. Around 30% of adults and 5% of children that require invasive ventilation die.(1-4) Survivors often report significant and sustained negative effects on their health-related quality of life.(5-9) The financial cost of an ICU stay is high, costing around £1500 per admission day with an average stay of five days.(2, 10-12)

In invasive mechanical ventilation, air is forcefully pushed into the lungs through positive pressure via a tracheal tube. The use of positive pressure comes with important risks, including increased infection risk, lung damage through volutrauma and barotrauma, cardiovascular effects, and muscle wasting.(13) Previous research has shown that the way in which invasive mechanical ventilation is delivered affects patient outcome. In 2000, the landmark ARDSNET tidal volume trial showed that use of lower tidal volumes (6 ml/kg of body weight) compared with traditional tidal volumes (12 ml/kg of body weight) in 861 adults with acute respiratory distress syndrome (ARDS) reduced mortality (31.0% v 39.8%, p=0.007) and increased the number of ventilator-free days.(14) Similarly, use of the prone position in adults with ARDS receiving invasive mechanical ventilation reduces mortality.(15) This evidence has led to the support of these strategies in UK and international guidelines.(16-18)

The desire to improve outcomes in patients receiving invasive mechanical ventilation has, in some cases, led to the adoption of ventilation technologies based on physiological principles, but without evidence of clinical benefit. High frequency oscillatory ventilation (HFOV) is a ventilation strategy in which very small tidal volumes are delivered at high-frequency, based on the idea that the use of these small tidal volumes would minimise the risk of barotrauma during ventilation.(19) It requires the purchase of an additional ventilator. Based on uncertainty as to its clinical effectiveness, the NIHR commissioned the OSCAR (OSCillation in ARDS) trial. The OSCAR NIHR report details that at least 25 UK intensive care units had purchased a high-frequency oscillator (2012 cost: ventilator cost £45,000 with a per-patient cost of £400), prior to any clear evidence of its clinical effectiveness.(19) The OSCAR trial randomised 795 adults with severe ARDS to either high-frequency oscillation or conventional ventilation. There was no statistically significant difference between the groups for the primary outcome of death at 30-days (HFOV 41.7% v standard care 41.1%, absolute difference 0.6 percentage points [95% confidence interval, −6.1 to 7.5]) or any secondary outcome, with no evidence that it was more cost-effective.(20) In contrast, a Canadian trial of 548 patients with moderate-severe ARDS showed that HFOV increased the risk of in-hospital mortality (HFOV 47% v standard care 35% , relative risk of death 1.33 [95% confidence interval, 1.09 to 1.64]).(21) These two landmark trials have led to international guidelines recommending against the use of HFOV.(16-18)

Airway pressure release ventilation is routinely available on many modern ventilators. As a ventilation mode, it applies prolonged periods of high pressure with intermittent pressure releases.(9) As such, it might reduce the risk of lung injury caused by the continuous alveolar opening and subsequent collapse that occur during conventional ventilation strategies.(22) In a recent systematic review which included five single-centre randomised controlled trials (330 patients), the use of airway pressure release ventilation compared with standard care increased ventilator free-days (mean difference 6.04, 95% confidence interval 2.12 to 9.96) and reduced mortality (risk difference 0.16, 95% confidence interval 0.02 to 0.29).(23) However, the authors highlight the low quality of evidence and state the need for further high-quality multicentre randomised controlled trials, such that the use of airway pressure release ventilation is not currently supported by clinical guidelines.(16-18) Despite it being of uncertain clinical benefit, a recent survey study has shown that it is routinely used in clinical practice.(24) The survey of 160 intensive care consultants found that 80% used the airway pressure release

ventilation on their intensive care unit, despite 83% stating that more evidence of clinical effectiveness was 'definitely' or 'probably' needed.

Paediatric intensivists face specific challenges in caring for ventilated patients as very limited evidence often means clinical practice and guidelines are based on expert consensus. (25-27)

We have defined an innovative ventilation technology as an approach to ventilation, including patient positioning strategies, where the uncertainty in the currently available evidence precludes making a recommendation for or against its use. We reviewed current clinical guidelines and drew on co-applicant expertise to propose examples of innovative technologies of relevance.(16-18, 25-27) Our examples include: awake prone positioning (non-COVID-19), airway pressure release ventilation, ultra-low tidal volume ventilation, closed-loop ventilation (e.g. adaptive support ventilation, neurally adjusted ventilatory assist), feedback loops/ processes, high-frequency jet ventilation (paediatrics), biomarker-guided strategies, and digital technologies (e.g. artificial intelligence).

The increasing volume of innovative ventilation technologies and associated evidence creates challenges for clinicians, patients, research funders, and service commissioners. The entirety of evidence needs to be appraised, assessed, and presented in a simple form so that it can be used by those who use and receive ventilation. Otherwise, there is a risk that some technologies may be adopted too early and potentially cause harm to patients, as was the case with high-frequency oscillatory ventilation. An additional risk is that emerging and promising strategies may not be identified and prioritised for research and development due to the high volume of emerging research in this area.

Aims and objectives

Research question:

What is the current evidence informing use of specific innovative ventilation technologies at different stages of the ventilation care pathway in adults and children, and to what extent are they clinically and cost-effective?

Aims

To conduct a comprehensive evidence synthesis to map current evidence underpinning innovative ventilation technologies across adults and children, and to appraise evidence on clinical and cost-effectiveness of promising technologies prioritised by key stakeholders.

Objectives

1. To undertake a scoping review to map the current evidence base for innovative ventilation technologies.
2. To undertake a collaborative prioritisation exercise with key stakeholders based on the findings of the scoping review to identify key research gaps that need to be addressed by a full evidence synthesis.
3. To undertake systematic reviews to determine the clinical and cost-effectiveness of four different innovative technologies.
4. To provide actionable findings to inform clinical decision-making, service commissioning decisions, and research prioritisation to immediately inform health care practice.

Study design

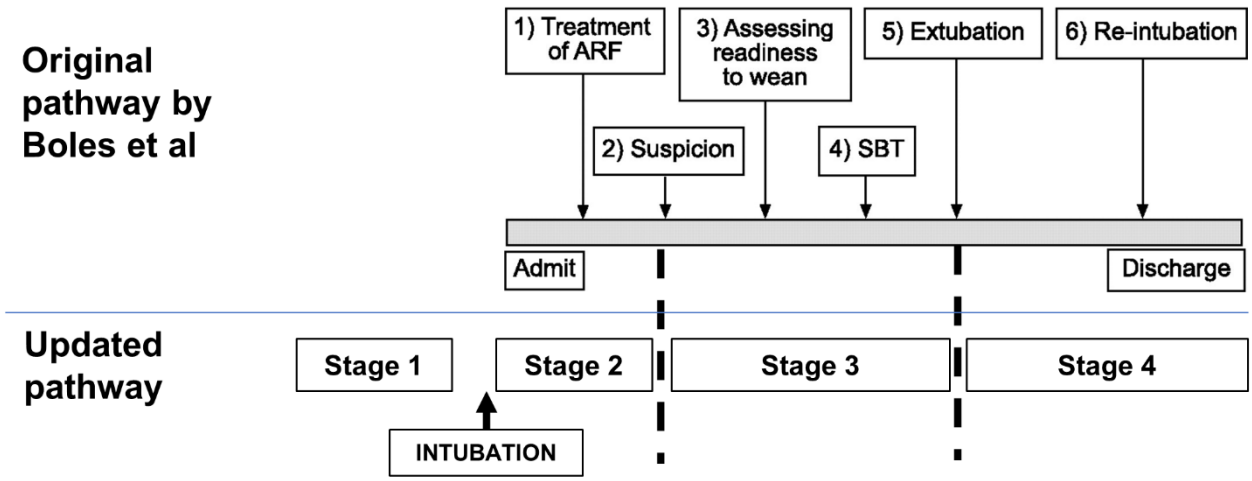
We plan to undertake an evidence synthesis, comprising two work packages.

Work package one (months 1-5) will consist of a scoping review in which we will collate and summarise evidence across all innovative ventilation strategies. We will present our findings as written summaries and using evidence maps.

In work package two (months 6-18), we will undertake systematic reviews in which we summarise the clinical and cost-effectiveness evidence of four innovative ventilation techniques prioritised by stakeholders. Where appropriate, we will undertake a meta-analysis to provide a pooled estimate of the treatment effect for each comparison. We will also consider the use of more advanced techniques such as network meta-analysis to inform comparative effectiveness and trial sequential analysis to help gauge the need for further evidence.

To support our evidence synthesis, we will use a conceptual model/ taxonomy of the ventilation care pathway to help illustrate the volume of evidence at each stage of the pathway. Boles and colleagues identified six stages in the ventilation care pathway from the point of tracheal intubation and commencement of invasive mechanical ventilation (see Figure 1).(28) To reflect the wider scope of our review, we will explore, as part of work package one, how best to refine the conceptual model/ taxonomy developed by Boles et al to better reflect the whole ventilation care pathway. We show both the original pathway and a potential modified pathway in Figure 1. The co-applicant team will work closely with the expert reference group to develop this revised model/ taxonomy.

Figure1. illustration of our proposed ventilation care pathway to help categorisation of interventions and original pathway developed by Boles and colleagues (28)



Stage one- innovative technologies to reduce risk of needing invasive ventilation or optimise timing tracheal intubation and start of invasive mechanical ventilation

Stage two- innovative technologies to support treatment of acute respiratory failure and minimise ventilator induced lung injury,

Stage three- innovative technologies to support the process of weaning from invasive ventilation

Stage four- innovative technologies to reduce risk of re-intubation

ARF: acute respiratory failure; SBT: spontaneous breathing trial

Expert reference group

We will convene an expert reference group to inform the project design, delivery, and dissemination. The expert reference group will include service commissioners (represented through NHS England), clinicians, and patients and carers with personal experience of invasive ventilation.

We will invite professional organisations (e.g., Intensive Care Society, Paediatric Intensive Care Society) to nominate clinician representatives. We will identify and invite patient contributors through our local patient and public involvement research group, which helped design this study, and our other existing networks, such as the NIHR Applied Research Collaboration West Midlands PPI Network. We anticipate total group membership will be ~10-15 people, including four patient contributors.

This group will meet at three key decision points throughout the project:

1. **Identification (month 1)-** The group will meet to agree terms of reference of the group and support the study team in identifying and mapping a list of innovative technologies that will be included in our scoping review. To support the process of classifying interventions, we will present and discuss our early ideas on how best to characterise the ventilation care pathway using a conceptual model/ taxonomy.

2. **Prioritisation (month 6)-** The group will review and discuss our ventilation conceptual model/ taxonomy, evidence summaries and maps generated in the scoping review (WP1). Group members will individually prioritise technologies to progress to a systematic review. In this prioritisation exercise, we will encourage members to consider:
    i. volume of available high-quality evidence;
    ii. absence of a recent high-quality systematic review;
    iii. relevance of the strategy to the NHS;
    iv. ease of implementation in the NHS,
    v. issues that are important to patients who receive ventilation and their carers.

    Group members will discuss their individual choices to reach group consensus facilitated by an expert research engagement facilitator.

3. **Interpretation (month 17)** We will present a summary of results to the group to assess interpretation and plans for dissemination. We will provide materials, such as infographics, to support dissemination of findings through member's organisations.

Work package 1- scoping review (months 1-5)

We will first conduct a scoping review to summarise the volume and nature of evidence underpinning innovative ventilation technologies. We will follow the latest methodological guidance for conducting scope review proposed by the Joanna Briggs Institute.(29) This widely adopted methodology builds on Arksey and O'Malley's seminal work on scoping studies (30) and subsequent development by Lavec and colleagues.(31) The methodology is considered a standard approach, which is acknowledged in the PRISMA Extension for Scoping Review (PRISMA-ScR).(32) We will use the PRISMA-ScR checklist to ensure the completeness of our scoping review report.

We will develop a draft list of innovative ventilation technologies through a review of relevant clinical guidelines, such as those developed by the Intensive Care Society, European Society of Intensive Care Medicine, Critical Care Society, Society of Critical Care Medicine, and other key professional organisations.(16, 18, 27, 33, 34) Our expert reference group will support us in refining this draft list and identifying other technologies. Through this process, we will develop a comprehensive list of innovative ventilation technologies to explore in this scoping review. The scoping review will focus on both clinical effectiveness and cost-effectiveness evidence.

Our population, concept, context (PCC) framework is:

Population: patients requiring invasive ventilation or at risk of requiring invasive ventilation.

Concept: innovative ventilation strategy, defined as an approach to ventilation that is not recommended by current clinical guidelines due to uncertainty of evidence or not yet addressed due to its novelty. It can cover ventilation techniques, patient positioning concepts, and digital technologies to optimise ventilation. Examples include: airway pressure release ventilation, ultra-low tidal volume ventilation, closed-loop ventilation (e.g. adaptive support ventilation, neurally adjusted ventilatory assist), and digital technologies (e.g. artificial intelligence).

Context: evidence related to clinical effectiveness and cost-effectiveness potentially applicable to UK settings.

Search strategy

Our information specialist (Court) will iteratively develop a search strategy, supported by clinical co-applicants. We will search key medical databases and clinical trial registries.(35)

Firstly, we will conduct systematic searches in a range of relevant bibliographic databases, based on the concepts of innovative ventilation technologies. Search concepts will include technologies such as awake prone positioning (non-COVID-19), airway pressure release ventilation, ultra-low tidal volume ventilation, closed-loop ventilation, high-frequency jet ventilation, biomarker-guided strategies digital technologies, together with word variations and synonyms.

Searches will combine keywords and, where appropriate, thesaurus (e.g., MeSH, EMTREE) terms. The search strategy will initially be developed in Ovid MEDLINE, before being adapted for other databases/interfaces, to include: Embase (Ovid), Science Citation Index and Conference Proceedings Citation Index- Science (Web of Science), CEA registry, ACM digital library, and the Cochrane Library. No language restrictions will be applied. Our search will focus on studies published since 2010 to avoid including historical interventions which proved either ineffective or impractical to implement in practice.

Grey literature will be identified via internet (Google) searches, ProQuest Dissertations & Theses Global database, proceedings of selected conferences of interest and websites of relevant organisations. Supplemental searches will be developed iteratively, as additional search terms, concepts and sources are identified; these may include specific projects, interventions, key authors, theories, or organisations. We will check reference lists of included studies and a selection of recent, relevant systematic reviews identified via the database searches. Forwards citation tracking from key publications of included studies (to identify citing papers) will also be undertaken, using Science Citation Index (Web of Science) and Scopus.

We will contact professional societies, research groups and search the NIHR funding and award database to identify other recent or forthcoming evidence.

Study selection

We will determine study eligibility for inclusion in the review, using the framework outlined in Table 1.

Table 1. eligibility criteria for studies in scoping review

	Inclusion criteria	Exclusion criteria
Population	Adults and children at risk of requiring, or currently receiving, invasive mechanical ventilation	Neonatal studies Animal studies
Intervention	Innovative ventilation technology (as per our definition above)	-
Comparator	Standard NHS care	Studies in which the comparator intervention is clearly not applicable to the UK NHS
Outcomes	Patient-reported outcomes (e.g. quality of life) Clinical effectiveness outcomes (e.g. mortality, safety), Cost-effectiveness outcome Surrogate outcome that provides information about intervention efficacy.	Surrogate outcomes with no association with clinical and patient reported outcomes
Study design	Randomised controlled trials Non-randomised comparative studies with a control group, Systematic reviews Economic evaluations. Eligible studies will include a comparison between an innovative ventilation strategy and standard care, or another innovative strategy.	Narrative review Commentary and opinion pieces without reporting new empirical data
Setting	Critical care unit (for innovative technologies where patient is receiving invasive mechanical ventilation) Acute hospital (for innovative technologies targeted at preventing the need for invasive mechanical ventilation in those at risk)	Invasive mechanical ventilation in the operating theatre, emergency department, or pre-hospital setting

We have excluded neonates from this evidence synthesis as the clinical indications for invasive mechanical ventilation and its use, are very different to those used in adults and children. We have decided to exclude animal studies as, whilst they can be helpful in identifying therapeutic targets for clinical testing, the generalisability of findings from animal models of invasive mechanical ventilation to humans is limited.(36, 37)

The focus of this scoping review is on evidence that might provide information about clinical and cost-effectiveness. However, we will identify and collate evidence on implementation, adoption, and user experience separately to inform our interpretation of the evidence.

Study classification and data charting

Eligible studies will be coded/charted based on key features, such as: innovative ventilation strategy type, comparator, stage in invasive mechanical ventilation care pathway, patient population, disease, study design and sample size, outcome measures, setting, sources of funding and conflicts of interest.

Where possible, the coding/charting will be informed by existing frameworks (with necessary adaption) such as the aforementioned classification of stages in mechanical ventilation care pathway modified from Boles et al. and the checklist of study design features for both randomised and non-randomised studies of interventions

recommended by the Cochrane Handbook.(38) However, given the broad scope of the review and the innovative nature of the interventions, it is important we remain open to the generation of new categories/codes inductively where needed. Potentially eligible studies identified through clinical trial registries and NIHR award registry that are ongoing or not yet published will be coded/charted in the same way.

For primary research that have reported study results, we will extract summaries of key findings and study conclusions – except where a systematic review covering the primary research has been published, in which case we will extract summaries of key findings from the systematic review instead.

No quality assessment will be undertaken for identified primary studies, in line with commonly adopted approaches to undertaking scoping reviews.(39) Systematic reviews meeting our inclusion criteria (if identified) will be quality assessed using AMSTAR-2 checklist, as this information (whether existing systematic reviews are well-conducted) will be required by the expert reference group and other stakeholders to inform prioritisation of topics for work package 2 of our evidence synthesis.(40) For cost-effectiveness studies, we will also extract information on type of analysis, perspective, time horizon, and modelling technique.

Data synthesis and output

We will synthesise and summarise data in two complementary ways; through narrative summaries and evidence maps.

Narrative summaries: We will develop a narrative written summary to describe the available evidence. We anticipate that a series of tables will be developed to help show the volume and nature of evidence for each innovative ventilation strategy across all patients and for key sub-groups (e.g. population type (adults/ children), underlying disease, and stage of the invasive ventilation care pathway).

Evidence maps: We will complement our narrative synthesis with evidence maps to provide a visual summary of all evidence across all patients and innovative technologies. (41, 42) We will produce separate evidence maps for key sub-groups, as described above. The extracted data will be compiled into a JSON file in EPPI Reviewer 4 and exported into an evidence map wizard, which will create the map with linkages between each strategy and outcome types. Each strategy (rows) will be mapped on to different outcomes (columns). The number and colour of the blocks in the evidence map will indicate the amount and quality of evidence of the link between a strategy and an outcome.

We will report findings in accordance with the PRISMA checklist for scoping reviews.(39) Our written summary output and evidence maps will be shared with the expert reference group to inform their prioritisation of which technologies should be evaluated in systematic reviews. We will host all output on our institutional website which is accessible to the public.

We will undertake the prioritisation process using Q-methodology. Q-methodology provides a framework to allow individual subjective viewpoints to be compared systematically.(43, 44) Expert reference group members (our stakeholders) will be asked to decide from the evidence summaries presented (Q statements), what topics are meaningful and significant from their perspective. To incorporate the views of both topic experts and patient contributors we will develop Q user informed statements which will be presented alongside the evidence summary Q statements. We will run a small pilot with 2-3 stakeholders to find out how easy participants find the

sorting of statements and their interpretation of the meaning of statements. Once the statements are generated, we will conduct the Q-sorting process. Using explicit terms of reference (e.g. volume/type of evidence, ease of implementation), stakeholders will be asked to sort statements into sets, i.e., most agreed/disagreed /least likely to implement, simple/already in practice, and directing them to select the statements that are most pertinent to their perspectives on ventilation technologies. Stakeholders will do this on a Q-grid, enabling them to sort statements on positive, negative, and neutral scales.(43) This process will generate a Q-sort for each stakeholder, which will then be correlated with the other stakeholders' Q-sorts, then factor-analysed to show similar orders of ranking by stakeholders. The analysis will then produce the common ranking of statements which will inform the reviews conducted in WP2.

Work package 2- systematic reviews (months 6-18)

We will evaluate four innovative technologies in formal systematic reviews. We have chosen four following discussion with the wider project team and advisors who are experts in evidence synthesis. It was deemed to be the maximum number achievable within the project timeframe.

Review protocol

Our systematic review method will be based on the approach described in the Cochrane Handbook and equivalent standards for cost-effectiveness reviews.(45, 46) For each systematic review topic, we will frame the research question using the PICOS (population, intervention, comparator, outcome, study design) framework, in consultation with the expert reference group.

An example PICOS framework is shown in Table 2.

Table 2. Example PICOS framework

Population	Adults with severe acute respiratory distress syndrome receiving invasive mechanical ventilation
Intervention	Airway pressure release ventilation
Comparator	Standard care
Outcome	Mortality, duration of invasive mechanical ventilation, duration of critical care stay, health-related quality of life, cost-effectiveness
Study design	Randomised controlled trials (clinical -effectiveness) Studies that undertook model-based economic analysis (cost-effectiveness)

We will prospectively register each systematic review with PROSPERO. The target population of each review may be adults, children, or both adults and children. For reviews that include both adults and children, we will analyse adult and child data separately, unless the expert reference group recommends a different strategy.

The protocol for each review will define the outcomes of interest, based on the nature of the patient population, intervention, and its stage in the ventilation care pathway. Outcome groups of interest include patient-reported outcomes, clinical outcomes, clinical process measures, and cost-effectiveness outcomes. Specific relevant outcomes include health-related quality of life, mortality, duration of mechanical ventilation, need for tracheal

intubation, and health economic outcomes. We will align outcomes with core outcome sets for ventilation studies (adult/paediatric) and paediatric critical care.(47, 48)

The review protocol will also detail study eligibility criteria, which will be developed in partnership with our expert reference group and will be aligned with the PICOS framework for each review. We anticipate that we will limit inclusion to randomised and non-randomised studies of interventions with a control group. We will not include animal studies.

The planned analysis strategy including any sub-group and sensitivity analyses will be detailed in review protocols and will be informed by the likely volume and type of evidence (see data analysis section below).

The individual systematic review protocols will be written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses- Protocol (PRISMA-P) checklist.(49)

Literature search, study screening, and selection

The project information specialist (Court) will determine the most appropriate approach to database searches, considering the initial scoping review searches, specific inclusion criteria for each systematic review, records of studies already identified, and information provided by the expert reference group. This will include whether we should develop individual search strategies tailored for each systematic review or a single broader search. At a minimum, we will search at least three databases (MEDLINE, EMBASE, Cochrane Library). We will target literature published since 2010 to reflect the innovative nature and rapid development of technologies. Searches will not be limited by publishing language.

Additional citations will be identified through citation tracking of eligible studies and relevant reviews, and searches of relevant grey literature sources. Systematic searches of trial registers, research funding databases, a systematic review registry and the internet will be used to identify unpublished studies.

Study screening and selection will be undertaken independently by two reviewers (Elfeky and Couper/Chen). Discrepancies will be resolved by discussion or referral to a third reviewer.

Data extraction and risk of bias assessment

General approach

For both the clinical-effectiveness and cost-effectiveness components of the review, two reviewers will independently assess risk of bias (Elfeky and Couper/Chen). Discrepancies will be resolved by discussion or referral to a third reviewer.

Data including study design features and quantitative outcomes of interest will be extracted on to a bespoke data extraction form which will be pre-piloted. Given the innovative nature of technologies, we will pay particular

attention to the description of study participants and their selection, and details of the intervention. Data extraction will be carried out by one reviewer and checked for accuracy by another.

Where key methodological details are not adequately reported (e.g., allocation concealment), we will contact the trial authors to obtain further information.

Clinical effectiveness

For randomised controlled trials, we will assess risk of bias using the revised Cochrane risk of bias tool (RoB2).(50) For non-randomised controlled studies, we will use the ROBINS-I tool.(51)

Cost effectiveness

Data will be extracted using an a priori pre-piloted data extraction sheet based on the items outlined in Wijnen et al., (46) by one reviewer and cross-checked by a second reviewer. Any disagreements will be resolved by discussion or by recourse to a third reviewer. Relevant information will be extracted on study details (e.g., title, author, and year of study), baseline characteristics (e.g., population, innovative technology, and comparator), methods (e.g., type of economic analysis, type of economic model, study perspective, resource use and costs and assumptions), results (e.g., base-case and sensitivity analysis results), discussion (e.g., study findings, comparison with other studies and limitations), and other (e.g., source of funding).

Decision analytical model studies will be appraised using the Philips checklist.(52) The Consolidated Health Economic Reporting Standards (CHEERS) checklist will be used to assess reporting quality of economic evaluation studies.(53)

Data synthesis

Clinical effectiveness outcomes

We plan to combine trial data in a meta-analysis to provide a pooled estimate of the treatment effect for each comparison and outcome. If study or clinical heterogeneity precludes meta-analysis, we will summarise findings in a narrative synthesis, ensuring reporting complies with best practice guidance. (54)

Where appropriate, we will perform more advanced syntheses, such as network meta-analysis for estimating comparative effectiveness for more than two ventilation strategies and trial sequential analysis for estimating optimal information size and the need for additional evidence. We will use Stata 17 for all meta- analyses. The Trial Sequential Analysis software developed by Copenhagen Trial Unit will be used to conduct trial sequential analysis.(55)

Pairwise meta-analyses- For each pair-wise comparison, we will synthesise data to obtain effect size estimates (e.g. RR or OR) and 95% confidence intervals (CIs) for dichotomous outcomes (e.g. mortality). We will also report risk differences with 95% CI. For continuous outcomes (e.g. length of ICU stay), mean difference and 95% CI will be calculated where feasible. Standardised mean differences (SMD, Cohen's d) will be considered where different

scales have been used to measure the same construct in different studies. We will use a random effects model to incorporate the assumption that different studies are estimating different, yet related, treatment effects.

Visual inspection of the forest plots and chi square test will be used to investigate the possibility of statistical heterogeneity. The I^2 statistic will be calculated to evaluate the proportion of total variance arising from between-study heterogeneity.

We anticipate there will be insufficient studies (<10) to use funnel plots and related methods to assess for publication bias/small study effects. We will highlight cases where a completed trial has not been published.

Network meta-analyses

Depending on the targeted patient populations and places in the care pathway, network meta-analyses (NMA) may be considered if different innovative ventilation technologies chosen for systematic reviews could be potentially used as competing/alternative treatment options. This might be the case, for example, if we wished to compare the clinical effectiveness of different types of closed loop ventilation. Provided that the included studies appear to be sufficiently similar with respect to the distribution of effect modifiers and form a connected network, we will conduct a random effects network meta-analysis to synthesise relevant evidence for each outcome, and obtain a comparative ranking of competing technologies /ventilation strategies.

We will use arm-level data and the binomial likelihood for dichotomous outcomes. We will assume a single heterogeneity parameter for each network. Results from the network meta-analysis will be presented as summary relative effect sizes (mean difference or odds ratio) along with 95% confidence intervals, derived assuming a normal distribution of the effects, for each possible pair of treatments. To interpret the level of heterogeneity, we will calculate prediction intervals, as these intervals could reflect the variation in treatment effects over different settings, including what effect is to be expected in patients in the future.(56) To rank the various treatments for each outcome, we will use the surface under the cumulative ranking curve (SUCRA) and the mean ranks.(57)

Trial sequential analysis

We will use trial sequential analysis (58) to estimate the optimal information size for a primary outcome of a potential future trial and to guard against the possibility of type I or type II statistical error

For the trial sequential analysis, we will assume a two-sided design using established design parameters (e.g. α of 0.05 and 90% power). For each analysis, we will work with our expert reference group to determine a clinically important effect size. The control group event probability will be based on the pooled estimate of event proportions in the control groups of included trials. We will estimate the required information size, namely the number of participants in the meta-analysis required to accept or reject the prespecified intervention effect and adjacent trial sequential monitoring boundaries for our pre-specified effect size. We will undertake sensitivity analyses to explore the effect of adjusting the clinically important effect size. We will also calculate the low-bias and heterogeneity (I^2)-adjusted information size (LBHIS).

We will estimate both the information size and apply the adjacent trial sequential monitoring boundaries. We will compare the accrued number of participants with the calculated information size and construct the cumulative Z-

curve (i.e., Z-statistics after each trial) of each meta-analysis and assess its crossing of Z = 1.96 (P = 0.05) and the monitoring boundaries with a random-effects model.

Subgroup analyses- In the protocol for each review, we will define relevant sub-groups of interest.

Potentially relevant sub-groups may be based on:

- Patient demographics (e.g. age, gender, ethnicity, social deprivation, body mass index, co-morbidities)
- Nature of respiratory failure (e.g. cause of respiratory failure, presence of acute respiratory distress syndrome),
- Severity of illness (e.g. PaO_2/ FiO_2 ratio, Acute Physiology and Chronic Health Evaluation (APACHE) II score).
- Study characteristics (e.g. study design, risk of bias)

We will explore potential differences between subgroups through subgroup analyses or meta-regression. Evidence on potential subgroup effects obtained from within-study comparisons is more reliable than those obtained from subgroup meta-analysis using trial-level data as the latter is more susceptible to confounding by study-level variables. Findings will be interpreted accordingly.

Cost-effectiveness outcomes

Due to the context-specific nature of economic evaluations, we will describe findings in a narrative synthesis supported by tabulation of study characteristics and findings. We will highlight issues related to applicability to UK setting, key drivers of cost-effectiveness, sources of uncertainty, and discuss recommendations for the conduct of future economic modelling studies.

GRADE certainty in evidence and presentation of findings

Overall certainty in clinical-effectiveness and cost-effectiveness evidence for each comparison and outcome will be evaluated using GRADE framework (59) which characterises the quality of a body of evidence on the basis of the study limitations, imprecision, inconsistency, indirectness and publication bias. The starting point for confidence in each estimate is high for randomised controlled trials, but may be downgraded according to the assessments of these five domains. GRADE assessment will be undertaken independently by two reviewers, with disagreements resolved through discussion or with the input of third reviewer. We will use the GRADEpro GDT tool to create GRADE evidence profiles and summary of findings tables (60) and use GRADE informative statements to communicate our findings.(61)

We will report each systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.(62)

Equality, diversity, and inclusivity (ED&I)

As an evidence synthesis project, we will not be recruiting participants.

We are, however, extremely cognisant that the way in which previous research was conducted may affect its generalisability to the communities served by NHS organisations. We also recognise that groups of people are routinely underserved by systematic review methods.

Whilst we cannot mitigate for exclusion in previously published research, we plan the following approach to addressing ED&I:

1. We will record whether studies included in work packages one or two record key demographic information, across any domain of the PROGRESS-plus concept (PROGRESS-Plus- Place of residence, Race/ethnicity/culture/language, Occupation, Gender or sex, Religion, Education, Socioeconomic status, Social capital, other factors associated with discrimination, exclusion, marginalisation or vulnerability (e.g. age, disability, pregnancy).(63). In study outputs, we will report the proportion of studies where this important information is adequately reported.
2. For work package two, we will record details about the study's approach to participant recruitment and potential issues in relation to inclusivity. We will also record whether key groups were excluded from the study based on characteristics highlighted in PROGRESS-Plus concept and whether this exclusion was adequately justified.(63) This will be specifically considered in our GRADE assessment of evidence certainty in the context of directness of evidence. Where appropriate, we will consider sub-group analyses using specific PROGRESS-plus domains.

Project management and patient/ public involvement

We will convene a project management group which will meet at least monthly over the project time span. This group, chaired by Couper/ Chen will comprise co-applicants. Our project Gantt chart (figure two) summarises key project milestones.

The project PPI co-applicant (Thompson) will provide day-to-day project support, ensuring that the project remains focussed on the interests of patients and members of the public. Our expert reference group membership will draw in additional patient and public members.

Figure two: detailed project plan

	Project month																			
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Overview of project																				
Expert reference group meetings																				
Work package one																				
Work package two																				
Work package 1- scoping review																				
Develop/ run searches																				
Study screening																				
Data extraction/ charting																				
Data synthesis																				
Generation of evidence maps																				
Publication of findings																				
Work package 2- systematic reviews																				
Review registration with PROSPERO																				
Develop/ run searches																				
Study screening																				
Data extraction																				
Data analysis																				
Publication of findings																				
Project management/ dissemination																				
Identify of expert reference group members																				
Contracting																				
Finalise and publish project protocol																				
Study management group meetings		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
HTA progress reporting																				
Dissemination activity																				
HTA report																				
Handover materials to prof. organisations																				

Dissemination

Our key audiences will be patients and the public, clinicians, research funders, and policy makers (NHS England and devolved nations). Project dissemination will be supported by our expert reference group. Our target audiences and planned study outputs are recorded in Table 3. We will make study materials available at the end of the project.

Table 3: project outputs

Type of output	Strategy to maximise impact
Presentations	We will target key national (e.g. Intensive Care Society) and international conferences (e.g. European Society of Intensive Care Medicine) to ensure results of our evidence synthesis reach professional groups. We will seek, where possible to share presentations simultaneously on-line to increase access. We anticipate presentations will be delivered by investigators, and patient and public partners.
Infographics/ lay summaries- lay audiences	We will develop infographics and accessible written summaries for lay audiences to facilitate communication of key findings and knowledge gaps. We will disseminate these through the university press office, our project website, intensive care charities, co-applicant/ expert reference group links, PPI groups and social media. We will send directly to key UK and European research funders to share with their PPI members.
Infographics- professional audiences	We will develop infographics for professional audiences that summarise key findings and knowledge gaps. We will disseminate these through professional organisations, co-applicant/ expert reference group links, social media, and our project website. We will send directly to key UK and European research funders.
Academic publications	In addition to the protocol, we will publish study findings and other key study information in open access, high impact, scientific journals.
Public engagement events	We will present information about the project at relevant public engagement events (e.g. Science Festivals, NIHR ARC-WM PPIE network, regional user events) to explain the importance of the research, how patients and public were involved, and to share the research findings and ongoing research gaps.
Guidelines	We will use co-applicant and expert reference group member links with national (e.g. NICE, NHS England, Intensive Care Society) and international (e.g. European Society of Intensive Care Medicine) guideline writing to flag key outputs, thereby ensuring our research informs clinical practice both locally and internationally.

Our comprehensive evidence synthesis of innovative ventilation technologies will provide actionable information to key groups to immediately inform health care practice, namely:

Clinicians and patients– our accessible evidence overviews will inform clinical decision-making regarding innovative technologies that they might be considering using/ implementing.

Research funders- our summary of evidence that underpins innovative technologies will inform decisions on prioritisation of technologies for future research funding.

Service commissioners- our systematic reviews will inform commissioning decision-making through independent and unbiased assessment of evidence on clinical and cost-effectiveness.

Ethical considerations

The proposed research is an evidence synthesis project that will use only data already in the public domain. Our proposed project does not raise any ethical concerns. There will be no requirement for any ethical or regulatory review.

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