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:	**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 **Intermediate Outcomes:** respiratory rate, PaO_2/FiO_2 ratio, SpO_2, pH, PaO_2, $PaCO_2$, treatment escalation, device intolerance **Cost/resource utilization** **Harms:** skin breakdown or pressure ulcers, gastric dysfunction, hospital-acquired pneumonia, compromised nutrition (enteral or parenteral nutrition), delirium, barotrauma
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:	Patient characteristics: age, race, gender Disease/diagnosis (e.g. COPD, cardiogenic pulmonary edema, immunosuppressed, post-extubation, post-surgery; hypoxic, hypercapnic, or mixed [hypoxic or hypercapnic] respiratory failure) Protocol/device settings (e.g., flow rate ≤30 vs. >30 L/min; treatment duration <6 vs. ≥6 hours)

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