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# **BMJ Open**

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

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### SCHOLARONE<sup>™</sup> Manuscripts

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4	1	Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a
5	2	scoping review
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56	46	syndrome, acute hypoxemic respiratory failure
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1 2		
2 3 4	47	
5 6	48	Abstract
7 8 9	49	Introduction: Titrated application of positive end expiratory pressure (PEEP) is an important part of
) 10 11	50	any mechanical ventilation strategy. However, the method by which the optimal PEEP is
12 13	51	determined and titrated varies widely. Methods for determining optimal PEEP have been assessed
14 15	52	using a variety of different study designs and patient populations. We will conduct a scoping review
16 17	53	to systematically identify all methods for determining optimal PEEP, and to identify the patient
18 19 20	54	populations, outcomes measured, and study designs utilized for each method. The goal will be to
21 22	55	identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to
23 24	56	further systematically synthesize and meta-analyze existing literature.
25 26	57	Methods and analysis: Using scoping review methodology, we will generate a comprehensive search
27 28 29	58	strategy based on inclusion and exclusion criteria generated using the Population, Concept, Context
30 31	59	framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of
32 33	60	Science, and Scopus). Three investigators will independently screen titles and abstracts, and two
34 35 26	61	investigators will independently complete full text review and data extraction. Included citations will
30 37 38	62	be categorized in terms of PEEP method, study design, patient population, and outcomes measured.
39 40	63	The methods for PEEP titration will be described in detail, including strengths and limitations.
41 42	64	Ethics and dissemination: Given this is a synthesis of existing literature, ethics approval is not
43 44	65	required. The results will be disseminated to stakeholders via presentation at local, regional, and
45 46 47	66	national levels, as well as publication in a high impact critical care journal. There is also the potential
48 49	67	to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by
50 51	68	societies.
52 53	69	Registration details: Scoping review protocol registered with Open Science Framework
54 55 56 57	70	(https://osf.io/atzqc)

1 2		
3 4	71	Strengths and limitations of this study (5 max)
5 6	72	• This study will rigorously describe studies testing methods of determining optimal PEEP.
7 8 0	73	Each method will be summarized with a description, its strengths, and limitations.
10 11 12 13 14 15 16 17 18	74	• Inclusion of many different study designs, not just randomized control trials will allow for
	75	identification of methods that are well studied or those that could be better studied.
	76	• A potential limitation is that given the broad nature of the review, there will be a large
	77	volume of studies to synthesize, and this may be challenging to summarize in one review.
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#### 95 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<sup>1</sup>. PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimizing atelectrauma<sup>2</sup>. 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<sup>2</sup>. Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output<sup>2</sup>. 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<sub>2</sub>) increased<sup>3</sup>. The investigators found no differences in terms of mortality or discharge home without ventilatory support<sup>3</sup>. The EXPRESS trial randomized patients with ARDS to a low PEEP strategy of 5-9 cmH<sub>2</sub>O vs a strategy that maximized PEEP while maintaining a plateau pressure between  $28-30 \text{ cmH}_2\text{O}^4$ . There was no difference in mortality or hospital discharge<sup>4</sup>. The LOVS trial randomized patients to a strategy of lower PEEP while maintaining plateau pressures under 30 cmH<sub>2</sub>O versus an open lung strategy involving recruitment maneuvers and high PEEP while maintaining plateau pressures under 40 cmH<sub>2</sub>O<sup>5</sup>. Again, no difference in mortality or duration of mechanical ventilation was demonstrated<sup>5</sup>. 

1		
2 3 4	119	Many other methods of PEEP titration have been described, however these have not been
5 6 7 8	120	rigorously tested through RCTs or been studied in terms of their impact on clinical outcomes <sup>6</sup> .
	121	Clinical practice guidelines regarding ventilator management in ARDS suggest higher PEEP may b
9 10 11	122	beneficial in patients with moderate-to-severe ARDS but acknowledge the optimal method for
12 13	123	PEEP titration is not yet clear <sup>7</sup> .
14 15	124	
16 17	125	Although many studies have used oxygenation as the primary physiological target when titrating
18 19 20	126	PEEP, other studies have proposed additional targets such as compliance <sup>8</sup> , driving pressure <sup>9</sup> , and
20 21 22	127	transpulmonary pressure <sup>10</sup> . Furthermore, a range of techniques are described to achieve these
23 24	128	targets, such as the use of esophageal balloons <sup>10</sup> , stress index <sup>11</sup> , or pressure-volume curves <sup>12</sup> . Lastly
25 26	129	the largest studies examining PEEP were conducted in ARDS patients, but the external validity to
27 28 29 30 31 32 33 34 35 36 37 38 39 40	130	other populations, such as those with normal lungs or acute hypoxemic respiratory failure without
	131	ARDS remains unclear. Previous systematic reviews have focused only on RCTs, thus excluding
	132	many studies examining alternative PEEP titration methods and physiological titration targets <sup>13-17</sup> .
	133	The use of alternative PEEP titration methods in broader non-ARDS patient populations has not
	134	been well synthesized by previous systematic or scoping reviews.
	135	
41 42	136	Scoping reviews are a form of knowledge synthesis that systematically search, select, and synthesize
43 44 45 46 47 48 49 50 51	137	knowledge around a research question that aims to map key concepts, types of evidence, and
	138	identify gaps in the literature <sup>18</sup> . The aims of this study are to use scoping review methodology to
	139	describe the methods of PEEP titration that have previously been studied, describe the patient
	140	populations they have been studied in, characterize the various clinical outcomes and endpoints
52 53	141	used, as well as describe the different study designs utilized. The results of the review will identify
54 55 56 57 58	142	knowledge gaps for future research in this area. For example, it will serve to identify the methods
59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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a)

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<sup>19</sup> where applicable. The scoping review itself will be prepared in accordance with the framework initially proposed by Arksey and O'Malley<sup>20</sup> with updates from Levac<sup>21</sup> and most recently updated by the Joanna Briggs Institute<sup>22</sup>. 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<sup>23</sup>. Identifying the research question In identifying a research question for the scoping review, we followed the recommended Population, Concept, Context (PCC) framework<sup>22</sup>. 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

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1 2		
3 4	167	those receiving invasive mechanical ventilation for non-pulmonary indications such as during
5 6	168	surgery will be included.
7 8	169	
9 10 11	170	b) The <u>primary concept</u> is to describe strategies used in setting or titration of PEEP on the
12 13	171	ventilator and the clinical and physiological outcomes associated with these different strategies.
14 15	172	Some examples of PEEP titration strategies include (but are not limited to): Using PEEP tables
16 17	173	(high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure,
18 19 20	174	pressure-volume curves and inflection points, esophageal balloons to measure transpulmonary
21 22	175	pressure, or various imaging modalities (CT or ultrasound or electrical impedance tomography).
23 24	176	The outcomes associated with the above-mentioned strategies will be broad and could include
25 26 27	177	clinical outcomes such as mortality, ICU length of stay, or duration of mechanical ventilation.
27 28 29	178	Other outcomes may relate to respiratory mechanics and physiology, including fraction of
30 31	179	inspired oxygen (FiO2), dead space, compliance, or oxygenation.
32 33	180	
34 35 26	181	c) The <u>context</u> will include those patients receiving planned or unplanned invasive mechanical
30 37 38	182	ventilation in the ICU, operating theater, or the emergency department. It will not be limited
39 40	183	based on duration of ventilation, geography, culture, or gender.
41 42	184	
43 44 45	185	Based on the above considerations, this scoping review will seek to answer the following question:
45 46 47	186	In hospitalized adults undergoing invasive mechanical ventilation, what are the strategies for determining optimal
48 49	187	positive end-expiratory pressure that currently exist in the literature. For these strategies, what patient populations
50 51	188	along with clinical and physiological outcomes have been studied, and what study designs have been used to examine
52 53	189	their efficacy and/or effectiveness?
54 55 56	190	
57 58		
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Popula	Inclusion	
1 op and	ion Adults undergoing invasive	Exclusion     Pediatric and peopatal popula
	<ul> <li>Any setting in hospital including intensive care unit, operating room, emergency department)</li> </ul>	<ul> <li>Non-invasive ventilation</li> <li>Single lung ventilation</li> <li>Home ventilation</li> <li>Animal studies</li> </ul>
Concep	<ul> <li>Study evaluates a method of setting optimal PEEP</li> <li>Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method</li> </ul>	• Studies that arbitrarily set PE at a certain value
Contex	t • Any geographic location	None
Eviden	<ul> <li>Primary research studies (including randomized controlled trials, cohort studies, cross-sectional studies, case series)</li> <li>Published abstracts will be included</li> </ul>	<ul> <li>Review articles</li> <li>Systematic reviews/meta-anal</li> <li>Case reports</li> <li>Editorial articles</li> <li>Articles for which we cannot obtain full text, or an English translation is not obtainable</li> </ul>
Table 1 framewo	- Inclusion and exclusion criteria, developed based rk	on the Population, Concept, Conte
Identifyi	ng relevant studies	
Based or	the inclusion and exclusion criteria, literature sear	cch strategies were developed by an o
librarian	(HLR) for MEDLINE, EMBASE, CENTRAL, W	7eb of Science, and Scopus. The sear
strategy	draft for MEDLINE can be seen in Supplemental	Material. The search strategy was pe
reviewed	by another librarian (ZAP) using the Peer Review	of Electronic Search Strategies (PR
guideline	e statement <sup>24</sup> . The search results in the different da	tabases will be exported to Endnote
and the	screening process will be completed using the syste	ematic review software Rayyan.

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205	Study selection
206	The workflow for study selection will be presented in a PRISMA flow diagram as well as in narrative
207	form. All titles and abstracts will be screened by at least two reviewers (between KP, SE, and TK).
208	Prior to completing screening of all titles, we will review 100 random selections to assess inter-rater
209	reliability and if there is a discrepancy, we will further clarify inclusion and exclusion criteria. After
210	title and abstract and screening is complete, disagreements will be resolved via discussion between
211	the three reviewers. After title and abstract screening is completed, the full text of all included
212	manuscripts will be reviewed independently by two reviewers (KP and SE) to confirm eligibility. At
213	this stage, the reason for exclusion will be recorded in the PRISMA diagram. In addition to
214	identifying articles through the search strategy, reference lists of included papers will be reviewed to
215	identify any other manuscripts that were not captured with the initial search. For any studies for
216	which the full manuscript is not accessible, an email will be sent to the corresponding author
217	requesting a copy of the manuscript. Manuscripts of another language will be translated to English
218	using Google Translate whenever possible <sup>25</sup> .
219	
220	Data extraction
221	Once included manuscripts are identified, relevant study data will be abstracted using a standardized
222	form. This form aims to collect all relevant variables of interest and was developed over several
223	iterations with input from all members of the team. It is based on a template suggested by the
224	Joanna Briggs Institute <sup>26</sup> . The key variables that will be extracted are summarized in Table 2. Two
225	reviewers (SE and KP) will independently extract data from five to ten studies to assess consistency
226	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.

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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 b	e abstracted from eligible studies included in the scoping review

#### 231 Presentation of results

232 Extracted data will be reported by using several different data displays. All included studies will be 233 aggregated in a table summarizing key study characteristics. This will include the setting, the study 234 design, country of origin, time period, patient population, and the method of PEEP selection, and 235 the outcomes measured. 236 Based on the number of studies within each setting and method of selection, we will stratify the data 237 for those with adequate number of studies. Data will be presented in terms of setting, patient 238 population and number of participants, study design (with focus on RCTs), outcomes (with focus on

239 clinical outcomes), trend over time in publishing, countries involved and most common publishing

240 journals. A table will also describe all RCTs in detail.

241 The methods for titrating PEEP will be presented in a table that describes how they were

242 performed, as well as benefits and limitations of each method. In addition, methods that have

243 insufficient numbers of studies to inform clinical practice will be discussed. Current gaps in the

244 literature, and opportunities for future research will be highlighted.

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5 6	246	Ethics and Dissemination
7 8	247	As this study will identify and review previously published literature, no research ethics board
9 10 11	248	approval is required.
12 13	249	
14 15	250	Patient and Public Involvement
16 17	251	This work describes existing research studies, and thus involves no patients or members of the
18 19 20	252	public.
20 21 22	253	
23 24	254	Implications
25 26	255	Given the rapidly growing body of evidence concerning methods of determining optimal PEEP,
27 28 29	256	there is a need to rigorously map the literature. This will be accomplished with this scoping review.
30 31	257	The results will be presented at local (departmental grand rounds), regional (Alberta Society of
32 33	258	Intensive Care Medicine meeting) and national critical care conferences (Critical Care Canada
34 35 26	259	Annual Forum) and will be submitted for publication in a peer reviewed critical care journal. It is
36 37 38	260	anticipated the study may identify certain methods of setting PEEP that have been studied
39 40	261	extensively and warrant further synthesis with systematic review and meta-analysis. It will also serve
41 42	262	to identify methods with potential benefit but where high-quality randomized trials have not been
43 44	263	conducted. This will guide future primary research studies. Clinicians will be able to use this
45 46 47	264	synthesis of studies to inform the development and implementation of an optimal PEEP protocol
48 49	265	within their hospital or region. The outputs will be relevant to many stakeholders within the
50 51	266	healthcare system, including bedside clinicians (including physicians, nurses, and respiratory
52 53	267	therapists), managers and team leads (who may be developing ventilator protocols and policies) as
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2 3 4	268	well as researchers and policy makers in the field who are responsible for development of clinical
5 6 7 8	269	practice guidelines.
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9 10 11	271	
12 13 14 15	272	Authors' contributions
	273	All authors contributed to study design. SE and KP drafted the protocol. All authors read, edited,
16 17	274	and approved the final protocol. KP is the guarantor of the protocol.
18 19 20	275	
20 21 22	276	Funding statement
23 24 25 26 27 28 29 30 31	277	This research received no specific grant from any funding agency in the public, commercial, or not-
	278	for-profit sectors.
	279	Competing interests statement
	280	None declared.
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Supplemental Material	
Stefan Edginton MD <sup>1</sup>	
Natalia Kruger BHSc <sup>1</sup>	
Henry Tom Stelfox MD PhD <sup>1,2</sup>	
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Sean M. Bagshaw MD MSc⁵	
Ken Kuljit Singh Parhar MD MSc <sup>1,2,6</sup>	
Supplemental Material #1 – Searc	n Strategy for MEDLINE developed with medic
norarian	

#### 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

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

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

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Section/topic	#		023.	Yes	No	number(s)	
ADMINISTRATIVE IN	FORMAT		Dov		-		
Title			vnlo				
Identification	1a	Identify the report as a protocol of a systematic review	adec	X		1	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	fro			N/A	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number Abstract	ne fe	X		69	
Authors		g. >	bn				
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide pays mailing address of corresponding author	çal	Х		29	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	bm	Х		261	
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Sources	5a	Indicate sources of financial or other support for the review	une	X		265	
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METHODS			ng fo	on 1			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and rep characteristics (e.g., years considered, language, publication status) to be used as crite eligibility for the review	ortes erias figs erias reio	August 2	X		Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with stud trial registers, or other grey literature sources) with planned dates of coverage	y d to	Dars,	X		195
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, includi limits, such that it could be repeated	ng ang	ned <b>S</b>	X		Figure 1
STUDY RECORDS		<u> </u>	erieu and o	Ided			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the		<u>ଟ୍</u> ୟି	Х		203
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewe each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	rs) Inin	augh	X		204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done ind in duplicate), any processes for obtaining and confirming data from investigators	epend	ently,	X		217
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sou pre-planned data assumptions and simplifications	urcens),	any	X		Figure 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of ma additional outcomes, with rationale	in and	1j.com	X		Figure 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including this will be done at the outcome or study level, or both; state how this information will b data synthesis	whether eussec	an tin			N/A
DATA			hno	ູ້			
	15a	Describe criteria under which study data will be quantitatively synthesized	logi	202			N/A
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures of handling data, and methods of combining data from studies, including any planned e of consistency (e.g., <i>I</i> <sup>2</sup> , Kendall's tau)	, nieth xplora	ads ∦gon			N/A
-	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, met regression)	a-	ce Bibl			N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		iogi	Х		227



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Section/topic	#	Checklist item	, includi	071871	Informatio Yes	n reported No	Line number(s)	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies reporting within studies)	ngeor L	ective P		Х	N/A	
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# **BMJ Open**

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-071871.R1
Article Type:	Protocol
Date Submitted by the Author:	05-May-2023
Complete List of Authors:	Edginton, Stefan; University of Calgary Cumming School of Medicine, Critical Care Medicine Kruger, Natalia; University of Calgary Cumming School of Medicine, Critical Care Medicine Stelfox, Tom; University of Calgary Cumming School of Medicine, Critical Care Medicine; University of Calgary Cumming School of Medicine, O'Brien Institute for Public Health Brochard, Laurent; University of Toronto Faculty of Medicine, Interdepartmental Division of Critical Care; Unity Health Toronto, Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute Zuege, Danny; University of Calgary Cumming School of Medicine, Critical Care Medicine Gaudet, Jonathan; University of Calgary Cumming School of Medicine, Critical Care Medicine Solverson, Kevin; University of Calgary Cumming School of Medicine, Critical Care Medicine Robertson, Helen; University of Calgary Cumming School of Medicine, Critical Care Medicine Fiest, Kirsten M.; University of Calgary Cumming School of Medicine, Critical Care Medicine Niven, Daniel; University of Calgary Cumming School of Medicine, Critical Care Medicine Niven, Daniel; University of Calgary Cumming School of Medicine, Critical Care Medicine Niven, Daniel; University of Calgary Cumming School of Medicine, O'Brien Institute for Public Health Bagshaw, Sean M.; University of Calgary Cumming School of Medicine, Critical Care Medicine Parhar, Ken Kuljit; University of Calgary Cumming School of Medicine, Critical Care Medicine
<b>Primary Subject Heading</b> :	Intensive care
Secondary Subject Heading:	Anaesthesia, Intensive care, Respiratory medicine, Evidence based practice
Keywords:	INTENSIVE & CRITICAL CARE, Adult anaesthesia < ANAESTHETICS, CLINICAL PHYSIOLOGY, EPIDEMIOLOGY

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1 2 3	Methods for Determination of Optimal Positive End Expiratory Pressure: a protocol for a scoping review
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6 7 8 9	Stefan Edginton MD <sup>1</sup> , Natalia Kruger BHSc <sup>1</sup> , Henry Tom Stelfox MD PhD <sup>1,2</sup> , Laurent Brochard, MD PhD <sup>3,4</sup> , Danny J. Zuege MD MSc <sup>1</sup> , Jonathan Gaudet MD MSc <sup>1</sup> , Kevin Solverson MD MSc <sup>1</sup> , Helen Lee Robertson MLIS <sup>1</sup> , Kirsten M. Fiest PhD <sup>1</sup> , Daniel J. Niven MD PhD <sup>1</sup> , Sean M. Bagshaw MD MSc <sup>5</sup> , Ken Kuljit S. Parhar MD MSc <sup>1,2,6</sup>
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	Word Count: 1905
	Keywords
	Mechanical ventilation, positive end-expiratory pressure, scoping review, acute respiratory distress
3	syndrome, acute hypoxemic respiratory failure
)	
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- 3 4	40	
5	41	Abstract
7 3	42	Introduction: Titrated application of positive end expiratory pressure (PEEP) is an important part of
9 10 11	43	any mechanical ventilation strategy. However, the method by which the optimal PEEP is
12 13	44	determined and titrated varies widely. Methods for determining optimal PEEP have been assessed
14 15	45	using a variety of different study designs and patient populations. We will conduct a scoping review
16 17	46	to systematically identify all methods for determining optimal PEEP, and to identify the patient
18 19 20	47	populations, outcomes measured, and study designs utilized for each method. The goal will be to
21 22	48	identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to
23 24	49	further systematically synthesize and meta-analyze existing literature.
25 26	50	Methods and analysis: Using scoping review methodology, we will generate a comprehensive search
27 28	51	strategy based on inclusion and exclusion criteria generated using the Population, Concept, Context
29 30 31	52	framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of
32 33	53	Science, and Scopus). Three investigators will independently screen titles and abstracts, and two
34 35	54	investigators will independently complete full text review and data extraction. Included citations will
36 37	55	be categorized in terms of PEEP method, study design, patient population, and outcomes measured.
38 39 10	56	The methods for PEEP titration will be described in detail, including strengths and limitations.
40 41 42	57	Ethics and dissemination: Given this is a synthesis of existing literature, ethics approval is not
43 44	58	required. The results will be disseminated to stakeholders via presentation at local, regional, and
45 46	59	national levels, as well as publication in a high impact critical care journal. There is also the potential
47 48 40	60	to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by
+9 50 51	61	societies.
52 53	62	Registration details: Scoping review protocol registered with Open Science Framework
54 55	63	(https://osf.io/atzqc)
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64	Strongths and limitations of this study (5 max)
04	Strengths and minitations of this study (5 max)
65	• This study will rigorously describe studies testing methods of determining optimal PEEP.
66	Each method will be summarized with a description, its strengths, and limitations.
67	• Inclusion of many different study designs, not just randomized control trials will allow for
68	identification of methods that are well studied or those that could be better studied.
69	• A potential limitation is that given the broad nature of the review, there will be a large
70	volume of studies to synthesize, and this may be challenging to summarize in one review.
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#### BMJ Open

#### 88 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<sup>1</sup>. PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimizing atelectrauma<sup>2</sup>. 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<sup>2</sup>. Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output<sup>2</sup>. 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<sub>2</sub>) increased<sup>3</sup>. The investigators found no differences in terms of mortality or discharge home without ventilatory support<sup>3</sup>. The EXPRESS trial randomized patients with ARDS to a low PEEP method of 5-9 cmH<sub>2</sub>O vs a method that maximized PEEP while maintaining a plateau pressure between  $28-30 \text{ cmH}_2\text{O}^4$ . There was no difference in mortality or hospital discharge<sup>4</sup>. The LOVS trial randomized patients to a method of lower PEEP while maintaining plateau pressures under 30 cmH<sub>2</sub>O versus an open lung method involving recruitment maneuvers and high PEEP while maintaining plateau pressures under 40 cmH<sub>2</sub>O<sup>5</sup>. Again, no difference in mortality or duration of mechanical ventilation was demonstrated<sup>5</sup>. 

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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<sup>6</sup>. 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<sup>7</sup>. Although many studies have used oxygenation as the primary physiological target when titrating PEEP, other studies have proposed additional targets such as compliance<sup>8</sup>, driving pressure<sup>9</sup>, and transpulmonary pressure<sup>10</sup>. Furthermore, a range of techniques are described to achieve these targets, such as the use of esophageal balloons<sup>10</sup>, stress index<sup>11</sup>, or pressure-volume curves<sup>12</sup>. 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<sup>13-17</sup>. 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

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<sup>18</sup>. 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

1 2		
2 3 4	136	that are currently well studied as well as other methods that show promise but are lacking in high
5 6	137	quality evidence such as randomized trials. Furthermore, this review could serve as the foundation
7 8 0	138	for future point prevalence studies or surveys that aim to map real world utilization of various
9 10 11	139	methods. It may also be used to inform policy and procedures within individual sites and could be
12 13	140	used as a resource in the development of clinical practice guidelines.
14 15	141	
16 17 19	142	Methods and analysis
18 19 20	143	
21 22	144	<u>Conceptual model</u>
23 24	145	This scoping review was registered using Open Science Framework (https://osf.io/atzqc).
25 26 27	146	Although no Enhancing the Quality and Transparency of Health Research (EQUATOR) guidance
27 28 29	147	on scoping review protocols exists, this protocol was prepared in accordance with the Preferred
30 31	148	Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement and
32 33	149	checklist <sup>19</sup> where applicable. The scoping review itself will be prepared in accordance with the
34 35 36	150	framework initially proposed by Arksey and O'Malley <sup>20</sup> with updates from Levac <sup>21</sup> and most recently
30 37 38	151	updated by the Joanna Briggs Institute <sup>22</sup> . The findings of our research will be reported in accordance
39 40	152	with the Preferred Reporting Items for Systematic Review and Meta-Analysis Scoping Review
41 42	153	(PRISMA-ScR) statement and checklist <sup>23</sup> .
43 44 45	154	
45 46 47	155	Identifying the research question
48 49	156	In identifying a research question for the scoping review, we followed the recommended Population,
50 51	157	Concept, Context (PCC) framework <sup>22</sup> .
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1 2			
- 3 4	159	a)	The population of interest involves adults (18 years of age or older) undergoing invasive
5 6 7 8 9 10 11 12 13 14 15	160		mechanical ventilation in hospital. Patients with ARDS, acute hypoxemic respiratory failure, and
	161		those receiving invasive mechanical ventilation for non-pulmonary indications such as during
	162		surgery will be included.
	163		
	164	b)	The primary concept is to describe methods used in setting or titration of PEEP on the
16 17	165		ventilator and the clinical and physiological outcomes associated with these different methods.
18 19 20	166		Some examples of PEEP titration methods include (but are not limited to): Using PEEP tables
20 21 22	167		(high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure,
23 24	168		pressure-volume curves and inflection points, esophageal balloons to measure transpulmonary
25 26 27 28 29 30 31 32 33 34 35 36 37 38	169		pressure, or various imaging modalities (CT or ultrasound or electrical impedance tomography).
	170		The outcomes associated with the above-mentioned methods will be broad and could include
	171		clinical outcomes such as mortality, ICU length of stay, or duration of mechanical ventilation.
	172		Other outcomes may relate to respiratory mechanics and physiology, including fraction of
	173		inspired oxygen (FiO2), dead space, compliance, or oxygenation.
	174		
39 40	175	c)	The <u>context</u> will include those patients receiving planned or unplanned invasive mechanical
41 42	176		ventilation in the ICU, operating theater, or the emergency department. It will not be limited
43 44	177		based on duration of ventilation, geography, culture, or gender.
45 46 47	178		
47 48 49	179	Ba	sed on the above considerations, this scoping review will seek to answer the following question:
50 51	180	In	hospitalized adults undergoing invasive mechanical ventilation, what are the methods for determining optimal
52 53 54 55	181	pos	itive end-expiratory pressure that currently exist in the literature. For these methods, what patient populations
50 57 58 59			

along with clinical and physiological outcomes have been studied, and what study designs have been used to examine

183 their efficacy and/or effectiveness?

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

	Inclusion	Exclusion
Population	<ul> <li>Patients undergoing invasive mechanical ventilation in hospital</li> <li>Any setting in hospital including intensive care unit, operating room, emergency department)</li> </ul>	<ul> <li>Pediatric and neonatal population</li> <li>Non-invasive ventilation</li> <li>Single lung ventilation</li> <li>Animal studies (with no human component)</li> </ul>
Concept	<ul> <li>Study evaluates a method of setting optimal PEEP</li> <li>Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method</li> </ul>	• Studies that arbitrarily set PEEP at a certain value (i.e. 5cmH <sub>2</sub> O)
Context	<ul><li>Any geographic location</li><li>Any duration of ventilation</li></ul>	• None
Types of Evidence	<ul> <li>Primary research studies (including randomized controlled trials, cohort studies, cross-sectional studies, case series)</li> <li>Published abstracts will be included</li> </ul>	• None
Fable 1 – Inclu ramework dentifying rele	usion and exclusion criteria, developed based o	n the Population, Concept, Context

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<sup>24</sup>. 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.

202 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<sup>25</sup>.

217 Data extraction

218 Once included manuscripts are identified, relevant study data will be abstracted using a standardized219 form. This form aims to collect all relevant variables of interest and was developed over several

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1 2							
2 3 4	220	0 iterations with input from all members of the team. It is based on a template suggested by th					
5 6	221	Joanna Briggs Institute <sup>26</sup> . The key variables that will be extracted are summarized in Table 2. Two					
/ 8 9	222	reviewers (SE and KP) will independently extract data from five to ten studies to assess consistency					
) 10 11	223	and to pilot test wh	ether the form needs to be adjusted to capture all the relevant data. Once data				
12 13	224	extraction has starte	ed, iterative refinement of the data abstraction form may be made to tailor to the				
14 15	225	data abstracted. Abs	stracted data will be collated in a Microsoft Excel spreadsheet.				
16		Domain	Categories				
10		Study identifiers	First author journal year of publication country of publication publication				
19 20		Study Identifiers	type				
21		Study design	Study type or design multicenter vs single center, country/countries of				
22		orday design	participants funding source				
23			participants, running source				
24 25		Participants	Number of participants, patient population, underlying disease severity, study				
25		1 un cherp un teo	setting				
27							
28		Results	Method (s) of selecting PEEP, comparator, tidal volumes within experimental				
29		10000000	and control groups				
30			and control groups				
31 32 33 34		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.				
35							
36 37 38	226 227	Table 2 – Data to b	e abstracted from eligible studies included in the scoping review				
39 40	228	Presentation of resu	<u>ilts</u>				
41 42 43	229	Extracted data will	be reported by using several different data displays. All included studies will be				
44 45	230	aggregated in a table	e summarizing key study characteristics. This will include the setting, the study				
46 47	231	design, country of c	origin, time period, patient population, the method of PEEP selection, and the				
48 49	232	2 outcomes measured.					
50 51 52	233	Based on the number of studies within each setting and method of selection, we will stratify the data					
52 53 54	234	for those with adequate number of studies. Data will be presented in terms of setting, patient					
55 56 57 58	235	nber of participants, study design (with focus on RCTs), outcomes (with focus on					
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3 4	236	clinical outcomes), trend over time in publishing, countries involved and most common publishing
5 6	237	journals. A table will also describe all RCTs in detail.
7 8 9 10 11 12 13 14 15	238	The methods for titrating PEEP will be presented in a table that describes how they were
	239	performed, as well as benefits and limitations of each method. In addition, methods that have
	240	insufficient numbers of studies to inform clinical practice will be discussed. Current gaps in the
	241	literature, and opportunities for future research will be highlighted.
16 17	242	
18 19	243	Ethics and Dissemination
20 21 22	244	As this study will identify and review previously published literature, no research ethics board
22 23 24	245	approval is required.
25 26	246	
27 28	247	Patient and Public Involvement
29 30 31 32 33	248	This work describes existing research studies, and thus involves no patients or members of the
	249	public.
34 35	250	
36 37	251	Implications
38 39 40	252	Given the rapidly growing body of evidence concerning methods of determining optimal PEEP,
40 41 42	253	there is a need to rigorously map the literature. This will be accomplished with this scoping review.
43 44	254	The results will be presented at local (departmental grand rounds), regional (Alberta Society of
45 46	255	Intensive Care Medicine meeting) and national critical care conferences (Critical Care Canada
47 48 40	256	Annual Forum) and will be submitted for publication in a peer reviewed critical care journal. It is
49 50 51	257	anticipated the study may identify certain methods of setting PEEP that have been studied
52 53	258	extensively and warrant further synthesis with systematic review and meta-analysis. The results of
54 55	259	this review will need to be interpreted within the limitations of scoping review methodology. These
56 57 58		

1 ว		
2 3 4	260	include lack of assessment of quality or risk of bias, and lack of quantitative meta-analysis of
5 6	261	outcomes. It will also serve to identify methods with potential benefit but where high-quality
7 8 0	262	randomized trials have not been conducted. This will guide future primary research studies.
9 10 11	263	Clinicians will be able to use this synthesis of studies to inform the development and
12 13	264	implementation of an optimal PEEP protocol within their hospital or region. The outputs will be
14 15	265	relevant to many stakeholders within the healthcare system, including bedside clinicians (including
16 17 19	266	physicians, nurses, and respiratory therapists), managers and team leads (who may be developing
10 19 20	267	ventilator protocols and policies) as well as researchers and policy makers in the field who are
21 22	268	responsible for development of clinical practice guidelines.
23 24	269	
25 26 27	270	
27 28 29	271	Authors' contributions
30 31	272	All authors (SE, NK, HS, LB, DZ, JG, KS, HLR, KF, DN, SB, KP) contributed to conception,
32 33	273	study design and planning. SE and KP drafted the protocol. All authors (SE, NK, HS, LB, DZ, JG,
34 35 36	274	KS, HLR, KF, DN, SB, KP) read, edited, and approved the final protocol. KP is the guarantor of
37 38	275	the protocol.
39 40	276	Funding statement
41 42	277	This research received no specific grant from any funding agency in the public, commercial, or not-
43 44 45	278	for-profit sectors.
46 47	279	Competing interests statement
48 49	280	None declared.
50 51	281	
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59 60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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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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## Ken Kuljit Singh Parhar MD MSc<sup>1,2,6</sup> Supplemental Material #1 – Search Strategy for MEDLINE developed with medical

Supplemental Material # librarian	#1 – Search Strategy for	MEDLINE developed with	1 medical 2

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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
5	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

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 **PRISMA-P 2015 Checklist** BMJ Open

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

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

		es se s	Informati	
Section/topic	#	Checklist item	informatio	on reported Line
		ted	Yes	No numbér(s)
ADMINISTRATIVE IN	FORMAT			
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 Abstract	X	69
Authors		9. ¥bn ∧		
Contact	За	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 protocolade tity as such and list changes; otherwise, state plan for documenting important protocol amengements	/	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 protection	X	265
INTRODUCTION		Age		
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
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		BMJ Open	hv convrigh				Page 20 2
Section/topic	#	Checklist item	- includi	074074	Information Yes	n reported No	Line number(s)
METHODS			na i	\$			
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 eligibility for the review	Epseic	2	X		Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study trial registers, or other grey literature sources) with planned dates of coverage		rs,	X		195
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including limits, such that it could be repeated		ned	Х		Figure 1
STUDY RECORDS			erieu				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the		w	X		203
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	B 語 S )	ugh	X		204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done indep in duplicate), any processes for obtaining and confirming data from investigators		ntly,	X		217
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sourd pre-planned data assumptions and simplifications	and s),	any	X		Figure 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main additional outcomes, with rationale	and a		X		Figure 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whethis will be done at the outcome or study level, or both; state how this information will be data synthesis	ethe sect	in			N/A
DATA			hno	3			
	15a	Describe criteria under which study data will be quantitatively synthesized		3			N/A
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, not of handling data, and methods of combining data from studies, including any planned exp of consistency (e.g., <i>I</i> <sup>2</sup> , Kendall's tau)	ieth Iora	ds on			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
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2 3 4	Section/topic	#	Checklist item	071871 c , includir		Informatio Yes	n reported No	Line number(s)
5 6 7	Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies reporting within studies)	, select Au	ive		Х	N/A
, 8 9	Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	gust 20 Enseig Ises rel				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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1 2 3 4	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
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3 4	40	
5 6	41	Abstract
7 8 0	42	Introduction: Titrated application of positive end expiratory pressure (PEEP) is an important part of
9 10 11	43	any mechanical ventilation strategy. However, the method by which the optimal PEEP is
12 13	44	determined and titrated varies widely. Methods for determining optimal PEEP have been assessed
14 15	45	using a variety of different study designs and patient populations. We will conduct a scoping review
16 17 18	46	to systematically identify all methods for determining optimal PEEP, and to identify the patient
19 20	47	populations, outcomes measured, and study designs utilized for each method. The goal will be to
21 22	48	identify gaps in the optimal PEEP literature and identify areas where there may be an opportunity to
23 24	49	further systematically synthesize and meta-analyze existing literature.
25 26 27	50	Methods and analysis: Using scoping review methodology, we will generate a comprehensive search
28 29	51	strategy based on inclusion and exclusion criteria generated using the Population, Concept, Context
30 31	52	framework. Five different databases will be searched (MEDLINE, EMBASE, CENTRAL, Web of
32 33	53	Science, and Scopus). Three investigators will independently screen titles and abstracts, and two
34 35 36	54	investigators will independently complete full text review and data extraction. Included citations will
37 38	55	be categorized in terms of PEEP method, study design, patient population, and outcomes measured.
39 40	56	The methods for PEEP titration will be described in detail, including strengths and limitations.
41 42	57	Ethics and dissemination: Given this is a synthesis of existing literature, ethics approval is not
43 44 45	58	required. The results will be disseminated to stakeholders via presentation at local, regional, and
45 46 47	59	national levels, as well as publication in a high impact critical care journal. There is also the potential
48 49	60	to impact local clinical care protocols and inform broader clinical practice guidelines undertaken by
50 51	61	societies.
52 53 54	62	Registration details: Scoping review protocol registered with Open Science Framework
55 56	63	(https://osf.io/atzqc)

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64	Strengths and limitations of this study (5 max)
65	• This study will rigorously describe studies testing methods of determining optimal PEEP.
66	Each method will be summarized with a description, its strengths, and limitations.
67	• Inclusion of many different study designs, not just randomized control trials will allow for
68	identification of methods that are well studied or those that could be better studied.
69	• A potential limitation is that given the broad nature of the review, there will be a large
70	volume of studies to synthesize, and this may be challenging to summarize in one review.
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#### 88 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<sup>1</sup>. PEEP can also reduce the risk of ventilator-induced lung injury (VILI) by minimizing atelectrauma<sup>2</sup>. 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<sup>2</sup>. Increased PEEP can elevate intrathoracic pressure which reduces venous return and cardiac output<sup>2</sup>. 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<sub>2</sub>) increased<sup>3</sup>. The investigators found no differences in terms of mortality or discharge home without ventilatory support<sup>3</sup>. The EXPRESS trial randomized patients with ARDS to a low PEEP method of 5-9 cmH<sub>2</sub>O vs a method that maximized PEEP while maintaining a plateau pressure between  $28-30 \text{ cmH}_2\text{O}^4$ . There was no difference in mortality or hospital discharge<sup>4</sup>. The LOVS trial randomized patients to a method of lower PEEP while maintaining plateau pressures under 30 cmH<sub>2</sub>O versus an open lung method involving recruitment maneuvers and high PEEP while maintaining plateau pressures under 40 cmH<sub>2</sub>O<sup>5</sup>. Again, no difference in mortality or duration of mechanical ventilation was demonstrated<sup>5</sup>. 

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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<sup>6</sup>. 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<sup>7</sup>. Although many studies have used oxygenation as the primary physiological target when titrating PEEP, other studies have proposed additional targets such as compliance<sup>8</sup>, driving pressure<sup>9</sup>, and transpulmonary pressure<sup>10</sup>. Furthermore, a range of techniques are described to achieve these targets, such as the use of esophageal balloons<sup>10</sup>, stress index<sup>11</sup>, or pressure-volume curves<sup>12</sup>. 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<sup>13-17</sup>. 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<sup>18</sup>. 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

1 2		
- 3 4	136	that are currently well studied as well as other methods that show promise but are lacking in high
5 6	137	quality evidence such as randomized trials. Furthermore, this review could serve as the foundation
7 8 0	138	for future point prevalence studies or surveys that aim to map real world utilization of various
9 10 11	139	methods. It may also be used to inform policy and procedures within individual sites and could be
12 13	140	used as a resource in the development of clinical practice guidelines.
14 15	141	
16 17	142	Methods and analysis
18 19 20	143	
21 22	144	<u>Conceptual model</u>
23 24	145	This scoping review was registered using Open Science Framework (https://osf.io/atzqc).
25 26 27	146	Although no Enhancing the Quality and Transparency of Health Research (EQUATOR) guidance
27 28 29	147	on scoping review protocols exists, this protocol was prepared in accordance with the Preferred
30 31	148	Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement and
32 33	149	checklist <sup>19</sup> where applicable. The scoping review itself will be prepared in accordance with the
34 35 36	150	framework initially proposed by Arksey and O'Malley <sup>20</sup> with updates from Levac <sup>21</sup> and most recently
37 38	151	updated by the Joanna Briggs Institute <sup>22</sup> . The findings of our research will be reported in accordance
39 40	152	with the Preferred Reporting Items for Systematic Review and Meta-Analysis Scoping Review
41 42	153	(PRISMA-ScR) statement and checklist <sup>23</sup> .
43 44 45	154	
45 46 47	155	Patient and Public Involvement
48 49	156	This work describes existing research studies, and thus involves no patients or members of the
50 51	157	public.
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1 2		
2 3 4	160	Identifying the research question
5 6	161	In identifying a research question for the scoping review, we followed the recommended Population,
7 8	162	Concept, Context (PCC) framework <sup>22</sup> .
9 10 11	163	
12 13	164	a) The population of interest involves adults (18 years of age or older) undergoing invasive
14 15	165	mechanical ventilation in hospital. Patients with ARDS, acute hypoxemic respiratory failure, and
16 17	166	those receiving invasive mechanical ventilation for non-pulmonary indications such as during
18 19 20	167	surgery will be included.
21 22	168	
23 24	169	b) The <u>primary concept</u> is to describe methods used in setting or titration of PEEP on the
25 26	170	ventilator and the clinical and physiological outcomes associated with these different methods.
27 28 29	171	Some examples of PEEP titration methods include (but are not limited to): Using PEEP tables
30 31	172	(high or low), measuring compliance (static or dynamic), driving pressure, plateau pressure,
32 33	173	pressure-volume curves and inflection points, esophageal balloons to measure transpulmonary
34 35 26	174	pressure, or various imaging modalities (CT or ultrasound or electrical impedance tomography).
30 37 38	175	The outcomes associated with the above-mentioned methods will be broad and could include
39 40	176	clinical outcomes such as mortality, ICU length of stay, or duration of mechanical ventilation.
41 42	177	Other outcomes may relate to respiratory mechanics and physiology, including fraction of
43 44	178	inspired oxygen (FiO2), dead space, compliance, or oxygenation.
45 46 47	179	
48 49	180	c) The <u>context</u> will include those patients receiving planned or unplanned invasive mechanical
50 51	181	ventilation in the ICU, operating theater, or the emergency department. It will not be limited
52 53	182	based on duration of ventilation, geography, culture, or gender.
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184	Based on the a	bove considerations, this scoping review will	seek to answer the following question:	
185	In hospitalized adults undergoing invasive mechanical ventilation, what are the methods for determining optimal			
186	positive end-expir	ratory pressure that currently exist in the literature. I	For these methods, what patient populations	
187	along with clinica	l and physiological outcomes have been studied, and n	what study designs have been used to examine	
188	their efficacy and	or effectiveness?		
189				
190	The inclusion a	and exclusion criteria and creation of a search	strategy were conducted as previously	
191	described for s	coping reviews <sup>22</sup> . The development of the cri	iteria was based on the PCC framework	
192	and can be seen	n in Table 1.		
		Inclusion	Exclusion	
	Population	<ul> <li>Patients undergoing invasive mechanical ventilation in hospital</li> <li>Any setting in hospital including intensive care unit, operating room, emergency department)</li> </ul>	<ul> <li>Pediatric and neonatal population</li> <li>Non-invasive ventilation</li> <li>Single lung ventilation</li> <li>Animal studies (with no human component)</li> </ul>	
	Concept	<ul> <li>Study evaluates a method of setting optimal PEEP</li> <li>Study reports an outcome (could be clinical or physiologic) associated with the setting of the PEEP by a specific method</li> <li>Any geographic location</li> </ul>	<ul> <li>Studies that arbitrarily set PEEP at a certain value (i.e. 5cmH<sub>2</sub>O)</li> <li>None</li> </ul>	
	Types of Evidence	<ul> <li>Any duration of ventilation</li> <li>Primary research studies (including randomized controlled trials, cohort studies, cross-sectional studies, case series)</li> <li>Published abstracts will be included</li> </ul>	• None	
193 194 195	Table 1 – Inclu framework	ision and exclusion criteria, developed based	on the Population, Concept, Context	
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198 <u>Identifying relevant studies</u>

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<sup>24</sup>. 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.

209 <u>Study selection</u>

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

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	221	requesting a copy o	of the manuscript. Manuscripts of another language will be translated to English			
	222	using Google Translate whenever possible <sup>25</sup> .				
	223					
0	224	Data extraction				
1 2 2	225	Once included man	nuscripts are identified, relevant study data will be abstracted using a standardized			
3 4 5	226	form. This form air	ms to collect all relevant variables of interest and was developed over several			
6 7	227	iterations with inpu	it from all members of the team. It is based on a template suggested by the			
8 9	228	Joanna Briggs Insti	tute <sup>26</sup> . The key variables that will be extracted are summarized in Table 2. Two			
20 21	229	reviewers (SE and I	KP) will independently extract data from five to ten studies to assess consistency			
.∠ !3 !4	230	and to pilot test wh	ether the form needs to be adjusted to capture all the relevant data. Once data			
25 26	231	extraction has start	ed, iterative refinement of the data abstraction form may be made to tailor to the			
27 28	232	data abstracted. Abstracted data will be collated in a Microsoft Excel spreadsheet.				
29 80						
1		Domain	Categories			
2		Study identifiers	First author, journal, year of publication, country of publication, publication type			
5 5 6 7		Study design	Study type or design, multicenter vs single center, country/countries of participants, funding source			
8 9 0		Participants	Number of participants, patient population, underlying disease severity, study setting			
-1 -2 -3 -4		Results	Method (s) of selecting PEEP, comparator, tidal volumes within experimental and control groups			
-5 -6 -7 -8		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.			
19 50 51	233 234	Table 2 – Data to b	be abstracted from eligible studies included in the scoping review			
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#### 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

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2 3 4	261	Annual Forum) and will be submitted for publication in a peer reviewed critical care journal. It is
5 6	262	anticipated the study may identify certain methods of setting PEEP that have been studied
7 8	263	extensively and warrant further synthesis with systematic review and meta-analysis. The results of
9 10 11	264	this review will need to be interpreted within the limitations of scoping review methodology. These
12 13	265	include lack of assessment of quality or risk of bias, and lack of quantitative meta-analysis of
14 15	266	outcomes. It will also serve to identify methods with potential benefit but where high-quality
16 17	267	randomized trials have not been conducted. This will guide future primary research studies.
18 19 20	268	Clinicians will be able to use this synthesis of studies to inform the development and
20 21 22	269	implementation of an optimal PEEP protocol within their hospital or region. The outputs will be
23 24	270	relevant to many stakeholders within the healthcare system, including bedside clinicians (including
25 26	271	physicians, nurses, and respiratory therapists), managers and team leads (who may be developing
27 28 20	272	ventilator protocols and policies) as well as researchers and policy makers in the field who are
29 30 31	273	responsible for development of clinical practice guidelines.
32 33	274	
34 35	275	Authors' contributions
36 37 38	276	All authors (SE, NK, HS, LB, DZ, JG, KS, HLR, KF, DN, SB, KP) contributed to conception,
30 39 40	277	study design and planning. SE and KP drafted the protocol. All authors (SE, NK, HS, LB, DZ, JG,
41 42	278	KS, HLR, KF, DN, SB, KP) read, edited, and approved the final protocol. KP is the guarantor of
43 44	279	the protocol.
45 46 47	280	Funding statement
47 48 49	281	This research received no specific grant from any funding agency in the public, commercial, or not-
50 51	282	for-profit sectors.
52 53	283	Competing interests statement
54 55	284	None declared.
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and

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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 Material #1 – Search Strategy for MEDLINE	2
Supplemental Material #2 – Search Strategy for EMBASE	3
Supplemental Material #3 – Search Strategy for CENTRAL	4
Supplemental Material #4 – Search Strategy for Scopus	5
Supplemental Material #5 – Search Strategy for Web of Science	6

#	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

Sur	plemental 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

nd-expiratory pressure*.tw,hw,sh. positive adj5 end expiratory pressure*).tw,hw,sh. positive adj2 endexpiratory pressure*).tw,hw,sh. pen lung adj3 (ventilat* or strateg* or pproach*)).tw,hw,sh. EEP*.tw,hw,sh. pen lung adj3 (ventilat* or strateg* or pproach*)).tw,hw,sh. tr/2-6 sepiratory mechanics.tw,hw,sh. high* or low* optim* or best or individual* or increment* r decrement* or open lung) adj5 (strateg* or applic* or pproach* or setting* or trial* or titrat* or level*)).tw,hw,sh. curve or curves or pressure or pressures) adj5 (driv* or ress* or PEEP* or oxygenat* or esophag*)).tw,hw,sh. oxygenation or ventilation) adj3 (index or indexes or idices)).tw,hw,sh. entilatory parameter*.tw,hw,sh. high* or low* optim* or best or individual* or increment* r decrement* or open lung) adj3 (PEEP* or positive end xpiratory pressure* or positive endexpiratory ressure*)).tw,hw,sh. tr/8-13 artificial* or mechanical*) adj3 (ventilat* or espirat*)).tw,hw,sh. MV or intubat*).tw,hw,sh. 5 or 16 and 14 and 17 sp child/ not (exp adult/ and exp child/) sp infant/ not (exp adult/ and exp infant/) up asimely ( and for a primely ( and hymens ()
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entilatory parameter*.tw,hw,sh. high* or low* optim* or best or individual* or increment* r decrement* or open lung) adj3 (PEEP* or positive end spiratory pressure* or positive endexpiratory ressure*)).tw,hw,sh. r/8-13 artificial* or mechanical*) adj3 (ventilat* or espirat*)).tw,hw,sh. MV or intubat*).tw,hw,sh. 5 or 16 and 14 and 17 sp child/ not (exp adult/ and exp child/) sp infant/ not (exp adult/ and exp infant/) ty arimels/ not (exp adult/ and exp infant/)
high* or low* optim* or best or individual* or increment* r decrement* or open lung) adj3 (PEEP* or positive end xpiratory pressure* or positive endexpiratory ressure*)).tw,hw,sh. r/8-13 artificial* or mechanical*) adj3 (ventilat* or espirat*)).tw,hw,sh. MV or intubat*).tw,hw,sh. 5 or 16 and 14 and 17 xp child/ not (exp adult/ and exp child/) xp infant/ not (exp adult/ and exp infant/) yp arimals/ not (exp adult/ and exp infant/)
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MV or intubat*).tw,hw,sh. 5 or 16 and 14 and 17 xp child/ not (exp adult/ and exp child/) xp infant/ not (exp adult/ and exp infant/) xp arimals/ not (exp animals/ and humans/)
5 or 16 and 14 and 17 xp child/ not (exp adult/ and exp child/) xp infant/ not (exp adult/ and exp infant/) xp animals/ not (exp adult/ and exp infant/)
and 14 and 17 xp child/ not (exp adult/ and exp child/) xp infant/ not (exp adult/ and exp infant/) xp animals/ not (exp animals/ and humans/)
xp child/ not (exp adult/ and exp child/)         xp infant/ not (exp adult/ and exp infant/)         xp animals/ not (ovp animals/ and humans/)
xp infant/ not (exp adult/ and exp infant/)
re animals ( not (are animals ( and hymans ()
xp annuals/ not (exp annuals/ and numans/)
r/19-21
8 not 22

### Supplemental Table #4 – Search Strategy for Scopus

(TITLE-ABS-KEY (end-expiratory-pressure\* OR (positive W/5 expiratorypressure\*) OR (positive W/2 endexpiratory-pressure\*) OR peep\* OR (openlung 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-endexpiratorypressure\*))))) 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"))

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Supplemental Table #5 – Search Strate	egy for Web of Science
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<u> </u>		
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	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	3.	((artificial* or mechanical*) NEAR/3 (ventilat* or
		respirat*)) (Topic) or (IMV or intubat*) (Topic)
4	ŀ.	#1 AND #2 AND #3

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 PRISMA-P 2015 Checklist
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Section/topic	#	Checklist item	20	Information reported Line			
			3	Yes	No	number(s)	
ADMINISTRATIVE INFORMATION			Dov				
Title			nlo				
Identification	1a	Identify the report as a protocol of a systematic review	adec	X		1	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	fro			N/A	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number Abstract		Х		69	
Authors							
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide pays mailing address of corresponding author	gal	Х		29	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	b M	Х		261	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol	tify tts			N/A	
Support			ы С				
Sources	5a	Indicate sources of financial or other support for the review	une	X		265	
Sponsor	5b	Provide name for the review funder and/or sponsor		Х		265	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protection	025 at	X		265	
INTRODUCTION		ů.	Aqe				
Rationale	6	Describe the rationale for the review in the context of what is already known	nce	Х		97	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Bibliogra	X		138	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	bhique de l	(	Biol The Op		



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Section/topic	#	Checklist item	includi	071871	Information Yes	reported No	Line number(s)
METHODS			ng fo	9 1			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and rep characteristics (e.g., years considered, language, publication status) to be used as crite eligibility for the review	ortes mo erias faseic	August 2	X		Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with stud trial registers, or other grey literature sources) with planned dates of coverage	y and to	Dars,	X		195
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, includin limits, such that it could be repeated	ng ang	ned	X		Figure 1
STUDY RECORDS			erieu and o	Ided			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the		<u>ଟ୍</u> ଟି୍୍	Х		203
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewe each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	rs) nin	augh	X		204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done ind in duplicate), any processes for obtaining and confirming data from investigators	epiend	ntly,	X		217
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sou pre-planned data assumptions and simplifications	urces),	gany	X		Figure 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of ma additional outcomes, with rationale	n and	nj.com	X		Figure 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including this will be done at the outcome or study level, or both; state how this information will b data synthesis	wheethe eussec	(สาว มี มาต			N/A
DATA	-		hno	j L			
	15a	Describe criteria under which study data will be quantitatively synthesized	logi	202			N/A
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures of handling data, and methods of combining data from studies, including any planned e of consistency (e.g., <i>I</i> <sup>2</sup> , Kendall's tau)	, meth xplora	5 ≇ds ∦gon			N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, met regression)	a-	ce Bibl			N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		iog	Х		227



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Section/topic	#	Checklist item	7187 inclu	Information reported		Line
			1 ol	Yes	No	number(s)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, reporting within studies)	selective P		X	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	gust 2 Enseig Ises re			N/A
			123. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographiqu nement Superieur (ABES) . ated to text and data mining, AI training, and similar technologies.			
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