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| | |

# Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a scoping review

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**Keywords**

Mechanical ventilation, positive end-expiratory pressure, scoping review, acute respiratory distress syndrome, acute hypoxemic respiratory failure

**Abstract**

Introduction: Titrated application of positive end expiratory pressure (PEEP) is an important part of any mechanical ventilation strategy. However, the method by which the optimal PEEP is determined and titrated varies widely. Methods for determining optimal PEEP have been assessed using a variety of different study designs and patient populations. We will conduct a scoping review to systematically identify all methods for determining optimal PEEP, and to identify the patient populations, outcomes measured, and study designs utilized for each method. The goal will be to identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to further systematically synthesize and meta-analyze existing literature.

Methods and analysis: Using scoping review methodology, we will generate a comprehensive search strategy based on inclusion and exclusion criteria generated using the Population, Concept, Context framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of Science, and Scopus). Three investigators will independently screen titles and abstracts, and two investigators will independently complete full text review and data extraction. Included citations will be categorized in terms of PEEP method, study design, patient population, and outcomes measured. The methods for PEEP titration will be described in detail, including strengths and limitations.

Ethics and dissemination: Given this is a synthesis of existing literature, ethics approval is not required. The results will be disseminated to stakeholders via presentation at local, regional, and national levels, as well as publication in a high impact critical care journal. There is also the potential to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by societies.

Registration details: Scoping review protocol registered with Open Science Framework (https://osf.io/atzqc)

**Strengths and limitations of this study (5 max)**

- This study will rigorously describe studies testing methods of determining optimal PEEP. Each method will be summarized with a description, its strengths, and limitations.
- Inclusion of many different study designs, not just randomized control trials will allow for identification of methods that are well studied or those that could be better studied.
- A potential limitation is that given the broad nature of the review, there will be a large volume of studies to synthesize, and this may be challenging to summarize in one review.

## Introduction

Titrated application of positive end-expiratory pressure (PEEP) during mechanical ventilation is a crucial part of any ventilatory strategy. PEEP can be beneficial in several ways. PEEP increases mean airway pressure which can improve oxygenation by recruiting collapsed alveoli and reducing intrapulmonary shunt[1]. PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimizing atelectrauma[2]. However, excessive PEEP can also have detrimental impacts through its effects on the respiratory and cardiac systems. Overdistension of the lungs from high PEEP can lead to VILI via barotrauma[2]. Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output[2]. Several methods exist to determine the best or optimal PEEP to apply during mechanical ventilation, but significant variability exists in terms of which methods are used by clinicians.

Several large randomized-controlled trials (RCTs) have assessed different strategies for selecting the best PEEP in patients with acute respiratory distress syndrome (ARDS). The ALVEOLI study randomized patients with ARDS to either low or high PEEP strategies based on pre-specified tables that titrated PEEP higher as the fraction of inspired oxygen ($FiO_2$) increased[3]. The investigators found no differences in terms of mortality or discharge home without ventilatory support[3]. The EXPRESS trial randomized patients with ARDS to a low PEEP strategy of 5-9 $cmH_2O$ vs a strategy that maximized PEEP while maintaining a plateau pressure between 28-30 $cmH_2O$[4]. There was no difference in mortality or hospital discharge[4]. The LOVS trial randomized patients to a strategy of lower PEEP while maintaining plateau pressures under 30 $cmH_2O$ versus an open lung strategy involving recruitment maneuvers and high PEEP while maintaining plateau pressures under 40 $cmH_2O$[5]. Again, no difference in mortality or duration of mechanical ventilation was demonstrated[5].

Many other methods of PEEP titration have been described, however these have not been rigorously tested through RCTs or been studied in terms of their impact on clinical outcomes[6]. Clinical practice guidelines regarding ventilator management in ARDS suggest higher PEEP may be beneficial in patients with moderate-to-severe ARDS but acknowledge the optimal method for PEEP titration is not yet clear[7].

Although many studies have used oxygenation as the primary physiological target when titrating PEEP, other studies have proposed additional targets such as compliance[8], driving pressure[9], and transpulmonary pressure[10]. Furthermore, a range of techniques are described to achieve these targets, such as the use of esophageal balloons[10], stress index[11], or pressure-volume curves[12]. Lastly, the largest studies examining PEEP were conducted in ARDS patients, but the external validity to other populations, such as those with normal lungs or acute hypoxemic respiratory failure without ARDS remains unclear. Previous systematic reviews have focused only on RCTs, thus excluding many studies examining alternative PEEP titration methods and physiological titration targets[13-17]. The use of alternative PEEP titration methods in broader non-ARDS patient populations has not been well synthesized by previous systematic or scoping reviews.

Scoping reviews are a form of knowledge synthesis that systematically search, select, and synthesize knowledge around a research question that aims to map key concepts, types of evidence, and identify gaps in the literature[18]. The aims of this study are to use scoping review methodology to describe the methods of PEEP titration that have previously been studied, describe the patient populations they have been studied in, characterize the various clinical outcomes and endpoints used, as well as describe the different study designs utilized. The results of the review will identify knowledge gaps for future research in this area. For example, it will serve to identify the methods

that are currently well studied as well as other methods that show promise but are lacking in high quality evidence such as randomized trials. It may also be used to inform policy and procedures within individual sites and could be used as a resource in the development of clinical practice guidelines.

## Methods and analysis

### Conceptual model

This scoping review was registered using Open Science Framework (https://osf.io/atzqc). Although no Enhancing the Quality and Transparency of Health Research (EQUATOR) guidance on scoping review protocols exists, this protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement and checklist[19] where applicable. The scoping review itself will be prepared in accordance with the framework initially proposed by Arksey and O'Malley[20] with updates from Levac[21] and most recently updated by the Joanna Briggs Institute[22]. The findings of our research will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Scoping Review (PRISMA-ScR) statement and checklist[23].

### Identifying the research question

In identifying a research question for the scoping review, we followed the recommended Population, Concept, Context (PCC) framework[22].

a) The population of interest involves adults (18 years of age or older) undergoing invasive mechanical ventilation in hospital. Patients with ARDS, acute hypoxemic respiratory failure, and

those receiving invasive mechanical ventilation for non-pulmonary indications such as during surgery will be included.

b) The primary concept is to describe strategies used in setting or titration of PEEP on the ventilator and the clinical and physiological outcomes associated with these different strategies. Some examples of PEEP titration strategies include (but are not limited to): Using PEEP tables (high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure, pressure-volume curves and inflection points, esophageal balloons to measure transpulmonary pressure, or various imaging modalities (CT or ultrasound or electrical impedance tomography). The outcomes associated with the above-mentioned strategies will be broad and could include clinical outcomes such as mortality, ICU length of stay, or duration of mechanical ventilation. Other outcomes may relate to respiratory mechanics and physiology, including fraction of inspired oxygen (FiO2), dead space, compliance, or oxygenation.

c) The context will include those patients receiving planned or unplanned invasive mechanical ventilation in the ICU, operating theater, or the emergency department. It will not be limited based on duration of ventilation, geography, culture, or gender.

Based on the above considerations, this scoping review will seek to answer the following question: *In hospitalized adults undergoing invasive mechanical ventilation, what are the strategies for determining optimal positive end-expiratory pressure that currently exist in the literature. For these strategies, what patient populations along with clinical and physiological outcomes have been studied, and what study designs have been used to examine their efficacy and/or effectiveness?*

The inclusion and exclusion criteria and creation of a search strategy were conducted as previously described for scoping reviews[22]. The development of the criteria was based on the PCC framework and can be seen in Table 1.

| | Inclusion | Exclusion |
|---|---|---|
| Population | • Adults undergoing invasive mechanical ventilation in hospital<br>• Any setting in hospital including intensive care unit, operating room, emergency department) | • Pediatric and neonatal population<br>• Non-invasive ventilation<br>• Single lung ventilation<br>• Home ventilation<br>• Animal studies |
| Concept | • Study evaluates a method of setting optimal PEEP<br>• Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method | • Studies that arbitrarily set PEEP at a certain value |
| Context | • Any geographic location | • None |
| Types of Evidence | • Primary research studies (including randomized controlled trials, cohort studies, cross-sectional studies, case series)<br>• Published abstracts will be included | • Review articles<br>• Systematic reviews/meta-analyses<br>• Case reports<br>• Editorial articles<br>• Articles for which we cannot obtain full text, or an English translation is not obtainable |

Table 1 – Inclusion and exclusion criteria, developed based on the Population, Concept, Context framework

Identifying relevant studies

Based on the inclusion and exclusion criteria, literature search strategies were developed by an expert librarian (HLR) for MEDLINE, EMBASE, CENTRAL, Web of Science, and Scopus. The search strategy draft for MEDLINE can be seen in Supplemental Material. The search strategy was peer-reviewed by another librarian (ZAP) using the Peer Review of Electronic Search Strategies (PRESS) guideline statement[24]. The search results in the different databases will be exported to Endnote 20 and the screening process will be completed using the systematic review software Rayyan.

Study selection

The workflow for study selection will be presented in a PRISMA flow diagram as well as in narrative form. All titles and abstracts will be screened by at least two reviewers (between KP, SE, and TK). Prior to completing screening of all titles, we will review 100 random selections to assess inter-rater reliability and if there is a discrepancy, we will further clarify inclusion and exclusion criteria. After title and abstract and screening is complete, disagreements will be resolved via discussion between the three reviewers. After title and abstract screening is completed, the full text of all included manuscripts will be reviewed independently by two reviewers (KP and SE) to confirm eligibility. At this stage, the reason for exclusion will be recorded in the PRISMA diagram. In addition to identifying articles through the search strategy, reference lists of included papers will be reviewed to identify any other manuscripts that were not captured with the initial search. For any studies for which the full manuscript is not accessible, an email will be sent to the corresponding author requesting a copy of the manuscript. Manuscripts of another language will be translated to English using Google Translate whenever possible[25].

Data extraction

Once included manuscripts are identified, relevant study data will be abstracted using a standardized form. This form aims to collect all relevant variables of interest and was developed over several iterations with input from all members of the team. It is based on a template suggested by the Joanna Briggs Institute[26]. The key variables that will be extracted are summarized in Table 2. Two reviewers (SE and KP) will independently extract data from five to ten studies to assess consistency and to pilot test whether the form needs to be adjusted to capture all the relevant data. Once data extraction has started, iterative refinement of the data abstraction form may be made to tailor to the data abstracted. Abstracted data will be collated in a Microsoft Excel spreadsheet.

| Domain | Categories |
|---|---|
| Study identifiers | First author, journal, year of publication, country of publication, publication type |
| Study design | Study type or design, multicenter vs single center, country/countries of participants, funding source |
| Participants | Number of participants, patient population, underlying disease severity, study setting |
| Results | Method (s) of selecting PEEP, comparator, tidal volumes within experimental and control groups |
| Outcomes | Clinical outcomes could include mortality, length of stay, ventilation outcomes or others. Respiratory or physiologic outcomes could include P/F ratio, oxygenation, compliance, plateau pressure, driving pressure, or others. |

Table 2 – Data to be abstracted from eligible studies included in the scoping review

Presentation of results

Extracted data will be reported by using several different data displays. All included studies will be aggregated in a table summarizing key study characteristics. This will include the setting, the study design, country of origin, time period, patient population, and the method of PEEP selection, and the outcomes measured.

Based on the number of studies within each setting and method of selection, we will stratify the data for those with adequate number of studies. Data will be presented in terms of setting, patient population and number of participants, study design (with focus on RCTs), outcomes (with focus on clinical outcomes), trend over time in publishing, countries involved and most common publishing journals. A table will also describe all RCTs in detail.

The methods for titrating PEEP will be presented in a table that describes how they were performed, as well as benefits and limitations of each method. In addition, methods that have insufficient numbers of studies to inform clinical practice will be discussed. Current gaps in the literature, and opportunities for future research will be highlighted.

## Ethics and Dissemination

As this study will identify and review previously published literature, no research ethics board approval is required.

### Patient and Public Involvement

This work describes existing research studies, and thus involves no patients or members of the public.

### Implications

Given the rapidly growing body of evidence concerning methods of determining optimal PEEP, there is a need to rigorously map the literature. This will be accomplished with this scoping review. The results will be presented at local (departmental grand rounds), regional (Alberta Society of Intensive Care Medicine meeting) and national critical care conferences (Critical Care Canada Annual Forum) and will be submitted for publication in a peer reviewed critical care journal. It is anticipated the study may identify certain methods of setting PEEP that have been studied extensively and warrant further synthesis with systematic review and meta-analysis. It will also serve to identify methods with potential benefit but where high-quality randomized trials have not been conducted. This will guide future primary research studies. Clinicians will be able to use this synthesis of studies to inform the development and implementation of an optimal PEEP protocol within their hospital or region. The outputs will be relevant to many stakeholders within the healthcare system, including bedside clinicians (including physicians, nurses, and respiratory therapists), managers and team leads (who may be developing ventilator protocols and policies) as

well as researchers and policy makers in the field who are responsible for development of clinical practice guidelines.

## Authors' contributions

All authors contributed to study design. SE and KP drafted the protocol. All authors read, edited, and approved the final protocol. KP is the guarantor of the protocol.

## Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Competing interests statement

None declared.

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## Supplemental Material

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Sean M. Bagshaw MD MSc[5]
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MEDLINE (3682 results)

| # | Query | Results from 4 Dec 2021 |
|---|---|---|
| 1 | end-expiratory pressure*.tw,kf,sh. | 6,843 |
| 2 | (positive adj5 expiratory pressure*).tw,kf,sh. | 6,868 |
| 3 | (positive adj2 endexpiratory pressure*).tw,kf,sh. | 46 |
| 4 | PEEP*.tw,kf. | 6,361 |
| 5 | (open lung adj3 (ventilat* or strateg* or approach*)).tw,kf. | 252 |
| 6 | or/1-5 | 9,963 |
| 7 | Respiratory Mechanics/ | 14,505 |
| 8 | ((high* or low* or optim* or individual* or increment* or decrement*) adj5 (strateg* or applic* or approach* or level* or trial* or titrat*)).tw,kf. | 1,520,428 |
| 9 | ((curve or curves or pressure or pressures) adj5 (driv* or stress* or PEEP* or oxygenat* or esophag*)).tw,kf,sh. | 33,868 |
| 10 | ((oxygenation or ventilation) adj3 (index or indexes or indices)).tw,kf. | 3,136 |
| 11 | ventilatory parameter*.tw,kf. | 957 |
| 12 | ((high* or low* or optim* or individual* or increment* or decrement* or restricted or liberal or algorithm* or level or levels or chang*) adj3 (PEEP* or positive end expiratory pressure* or positive endexpiratory pressure*)).tw,kf. | 3,075 |
| 13 | or/7-12 | 1,568,238 |
| 14 | exp Respiration, Artificial/ or Ventilators, Mechanical/ | 90,036 |
| 15 | ((artificial* or mechanical*) adj3 (ventilat* or respirat*)).tw,kf. | 69,839 |
| 16 | Intubation, Intratracheal/ | 38,052 |
| 17 | (IMV or intubat*).tw,kf. | 63,761 |
| 18 | or/14-17 | 191,843 |
| 19 | 6 and 13 and 18 | 5,505 |
| 20 | exp Child/ not (exp Adult/ and exp Child/) | 1,297,508 |
| 21 | exp Infant/ not (exp Adult/ and exp Infant/) | 876,186 |
| 22 | exp Animals/ not (exp Animals/ and Humans/) | 4,924,219 |
| 23 | or/20-22 | 6,702,675 |
| 24 | 19 not 23 | 3,682 |

## Supplemental Material #1 – Search Strategy for MEDLINE developed with medical librarian

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in: Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | X | ☐ | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | ☐ | N/A |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | X | ☐ | 69 |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | X | ☐ | 29 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | X | ☐ | 261 |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | ☐ | ☐ | N/A |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | X | ☐ | 265 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | X | ☐ | 265 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | X | ☐ | 265 |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | X | ☐ | 97 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | X | ☐ | 138 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | X | ☐ | Table 1 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | X | ☐ | 195 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | X | ☐ | Figure 1 |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | X | ☐ | 203 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | X | ☐ | 204 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | X | ☐ | 217 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | X | ☐ | Figure 2 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | X | ☐ | Figure 2 |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ☐ | ☐ | N/A |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | ☐ | ☐ | N/A |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall's tau) | ☐ | ☐ | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | ☐ | ☐ | N/A |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | X | ☐ | 227 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☐ | X | N/A |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | ☐ | N/A |

BMJ Open

# Methods for Determination of Optimal Positive End-Expiratory Pressure: a protocol for a scoping review

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| Primary Subject Heading: | Intensive care |
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| Keywords: | INTENSIVE & CRITICAL CARE, Adult anaesthesia < ANAESTHETICS, CLINICAL PHYSIOLOGY, EPIDEMIOLOGY |
| | |

# Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a scoping review

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**Keywords**

Mechanical ventilation, positive end-expiratory pressure, scoping review, acute respiratory distress syndrome, acute hypoxemic respiratory failure

## Abstract

Introduction: Titrated application of positive end expiratory pressure (PEEP) is an important part of any mechanical ventilation strategy. However, the method by which the optimal PEEP is determined and titrated varies widely. Methods for determining optimal PEEP have been assessed using a variety of different study designs and patient populations. We will conduct a scoping review to systematically identify all methods for determining optimal PEEP, and to identify the patient populations, outcomes measured, and study designs utilized for each method. The goal will be to identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to further systematically synthesize and meta-analyze existing literature.

Methods and analysis: Using scoping review methodology, we will generate a comprehensive search strategy based on inclusion and exclusion criteria generated using the Population, Concept, Context framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of Science, and Scopus). Three investigators will independently screen titles and abstracts, and two investigators will independently complete full text review and data extraction. Included citations will be categorized in terms of PEEP method, study design, patient population, and outcomes measured. The methods for PEEP titration will be described in detail, including strengths and limitations.

Ethics and dissemination: Given this is a synthesis of existing literature, ethics approval is not required. The results will be disseminated to stakeholders via presentation at local, regional, and national levels, as well as publication in a high impact critical care journal. There is also the potential to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by societies.

Registration details: Scoping review protocol registered with Open Science Framework (https://osf.io/atzqc)

**Strengths and limitations of this study (5 max)**

- This study will rigorously describe studies testing methods of determining optimal PEEP. Each method will be summarized with a description, its strengths, and limitations.
- Inclusion of many different study designs, not just randomized control trials will allow for identification of methods that are well studied or those that could be better studied.
- A potential limitation is that given the broad nature of the review, there will be a large volume of studies to synthesize, and this may be challenging to summarize in one review.

## Introduction

Titrated application of positive end-expiratory pressure (PEEP) during mechanical ventilation is a crucial part of any ventilatory strategy. PEEP can be beneficial in several ways. PEEP increases mean airway pressure which can improve oxygenation by recruiting collapsed alveoli and reducing intrapulmonary shunt[1]. PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimizing atelectrauma[2]. However, excessive PEEP can also have detrimental impacts through its effects on the respiratory and cardiac systems. Overdistension of the lungs from high PEEP can lead to VILI via barotrauma[2]. Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output[2]. Several methods exist to determine the best or optimal PEEP to apply during mechanical ventilation, but significant variability exists in terms of which methods are used by clinicians.

Several large randomized-controlled trials (RCTs) have assessed different methods for selecting the best PEEP in patients with acute respiratory distress syndrome (ARDS). The ALVEOLI study randomized patients with ARDS to either low or high PEEP methods based on pre-specified tables that titrated PEEP higher as the fraction of inspired oxygen ($FiO_2$) increased[3]. The investigators found no differences in terms of mortality or discharge home without ventilatory support[3]. The EXPRESS trial randomized patients with ARDS to a low PEEP method of 5-9 $cmH_2O$ vs a method that maximized PEEP while maintaining a plateau pressure between 28-30 $cmH_2O$[4]. There was no difference in mortality or hospital discharge[4]. The LOVS trial randomized patients to a method of lower PEEP while maintaining plateau pressures under 30 $cmH_2O$ versus an open lung method involving recruitment maneuvers and high PEEP while maintaining plateau pressures under 40 $cmH_2O$[5]. Again, no difference in mortality or duration of mechanical ventilation was demonstrated[5].

Many other methods of PEEP titration have been described, however these have not been rigorously tested through RCTs or been studied in terms of their impact on clinical outcomes[6]. Clinical practice guidelines regarding ventilator management in ARDS suggest higher PEEP may be beneficial in patients with moderate-to-severe ARDS but acknowledge the optimal method for PEEP titration is not yet clear[7].

Although many studies have used oxygenation as the primary physiological target when titrating PEEP, other studies have proposed additional targets such as compliance[8], driving pressure[9], and transpulmonary pressure[10]. Furthermore, a range of techniques are described to achieve these targets, such as the use of esophageal balloons[10], stress index[11], or pressure-volume curves[12]. Lastly, the largest studies examining PEEP were conducted in ARDS patients, but the external validity to other populations, such as those with normal lungs or acute hypoxemic respiratory failure without ARDS remains unclear. Previous systematic reviews have focused only on RCTs, thus excluding many studies examining alternative PEEP titration methods and physiological titration targets[13-17]. To date, there has not been a comprehensive review that has synthesized all known PEEP titration methods, regardless of patient population or study design.

Scoping reviews are a form of knowledge synthesis that systematically search, select, and synthesize knowledge around a research question that aims to describe key concepts, types of evidence, and identify gaps in the literature[18]. The aims of this study are to use scoping review methodology to describe the methods of PEEP titration that have previously been studied, describe the patient populations they have been studied in, characterize the various clinical outcomes and endpoints used, as well as describe the different study designs utilized. The results of the review will identify knowledge gaps for future research in this area. For example, it will serve to identify the methods

that are currently well studied as well as other methods that show promise but are lacking in high quality evidence such as randomized trials. Furthermore, this review could serve as the foundation for future point prevalence studies or surveys that aim to map real world utilization of various methods. It may also be used to inform policy and procedures within individual sites and could be used as a resource in the development of clinical practice guidelines.

## Methods and analysis

### Conceptual model

This scoping review was registered using Open Science Framework (https://osf.io/atzqc). Although no Enhancing the Quality and Transparency of Health Research (EQUATOR) guidance on scoping review protocols exists, this protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement and checklist[19] where applicable. The scoping review itself will be prepared in accordance with the framework initially proposed by Arksey and O'Malley[20] with updates from Levac[21] and most recently updated by the Joanna Briggs Institute[22]. The findings of our research will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Scoping Review (PRISMA-ScR) statement and checklist[23].

### Identifying the research question

In identifying a research question for the scoping review, we followed the recommended Population, Concept, Context (PCC) framework[22].

a) The population of interest involves adults (18 years of age or older) undergoing invasive mechanical ventilation in hospital. Patients with ARDS, acute hypoxemic respiratory failure, and those receiving invasive mechanical ventilation for non-pulmonary indications such as during surgery will be included.

b) The primary concept is to describe methods used in setting or titration of PEEP on the ventilator and the clinical and physiological outcomes associated with these different methods. Some examples of PEEP titration methods include (but are not limited to): Using PEEP tables (high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure, pressure-volume curves and inflection points, esophageal balloons to measure transpulmonary pressure, or various imaging modalities (CT or ultrasound or electrical impedance tomography). The outcomes associated with the above-mentioned methods will be broad and could include clinical outcomes such as mortality, ICU length of stay, or duration of mechanical ventilation. Other outcomes may relate to respiratory mechanics and physiology, including fraction of inspired oxygen (FiO2), dead space, compliance, or oxygenation.

c) The context will include those patients receiving planned or unplanned invasive mechanical ventilation in the ICU, operating theater, or the emergency department. It will not be limited based on duration of ventilation, geography, culture, or gender.

Based on the above considerations, this scoping review will seek to answer the following question: *In hospitalized adults undergoing invasive mechanical ventilation, what are the methods for determining optimal positive end-expiratory pressure that currently exist in the literature. For these methods, what patient populations*

*along with clinical and physiological outcomes have been studied, and what study designs have been used to examine their efficacy and/or effectiveness?*

The inclusion and exclusion criteria and creation of a search strategy were conducted as previously described for scoping reviews[22]. The development of the criteria was based on the PCC framework and can be seen in Table 1.

| | Inclusion | Exclusion |
|---|---|---|
| Population | • Patients undergoing invasive mechanical ventilation in hospital<br>• Any setting in hospital including intensive care unit, operating room, emergency department) | • Pediatric and neonatal population<br>• Non-invasive ventilation<br>• Single lung ventilation<br>• Animal studies (with no human component) |
| Concept | • Study evaluates a method of setting optimal PEEP<br>• Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method | • Studies that arbitrarily set PEEP at a certain value (i.e. 5cm$H_2O$) |
| Context | • Any geographic location<br>• Any duration of ventilation | • None |
| Types of Evidence | • Primary research studies (including randomized controlled trials, cohort studies, cross-sectional studies, case series)<br>• Published abstracts will be included | • None |

Table 1 – Inclusion and exclusion criteria, developed based on the Population, Concept, Context framework

Identifying relevant studies

Based on the inclusion and exclusion criteria, literature search strategies were developed by an expert librarian (HLR) for MEDLINE, EMBASE, CENTRAL, Web of Science, and Scopus. Articles will be included from inception of databases up until the date of the search. The search strategy draft for MEDLINE can be seen in Supplemental Material. The search strategy was peer-reviewed by another

librarian (ZAP) using the Peer Review of Electronic Search Strategies (PRESS) guideline statement[24]. The search results in the different databases will be exported to Endnote 20 and the screening process will be completed using the systematic review software Rayyan. The initial database search will be conducted early May 2023 and may be updated as needed depending on the duration between initial search and completion of the project.

Study selection

The workflow for study selection will be presented in a PRISMA flow diagram as well as in narrative form. All titles and abstracts will be screened by at least two reviewers (between KP, SE, and TK). Prior to completing screening of all titles, we will review 100 random selections to assess inter-rater reliability and if there is a discrepancy, we will further clarify inclusion and exclusion criteria. After title and abstract and screening is complete, disagreements will be resolved via discussion between the three reviewers. After title and abstract screening is completed, the full text of all included manuscripts will be reviewed independently by two reviewers (KP and SE) to confirm eligibility. At this stage, the reason for exclusion will be recorded in the PRISMA diagram. In addition to identifying articles through the search strategy, reference lists of included papers will be reviewed to identify any other manuscripts that were not captured with the initial search. For any studies for which the full manuscript is not accessible, an email will be sent to the corresponding author requesting a copy of the manuscript. Manuscripts of another language will be translated to English using Google Translate whenever possible[25].

Data extraction

Once included manuscripts are identified, relevant study data will be abstracted using a standardized form. This form aims to collect all relevant variables of interest and was developed over several

iterations with input from all members of the team. It is based on a template suggested by the Joanna Briggs Institute[26]. The key variables that will be extracted are summarized in Table 2. Two reviewers (SE and KP) will independently extract data from five to ten studies to assess consistency and to pilot test whether the form needs to be adjusted to capture all the relevant data. Once data extraction has started, iterative refinement of the data abstraction form may be made to tailor to the data abstracted. Abstracted data will be collated in a Microsoft Excel spreadsheet.

| Domain | Categories |
|---|---|
| Study identifiers | First author, journal, year of publication, country of publication, publication type |
| Study design | Study type or design, multicenter vs single center, country/countries of participants, funding source |
| Participants | Number of participants, patient population, underlying disease severity, study setting |
| Results | Method (s) of selecting PEEP, comparator, tidal volumes within experimental and control groups |
| Outcomes | Clinical outcomes could include mortality, length of stay, ventilation outcomes or others. Respiratory or physiologic outcomes could include P/F ratio, oxygenation, compliance, plateau pressure, driving pressure, or others. |

Table 2 – Data to be abstracted from eligible studies included in the scoping review

Presentation of results

Extracted data will be reported by using several different data displays. All included studies will be aggregated in a table summarizing key study characteristics. This will include the setting, the study design, country of origin, time period, patient population, the method of PEEP selection, and the outcomes measured.

Based on the number of studies within each setting and method of selection, we will stratify the data for those with adequate number of studies. Data will be presented in terms of setting, patient population and number of participants, study design (with focus on RCTs), outcomes (with focus on

clinical outcomes), trend over time in publishing, countries involved and most common publishing journals. A table will also describe all RCTs in detail.

The methods for titrating PEEP will be presented in a table that describes how they were performed, as well as benefits and limitations of each method. In addition, methods that have insufficient numbers of studies to inform clinical practice will be discussed. Current gaps in the literature, and opportunities for future research will be highlighted.

**Ethics and Dissemination**

As this study will identify and review previously published literature, no research ethics board approval is required.

Patient and Public Involvement

This work describes existing research studies, and thus involves no patients or members of the public.

Implications

Given the rapidly growing body of evidence concerning methods of determining optimal PEEP, there is a need to rigorously map the literature. This will be accomplished with this scoping review. The results will be presented at local (departmental grand rounds), regional (Alberta Society of Intensive Care Medicine meeting) and national critical care conferences (Critical Care Canada Annual Forum) and will be submitted for publication in a peer reviewed critical care journal. It is anticipated the study may identify certain methods of setting PEEP that have been studied extensively and warrant further synthesis with systematic review and meta-analysis. The results of this review will need to be interpreted within the limitations of scoping review methodology. These

include lack of assessment of quality or risk of bias, and lack of quantitative meta-analysis of outcomes. It will also serve to identify methods with potential benefit but where high-quality randomized trials have not been conducted. This will guide future primary research studies. Clinicians will be able to use this synthesis of studies to inform the development and implementation of an optimal PEEP protocol within their hospital or region. The outputs will be relevant to many stakeholders within the healthcare system, including bedside clinicians (including physicians, nurses, and respiratory therapists), managers and team leads (who may be developing ventilator protocols and policies) as well as researchers and policy makers in the field who are responsible for development of clinical practice guidelines.

**Authors' contributions**

All authors (SE, NK, HS, LB, DZ, JG, KS, HLR, KF, DN, SB, KP) contributed to conception, study design and planning. SE and KP drafted the protocol. All authors (SE, NK, HS, LB, DZ, JG, KS, HLR, KF, DN, SB, KP) read, edited, and approved the final protocol. KP is the guarantor of the protocol.

**Funding statement**

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**Competing interests statement**

None declared.

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# Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a scoping review

## Supplemental Material

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Kirsten M. Fiest PhD[1]
Daniel J Niven MD PhD[1]
Sean M. Bagshaw MD MSc[5]
Ken Kuljit Singh Parhar MD MSc[1,2,6]

MEDLINE (3682 results)

| # | Query | Results from 4 Dec 2021 |
|---|---|---|
| 1 | end-expiratory pressure*.tw,kf,sh. | 6,843 |
| 2 | (positive adj5 expiratory pressure*).tw,kf,sh. | 6,868 |
| 3 | (positive adj2 endexpiratory pressure*).tw,kf,sh. | 46 |
| 4 | PEEP*.tw,kf. | 6,361 |
| 5 | (open lung adj3 (ventilat* or strateg* or approach*)).tw,kf. | 252 |
| 6 | or/1-5 | 9,963 |
| 7 | Respiratory Mechanics/ | 14,505 |
| 8 | ((high* or low* or optim* or individual* or increment* or decrement*) adj5 (strateg* or applic* or approach* or level* or trial* or titrat*)).tw,kf. | 1,520,428 |
| 9 | ((curve or curves or pressure or pressures) adj5 (driv* or stress* or PEEP* or oxygenat* or esophag*)).tw,kf,sh. | 33,868 |
| 10 | ((oxygenation or ventilation) adj3 (index or indexes or indices)).tw,kf. | 3,136 |
| 11 | ventilatory parameter*.tw,kf. | 957 |
| 12 | ((high* or low* or optim* or individual* or increment* or decrement* or restricted or liberal or algorithm* or level or levels or chang*) adj3 (PEEP* or positive end expiratory pressure* or positive endexpiratory pressure*)).tw,kf. | 3,075 |
| 13 | or/7-12 | 1,568,238 |
| 14 | exp Respiration, Artificial/ or Ventilators, Mechanical/ | 90,036 |
| 15 | ((artificial* or mechanical*) adj3 (ventilat* or respirat*)).tw,kf. | 69,839 |
| 16 | Intubation, Intratracheal/ | 38,052 |
| 17 | (IMV or intubat*).tw,kf. | 63,761 |
| 18 | or/14-17 | 191,843 |
| 19 | 6 and 13 and 18 | 5,505 |
| 20 | exp Child/ not (exp Adult/ and exp Child/) | 1,297,508 |
| 21 | exp Infant/ not (exp Adult/ and exp Infant/) | 876,186 |
| 22 | exp Animals/ not (exp Animals/ and Humans/) | 4,924,219 |
| 23 | or/20-22 | 6,702,675 |
| 24 | 19 not 23 | 3,682 |

**Supplemental Material #1 – Search Strategy for MEDLINE developed with medical librarian**

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in: Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | X | ☐ | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | ☐ | N/A |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | X | ☐ | 69 |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | X | ☐ | 29 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | X | ☐ | 261 |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | ☐ | ☐ | N/A |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | X | ☐ | 265 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | X | ☐ | 265 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | X | ☐ | 265 |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | X | ☐ | 97 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | X | ☐ | 138 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | X | ☐ | Table 1 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | X | ☐ | 195 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | X | ☐ | Figure 1 |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | X | ☐ | 203 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | X | ☐ | 204 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | X | ☐ | 217 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | X | ☐ | Figure 2 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | X | ☐ | Figure 2 |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ☐ | ☐ | N/A |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | ☐ | ☐ | N/A |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall's tau) | ☐ | ☐ | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | ☐ | ☐ | N/A |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | X | ☐ | 227 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☐ | X | N/A |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | ☐ | N/A |

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# Methods for Determination of Optimal Positive End-Expiratory Pressure: a protocol for a scoping review

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# Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a scoping review

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Mechanical ventilation, positive end-expiratory pressure, scoping review, acute respiratory distress syndrome, acute hypoxemic respiratory failure

## Abstract

Introduction: Titrated application of positive end expiratory pressure (PEEP) is an important part of any mechanical ventilation strategy. However, the method by which the optimal PEEP is determined and titrated varies widely. Methods for determining optimal PEEP have been assessed using a variety of different study designs and patient populations. We will conduct a scoping review to systematically identify all methods for determining optimal PEEP, and to identify the patient populations, outcomes measured, and study designs utilized for each method. The goal will be to identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to further systematically synthesize and meta-analyze existing literature.

Methods and analysis: Using scoping review methodology, we will generate a comprehensive search strategy based on inclusion and exclusion criteria generated using the Population, Concept, Context framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of Science, and Scopus). Three investigators will independently screen titles and abstracts, and two investigators will independently complete full text review and data extraction. Included citations will be categorized in terms of PEEP method, study design, patient population, and outcomes measured. The methods for PEEP titration will be described in detail, including strengths and limitations.

Ethics and dissemination: Given this is a synthesis of existing literature, ethics approval is not required. The results will be disseminated to stakeholders via presentation at local, regional, and national levels, as well as publication in a high impact critical care journal. There is also the potential to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by societies.

Registration details: Scoping review protocol registered with Open Science Framework (https://osf.io/atzqc)

**Strengths and limitations of this study (5 max)**

- This study will rigorously describe studies testing methods of determining optimal PEEP. Each method will be summarized with a description, its strengths, and limitations.
- Inclusion of many different study designs, not just randomized control trials will allow for identification of methods that are well studied or those that could be better studied.
- A potential limitation is that given the broad nature of the review, there will be a large volume of studies to synthesize, and this may be challenging to summarize in one review.

## Introduction

Titrated application of positive end-expiratory pressure (PEEP) during mechanical ventilation is a crucial part of any ventilatory strategy. PEEP can be beneficial in several ways. PEEP increases mean airway pressure which can improve oxygenation by recruiting collapsed alveoli and reducing intrapulmonary shunt[1]. PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimizing atelectrauma[2]. However, excessive PEEP can also have detrimental impacts through its effects on the respiratory and cardiac systems. Overdistension of the lungs from high PEEP can lead to VILI via barotrauma[2]. Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output[2]. Several methods exist to determine the best or optimal PEEP to apply during mechanical ventilation, but significant variability exists in terms of which methods are used by clinicians.

Several large randomized-controlled trials (RCTs) have assessed different methods for selecting the best PEEP in patients with acute respiratory distress syndrome (ARDS). The ALVEOLI study randomized patients with ARDS to either low or high PEEP methods based on pre-specified tables that titrated PEEP higher as the fraction of inspired oxygen ($FiO_2$) increased[3]. The investigators found no differences in terms of mortality or discharge home without ventilatory support[3]. The EXPRESS trial randomized patients with ARDS to a low PEEP method of 5-9 $cmH_2O$ vs a method that maximized PEEP while maintaining a plateau pressure between 28-30 $cmH_2O$[4]. There was no difference in mortality or hospital discharge[4]. The LOVS trial randomized patients to a method of lower PEEP while maintaining plateau pressures under 30 $cmH_2O$ versus an open lung method involving recruitment maneuvers and high PEEP while maintaining plateau pressures under 40 $cmH_2O$[5]. Again, no difference in mortality or duration of mechanical ventilation was demonstrated[5].

Many other methods of PEEP titration have been described, however these have not been rigorously tested through RCTs or been studied in terms of their impact on clinical outcomes[6]. Clinical practice guidelines regarding ventilator management in ARDS suggest higher PEEP may be beneficial in patients with moderate-to-severe ARDS but acknowledge the optimal method for PEEP titration is not yet clear[7].

Although many studies have used oxygenation as the primary physiological target when titrating PEEP, other studies have proposed additional targets such as compliance[8], driving pressure[9], and transpulmonary pressure[10]. Furthermore, a range of techniques are described to achieve these targets, such as the use of esophageal balloons[10], stress index[11], or pressure-volume curves[12]. Lastly, the largest studies examining PEEP were conducted in ARDS patients, but the external validity to other populations, such as those with normal lungs or acute hypoxemic respiratory failure without ARDS remains unclear. Previous systematic reviews have focused only on RCTs, thus excluding many studies examining alternative PEEP titration methods and physiological titration targets[13-17]. To date, there has not been a comprehensive review that has synthesized all known PEEP titration methods, regardless of patient population or study design.

Scoping reviews are a form of knowledge synthesis that systematically search, select, and synthesize knowledge around a research question that aims to describe key concepts, types of evidence, and identify gaps in the literature[18]. The aims of this study are to use scoping review methodology to describe the methods of PEEP titration that have previously been studied, describe the patient populations they have been studied in, characterize the various clinical outcomes and endpoints used, as well as describe the different study designs utilized. The results of the review will identify knowledge gaps for future research in this area. For example, it will serve to identify the methods

that are currently well studied as well as other methods that show promise but are lacking in high quality evidence such as randomized trials. Furthermore, this review could serve as the foundation for future point prevalence studies or surveys that aim to map real world utilization of various methods. It may also be used to inform policy and procedures within individual sites and could be used as a resource in the development of clinical practice guidelines.

## Methods and analysis

### Conceptual model

This scoping review was registered using Open Science Framework (https://osf.io/atzqc). Although no Enhancing the Quality and Transparency of Health Research (EQUATOR) guidance on scoping review protocols exists, this protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement and checklist[19] where applicable. The scoping review itself will be prepared in accordance with the framework initially proposed by Arksey and O'Malley[20] with updates from Levac[21] and most recently updated by the Joanna Briggs Institute[22]. The findings of our research will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Scoping Review (PRISMA-ScR) statement and checklist[23].

### Patient and Public Involvement

This work describes existing research studies, and thus involves no patients or members of the public.

Identifying the research question

In identifying a research question for the scoping review, we followed the recommended Population, Concept, Context (PCC) framework[22].

a) The population of interest involves adults (18 years of age or older) undergoing invasive mechanical ventilation in hospital. Patients with ARDS, acute hypoxemic respiratory failure, and those receiving invasive mechanical ventilation for non-pulmonary indications such as during surgery will be included.

b) The primary concept is to describe methods used in setting or titration of PEEP on the ventilator and the clinical and physiological outcomes associated with these different methods. Some examples of PEEP titration methods include (but are not limited to): Using PEEP tables (high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure, pressure-volume curves and inflection points, esophageal balloons to measure transpulmonary pressure, or various imaging modalities (CT or ultrasound or electrical impedance tomography). The outcomes associated with the above-mentioned methods will be broad and could include clinical outcomes such as mortality, ICU length of stay, or duration of mechanical ventilation. Other outcomes may relate to respiratory mechanics and physiology, including fraction of inspired oxygen (FiO2), dead space, compliance, or oxygenation.

c) The context will include those patients receiving planned or unplanned invasive mechanical ventilation in the ICU, operating theater, or the emergency department. It will not be limited based on duration of ventilation, geography, culture, or gender.

Based on the above considerations, this scoping review will seek to answer the following question: *In hospitalized adults undergoing invasive mechanical ventilation, what are the methods for determining optimal positive end-expiratory pressure that currently exist in the literature. For these methods, what patient populations along with clinical and physiological outcomes have been studied, and what study designs have been used to examine their efficacy and/or effectiveness?*

The inclusion and exclusion criteria and creation of a search strategy were conducted as previously described for scoping reviews[22]. The development of the criteria was based on the PCC framework and can be seen in Table 1.

| | Inclusion | Exclusion |
|---|---|---|
| Population | • Patients undergoing invasive mechanical ventilation in hospital<br>• Any setting in hospital including intensive care unit, operating room, emergency department) | • Pediatric and neonatal population<br>• Non-invasive ventilation<br>• Single lung ventilation<br>• Animal studies (with no human component) |
| Concept | • Study evaluates a method of setting optimal PEEP<br>• Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method | • Studies that arbitrarily set PEEP at a certain value (i.e. 5cm$H_2O$) |
| Context | • Any geographic location<br>• Any duration of ventilation | • None |
| Types of Evidence | • Primary research studies (including randomized controlled trials, cohort studies, cross-sectional studies, case series)<br>• Published abstracts will be included | • None |

Table 1 – Inclusion and exclusion criteria, developed based on the Population, Concept, Context framework

Identifying relevant studies

Based on the inclusion and exclusion criteria, literature search strategies were developed by an expert librarian (HLR) for MEDLINE, EMBASE, CENTRAL, Web of Science, and Scopus. Articles will be included from inception of databases up until the date of the search. The search strategy draft for all databases can be seen in Supplemental Material (Table S1-S5). The search strategy was peer-reviewed by another librarian (ZAP) using the Peer Review of Electronic Search Strategies (PRESS) guideline statement[24]. The search results in the different databases will be exported to Endnote 20 and the screening process will be completed using the systematic review software Rayyan. The initial database search will be conducted early May 2023 and may be updated as needed depending on the duration between initial search and completion of the project.

Study selection

The workflow for study selection will be presented in a PRISMA flow diagram as well as in narrative form. All titles and abstracts will be screened by at least two reviewers (between KP, SE, and TK). Prior to completing screening of all titles, we will review 100 random selections to assess inter-rater reliability and if there is a discrepancy, we will further clarify inclusion and exclusion criteria. After title and abstract and screening is complete, disagreements will be resolved via discussion between the three reviewers. After title and abstract screening is completed, the full text of all included manuscripts will be reviewed independently by two reviewers (KP and SE) to confirm eligibility. At this stage, the reason for exclusion will be recorded in the PRISMA diagram. In addition to identifying articles through the search strategy, reference lists of included papers will be reviewed to identify any other manuscripts that were not captured with the initial search. For any studies for which the full manuscript is not accessible, an email will be sent to the corresponding author

requesting a copy of the manuscript. Manuscripts of another language will be translated to English using Google Translate whenever possible[25].

Data extraction

Once included manuscripts are identified, relevant study data will be abstracted using a standardized form. This form aims to collect all relevant variables of interest and was developed over several iterations with input from all members of the team. It is based on a template suggested by the Joanna Briggs Institute[26]. The key variables that will be extracted are summarized in Table 2. Two reviewers (SE and KP) will independently extract data from five to ten studies to assess consistency and to pilot test whether the form needs to be adjusted to capture all the relevant data. Once data extraction has started, iterative refinement of the data abstraction form may be made to tailor to the data abstracted. Abstracted data will be collated in a Microsoft Excel spreadsheet.

| Domain | Categories |
|---|---|
| Study identifiers | First author, journal, year of publication, country of publication, publication type |
| Study design | Study type or design, multicenter vs single center, country/countries of participants, funding source |
| Participants | Number of participants, patient population, underlying disease severity, study setting |
| Results | Method (s) of selecting PEEP, comparator, tidal volumes within experimental and control groups |
| Outcomes | Clinical outcomes could include mortality, length of stay, ventilation outcomes or others. Respiratory or physiologic outcomes could include P/F ratio, oxygenation, compliance, plateau pressure, driving pressure, or others. |

Table 2 – Data to be abstracted from eligible studies included in the scoping review

Presentation of results

Extracted data will be reported by using several different data displays. All included studies will be aggregated in a table summarizing key study characteristics. This will include the setting, the study design, country of origin, time period, patient population, the method of PEEP selection, and the outcomes measured.

Based on the number of studies within each setting and method of selection, we will stratify the data for those with adequate number of studies. Data will be presented in terms of setting, patient population and number of participants, study design (with focus on RCTs), outcomes (with focus on clinical outcomes), trend over time in publishing, countries involved and most common publishing journals. A table will also describe all RCTs in detail.

The methods for titrating PEEP will be presented in a table that describes how they were performed, as well as benefits and limitations of each method. In addition, methods that have insufficient numbers of studies to inform clinical practice will be discussed. Current gaps in the literature, and opportunities for future research will be highlighted.

## Ethics and Dissemination

As this study will identify and review previously published literature, no research ethics board approval is required.

Implications

Given the rapidly growing body of evidence concerning methods of determining optimal PEEP, there is a need to rigorously map the literature. This will be accomplished with this scoping review. The results will be presented at local (departmental grand rounds), regional (Alberta Society of Intensive Care Medicine meeting) and national critical care conferences (Critical Care Canada

Annual Forum) and will be submitted for publication in a peer reviewed critical care journal. It is anticipated the study may identify certain methods of setting PEEP that have been studied extensively and warrant further synthesis with systematic review and meta-analysis. The results of this review will need to be interpreted within the limitations of scoping review methodology. These include lack of assessment of quality or risk of bias, and lack of quantitative meta-analysis of outcomes. It will also serve to identify methods with potential benefit but where high-quality randomized trials have not been conducted. This will guide future primary research studies. Clinicians will be able to use this synthesis of studies to inform the development and implementation of an optimal PEEP protocol within their hospital or region. The outputs will be relevant to many stakeholders within the healthcare system, including bedside clinicians (including physicians, nurses, and respiratory therapists), managers and team leads (who may be developing ventilator protocols and policies) as well as researchers and policy makers in the field who are responsible for development of clinical practice guidelines.

**Authors' contributions**

All authors (SE, NK, HS, LB, DZ, JG, KS, HLR, KF, DN, SB, KP) contributed to conception, study design and planning. SE and KP drafted the protocol. All authors (SE, NK, HS, LB, DZ, JG, KS, HLR, KF, DN, SB, KP) read, edited, and approved the final protocol. KP is the guarantor of the protocol.

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**Competing interests statement**

None declared.

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# Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a scoping review

## Supplemental Material

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## Supplemental Table #1 – Search Strategy for MEDLINE

| # | Query |
|---|---|
| 1 | end-expiratory pressure*.tw,kf,sh. |
| 2 | (positive adj5 expiratory pressure*).tw,kf,sh. |
| 3 | (positive adj2 endexpiratory pressure*).tw,kf,sh. |
| 4 | PEEP*.tw,kf. |
| 5 | (open lung adj3 (ventilat* or strateg* or approach*)).tw,kf. |
| 6 | or/1-5 |
| 7 | Respiratory Mechanics/ |
| 8 | ((high* or low* or optim* or individual* or increment* or decrement*) adj5 (strateg* or applic* or approach* or level* or trial* or titrat*)).tw,kf. |
| 9 | ((curve or curves or pressure or pressures) adj5 (driv* or stress* or PEEP* or oxygenat* or esophag*)).tw,kf,sh. |
| 10 | ((oxygenation or ventilation) adj3 (index or indexes or indices)).tw,kf. |
| 11 | ventilatory parameter*.tw,kf. |
| 12 | ((high* or low* or optim* or individual* or increment* or decrement* or restricted or liberal or algorithm* or level or levels or chang*) adj3 (PEEP* or positive end expiratory pressure* or positive endexpiratory pressure*)).tw,kf. |
| 13 | or/7-12 |
| 14 | exp Respiration, Artificial/ or Ventilators, Mechanical/ |
| 15 | ((artificial* or mechanical*) adj3 (ventilat* or respirat*)).tw,kf. |
| 16 | Intubation, Intratracheal/ |
| 17 | (IMV or intubat*).tw,kf. |
| 18 | or/14-17 |
| 19 | 6 and 13 and 18 |
| 20 | exp Child/ not (exp Adult/ and exp Child/) |
| 21 | exp Infant/ not (exp Adult/ and exp Infant/) |
| 22 | exp Animals/ not (exp Animals/ and Humans/) |
| 23 | or/20-22 |
| 24 | 19 not 23 |

## Supplemental Table #2 – Search Strategy for EMBASE

| # | Query |
|---|---|
| 1 | positive end expiratory pressure ventilation/ |
| 2 | end-expiratory pressure*.tw,kf. |
| 3 | (positive adj5 end expiratory pressure*).tw,kf. |
| 4 | (positive adj2 endexpiratory pressure*).tw,kf. |
| 5 | PEEP*.tw,kf. |
| 6 | open lung ventilation/ |
| 7 | (open lung adj3 (ventilat* or strateg* or approach*)).tw,kf. |
| 8 | or/1-7 |
| 9 | breathing mechanics/ |
| 10 | ((high* or low* or optim* or individual* or increment* or decrement*) adj5 (strateg* or applic* or approach* or trial* or titrat* or level*)).tw,kf. |
| 11 | ((curve or curves or pressure or pressures) adj5 (driv* or stress* or PEEP* or oxygenat* or esophag*)).tw,kf. |
| 12 | ((oxygenation or ventilation) adj3 (index or indexes or indices)).tw,kf. |
| 13 | ventilatory parameter*.tw,kf. |
| 14 | ((high* or low* or optim* or individual* or increment* or decrement* or restricted or liberal or algorithm* or level or levels or chang*) adj3 (PEEP* or positive end expiratory pressure* or positive endexpiratory pressure*)).tw,kf. |
| 15 | or/9-14 |
| 16 | exp artificial ventilation/ or mechanical ventilator/ |
| 17 | ((artificial* or mechanical*) adj3 (ventilat* or respirat*)).tw,kf. |
| 18 | endotracheal intubation/ |
| 19 | (IMV or intubat*).tw,kf. |
| 20 | or/16-19 |
| 21 | 8 and 15 and 20 |
| 22 | exp child/ not ((exp adult/ or exp aged/) and exp child/) |
| 23 | exp infant/ not ((exp adult/ or exp aged/) and exp infant/) |
| 24 | exp animals/ not (exp animals/ and humans/) |
| 25 | 22 or 23 or 24 |
| 26 | 21 not 25 |

## Supplemental Table #3 – Search Strategy for CENTRAL

| # | Query |
|---|---|
| 1 | end-expiratory pressure*.tw,hw,sh. |
| 2 | (positive adj5 end expiratory pressure*).tw,hw,sh. |
| 3 | (positive adj2 endexpiratory pressure*).tw,hw,sh. |
| 4 | (open lung adj3 (ventilat* or strateg* or approach*)).tw,hw,sh. |
| 5 | PEEP*.tw,hw,sh. |
| 6 | (open lung adj3 (ventilat* or strateg* or approach*)).tw,hw,sh. |
| 7 | or/2-6 |
| 8 | respiratory mechanics.tw,hw,sh. |
| 9 | ((high* or low* optim* or best or individual* or increment* or decrement* or open lung) adj5 (strateg* or applic* or approach* or setting* or trial* or titrat* or level*)).tw,hw,sh. |
| 10 | ((curve or curves or pressure or pressures) adj5 (driv* or stress* or PEEP* or oxygenat* or esophag*)).tw,hw,sh. |
| 11 | ((oxygenation or ventilation) adj3 (index or indexes or indices)).tw,hw,sh. |
| 12 | ventilatory parameter*.tw,hw,sh. |
| 13 | ((high* or low* optim* or best or individual* or increment* or decrement* or open lung) adj3 (PEEP* or positive end expiratory pressure* or positive endexpiratory pressure*)).tw,hw,sh. |
| 14 | or/8-13 |
| 15 | ((artificial* or mechanical*) adj3 (ventilat* or respirat*)).tw,hw,sh. |
| 16 | (IMV or intubat*).tw,hw,sh. |
| 17 | 15 or 16 |
| 18 | 7 and 14 and 17 |
| 19 | exp child/ not (exp adult/ and exp child/) |
| 20 | exp infant/ not (exp adult/ and exp infant/) |
| 21 | exp animals/ not (exp animals/ and humans/) |
| 22 | or/19-21 |
| 23 | 18 not 22 |

## Supplemental Table #4 – Search Strategy for Scopus

```
( TITLE-ABS-KEY ( end-expiratory-pressure* OR ( positive W/5 expiratory-
pressure* ) OR ( positive W/2 endexpiratory-pressure* ) OR peep* OR ( open-
lung W/3 ( ventilat* OR strateg* OR approach* ) ) ) ) AND ( ( TITLE-ABS-
KEY ( respiratory-mechanics OR ventilatory-parameter* ) OR TITLE-ABS-
KEY ( ( ( high* OR low* OR optim* OR individual* OR increment* OR decrement* )
W/5 ( strateg* OR applic* OR approach* OR level* OR trial* OR titrat* ) ) ) OR TITL
E-ABS-
KEY ( ( ( curve OR curves OR pressure OR pressures ) W/5 ( driv* OR stress* OR pee
p* OR oxygenat* OR esophag* ) ) . ) OR TITLE-ABS-
KEY ( ( ( oxygenation OR ventilation ) W/3 ( index OR indexes OR indices ) ) ) OR TIT
LE-ABS-
KEY ( ( ( high* OR low* OR optim* OR individual* OR increment* OR decrement* O
R restricted OR liberal OR algorithm* OR level OR levels OR chang* ) W/3 ( peep* O
R positive-end-expiratory-pressure* OR positive-endexpiratory-
pressure* ) ) ) ) ) AND ( ( TITLE-ABS-
KEY ( ( ( artificial* OR mechanical* ) W/3 ( ventilat* OR respirat* ) ) ) OR TITLE-ABS-
KEY ( ( imv OR intubat* ) ) ) ) AND ( EXCLUDE ( SRCTYPE , "k" ) OR EXCLUDE ( S
RCTYPE , "Undefined" ) ) AND ( LIMIT-TO ( DOCTYPE , "ar" ) OR LIMIT-
TO ( DOCTYPE , "re" ) OR LIMIT-TO ( DOCTYPE , "cp" ) ) AND ( LIMIT-
TO ( SUBJAREA , "MEDI" ) OR EXCLUDE ( SUBJAREA , "AGRI" ) OR EXCLUDE (
SUBJAREA , "ARTS" ) OR EXCLUDE ( SUBJAREA , "CENG" ) OR EXCLUDE ( SUBJ
AREA , "CHEM" ) OR EXCLUDE ( SUBJAREA , "COMP" ) OR EXCLUDE ( SUBJAR
EA , "DECI" ) OR EXCLUDE ( SUBJAREA , "DENT" ) OR EXCLUDE ( SUBJAREA ,
"EART" ) OR EXCLUDE ( SUBJAREA , "ENGI" ) OR EXCLUDE ( SUBJAREA , "IMM
U" ) OR EXCLUDE ( SUBJAREA , "SOCI" ) OR EXCLUDE ( SUBJAREA , "PSYC" ) O
R EXCLUDE ( SUBJAREA , "ENVI" ) OR EXCLUDE ( SUBJAREA , "VETE" ) OR EX
CLUDE ( SUBJAREA , "MATE" ) OR EXCLUDE ( SUBJAREA , "PHYS" ) )
```

Supplemental Table #5 – Search Strategy for Web of Science

| | |
|---|---|
| 1. | end-expiratory pressure* OR (positive NEAR/5 expiratory pressure*) OR (positive NEAR/2 endexpiratory pressure*) OR PEEP* OR (open lung NEAR/3 (ventilat* or strateg* or approach*)) (Topic) |
| 2. | TS=(((high* or low* or optim* or individual* or increment* or decrement*) NEAR/5 (strateg* or applic* or approach* or level* or trial* or titrat*))) OR TS=(((curve or curves or pressure or pressures) NEAR/5 (driv* or stress* or PEEP* or oxygenat* or esophag*))) OR TS=(((oxygenation or ventilation) NEAR/3 (index or indexes or indices))) OR TS=(ventilatory-parameter*) OR TS=(((high* or low* or optim* or individual* or increment* or decrement* or restricted or liberal or algorithm* or level or levels or chang*) NEAR/3 (PEEP* or positive-end-expiratory-pressure* or positive-endexpiratory-pressure*))) |
| 3. | ((artificial* or mechanical*) NEAR/3 (ventilat* or respirat*)) (Topic) or (IMV or intubat*) (Topic) |
| 4. | #1 AND #2 AND #3 |

# PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in: Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **ADMINISTRATIVE INFORMATION** | | | | | |
| **Title** | | | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | X | ☐ | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | ☐ | ☐ | N/A |
| **Registration** | 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | X | ☐ | 69 |
| **Authors** | | | | | |
| Contact | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | X | ☐ | 29 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | X | ☐ | 261 |
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | ☐ | ☐ | N/A |
| **Support** | | | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | X | ☐ | 265 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | X | ☐ | 265 |
| Role of sponsor/funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | X | ☐ | 265 |
| **INTRODUCTION** | | | | | |
| **Rationale** | 6 | Describe the rationale for the review in the context of what is already known | X | ☐ | 97 |
| **Objectives** | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | X | ☐ | 138 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **METHODS** | | | | | |
| **Eligibility criteria** | 8 | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | X | ☐ | Table 1 |
| **Information sources** | 9 | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | X | ☐ | 195 |
| **Search strategy** | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | X | ☐ | Figure 1 |
| ***STUDY RECORDS*** | | | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | X | ☐ | 203 |
| Selection process | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | X | ☐ | 204 |
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | X | ☐ | 217 |
| **Data items** | 12 | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | X | ☐ | Figure 2 |
| **Outcomes and prioritization** | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | X | ☐ | Figure 2 |
| **Risk of bias in individual studies** | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | ☐ | ☐ | N/A |
| ***DATA*** | | | | | |
| **Synthesis** | 15a | Describe criteria under which study data will be quantitatively synthesized | ☐ | ☐ | N/A |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall's tau) | ☐ | ☐ | N/A |
| | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | ☐ | ☐ | N/A |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | X | ☐ | 227 |

| Section/topic | # | Checklist item | Information reported | | Line number(s) |
|---|---|---|---|---|---|
| | | | Yes | No | |
| **Meta-bias(es)** | 16 | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | ☐ | X | N/A |
| **Confidence in cumulative evidence** | 17 | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | ☐ | ☐ | N/A |