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High-flow nasal oxygen (HFNO) for hospitalized patients: a systematic review protocol

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Manuscripts

HFNO for hospitalized patients: a systematic review protocol
Date: 10/15/19

PROTOCOL:

High-flow nasal oxygen (HFNO) for hospitalized patients: a systematic review protocol

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3 36 **ABSTRACT**
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5
6 38 **Introduction**
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8 39 High-flow nasal oxygen (HFNO) therapy use in adults hospitalized with acute respiratory
9
10 40 failure (ARF) is increasing. However, evidence to support widespread use of HFNO compared
11
12 41 to noninvasive ventilation (NIV) and conventional oxygen therapy (COT) is lacking. This protocol
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14 42 describes the methods for a systematic evidence review regarding the comparative
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16 43 effectiveness and harms of HFNO compared to NIV or COT for the management of ARF in
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18 44 hospitalized adult patients.
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23 46 **Methods and analysis**
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25 47 We searched MEDLINE®, Embase, CINAHL, and Cochrane Library for randomized-
26
27 48 controlled trials (RCTs) of adult patients hospitalized with ARF defined as SpO₂ <90%,
28
29 49 PaO₂:FiO₂ ratio ≤300, PaO₂ ≤60 mmHg, or PaCO₂ ≥45 mmHg. The intervention is HFNO
30
31 50 (humidified oxygen, flow rate ≥20 L/min) compared to NIV or COT. The critical outcomes are:
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33 51 mortality, hospital-acquired pneumonia, intubation/reintubation (days of intubation), intensive
34
35 52 care unit (ICU) admission and ICU transfers, patient comfort, and hospital length of stay. The
36
37 53 important outcomes are: delirium, 30-day hospital readmissions, barotrauma, compromised
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39 54 nutrition, gastric dysfunction, independence at discharge, discharge, and skin breakdown or
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41 55 pressure ulcers. Where possible and appropriate, meta-analysis will be performed for each
42
43 56 outcome.
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48 58 **Conclusion**
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50 59 This systematic review will provide a comprehensive evaluation of the evidence
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52 60 regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the
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54 61 management of ARF in hospitalized adult patients to inform clinical practice and to identify
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- 87 ▪ The relative heterogeneity of the populations, diagnoses, settings, and outcome
- 88 measures assessed by the individual studies that will be included in this systematic
- 89 review may preclude meaningful subgroup analyses.

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91 INTRODUCTION

92 High-flow nasal oxygen (HFNO) therapy is a mode of noninvasive oxygen support that
93 has been used in neonatal and pediatric settings for over a decade. In recent years, HFNO use
94 in adults hospitalized with acute respiratory failure (ARF) has been increasing. HFNO delivers
95 warmed, humidified oxygen with fraction of inspired oxygen (FiO₂) up to 1.0 and maximum flow
96 rate of 60 L/min. Several potential physiologic advantages of HFNO over noninvasive ventilation
97 (NIV) and conventional oxygen therapy (COT) have been proposed. These include patient
98 comfort (1, 2), improved oxygenation and ventilation (3, 4), clearance of airway secretions (5, 6),
99 and reduced work of breathing (2, 7, 8). These theoretical benefits are attributed to HFNO
100 delivery through small, pliable nasal cannula, washout of anatomic dead space (9), high oxygen
101 flow rates (10, 11), generation of positive-end expiratory pressure (PEEP) (12-16), and heated
102 humidification.

103 Given the increasing use of HFNO and the lack of robust evidence to support its
104 widespread use in adult patients with ARF, the Minnesota Evidence Dissemination Center was
105 commissioned by the American College of Physicians (ACP) to systematically review the
106 evidence regarding the comparative effectiveness and harms of HFNO compared to NIV or
107 COT for the management of ARF in hospitalized adult patients. With input from the ACP-Clinical
108 Guidelines Committee (ACP-CGC) (17) and a technical expert panel (TEP), we developed the
109 following key questions (KQ):

110 KQ 1. What is the comparative effectiveness of HFNO versus NIV or COT for hospitalized
111 patients with ARF? Does comparative effectiveness of HFNO vary by patient
112 characteristics, disease/diagnosis characteristics, protocol/device settings, or location of
113 administration?

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115 KQ 2. What are the harms of HFNO versus NIV or COT for hospitalized patients with
116 ARF? Do harms vary by patient characteristics, disease/diagnosis, protocol/device
117 settings, or location of administration?

118

119 **METHODS**

120 In accordance with the guidelines, our systematic review protocol was registered with
121 the International Prospective Register of Systematic Reviews (PROSPERO) on August 8, 2019.
122 We will report our findings according to the Preferred Reporting Items for Systematic Reviews
123 and Meta-Analyses (PRISMA) 2009 statement (18).

124

125 **Eligibility criteria**

126 All studies included in this systematic review will be selected in accordance with the
127 PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Study Design) framework:

128

129 ***Population***

130 We will include all adult patients (age ≥ 18 years) with ARF at the time of study enrollment,
131 defined as $SpO_2 < 90\%$, $PaO_2:FIO_2$ ratio ≤ 300 , $PaO_2 \leq 60$ mmHg, or $PaCO_2 \geq 45$ mmHg.

132

133 ***Intervention***

134 The intervention of interest is HFNO, defined as humidified oxygen with flow rates ≥ 20
135 L/min.

136

137 ***Comparators***

138 We will compare HFNO to NIV (continuous or bilevel positive airway pressure ventilation
139 [CPAP or BiPAP®]) or COT (e.g. oxygen delivered through nasal cannula, simple face
140 mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask, etc).

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5 142 **Outcome measures**

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7 143 We will examine several patient-related outcomes and intermediate outcomes. With input
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9 144 from the ACP-CGC that included nonphysician public representatives, outcomes were
10
11 145 identified as critical or important. The critical outcomes are: mortality, hospital-acquired
12
13 146 pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU)
14
15 147 admission and ICU transfers, patient comfort, and hospital length of stay. The important
16
17 148 outcomes are: delirium, 30-day hospital readmissions, barotrauma (pneumothorax,
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19 149 pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury), compromised
20
21 150 nutrition (enteral or parenteral nutrition), gastric dysfunction (placement of nasogastric
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23 151 tube, abdominal distension, nausea, or vomiting), functional independence at discharge,
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25 152 discharge disposition (home, assisted-living facility, nursing home, or long-term care
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27 153 hospital), and skin breakdown or pressure ulcers. Intermediate outcomes are: respiratory
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29 154 rate, PaO₂/FiO₂ ratio, SpO₂, pH, PaO₂, and PCO₂.

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35 156 **Timing**

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37 157 We will include patients hospitalized for ARF or who developed ARF while hospitalized,
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39 158 including patients with ARF post-extubation or post-surgery. We will exclude studies
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41 159 evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.

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45 161 **Setting**

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47 162 We will include studies that randomized patients in the hospital (including hospital wards,
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49 163 intermediate/step-down units, and intensive care units) and emergency department.

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53 165 **Study design**

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166 Randomized controlled trials (RCTs) with full-text reports in English will be included. We
167 will exclude non-randomized trials and observational studies.

168

169 **Data sources and search strategy**

170 We searched MEDLINE®, Embase, CINAHL, and Cochrane Library from January 2000
171 to August 2019. The literature search will be updated prior to preparation of the final report. The
172 search strategy for the MEDLINE® search is provided in Appendix A. We will search references
173 of the primary studies and published systematic reviews for relevant studies. We will also
174 search ClinicalTrials.gov and conference proceedings for unpublished or ongoing clinical trials.

175

176 **Study selection process**

177 We will conduct the study selection in two stages: stage one is abstract triage and stage
178 two is full-text triage. All studies in stage one and stage two of the study selection process will
179 be reviewed independently by two members of the review team. Abstracts included by one
180 reviewer will move on to full-text review. At the full text review stage, both reviewers must agree
181 on study inclusion or exclusion. Disagreements will be resolved through discussion and
182 evaluation by a third reviewer, if needed.

183

184 **Data extraction and management**

185 Data extraction forms will be piloted by three members of the review team. Final data
186 extraction will be conducted by one investigator with verification by a second team member.
187 Disagreements in data extraction will be resolved by consensus that includes the senior
188 investigator (TJW). Data that will be extracted include information related to study
189 characteristics (primary author, year published, country, funding source, setting, and study
190 population); participant inclusion and exclusion criteria; descriptions of intervention and
191 comparator (oxygen therapy or NIV settings, adjustment parameters, and follow-up duration);

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192 participant demographics (age, race/ethnicity, gender, comorbidities, and baseline physiologic
193 parameters such as SpO₂, respiratory rate, PaO₂/FiO₂ ratio, pH, PaO₂, and PCO₂); and outcome
194 data (patient-centered outcomes and intermediate outcomes). The data extraction form with the
195 full list of information that will be extracted is provided in Appendix B. Data extraction will be
196 stratified by setting; depending on data availability, we will also stratify data by comparator and
197 by diagnosis or underlying disease.

198

199 **Data synthesis and analysis**

200 We will examine the clinical and methodological heterogeneity to determine
201 appropriateness of quantitative synthesis. Analyses will be conducted by a systematic review
202 methodologist. We will use Comprehensive Meta Analysis V.3 or R for pooled analyses. We will
203 calculate risk ratios and Peto odds ratios (for rare events) and corresponding 95% confidence
204 intervals for categorical outcomes. Mean and standardized mean difference will be calculated
205 for continuous outcomes. Heterogeneity will be assessed by using the I² test. An I² statistic of 75
206 or greater may indicate substantial heterogeneity. If heterogeneity exists, we will conduct
207 sensitivity analyses to explore potential causes of heterogeneity. We will pool studies with
208 clinically homogeneous (population, intervention, setting, outcome measures) studies with
209 sufficient outcomes information. We will also pool data from studies deemed of low to moderate
210 risk of bias (ROB). We will extract data from high ROB studies and include them in sensitivity
211 analyses. If quantitative synthesis is not appropriate, findings will be summarized narratively.

212

213 **Assessment of bias in individual studies**

214 We will assess the risk of bias using a modification of the Cochrane guidance for
215 randomized trials (19). Components of risk of bias assessment will include sequence
216 generation, allocation concealment, blinding, attrition, and appropriateness of analytic methods.
217 One reviewer will conduct risk of bias assessments at the study level and will be verified by a

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218 second reviewer. Disagreements will be resolved through discussion and evaluation by a third
219 reviewer. If appropriate, we may conduct sensitivity analyses excluding high risk of bias studies.

220 We will attempt to reduce the risk of publication bias by doing a comprehensive search
221 across multiple data bases and with input from ACP-CGC and TEP members. We do not
222 anticipate that there will be sufficient studies by population, intervention, and outcome to
223 conduct funnel plots assessing for publication bias across studies. We will look at protocol
224 papers, where available, to assess whether outcomes were pre-specified and whether all
225 outcomes are reported.

226

227 **Assessment of the certainty of the body of evidence**

228 We will use the Grading of Recommendations, Assessment, Development, and
229 Evaluation (GRADE) methodology to rate overall certainty of evidence for the critical outcomes
230 identified by the ACP as high, moderate, low, or very low (20, 21).

231

232 **Patient and public involvement**

233 The list of patient-centered outcomes that will be evaluated in this systematic evidence
234 review was developed and rated as critical or important with input from nonphysician public
235 representatives.

236

237 **Ethics and dissemination**

238 No ethical approval will be needed because we will be using data from previously
239 published studies in which informed consent was obtained by the primary investigators. We will
240 publish our results in a peer-reviewed journal.

241

242 **CONCLUSION**

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243 This systematic review will provide a comprehensive evaluation of the evidence
244 regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the
245 management of ARF in hospitalized adult patients to inform clinical practice and to identify
246 research gaps in the management of acute respiratory failure in hospitalized adults. The results
247 will inform the work of the ACP-CGC in their development of a clinical guideline related to use of
248 HFNO in adult patients with ARF.

249
250 **Author contributions:** TJW is the guarantor. AKB, AM, NG, BNM, TJW contributed to study
251 design and the PROSPERO protocol. NG developed the search strategy and the risk of bias
252 assessment strategy. BNM and NG developed the data extraction tables. AKB drafted the
253 protocol manuscript. AKB and AM provided expertise on acute respiratory failure management.
254 RM provided statistical expertise. All authors provided critical revisions and approved the final
255 manuscript.

256
257 **Support:** This review is funded by a contract with the American College of Physicians (ACP).
258 The ACP-Clinical Guideline Committee (CGC) assisted in the development of key questions,
259 study inclusion criteria, and outcome measures of interest but will not be involved in data
260 collection, analysis, or manuscript preparation.

261
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263 public representatives, and the technical expert panel (TEP) members who have provided
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265 Andrew Dunn, MD, MPH, SFHM, MACP; Matthew G. Drake, MD; and Robert C. Hyzy, MD.

266
267 **Competing interests:** TJW is Chair of the ACP-CGC. He will be recused from voting on or
268 authoring the ACP guidelines. All other authors have no conflict of interests to declare.

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Data statement: Data sharing is not applicable as no datasets were generated and/or analyzed for this protocol paper.

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Appendix A. MEDLINE® search strategy

- 1 (high flow nasal adj2 (cannula\$ or oxygen\$ or therap\$ or insufflation\$)).mp.
- 2 high flow therapy.mp.
- 3 nasal high flow.mp.
- 4 high flow oxygen.mp.
- 5 (humidified high flow or humidified oxygen).mp.
- 6 (HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
- 7 (Vapotherm or Optiflow or "Comfort Flo").ti,ab.
- 8 or/1-7
- 9 remove duplicates from 8
- 10 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
- 11 (random\$ adj (enroll\$ or assign\$ or allocat\$)).ti,ab.
- 12 ((randomi#ed or controlled or clinical) adj2 trial\$).ti,ab.
- 13 or/10-12
- 14 9 and 13
- 15 (meta-analy\$ or metaanaly\$ or meta analy\$).ti,ab.
- 16 exp Meta-Analysis/
- 17 (systematic adj2 (review\$ or overview\$)).ti,ab.
- 18 (rapid review or meta synthesis or metasyntesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
- 19 or/15-18
- 20 9 and 19
- 21 limit 14 to english language
- 22 limit 21 to yr="1995 -Current"
- 23 limit 22 to "all child (0 to 18 years)"
- 24 limit 23 to "all adult (19 plus years)"
- 25 22 not 23
- 26 24 or 25
- 27 limit 20 to english language
- 28 limit 27 to yr="2015 -Current"
- 29 limit 28 to "all child (0 to 18 years)"
- 30 limit 29 to "all adult (19 plus years)"
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Appendix B. Data extraction tables

Table 1. Study Characteristics

Author, year Country Funding Setting Special population Risk of Bias	Inclusion/Exclusion Criteria	Intervention (n) Comparator (n) Follow-up (primary outcome)	Demographics
	Inclusion: Exclusion:	Intervention: Comparator: Follow-up:	N= Age (mean): Race/ethnicity (%): White: Black: Other: Gender (% male): Comorbidities (%): Chronic Respiratory Failure: COPD: Congestive Heart Failure: Comorbidity Index: Baseline characteristics: SpO ₂ : Respiratory Rate: PaO ₂ /FiO ₂ ratio: pH: PaO ₂ : PaCO ₂ :

Table 2. Risk of Bias Assessment for Included Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias

Table 3. Treatment Characteristics

Author Year Setting Follow-up Comparator	Adherence to treatment—describe measure		Treatment Settings				Treatment Weaning Criteria	
	Intervention	Control	Protocol		Received		Intervention	Control
			Intervention	Control	Intervention	Control		
			Flow Rate: FiO2: Temperature: Duration:	Flow Rate: FiO2: Temperature: : Duration:	Flow Rate: FiO2: Temperature: Duration:	Flow Rate: FiO2: Temperature: : Duration:		

Table 4: Patient-Centered Outcomes, Part 1

Author Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N) (mean # of days)				Length of Hospital Stay (mean # of days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

Table 5: Patient-Centered Outcomes, Part 2

Author Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Intubation % (n/N) (mean # of days)				Patient Comfort (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

Table 6: Patient-Centered Outcomes, Part 3

Author Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)—describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control

Table 7: Patient-Centered Outcomes, Part 4

Author Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

Table 8: Patient-Centered Outcomes, Part 5

Author Year Setting Follow-up Comparator	Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control

Table 9: Intermediate Outcomes, Part 1

Author Year Setting Follow-up Comparator	Respiratory Rate (mean, SD)		PaO ₂ /FiO ₂ ratio (mean, SD)		SpO ₂ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

Table 10: Intermediate Outcomes, Part 2

Author Year Setting Follow-up Comparator	pH (mean, SD)		PaO ₂ (mean, SD)		PaCO ₂ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

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PRISMA-P 2015 Checklist

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

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	71. Awaiting registration number.
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	25-31
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	250-255
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	N/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	92-107

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	110-117
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	125-167
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	169-174
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	169-174
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	184-197
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	176-182
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	184-197
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	184-197
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	142-154
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	213-225
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	199-211
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	199-211

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	199-211
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	211
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-225
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-230

BMJ Open

Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: a systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034956.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Nov-2019
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Respiratory medicine, Intensive care, Evidence based practice
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), INTERNAL MEDICINE, INTENSIVE & CRITICAL CARE, Adult thoracic medicine < THORACIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult intensive & critical care < INTENSIVE & CRITICAL CARE

SCHOLARONE™
Manuscripts

PROTOCOL:**Effectiveness and harms of high-flow nasal oxygen (HFNO)
for acute respiratory failure: a systematic review protocol****Authors' full names:**

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36 **ABSTRACT**

38 **Introduction**

39 High-flow nasal oxygen (HFNO) use in adults hospitalized with acute respiratory failure
40 (ARF) is increasing. However, evidence to support widespread use of HFNO compared to
41 noninvasive ventilation (NIV) and conventional oxygen therapy (COT) is unclear. This protocol
42 describes the methods for a systematic evidence review regarding the comparative
43 effectiveness and harms of HFNO compared to NIV or COT for the management of ARF in
44 hospitalized adult patients.

46 **Methods and analysis**

47 We will search MEDLINE®, Embase, CINAHL, and Cochrane Library for randomized-
48 controlled trials (RCTs) of adult patients hospitalized with ARF or who developed ARF while
49 hospitalized. ARF will be defined as $SpO_2 < 90\%$, $PaO_2:FiO_2$ ratio ≤ 300 , $PaO_2 \leq 60$ mmHg, or
50 $PaCO_2 \geq 45$ mmHg. The intervention is HFNO (humidified oxygen, flow rate ≥ 20 L/min)
51 compared separately to NIV or COT. The critical outcomes are: all-cause mortality, hospital-
52 acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU)
53 admission/transfers, patient comfort, and hospital length of stay. The important outcomes are:
54 delirium, 30-day hospital readmissions, barotrauma, compromised nutrition (enteral or
55 parenteral nutrition), gastric dysfunction, functional independence at discharge, and skin
56 breakdown or pressure ulcers. We will calculate risk ratios and Peto odds ratios (for rare events)
57 and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized
58 mean difference will be calculated for continuous outcomes. Where possible and appropriate,
59 meta-analysis will be performed for each outcome.

61 **Conclusion**

1
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3 62 This systematic review will provide a comprehensive evaluation of the evidence
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5 63 regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the
6
7 64 management of ARF in hospitalized adult patients to inform clinical practice and to identify
8
9 65 research gaps in the management of ARF in hospitalized adults. The results will inform the work
10
11 66 of the ACP-CGC in their development of a clinical guideline related to use of HFNO in adult
12
13 67 patients with ARF.
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17 69 **Ethics and dissemination**

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20 70 No ethical approval will be needed because we will be using data from previously
21
22 71 published studies in which informed consent was obtained by the primary investigators. We will
23
24 72 publish our results in a peer-reviewed journal.
25

26 73

27
28 74 **PROSPERO registration:** CRD42019146691
29

30 75

31
32 76 **MeSH keywords:** systematic review; oxygen inhalation therapy; respiratory failure; respiratory
33
34 77 tract diseases; positive-pressure respiration; high-flow nasal oxygen
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39 79 **Word count:** 1,969
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41 80

42 81 **Strengths and limitations of this study:**

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45 82
 - 46 83 ■ We will compare high-flow nasal oxygen (HFNO) to both noninvasive ventilation and
 - 47 84 ■ We will evaluate the efficacy and harms of HFNO in a wide-range of clinical conditions
 - 48 85 (e.g. chronic obstructive pulmonary disease, cardiogenic pulmonary edema,
 - 49 86 immunosuppressed, post-surgery, post-extubation, etc.) and multiple clinical settings

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2
3 87 (emergency department, intensive care unit, intermediate/step-down unit, and hospital
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5 88 ward).

6
7 89 ▪ The comprehensive list of clinically-relevant outcomes that will be evaluated in this
8
9 90 systematic evidence review was developed with input from physician and nonphysician
10
11 91 public representatives.

12
13 92 ▪ This systematic evidence review of HFNO will be limited to studies evaluating patients
14
15 93 who meet criteria for acute respiratory failure.

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17 94 ▪ We will exclude studies that evaluated HFNO for oxygenation support before
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19 95 (preoxygenation) and during intubation.
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97 INTRODUCTION

98 High-flow nasal oxygen (HFNO) therapy is a mode of noninvasive oxygen support that
99 has been used in neonatal and pediatric settings for over a decade. In recent years, HFNO use
100 in adults hospitalized with acute respiratory failure (ARF) has been increasing. HFNO delivers
101 warmed, humidified oxygen with fraction of inspired oxygen (FiO₂) up to 1.0 and maximum flow
102 rate of 60 L/min. Several potential physiologic advantages of HFNO over noninvasive ventilation
103 (NIV) and conventional oxygen therapy (COT) have been proposed (1, 2). These include patient
104 comfort (3-5), improved oxygenation and ventilation (6, 7), clearance of airway secretions (8, 9),
105 and reduced work of breathing (4, 10, 11). These theoretical benefits are attributed to HFNO
106 delivery through small, pliable nasal cannula, washout of anatomic dead space (12), high
107 oxygen flow rates (13, 14), generation of low level positive-end expiratory pressure (PEEP) (15-
108 19), and heated humidification.

109 Given the increasing use of HFNO and the lack of robust evidence to support its
110 widespread use in adult patients with ARF, the Minnesota Evidence Synthesis and
111 Dissemination Center was commissioned by the American College of Physicians (ACP) to
112 systematically review the evidence regarding the comparative effectiveness and harms of
113 HFNO compared to NIV or COT for the management of ARF in hospitalized adult patients.
114 Compared to existing reviews in this area, this systematic evidence review will include a broader
115 scope that will compare HFNO to both NIV and COT, assess a wider range of clinical conditions
116 in multiple clinical settings, and evaluate a more comprehensive list of key clinical outcomes.
117 Furthermore, an updated review will include evidence from recently published clinical trials. This
118 systematic review will be used by the ACP-Clinical Guidelines Committee (ACP-CGC) to
119 develop a clinical practice guideline for the use of HFNO in acute respiratory failure. With input
120 from the ACP-Clinical Guidelines Committee (ACP-CGC) (20) and a technical expert panel
121 (TEP), we developed the following key questions (KQ):

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3 122 KQ 1. What is the comparative effectiveness of HFNO versus NIV or COT for hospitalized
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5 123 patients with ARF? Does comparative effectiveness of HFNO vary by patient
6
7 124 characteristics, disease/diagnosis characteristics, protocol/device settings, or location of
8
9 125 administration?
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12
13 127 KQ 2. What are the harms of HFNO versus NIV or COT for hospitalized patients with
14
15 128 ARF? Do harms vary by patient characteristics, disease/diagnosis, protocol/device
16
17 129 settings, or location of administration?
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21 131 **METHODS**

22 132 In accordance with the guidelines, our systematic review protocol was registered with
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24 133 the International Prospective Register of Systematic Reviews (PROSPERO) on August 8, 2019.
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26 134 We will report our findings according to the Preferred Reporting Items for Systematic Reviews
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28 135 and Meta-Analyses (PRISMA) 2009 statement (21).
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32 137 **Eligibility criteria**

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35 138 All studies that will be included in this systematic review will be selected in accordance
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37 139 with the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Study Design)
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39 140 framework (Appendix A). A study will be included if at least 75% of the participants meet the
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41 141 inclusion criteria.
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45 143 **Population**

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47 144 We will include all adult patients (age ≥ 18 years) with ARF at the time of study enrollment.
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49 145 A study will be included if at least one criterion for ARF is met: $SpO_2 < 90\%$, $PaO_2:FIO_2$
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51 146 ratio ≤ 300 , $PaO_2 \leq 60$ mmHg, or $PaCO_2 \geq 45$ mmHg.
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3 148 **Intervention**

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5 149 The intervention of interest is HFNO, defined as humidified oxygen with flow rates ≥ 20
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7 150 L/min.
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11 152 **Comparators**

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13 153 We will compare HFNO vs. NIV (continuous or bilevel positive airway pressure ventilation
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15 154 [CPAP or BiPAP®]) and HFNO vs. COT (e.g. oxygen delivered through nasal cannula,
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17 155 simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask,
18
19 156 etc.).
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24 158 **Outcome measures**

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26 159 We will examine several patient-related outcomes and intermediate outcomes. With input
27
28 160 from the ACP-CGC that included physician and nonphysician public representatives,
29
30 161 outcomes were identified as critical or important. The critical outcomes are: all-cause
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32 162 mortality (in-hospital and the longest available through 90 days), hospital-acquired
33
34 163 pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU)
35
36 164 admission/transfers, patient comfort, and hospital length of stay. The important outcomes
37
38 165 are: delirium, 30-day hospital readmissions, barotrauma (pneumothorax,
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40 166 pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury), compromised
41
42 167 nutrition (enteral or parenteral nutrition), gastric dysfunction (placement of nasogastric
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44 168 tube, abdominal distension, nausea, or vomiting), functional independence at discharge,
45
46 169 discharge disposition (home, assisted-living facility, nursing home, or long-term care
47
48 170 hospital), and skin breakdown or pressure ulcers. Intermediate outcomes are: respiratory
49
50 171 rate, $\text{PaO}_2/\text{FiO}_2$ ratio, SpO_2 , pH, PaO_2 , PCO_2 , treatment escalation, and device
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52 172 intolerance. If multiple points are reported, we will categorize these as “short” (first time
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3 173 point) and “longer” (last time point) term outcomes. We will also explore analyses based
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5 174 on commonly reported time points.
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9 176 ***Timing***

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11 177 We will include patients hospitalized for ARF or who developed ARF while hospitalized,
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13 178 including patients with ARF post-extubation or post-surgery. We will exclude studies
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15 179 evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.
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20 181 ***Setting***

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22 182 We will include studies that randomized patients in the hospital (including hospital wards,
23
24 183 intermediate/step-down units, and intensive care units) and emergency department.
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28 185 ***Study design***

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30 186 Randomized controlled trials (RCTs) including crossover RCTs and cluster RCTs with full-
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32 187 text reports in English will be included. We will exclude non-randomized trials and
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34 188 observational studies.
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39 190 **Data sources and search strategy**

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41 191 We will search MEDLINE®, Embase, CINAHL, and Cochrane Library from January 2000
42
43 192 to August 2019. HFNO was not widely used in adults prior to 2000.” The literature search will be
44
45 193 updated prior to preparation of the final report. The search strategy for the MEDLINE® search is
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47 194 provided in Appendix B. We will search references of the primary studies and published
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49 195 systematic reviews for relevant studies. We will also search ClinicalTrials.gov for recently
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51 196 completed or ongoing clinical trials.
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56 198 **Study selection process**

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3 199 We will conduct the study selection in two stages: stage one is abstract triage and stage
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5 200 two is full-text triage. All studies in stage one and stage two of the study selection process will
6
7 201 be reviewed independently by two members of the review team. Abstracts included by one
8
9 202 reviewer will move on to full-text review. At the full text review stage, both reviewers must agree
10
11 203 on study inclusion or exclusion. Disagreements will be resolved through discussion and
12
13 204 evaluation by a third reviewer, if needed.
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17 18 206 **Data extraction and management**

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20 207 Data extraction forms will be piloted by three members of the review team. Final data
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22 208 extraction will be conducted by one investigator with verification by a second team member.
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24 209 Disagreements in data extraction will be resolved by consensus that includes the senior
25
26 210 investigator (TJW). Data that will be extracted include information related to study
27
28 211 characteristics (primary author, year published, country, funding source, setting, and study
29
30 212 population); participant inclusion and exclusion criteria; descriptions of intervention and
31
32 213 comparator (oxygen therapy or NIV settings, adjustment parameters, and follow-up duration);
33
34 214 participant demographics (age, race/ethnicity, gender, comorbidities, and baseline physiologic
35
36 215 parameters such as SpO₂, respiratory rate, PaO₂/FiO₂ ratio, pH, PaO₂, and PCO₂); and outcome
37
38 216 data (patient-centered outcomes and intermediate outcomes). The data extraction form with the
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40 217 full list of information that will be extracted is provided in Appendix C. Data will be extracted
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42 218 similarly for all eligible studies and then subgroup analyses will be performed.
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46 47 220 **Data synthesis and analysis**

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49 221 We will examine the clinical and methodological heterogeneity to determine
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51 222 appropriateness of quantitative synthesis. Cluster RCTs will be evaluated for statistical
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53 223 measures that adjust for clustering. Analyses will be conducted by a systematic review
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55 224 methodologist. We will use Comprehensive Meta Analysis V.3 or R for pooled analyses. We will
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3 225 calculate risk ratios and Peto odds ratios (for rare events) and corresponding 95% confidence
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5 226 intervals for categorical outcomes. Mean and standardized mean difference will be calculated
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7 227 for continuous outcomes. Heterogeneity will be assessed by using the I^2 statistic, Chi-squared
8
9 228 test, and visual inspection of the forest plots. An I^2 statistic of 75 or greater may indicate
10
11 229 substantial heterogeneity. If heterogeneity exists, we will conduct sensitivity analyses to explore
12
13 230 potential causes of heterogeneity. We will pool clinically homogeneous (population, intervention,
14
15 231 setting, outcome measures) studies with sufficient outcomes information. We will also pool data
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17 232 from studies deemed of low to moderate risk of bias (ROB). We will extract data from high ROB
18
19 233 studies and include them in sensitivity analyses. If quantitative synthesis is not appropriate,
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21 234 findings will be summarized narratively.
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26 236 **Subgroup analysis**

28 237 If sufficient data allows, we plan to perform analysis on the following subgroups of
29
30 238 interest: (1) noninvasive ventilator (NIV) vs. conventional oxygen therapy (COT); (2) emergency
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32 239 department (ED), ICU, hospital ward/step down, or mixed settings; (3) chronic obstructive
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34 240 pulmonary disease (COPD), cardiogenic pulmonary edema/acute decompensated heart failure,
35
36 241 pneumonia, obese, post-extubation, post-surgical, immunocompromised, (4) hypoxic,
37
38 242 hypercapnic, and mixed (hypoxic or hypercapnic) respiratory failure; (5) treatment duration <6
39
40 243 vs. ≥6 hours; and (6) lower (≤30 L/min) vs. higher (>30 L/min) flow settings.
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43 244 We hypothesize that: (1) HFNO is more beneficial than COT, but is as effective, though
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45 245 less comfortable, than NIV; (2) the efficacy of HFNO is likely the same as NIV, but better than
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47 246 COT, in different settings; (3) HFNO is as effective as NIV in COPD, pneumonia, post-
48
49 247 extubation, and post-surgical patients; (4) HFNO is less effective than NIV in cardiogenic
50
51 248 pulmonary edema and obesity due to lower level of PEEP; (5) HFNO is more effective than
52
53 249 COT in most disease states; (6) HFNO is more effective and less harmful than NIV in hypoxic
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55 250 respiratory failure, but is less effective in hypercapnic and mixed hypoxic and hypercapnic
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3 251 respiratory failure; and (7) higher flow (>30 L/min) is more effective, but is less comfortable, than
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5 252 lower flow (\leq 30 L/min) settings. If subgroup analyses are performed, we will assess subgroup
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7 253 effects with an I^2 statistic for subgroup differences. The I^2 statistic delineates the percentage of
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9 254 variability in the estimates of effect between the different subgroups that is due to real subgroup
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11 255 differences (as opposed to sampling error).
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15 16 257 **Assessment of bias in individual studies**

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18 258 We will assess the risk of bias using a modification of the Cochrane guidance for
19
20 259 randomized trials (22). Individual elements will be rated low, unclear, or high risk of bias. Our
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22 260 modification of the tool is to identify overall study risk of bias as low, moderate, or high. A study
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24 261 with unclear elements will be considered moderate risk of bias. Components of risk of bias
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26 262 assessment will include sequence generation, allocation concealment, blinding, attrition, and
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28 263 appropriateness of analytic methods. One reviewer will conduct risk of bias assessments at the
29
30 264 study level and will be verified by a second reviewer. Disagreements will be resolved through
31
32 265 discussion and evaluation by a third reviewer. If appropriate, we may conduct sensitivity
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34 266 analyses excluding high risk of bias studies.
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37 267 We will attempt to reduce the risk of publication bias by doing a comprehensive search
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39 268 across multiple data bases and with input from ACP-CGC and TEP members. We will conduct
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41 269 funnel plot analysis to assess for publication bias across studies if sufficient studies are found.
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43 270 We will look at protocol papers, where available, to assess whether outcomes were pre-
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45 271 specified and whether all outcomes are reported.
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49 50 273 **Assessment of the certainty of the body of evidence**

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52 274 We will use the Grading of Recommendations, Assessment, Development, and
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54 275 Evaluation (GRADE) methodology to rate overall certainty of evidence for the critical outcomes
55
56 276 identified by the ACP as high, moderate, low, or very low (23, 24).
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45 278 **Patient and public involvement**

7 279 The list of patient-centered outcomes that will be evaluated in this systematic evidence
8 review was developed and rated as critical or important with input from nonphysician public
9 representatives.
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15 283 **Ethics and dissemination**

17 284 No ethical approval will be needed because we will be using data from previously
18 published studies in which informed consent was obtained by the primary investigators. We will
19 publish our results in a peer-reviewed journal.
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26 288 **CONCLUSION**

27 289 This systematic review will provide a comprehensive evaluation of the evidence
28 regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the
29 management of ARF in hospitalized adult patients to inform clinical practice and to identify
30 research gaps in the management of acute respiratory failure in hospitalized adults. The results
31 will inform the work of the ACP-CGC in their development of a clinical guideline related to use of
32 HFNO in adult patients with ARF.
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39 296 **Author contributions:** TJW is the guarantor. AKB, AM, NG, BNM, TJW contributed to study
40 design and the PROSPERO protocol. NG developed the search strategy and the risk of bias
41 assessment strategy. BNM and NG developed the data extraction tables. AKB drafted the
42 protocol manuscript. AKB and AM provided expertise on acute respiratory failure management.
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2
3 303 **Support:** This review is funded by a contract with the American College of Physicians (ACP).
4
5 304 The ACP-Clinical Guideline Committee (CGC) assisted in the development of key questions,
6
7 305 study inclusion criteria, and outcome measures of interest but will not be involved in data
8
9 306 collection, analysis, or manuscript preparation.
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22 312
23
24 313 **Competing interests:** TJW is Chair of the ACP-CGC. He will be recused from voting on or
25
26 314 authoring the ACP guidelines. All other authors have no conflict of interests to declare.
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31 316 **Data statement:** Data sharing is not applicable as no datasets were generated and/or analyzed
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33 317 for this protocol paper.
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For peer review only

Appendix A. Key Questions and PICOTS

KEY QUESTIONS

1) What is the comparative effectiveness of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen for hospitalized patients?

1a) Does comparative effectiveness of high flow nasal oxygen vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

2) What are the harms of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®), invasive mechanical ventilation, or conventional oxygen for hospitalized patients?

2a) Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

PICOTS	
Population:	Hospitalized adult patients with acute respiratory failure (ARF). ARF defined as SpO ₂ <90%, PaO ₂ :FiO ₂ ratio ≤300, PaO ₂ ≤60 mmHg, or PaCO ₂ ≥45 mmHg
Intervention:	High flow nasal oxygen (humidified, ≥20 l/min)
Comparators:	Noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen (e.g., simple, Venturi, or nonrebreather oxygen masks)
Outcomes:	<p>Patient-centered Outcomes: all-cause mortality (in-hospital and 90 day), intubation/reintubation (days of intubation), hospital length of stay, ICU admissions/transfers (ICU days), patient comfort, hospital readmissions (30 day) (e.g., all-cause, pneumonia), functional independence at discharge (e.g., scale scores, measures of independence/activities of daily living), discharge disposition</p> <p>Intermediate Outcomes: respiratory rate, PaO₂/FiO₂ ratio, SpO₂, pH, PaO₂, PaCO₂, treatment escalation, device intolerance</p> <p>Cost/resource utilization</p> <p>Harms: skin breakdown or pressure ulcers, gastric dysfunction, hospital-acquired pneumonia, compromised nutrition (enteral or parenteral nutrition), delirium, barotrauma</p>
Timing:	Hospitalization for ARF or development of ARF while hospitalized; immediate post-extubation; post-surgery. Exclude pre-intubation/pre-oxygenation and HFNO oxygenation support during intubation
Setting:	Hospital (including ICU, step down units, hospital wards), emergency department
Study Design:	Randomized controlled trials, including crossover RCTs and cluster RCTs
Subgroups:	<p>Patient characteristics: age, race, gender</p> <p>Disease/diagnosis (e.g. COPD, cardiogenic pulmonary edema, immunosuppressed, post-extubation, post-surgery; hypoxic, hypercapnic, or mixed [hypoxic or hypercapnic] respiratory failure)</p> <p>Protocol/device settings (e.g., flow rate ≤30 vs. >30 L/min; treatment duration <6 vs. ≥6 hours)</p>

BiPAP=Bilevel Positive Airway Pressure; CPAP=continuous positive airway pressure; ICU=intensive care unit; COPD= chronic obstructive pulmonary disease

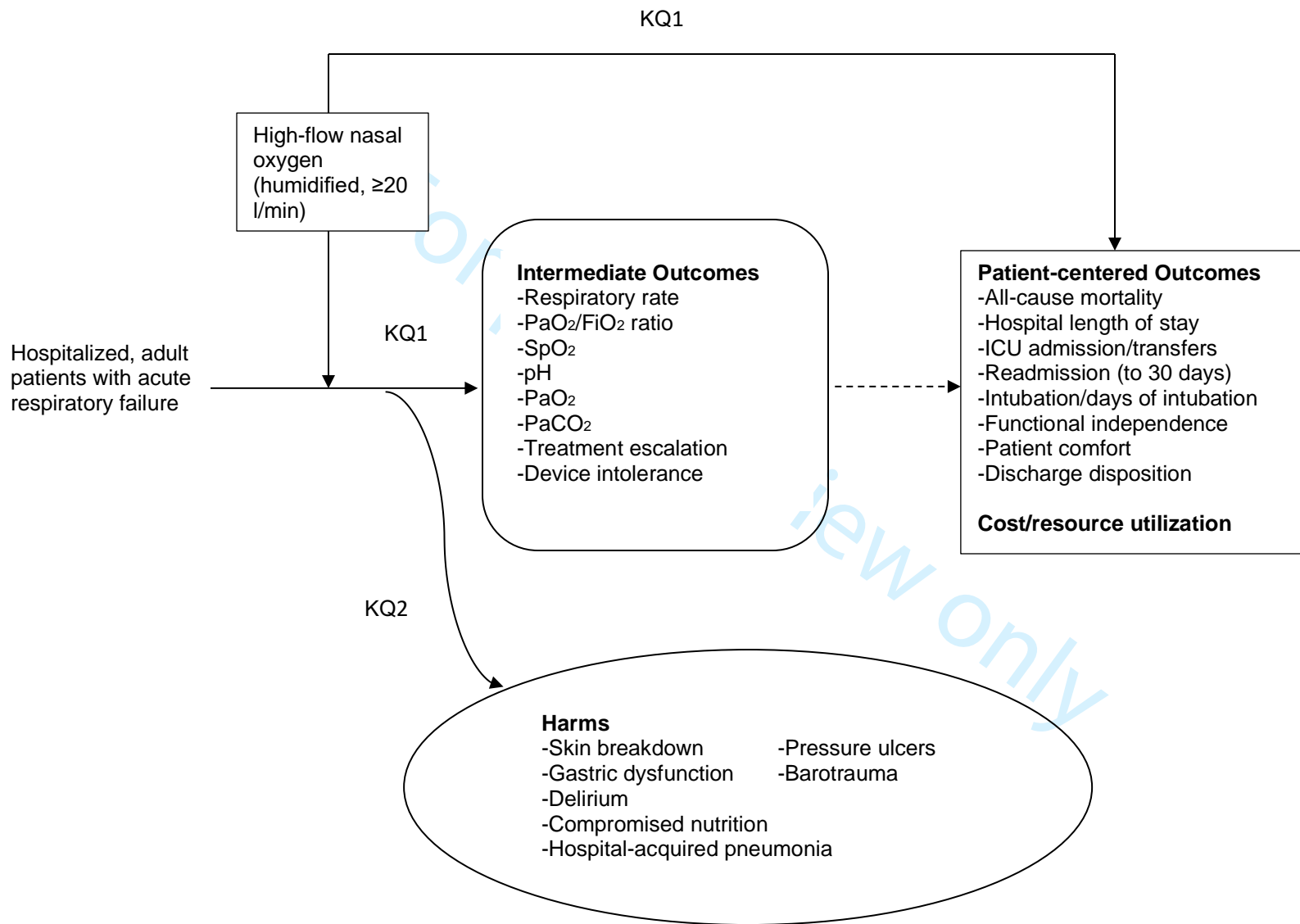
LITERATURE SEARCH

RCTs: We will search MEDLINE, Embase, CINAHL, and Cochrane Library from 2000 to August 2019

Clinicaltrials.gov for recently completed and/or on-going trials

Reference lists from relevant systematic reviews for references missed by our database searches

Analytic Framework



Appendix B. MEDLINE® search strategy

- 1 (high flow nasal adj2 (cannula\$ or oxygen\$ or therap\$ or insufflation\$)).mp.
- 2 high flow therapy.mp.
- 3 nasal high flow.mp.
- 4 high flow oxygen.mp.
- 5 (humidified high flow or humidified oxygen).mp.
- 6 (HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
- 7 (Vapotherm or Optiflow or "Comfort Flo").ti,ab.
- 8 or/1-7
- 9 remove duplicates from 8
- 10 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
- 11 (random\$ adj (enroll\$ or assign\$ or allocat\$)).ti,ab.
- 12 ((randomi#ed or controlled or clinical) adj2 trial\$).ti,ab.
- 13 or/10-12
- 14 9 and 13
- 15 (meta-analy\$ or metaanaly\$ or meta analy\$).ti,ab.
- 16 exp Meta-Analysis/
- 17 (systematic adj2 (review\$ or overview\$)).ti,ab.
- 18 (rapid review or meta synthesis or metasyntesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
- 19 or/15-18
- 20 9 and 19
- 21 limit 14 to english language
- 22 limit 21 to yr="1995 -Current"
- 23 limit 22 to "all child (0 to 18 years)"
- 24 limit 23 to "all adult (19 plus years)"
- 25 22 not 23
- 26 24 or 25
- 27 limit 20 to english language
- 28 limit 27 to yr="2015 -Current"
- 29 limit 28 to "all child (0 to 18 years)"
- 30 limit 29 to "all adult (19 plus years)"
- 31 28 not 29
- 32 30 or 31

Appendix C. Data extraction forms

Table 1. Study Characteristics

Author, year Country Funding Setting Special population Risk of Bias rating	Inclusion/Exclusion Criteria	Intervention (n) Comparator (n) Follow-up (primary outcome)	Demographics
	Inclusion: Exclusion:	Intervention: Comparator: Follow-up:	N= Age (mean): Race/ethnicity (%): White: Black: Other: Gender (% male): Comorbidities (%): Chronic Respiratory Failure: COPD: Congestive Heart Failure: Comorbidity Index: Baseline characteristics: SpO ₂ : Respiratory Rate: PaO ₂ /FiO ₂ ratio: pH: PaO ₂ : PaCO ₂ :

Table 2. Risk of Bias Assessment for Included Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias

Table 3. Treatment Characteristics

Author Year Setting Follow-up Comparator	Adherence/Intolerance describe measure		Treatment Settings				Treatment Weaning Criteria		
	Intervention	Control	Protocol		Received		Provider Discretion	Protocol or Definition	Not Reported

COT=conventional oxygen therapy; HFFM=high-flow face mask; HFNC=high-flow nasal cannula; NIV=non-invasive ventilation; NR=not reported; PEEP=positive end-expiratory pressure

Table 4: Patient-Centered Outcomes, Part 1

Author Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N) (mean # of days)				Length of Hospital Stay (mean # of days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=Non-invasive ventilation; N/A=not applicable; NR=not reported; RD=risk difference; SD=standard deviation

Table 5: Patient-Centered Outcomes, Part 2

Author Year Setting Follow-up Comparator	Treatment Escalation (describe) % (n/N)		Intubation % (n/N) (mean # of days)				Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; VAS=visual analog scale

Table 6: Patient-Centered Outcomes, Part 3

Author Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)—describe measure		Patient Comfort (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant

Discharge Disposition: home, assisted living facility, nursing home, long-term care hospital

Table 7: Patient-Centered Outcomes, Part 4

Author Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported

Compromised Nutrition: (enteral/parenteral nutrition or days without nutrition)

Gastric Dysfunction: (placement of a nasogastric tube for decompression or treatment of abdominal distension/nausea/vomiting)

Table 8: Patient-Centered Outcomes, Part 5

Author Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; N/A=not applicable; NR=not reported

Barotrauma: (pneumothorax, pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury)

Table 9: Intermediate Outcomes, Part 1

Author Year Setting Follow-up Comparator	Respiratory Rate (mean, SD)		PaO ₂ /FiO ₂ ratio (mean, SD)		SpO ₂ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant; SD=standard deviation

Table 10: Intermediate Outcomes, Part 2

Author Year Setting Follow-up Comparator	pH (mean, SD)		PaO ₂ (mean, SD)		PaCO ₂ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported; SD=standard deviation

PRISMA-P 2015 Checklist

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

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	74	74
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	25-31
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	295-300
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	N/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-305
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-305
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-305
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	98-121

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	122-129
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	125-167
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	137-187
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	189-195
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	205-217
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	197-203
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	205-217
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	209-216 157-173
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	157-173
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	256-270
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	219-233

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	199-211
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	219-242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	232-233
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	266-270
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	272-275

BMJ Open

Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: a systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034956.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Dec-2019
Complete List of Authors:	Baldomero, Arianne; Minneapolis VA Health Care System; University of Minnesota, Pulmonary, Allergy, Critical Care, and Sleep Medicine Melzer, Anne; Minneapolis VA Health Care System; University of Minnesota, Pulmonary, Allergy, Critical Care, and Sleep Medicine Greer, Nancy; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research Majeski, Brittany; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research Macdonald, Roderick; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research Wilt, Timothy; Minneapolis VA Health Care System, Center for Care Delivery and Outcomes Research; University of Minnesota, Department of Medicine
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Respiratory medicine, Intensive care, Evidence based practice
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), INTERNAL MEDICINE, INTENSIVE & CRITICAL CARE, Adult thoracic medicine < THORACIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult intensive & critical care < INTENSIVE & CRITICAL CARE

SCHOLARONE™
Manuscripts

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36 **ABSTRACT**

38 **Introduction**

39 High-flow nasal oxygen (HFNO) use in adults hospitalized with acute respiratory failure
40 (ARF) is increasing. However, evidence to support widespread use of HFNO compared to
41 noninvasive ventilation (NIV) and conventional oxygen therapy (COT) is unclear. This protocol
42 describes the methods for a systematic evidence review regarding the comparative
43 effectiveness and harms of HFNO compared to NIV or COT for the management of ARF in
44 hospitalized adult patients.

46 **Methods and analysis**

47 We will search MEDLINE®, Embase, CINAHL, and Cochrane Library for randomized-
48 controlled trials (RCTs) of adult patients hospitalized with ARF or who developed ARF while
49 hospitalized. ARF will be defined as $SpO_2 < 90\%$, $PaO_2:FiO_2$ ratio ≤ 300 , $PaO_2 \leq 60$ mmHg, or
50 $PaCO_2 \geq 45$ mmHg. The intervention is HFNO (humidified oxygen, flow rate ≥ 20 L/min)
51 compared separately to NIV or COT. The critical outcomes are: all-cause mortality, hospital-
52 acquired pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU)
53 admission/transfers, patient comfort, and hospital length of stay. The important outcomes are:
54 delirium, 30-day hospital readmissions, barotrauma, compromised nutrition (enteral or
55 parenteral nutrition), gastric dysfunction, functional independence at discharge, and skin
56 breakdown or pressure ulcers. We will calculate risk ratios and Peto odds ratios (for rare events)
57 and corresponding 95% confidence intervals for categorical outcomes. Mean and standardized
58 mean difference will be calculated for continuous outcomes. Where possible and appropriate,
59 meta-analysis will be performed for each outcome.

61 **Conclusion**

1
2
3 62 This systematic review will provide a comprehensive evaluation of the evidence
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5 63 regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the
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7 64 management of ARF in hospitalized adult patients to inform clinical practice and to identify
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9 65 research gaps in the management of ARF in hospitalized adults. The results will inform the work
10
11 66 of the ACP-CGC in their development of a clinical guideline related to use of HFNO in adult
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13 67 patients with ARF.
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17 69 **Ethics and dissemination**

19
20 70 No ethical approval will be needed because we will be using data from previously
21
22 71 published studies in which informed consent was obtained by the primary investigators. We will
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24 72 publish our results in a peer-reviewed journal.
25

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28 74 **PROSPERO registration:** CRD42019146691
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30 75

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32 76 **MeSH keywords:** systematic review; oxygen inhalation therapy; respiratory failure; respiratory
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34 77 tract diseases; positive-pressure respiration; high-flow nasal oxygen
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36 78

37
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39 79 **Word count:** 1,969
40

41 80

42 81 **Strengths and limitations of this study:**

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45 82
 - We will compare high-flow nasal oxygen (HFNO) to both noninvasive ventilation and
- 46
47 83 conventional oxygen therapy.
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49 84
 - We will evaluate the efficacy and harms of HFNO in a wide-range of clinical conditions
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51 85 (e.g. chronic obstructive pulmonary disease, cardiogenic pulmonary edema,
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53 86 immunosuppressed, post-surgery, post-extubation, etc.) and multiple clinical settings
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3 87 (emergency department, intensive care unit, intermediate/step-down unit, and hospital
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5 88 ward).

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7 89 ▪ The comprehensive list of clinically-relevant outcomes that will be evaluated in this
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9 90 systematic evidence review was developed with input from physician and nonphysician
10
11 91 public representatives.

12
13 92 ▪ This systematic evidence review of HFNO will be limited to studies evaluating patients
14
15 93 who meet criteria for acute respiratory failure.

16
17 94 ▪ We will exclude studies that evaluated HFNO for oxygenation support before
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19 95 (preoxygenation) and during intubation.
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97 INTRODUCTION

98 High-flow nasal oxygen (HFNO) therapy is a mode of noninvasive oxygen support that
99 has been used in neonatal and pediatric settings for over a decade. In recent years, HFNO use
100 in adults hospitalized with acute respiratory failure (ARF) has been increasing. HFNO delivers
101 warmed, humidified oxygen with fraction of inspired oxygen (FiO₂) up to 1.0 and maximum flow
102 rate of 60 L/min. Several potential physiologic advantages of HFNO over noninvasive ventilation
103 (NIV) and conventional oxygen therapy (COT) have been proposed (1, 2). These include patient
104 comfort (3-5), improved oxygenation and ventilation (6, 7), clearance of airway secretions (8, 9),
105 and reduced work of breathing (4, 10, 11). These theoretical benefits are attributed to HFNO
106 delivery through small, pliable nasal cannula, washout of anatomic dead space (12), high
107 oxygen flow rates (13, 14), generation of low level positive-end expiratory pressure (PEEP) (15-
108 19), and heated humidification.

109 Given the increasing use of HFNO and the lack of robust evidence to support its
110 widespread use in adult patients with ARF, the Minnesota Evidence Synthesis and
111 Dissemination Center was commissioned by the American College of Physicians (ACP) to
112 systematically review the evidence regarding the comparative effectiveness and harms of
113 HFNO compared to NIV or COT for the management of ARF in hospitalized adult patients.
114 Compared to existing reviews in this area, this systematic evidence review will include a broader
115 scope that will compare HFNO to both NIV and COT, assess a wider range of clinical conditions
116 in multiple clinical settings, and evaluate a more comprehensive list of key clinical outcomes.
117 Furthermore, an updated review will include evidence from recently published clinical trials. This
118 systematic review will be used by the ACP-Clinical Guidelines Committee (ACP-CGC) to
119 develop a clinical practice guideline for the use of HFNO in acute respiratory failure. With input
120 from the ACP-Clinical Guidelines Committee (ACP-CGC) (20) and a technical expert panel
121 (TEP), we developed the following key questions (KQ):

1
2
3 122 KQ 1. What is the comparative effectiveness of HFNO versus NIV or COT for hospitalized
4
5 123 patients with ARF? Does comparative effectiveness of HFNO vary by patient
6
7 124 characteristics, disease/diagnosis characteristics, protocol/device settings, or location of
8
9 125 administration?
10

11 126
12
13 127 KQ 2. What are the harms of HFNO versus NIV or COT for hospitalized patients with
14
15 128 ARF? Do harms vary by patient characteristics, disease/diagnosis, protocol/device
16
17 129 settings, or location of administration?
18
19

20 130

21 131 **METHODS**

22 132 In accordance with the guidelines, our systematic review protocol was registered with
23
24 133 the International Prospective Register of Systematic Reviews (PROSPERO) on August 8, 2019.
25
26 134 We will report our findings according to the Preferred Reporting Items for Systematic Reviews
27
28 135 and Meta-Analyses (PRISMA) 2009 statement (21).
29
30

31 136

32 137 **Eligibility criteria**

33
34
35 138 All studies that will be included in this systematic review will be selected in accordance
36
37 139 with the PICOTS (Population, Intervention, Comparison, Outcomes, Timing, Study Design)
38
39 140 framework (Appendix A). A study will be included if at least 75% of the participants meet the
40
41 141 inclusion criteria.
42
43

44 142

45 143 **Population**

46
47 144 We will include all adult patients (age ≥ 18 years) with ARF at the time of study enrollment.
48
49 145 A study will be included if at least one criterion for ARF is met: $SpO_2 < 90\%$, $PaO_2:FIO_2$
50
51 146 ratio ≤ 300 , $PaO_2 \leq 60$ mmHg, or $PaCO_2 \geq 45$ mmHg.
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3 148 **Intervention**

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5 149 The intervention of interest is HFNO, defined as humidified oxygen with flow rates ≥ 20
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7 150 L/min.
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11 152 **Comparators**

12
13 153 We will compare HFNO vs. NIV (continuous or bilevel positive airway pressure ventilation
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15 [CPAP or BiPAP®]) and HFNO vs. COT (e.g. oxygen delivered through nasal cannula,
16 154
17 simple face mask, air-entrainment mask, partial rebreathing mask, non-rebreather mask,
18 155
19 etc.).
20 156
21

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23
24 158 **Outcome measures**

25
26 159 We will examine several patient-related outcomes and intermediate outcomes. With input
27
28 160 from the ACP-CGC that included physician and nonphysician public representatives,
29
30 161 outcomes were identified as critical or important. The critical outcomes are: all-cause
31
32 162 mortality (in-hospital and the longest available through 90 days), hospital-acquired
33
34 163 pneumonia, intubation/reintubation (days of intubation), intensive care unit (ICU)
35
36 164 admission/transfers, patient comfort, and hospital length of stay. The important outcomes
37
38 165 are: delirium, 30-day hospital readmissions, barotrauma (pneumothorax,
39
40 166 pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury), compromised
41
42 167 nutrition (enteral or parenteral nutrition), gastric dysfunction (placement of nasogastric
43
44 168 tube, abdominal distension, nausea, or vomiting), functional independence at discharge,
45
46 169 discharge disposition (home, assisted-living facility, nursing home, or long-term care
47
48 170 hospital), and skin breakdown or pressure ulcers. Intermediate outcomes are: respiratory
49
50 171 rate, $\text{PaO}_2/\text{FiO}_2$ ratio, SpO_2 , pH, PaO_2 , PCO_2 , treatment escalation, and device
51
52 172 intolerance. If multiple points are reported, we will categorize these as “short” (first time
53
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1
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3 173 point) and “longer” (last time point) term outcomes. We will also explore analyses based
4
5 174 on commonly reported time points.
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8
9 176 ***Timing***

10
11 177 We will include patients hospitalized for ARF or who developed ARF while hospitalized,
12
13 178 including patients with ARF post-extubation or post-surgery. We will exclude studies
14
15 179 evaluating HFNO for oxygenation support before (preoxygenation) and during intubation.
16
17 180

18
19
20 181 ***Setting***

21
22 182 We will include studies that randomized patients in the hospital (including hospital wards,
23
24 183 intermediate/step-down units, and intensive care units) and emergency department.
25

26 184

27
28 185 ***Study design***

29
30 186 Randomized controlled trials (RCTs) including crossover RCTs and cluster RCTs with full-
31
32 187 text reports in English will be included. We will exclude non-randomized trials and
33
34 188 observational studies.
35

36 189

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38
39 190 **Data sources and search strategy**

40
41 191 We will search MEDLINE[®], Embase, CINAHL, and Cochrane Library from January 2000
42
43 192 to August 2019. HFNO was not widely used in adults prior to 2000.” The literature search will be
44
45 193 updated prior to preparation of the final report. The search strategy for the MEDLINE[®] search is
46
47 194 provided in Appendix B. We will search references of the primary studies and published
48
49 195 systematic reviews for relevant studies. We will also search ClinicalTrials.gov for recently
50
51 196 completed or ongoing clinical trials.
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55
56 198 **Study selection process**

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2
3 199 We will conduct the study selection in two stages: stage one is abstract triage and stage
4
5 200 two is full-text triage. All studies in stage one and stage two of the study selection process will
6
7 201 be reviewed independently by two members of the review team. Abstracts included by one
8
9 202 reviewer will move on to full-text review. At the full text review stage, both reviewers must agree
10
11 203 on study inclusion or exclusion. Disagreements will be resolved through discussion and
12
13 204 evaluation by a third reviewer, if needed.
14
15
16 205

17 18 206 **Data extraction and management**

19
20 207 Data extraction forms will be piloted by three members of the review team. Final data
21
22 208 extraction will be conducted by one investigator with verification by a second team member.
23
24 209 Disagreements in data extraction will be resolved by consensus that includes the senior
25
26 210 investigator (TJW). Data that will be extracted include information related to study
27
28 211 characteristics (primary author, year published, country, funding source, setting, and study
29
30 212 population); participant inclusion and exclusion criteria; descriptions of intervention and
31
32 213 comparator (oxygen therapy or NIV settings, adjustment parameters, and follow-up duration);
33
34 214 participant demographics (age, race/ethnicity, gender, comorbidities, and baseline physiologic
35
36 215 parameters such as SpO₂, respiratory rate, PaO₂/FiO₂ ratio, pH, PaO₂, and PCO₂); and outcome
37
38 216 data (patient-centered outcomes and intermediate outcomes). The data extraction form with the
39
40 217 full list of information that will be extracted is provided in Appendix C. Data will be extracted
41
42 218 similarly for all eligible studies and then subgroup analyses will be performed.
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45 219

46 47 220 **Data synthesis and analysis**

48
49 221 We will examine the clinical and methodological heterogeneity to determine
50
51 222 appropriateness of quantitative synthesis. Cluster RCTs will be evaluated for statistical
52
53 223 measures that adjust for clustering. Analyses will be conducted by a systematic review
54
55 224 methodologist. We will use Comprehensive Meta Analysis V.3 or R for pooled analyses. We will
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3 225 calculate risk ratios and Peto odds ratios (for rare events) and corresponding 95% confidence
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5 226 intervals for categorical outcomes. Mean and standardized mean difference will be calculated
6
7 227 for continuous outcomes. Heterogeneity will be assessed by using the I^2 statistic, Chi-squared
8
9 228 test, and visual inspection of the forest plots. An I^2 statistic of 75% or greater may indicate
10
11 229 substantial heterogeneity. If heterogeneity exists, we will conduct subgroup analyses to explore
12
13 230 potential causes of heterogeneity. We will pool clinically homogeneous (population, intervention,
14
15 231 setting, outcome measures) studies with sufficient outcomes information. Our primary analysis
16
17 232 will include studies deemed of low to moderate risk of bias. We will conduct sensitivity analyses
18
19 233 that includes data from studies deemed to be high risk of bias. For analyses involving two
20
21 234 subgroups, Chi-squared test will be used to assess differences between the groups. If
22
23 235 applicable, when there are more than two subgroups, meta-regression will be applied to explore
24
25 236 the relationship between the subgroup characteristics and the treatment effects (22). Meta-
26
27 237 regression will only be considered if there are more than ten studies in a meta-analysis. Meta-
28
29 238 regression will be performed using the 'metafor' package for R. If quantitative synthesis is not
30
31 239 appropriate, findings will be summarized narratively.
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241 **Subgroup analysis**

38
39 242 If sufficient data allows, we plan to perform analysis on the following subgroups of
40
41 243 interest: (1) noninvasive ventilator (NIV) vs. conventional oxygen therapy (COT); (2) emergency
42
43 244 department (ED), ICU, hospital ward/step down, or mixed settings; (3) chronic obstructive
44
45 245 pulmonary disease (COPD), cardiogenic pulmonary edema/acute decompensated heart failure,
46
47 246 pneumonia, obese, post-extubation, post-surgical, immunocompromised, (4) hypoxic,
48
49 247 hypercapnic, and mixed (hypoxic or hypercapnic) respiratory failure; (5) treatment duration <6
50
51 248 vs. ≥6 hours; and (6) lower (≤30 L/min) vs. higher (>30 L/min) flow settings.

53
54 249 We hypothesize that: (1) HFNO is more beneficial than COT, but is as effective, though
55
56 250 less comfortable, than NIV; (2) the efficacy of HFNO is likely the same as NIV, but better than
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3 251 COT, in different settings; (3) HFNO is as effective as NIV in COPD, pneumonia, post-
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5 252 extubation, and post-surgical patients; (4) HFNO is less effective than NIV in cardiogenic
6
7 253 pulmonary edema and obesity due to lower level of PEEP; (5) HFNO is more effective than
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9 254 COT in most disease states; (6) HFNO is more effective and less harmful than NIV in hypoxic
10
11 255 respiratory failure, but is less effective in hypercapnic and mixed hypoxic and hypercapnic
12
13 256 respiratory failure; and (7) higher flow (>30 L/min) is more effective, but is less comfortable, than
14
15 257 lower flow (≤ 30 L/min) settings. If subgroup analyses are performed, we will assess subgroup
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17 258 effects with an I^2 statistic for subgroup differences. The I^2 statistic delineates the percentage of
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19 259 variability in the estimates of effect between the different subgroups that is due to real subgroup
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21 260 differences (as opposed to sampling error).
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262 **Assessment of bias in individual studies**

263 We will assess the risk of bias using a modification of the Cochrane guidance for
264 randomized trials (23). Individual elements will be rated low, unclear, or high risk of bias. Our
265 modification of the tool is to identify overall study risk of bias as low, moderate, or high. A study
266 with unclear elements will be considered moderate risk of bias. Components of risk of bias
267 assessment will include sequence generation, allocation concealment, blinding, attrition, and
268 appropriateness of analytic methods. One reviewer will conduct risk of bias assessments at the
269 study level and will be verified by a second reviewer. Disagreements will be resolved through
270 discussion and evaluation by a third reviewer. If appropriate, we may conduct sensitivity
271 analyses excluding high risk of bias studies.

272 We will attempt to reduce the risk of publication bias by doing a comprehensive search
273 across multiple data bases and with input from ACP-CGC and TEP members. We will conduct
274 funnel plot analysis to assess for publication bias across studies if sufficient studies are found.
275 We will look at protocol papers, where available, to assess whether outcomes were pre-
276 specified and whether all outcomes are reported.

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3 277
45 278 **Assessment of the certainty of the body of evidence**

6
7 279 We will use the Grading of Recommendations, Assessment, Development, and
8
9 280 Evaluation (GRADE) methodology to rate overall certainty of evidence for the critical outcomes
10
11 281 identified by the ACP as high, moderate, low, or very low (24, 25).
12

13 282

14 283 **Patient and public involvement**

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16 284 The list of patient-centered outcomes that will be evaluated in this systematic evidence
17
18 285 review was developed and rated as critical or important with input from nonphysician public
19
20 286 representatives.
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22 287

23 288 **Ethics and dissemination**

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26 289 No ethical approval will be needed because we will be using data from previously
27
28 290 published studies in which informed consent was obtained by the primary investigators. We will
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30 291 publish our results in a peer-reviewed journal.
31

32 292

33 293 **CONCLUSION**

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36 294 This systematic review will provide a comprehensive evaluation of the evidence
37
38 295 regarding the comparative effectiveness and harms of HFNO compared to NIV or COT for the
39
40 296 management of ARF in hospitalized adult patients to inform clinical practice and to identify
41
42 297 research gaps in the management of acute respiratory failure in hospitalized adults. The results
43
44 298 will inform the work of the ACP-CGC in their development of a clinical guideline related to use of
45
46 299 HFNO in adult patients with ARF.
47

48 300

49
50 301 **Author contributions:** TJW is the guarantor. AKB, AM, NG, BNM, TJW contributed to study
51
52 302 design and the PROSPERO protocol. NG developed the search strategy and the risk of bias
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3 303 assessment strategy. BNM and NG developed the data extraction tables. AKB drafted the
4
5 304 protocol manuscript. AKB and AM provided expertise on acute respiratory failure management.
6
7 305 RM provided statistical expertise. All authors provided critical revisions and approved the final
8
9 306 manuscript.

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15
16 309 The ACP-Clinical Guideline Committee (CGC) assisted in the development of key questions,
17
18 310 study inclusion criteria, and outcome measures of interest but will not be involved in data
19
20 311 collection, analysis, or manuscript preparation.

21
22 312

23
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25
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27
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29
30 316 Andrew Dunn, MD, MPH, SFHM, MACP; Matthew G. Drake, MD; and Robert C. Hyzy, MD.

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35 318 **Competing interests:** TJW is Chair of the ACP-CGC. He will be recused from voting on or
36
37 319 authoring the ACP guidelines. All other authors have no conflict of interests to declare.

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41 321 **Data statement:** Data sharing is not applicable as no datasets were generated and/or analyzed
42
43 322 for this protocol paper.

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Appendix A. Key Questions and PICOTS

KEY QUESTIONS

1) What is the comparative effectiveness of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen for hospitalized patients?

1a) Does comparative effectiveness of high flow nasal oxygen vary by patient characteristics, disease/diagnosis characteristics, protocol/device settings, or location of administration?

2) What are the harms of high flow nasal oxygen versus noninvasive positive pressure ventilation (CPAP, BiPAP®), invasive mechanical ventilation, or conventional oxygen for hospitalized patients?

2a) Do harms vary by patient characteristics, disease/diagnosis, protocol/device settings, or location of administration?

PICOTS	
Population:	Hospitalized adult patients with acute respiratory failure (ARF). ARF defined as SpO ₂ <90%, PaO ₂ :FiO ₂ ratio ≤300, PaO ₂ ≤60 mmHg, or PaCO ₂ ≥45 mmHg
Intervention:	High flow nasal oxygen (humidified, ≥20 l/min)
Comparators:	Noninvasive positive pressure ventilation (CPAP, BiPAP®) or conventional oxygen (e.g., simple, Venturi, or nonrebreather oxygen masks)
Outcomes:	<p>Patient-centered Outcomes: all-cause mortality (in-hospital and 90 day), intubation/reintubation (days of intubation), hospital length of stay, ICU admissions/transfers (ICU days), patient comfort, hospital readmissions (30 day) (e.g., all-cause, pneumonia), functional independence at discharge (e.g., scale scores, measures of independence/activities of daily living), discharge disposition</p> <p>Intermediate Outcomes: respiratory rate, PaO₂/FiO₂ ratio, SpO₂, pH, PaO₂, PaCO₂, treatment escalation, device intolerance</p> <p>Cost/resource utilization</p> <p>Harms: skin breakdown or pressure ulcers, gastric dysfunction, hospital-acquired pneumonia, compromised nutrition (enteral or parenteral nutrition), delirium, barotrauma</p>
Timing:	Hospitalization for ARF or development of ARF while hospitalized; immediate post-extubation; post-surgery. Exclude pre-intubation/pre-oxygenation and HFNO oxygenation support during intubation
Setting:	Hospital (including ICU, step down units, hospital wards), emergency department
Study Design:	Randomized controlled trials, including crossover RCTs and cluster RCTs
Subgroups:	<p>Patient characteristics: age, race, gender</p> <p>Disease/diagnosis (e.g. COPD, cardiogenic pulmonary edema, immunosuppressed, post-extubation, post-surgery; hypoxic, hypercapnic, or mixed [hypoxic or hypercapnic] respiratory failure)</p> <p>Protocol/device settings (e.g., flow rate ≤30 vs. >30 L/min; treatment duration <6 vs. ≥6 hours)</p>

BiPAP=Bilevel Positive Airway Pressure; CPAP=continuous positive airway pressure; ICU=intensive care unit; COPD= chronic obstructive pulmonary disease

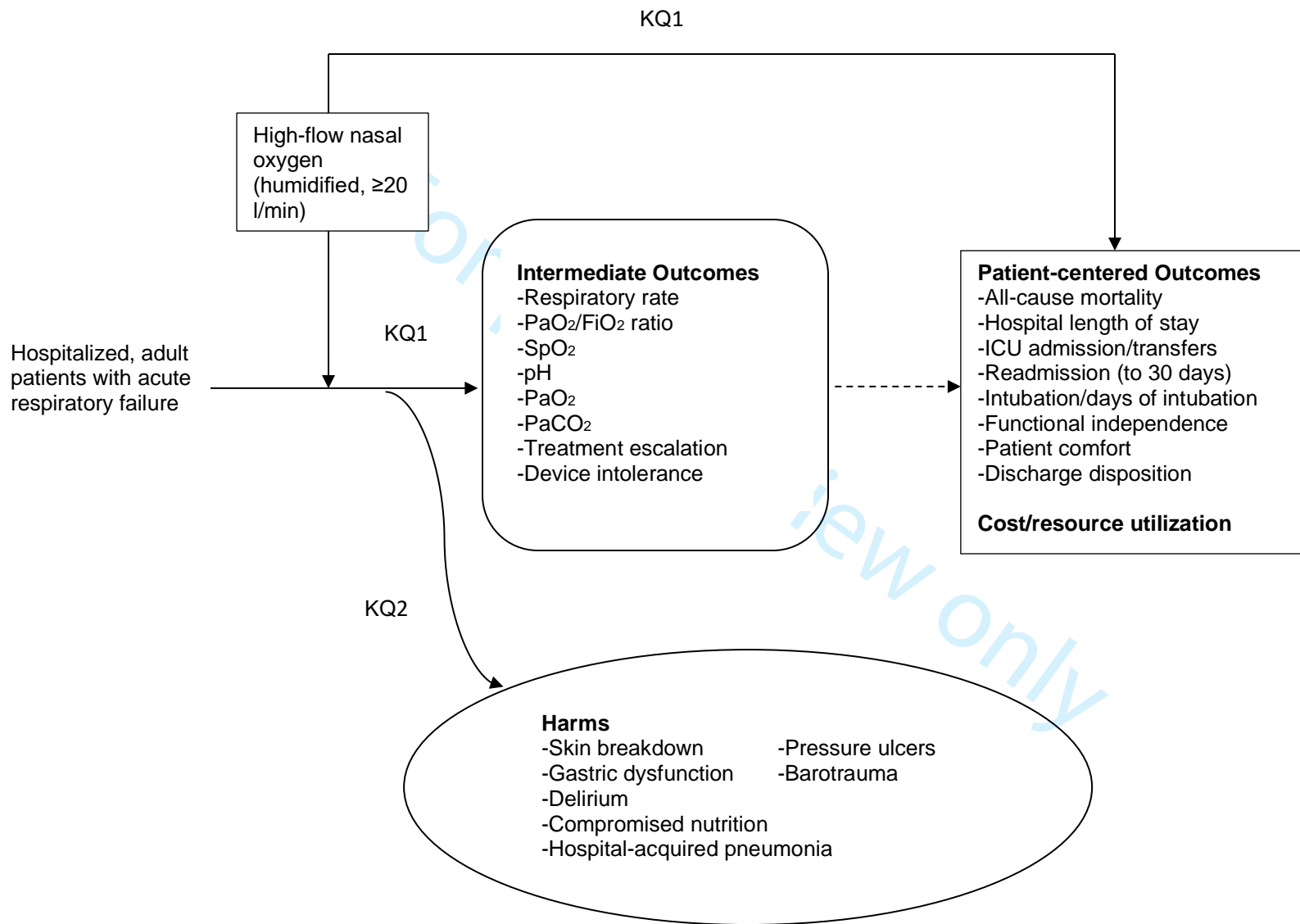
LITERATURE SEARCH

RCTs: We will search MEDLINE, Embase, CINAHL, and Cochrane Library from 2000 to August 2019

Clinicaltrials.gov for recently completed and/or on-going trials

Reference lists from relevant systematic reviews for references missed by our database searches

Analytic Framework



Appendix B. MEDLINE® search strategy

- 1 (high flow nasal adj2 (cannula\$ or oxygen\$ or therap\$ or insufflation\$)).mp.
- 2 high flow therapy.mp.
- 3 nasal high flow.mp.
- 4 high flow oxygen.mp.
- 5 (humidified high flow or humidified oxygen).mp.
- 6 (HFNC or HHFNC or HFNT or NHF or HFNO or HFOT or HFNOT).ti,ab.
- 7 (Vapotherm or Optiflow or "Comfort Flo").ti,ab.
- 8 or/1-7
- 9 remove duplicates from 8
- 10 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab.
- 11 (random\$ adj (enroll\$ or assign\$ or allocat\$)).ti,ab.
- 12 ((randomi#ed or controlled or clinical) adj2 trial\$).ti,ab.
- 13 or/10-12
- 14 9 and 13
- 15 (meta-analy\$ or metaanaly\$ or meta analy\$).ti,ab.
- 16 exp Meta-Analysis/
- 17 (systematic adj2 (review\$ or overview\$)).ti,ab.
- 18 (rapid review or meta synthesis or metasyntesis or meta-synthesis or umbrella review or integrative review or data synthesis or review of reviews).ti,ab.
- 19 or/15-18
- 20 9 and 19
- 21 limit 14 to english language
- 22 limit 21 to yr="1995 -Current"
- 23 limit 22 to "all child (0 to 18 years)"
- 24 limit 23 to "all adult (19 plus years)"
- 25 22 not 23
- 26 24 or 25
- 27 limit 20 to english language
- 28 limit 27 to yr="2015 -Current"
- 29 limit 28 to "all child (0 to 18 years)"
- 30 limit 29 to "all adult (19 plus years)"
- 31 28 not 29
- 32 30 or 31

Appendix C. Data extraction forms

Table 1. Study Characteristics

Author, year Country Funding Setting Special population Risk of Bias rating	Inclusion/Exclusion Criteria	Intervention (n) Comparator (n) Follow-up (primary outcome)	Demographics
	Inclusion: Exclusion:	Intervention: Comparator: Follow-up:	N= Age (mean): Race/ethnicity (%): White: Black: Other: Gender (% male): Comorbidities (%): Chronic Respiratory Failure: COPD: Congestive Heart Failure: Comorbidity Index: Baseline characteristics: SpO ₂ : Respiratory Rate: PaO ₂ /FiO ₂ ratio: pH: PaO ₂ : PaCO ₂ :

Table 2. Risk of Bias Assessment for Included Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias

Table 3. Treatment Characteristics

Author Year Setting Follow-up Comparator	Adherence/Intolerance describe measure		Treatment Settings				Treatment Weaning Criteria		
	Intervention	Control	Protocol		Received		Provider Discretion	Protocol or Definition	Not Reported

COT=conventional oxygen therapy; HFFM=high-flow face mask; HFNC=high-flow nasal cannula; NIV=non-invasive ventilation; NR=not reported; PEEP=positive end-expiratory pressure

Table 4: Patient-Centered Outcomes, Part 1

Author Year Setting Follow-up Comparator	All-cause Mortality % (n/N)		ICU Admissions and/or Transfers % (n/N) (mean # of days)				Length of Hospital Stay (mean # of days)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=Non-invasive ventilation; N/A=not applicable; NR=not reported; RD=risk difference; SD=standard deviation

Table 5: Patient-Centered Outcomes, Part 2

Author Year Setting Follow-up Comparator	Treatment Escalation (describe) % (n/N)		Intubation % (n/N) (mean # of days)				Intubation Criteria		
	Intervention	Control	Intervention	Control	Intervention	Control	Provider Discretion	Protocol or Definition	Not Reported

CI=confidence interval; COT=conventional oxygen therapy; ED=emergency department; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; VAS=visual analog scale

Table 6: Patient-Centered Outcomes, Part 3

Author Year Setting Follow-up Comparator	Discharge Disposition % (n/N for each location)		Hospital Readmissions (30 day) % (n/N)		Functional Independence (mean, SD)—describe measure		Patient Comfort (mean, SD) – describe measure	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant

Discharge Disposition: home, assisted living facility, nursing home, long-term care hospital

Table 7: Patient-Centered Outcomes, Part 4

Author Year Setting Follow-up Comparator	Compromised Nutrition				Gastric Dysfunction			
	% (n/N)		# days w/o nutrition		% (n/N) with placement of nasogastric tube		% (n/N) with nausea, vomiting, or abdominal distension	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported

Compromised Nutrition: (enteral/parenteral nutrition or days without nutrition)

Gastric Dysfunction: (placement of a nasogastric tube for decompression or treatment of abdominal distension/nausea/vomiting)

Table 8: Patient-Centered Outcomes, Part 5

Author Year Setting Follow-up Comparator	Hospital-acquired Pneumonia % (n/N)		Barotrauma % (n/N)		Skin Breakdown or Pressure Ulcers % (n/N)		Delirium % (n/N)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; N/A=not applicable; NR=not reported

Barotrauma: (pneumothorax, pneumomediastinum, pneumoperitoneum, or ventilator-induced lung injury)

Table 9: Intermediate Outcomes, Part 1

Author Year Setting Follow-up Comparator	Respiratory Rate (mean, SD)		PaO ₂ /FiO ₂ ratio (mean, SD)		SpO ₂ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; NIV=non-invasive ventilation; NR=not reported; NS=not statistically significant; SD=standard deviation

Table 10: Intermediate Outcomes, Part 2

Author Year Setting Follow-up Comparator	pH (mean, SD)		PaO ₂ (mean, SD)		PaCO ₂ (mean, SD)	
	Intervention	Control	Intervention	Control	Intervention	Control

COT=conventional oxygen therapy; ED=emergency department; ICU=intensive care unit; NIV=non-invasive ventilation; NR=not reported; SD=standard deviation

PRISMA-P 2015 Checklist

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

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/a
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	74	74
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	7-31
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	301-306
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	N/a
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	308-311
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	308-311
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	308-311
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	98-121

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	122-129
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	137-188
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	190-196
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	190-196
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	206-218
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	198-204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	206-218
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-217 158-174
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	158-174
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	262-276
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-238

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-238
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	231-260
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	238-239
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	272-276
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	278-281