Effective Health Care

Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal Cardiopulmonary Resuscitation (ECPR)

Results of Topic Selection Process & Next Steps

The nominator, Extracorporeal Life Support Organization (ELSO), is interested in a new evidence review on Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal Cardiopulmonary Resuscitation (ECPR) to inform an update of their clinical practice guidelines.

While the nomination met all selection criteria, it was not prioritized for development as a new review at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal Cardiopulmonary Resuscitation (ECPR), #764

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary

- This nomination meets the selection criteria of appropriateness and importance, impact, and value.
- We found an in-process duplicative review for KQ 2; reviews identified for KQ 4 were not considered duplicative because they did not address the spectrum of population and intervention characteristics of interest to the nominator.
- A new review is feasible. The evidence base is likely small. Most of the studies lacked a comparator group, and focused on individuals who had received the intervention.

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Background

Acute respiratory distress syndrome (ARDS) is a severe lung disease that occurs within one week of clinical insult or onset of respiratory symptoms); has radiographic changes (bilateral opacities not fully explained by effusions, consolidation, or atelectasis); has pulmonary edema not fully explained by cardiac failure or fluid overload; and severity based on the PaO2/FiO2 ratio on 5 cm of continuous positive airway pressure (CPAP). About 5% of hospitalized mechanically ventilated adults have ARDS.[1] Hospital mortality was 34.9% (95% CI, 31.4%-38.5%) for those with mild, 40.3% (95% CI, 37.4%-43.3%) for those with moderate, and 46.1% (95% CI, 41.9%-50.4%) for those with severe ARDS.[2]

Pediatric Acute Respiratory Distress Syndrome (PARDS) is an acute, diffuse, inflammatory lung injury caused by diverse pulmonary and non-pulmonary etiologies in children. Like ARDS it occurs within one week of clinical insult, and is characterized by hypoxemia, bilateral opacities on the chest x-ray, decreased lung compliance and increased physiological dead space.[3] It affects 1-4% of children undergoing mechanical ventilation[4], and a systematic review recently reported mortality of 24%.[5]

Extracorporeal membranous oxygenation (ECMO) is a mechanical system used to provide support to failing lungs or heart. During the management of severe respiratory failure, ECMO draws blood from the venous system, oxygenates it outside of the body, and returns oxygenated blood to systemic circulation without it having to pass through the pulmonary circulation. During venovenous ECMO the blood is extracted from a cannula inserted into a major vein (the inferior vena cava or the superior vena cava). The blood after oxygenation is returned back to a major vein or the right atrium. This technique supports the lung function but not the cardiac function, and is the most common form of ECMO used in ARDS patients.

Out-of-hospital cardiac arrest ranges from 20 to 140 per 100 000 people, and survival ranges from 2% to 11%. In the US over 500 000 children and adults experience a cardiac arrest, and <15% survive.[6] Extracorporeal cardiopulmonary resuscitation (ECPR), providing mechanical circulatory support, may improve the likelihood of survival among those with refractory cardiac arrest in the hospital and out of the hospital.

Nominator and Stakeholder Engagement: The nominator, Extracorporeal Life Support Organization (ELSO), wishes to update their guidelines with a more rigorous approach using an AHRQ systematic review given the larger evidence base on ECMO and ECPR. They are forming a taskforce for two guideline updates: one on ECMO and another on ECPR. The nominator shared a 2014 systematic review on ECMO for adults with ARDS; ideally an updated review would include results from the recently completed Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) study (https://clinicaltrials.gov/ct2/show/NCT01470703).

The key questions for this nomination are:

KQ 1: What is the effectiveness of extracorporeal membrane oxygenation (ECMO) for children with pediatric acute respiratory distress syndrome (PARDS) unresponsive to conventional mechanical ventilation? Among those who received ECMO, does effectiveness vary by patient or intervention characteristics?
KQ 2: What is the effectiveness of ECMO for adults with acute respiratory distress syndrome (ARDS) unresponsive to conventional mechanical ventilation?
KQ 3: What is the effectiveness of extracorporeal cardiopulmonary resuscitation (ECPR) for children with a witnessed cardiac arrest refractory to cardiopulmonary resuscitation (CPR)? Among those who received ECPR does effectiveness vary by patient or intervention characteristics?

KQ 4: What is the effectiveness of ECPR for adults with a witnessed cardiac arrest refractory to CPR? Among those who received ECPR does effectiveness vary by patient or intervention characteristics?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICO) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	**1. ECMO, PARDS**	**2. ECMO, ARDS**	**3. ECPR vs. CPR in children**	**4. ECPR vs. CPR in adults**
Population	Children 30 days to 18 years old with PARDS Patient characteristics: age, Pre-ECMO severity of illness, acidosis	Adults 18 years old and older with ARDS Patient characteristics: age, Pre-ECMO severity of illness, acidosis	Children up to 18 years old with a witnessed cardiac arrest, refractory to conventional CPR Patient characteristics: age, duration of CPR, Pre-ECMO severity of illness, in-hospital vs. out of hospital cardiac arrest	Adults 18 years old and older with a witnessed cardiac arrest, refractory to conventional CPR Patient characteristics: age, duration of CPR, Pre-ECMO severity of illness, in-hospital vs. out of hospital cardiac arrest
Interventions	Extracorporeal membrane oxygenation Intervention characteristics: cannulation site, in-house team, ECMO prime	Extracorporeal membrane oxygenation Intervention characteristics: cannulation site, in-house team, ECMO prime	Extracorporeal cardiopulmonary resuscitation Intervention characteristics: cannulation site, in-house team, ECMO prime, co-interventions (therapeutic hypothermia, percutaneous cardiac catheterization)	Extracorporeal cardiopulmonary resuscitation Intervention characteristics: cannulation site, in-house team, ECMO prime, co-interventions (therapeutic hypothermia, percutaneous cardiac catheterization)
Comparators	• Conventional mechanical ventilation including high frequency oscillatory ventilation and high frequency jet ventilation • Other intervention	• Conventional mechanical ventilation including high frequency oscillatory ventilation and high frequency jet ventilation • Other intervention	CPR	CPR

Key Questions	1. ECMO, PARDS	2. ECMO, ARDS	3. ECPR vs. CPR in children	4. ECPR vs. CPR in adults
Outcomes	• Mortality • Survival to hospital discharge • Hospital and PICU length of stay • Long-term function • Readmissions • Adverse effects of treatment (such as systemic emboli, organ injury, bleeding, infection)	• Mortality • Survival to hospital discharge • Hospital and ICU length of stay • Readmissions • Adverse effects of treatment (such as systemic emboli, organ injury, bleeding, infection)	• Return of spontaneous circulation • Mortality • Survival to hospital discharge • Hospital and PICU length of stay • Readmissions • Adverse effects of treatment (such as systemic emboli, organ injury, bleeding, infection) • Functional status at discharge (PCPC or POPC scores) • Neurodevelopmental outcomes at follow-up	• Return of spontaneous circulation • Mortality • Survival to hospital discharge • Hospital and ICU length of stay • Readmissions • Adverse effects of treatment (such as systemic emboli, organ injury, bleeding, infection) • Functional status at discharge

Abbreviations: ARDS=acute respiratory distress syndrome; CPR=cardiopulmonary resuscitation; ECMO=extracorporeal membrane oxygenation; ECPR=extracorporeal cardiopulmonary resuscitation; ICU=intensive care unit; PARDS=pediatric acute respiratory distress syndrome; PICU=pediatric intensive care unit;

Methods

We assessed nomination, Extracorporeal Membrane Oxygenation (ECMO) and Extracorporeal Cardiopulmonary Resuscitation (ECPR), for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature scan in PubMed from March 2013 to March 2018. A research librarian at the Scientific Resource Center developed a search strategy. We reviewed all identified titles and abstracts for inclusion to assess the size and scope of a potential evidence review. Because of the limited evidence, we broadened the search for patient and intervention characteristics and did not require a non-ECMO or non-ECPR comparator. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic (Appendix A).

Desirability of New Review/Duplication

A new evidence review on would partly duplicate an existing product. See Table 2, Duplication column.

We identified four systematic reviews related to use of ECMO in adults (KQ 2). Two reviews are considered duplicative: a 2015 Cochrane systematic review,[7] that includes the same RCTs in the 2014 Munshi et al systematic review[8] referenced by the nominator; and an update to Munshi et al[8], with plans to begin after the results of the EOLIA study (https://clinicaltrials.gov/ct2/show/NCT01470703) are released in May 2018[9]. The Munshi et al review[8] informed an American Thoracic Society guideline on the same topic[10].

We identified five systematic reviews on ECPR in adults (KQ 4). Three focused on ECPR vs. CPR[11-13]; one focused on factors affecting outcomes of those receiving ECPR for an in hospital cardiac arrest[14]; and one focused on factors affecting outcomes for ECPR for out-of-hospital cardiac arrest[15]. However these reviews did not look at the range of subgroups and intervention characteristics of interest to the nominator.

No SR were identified on ECMO or ECPR in children (KQ 1 and 3).

Impact of a New Evidence Review

A new systematic review may have high impact. There is uncertainty about individuals who would most benefit from this intervention and whether intervention characteristics influence outcomes.

Feasibility of a New Evidence Review

A new evidence review is feasible (Table 2, feasibility column). We estimate that the size will be small to medium. We identified 58 studies across three key questions, with the most related to KQ 4. Ten studies included a non-ECMO or ECPR comparison group. Some only had data for a single institution or region. Studies often included mixed populations including infants, and results were not always reported in abstracts by age group. However for completeness, these studies are included. Some studies identified overlapped with those included in the systematic reviews identified earlier.

We identified 7 studies relevant to KQ 1 (ECMO for PARDS). Only one had a non-ECMO comparison group[16]. The remaining studies focused on the effect patient and intervention characteristics of those that received ECMO on outcomes. Characteristics described included duration of ECMO support, pre-ECMO acidosis, facility volume, and single vessel cannulation.

We identified 12 studies on KQ 3 (ECPR in children); two had a conventional CPR comparison group[17, 18]. Characteristics described included underlying etiology, lactate levels, need for hemodialysis, acidosis, duration of CPR, location of CPR, age, and use of therapeutic hypothermia.

For KQ 4, we identified 42 studies. Seven included a conventional CPR comparison group[19-25]. The other studies of the studies focused on patient and intervention characteristics for only those who received ECPR. Seventeen[19, 21, 25-38] focused on those with in-hospital cardiac arrests; 11[20, 22, 24, 39-47] on out of hospital cardiac arrests; four[23, 48-50] on both; and the remainder were unclear from the abstract[51-60]. Characteristics described included use of co-interventions such as therapeutic hypothermia and percutaneous cardiac catheterization; and patient characteristics such as location of cardiac arrest, duration of CPR, and BMI.

Table 2. Key questions and Results for Duplication and Feasibility

Key Question	Duplication (3/2015-3/2018)	Feasibility (3/2013-3/2018)
KQ 1: ECMO, children with PARDS	Total number of identified systematic reviews: 0	Size/scope of review Relevant Studies Identified: 7 • Cohort study with non-ECMO comparator-1[16] • Cohort study ECMO only-6[54, 61-65] Clinicaltrials.gov-0
KQ 2: ECMO, adults with ARDS	Total number of identified systematic reviews: 4 • Completed systematic review-3[7, 66, 67] • In-process systematic review-1[9]	NA
KQ 3: ECPR, children	Total number of identified systematic reviews: 0	Size/scope of review Relevant Studies Identified: 12 • Cohort study with CCPR comparator-2[17, 18] • Cohort study ECPR only-10[53, 54, 68-75] Clinicaltrials.gov: 0
KQ 4: ECPR, adults	Total number of identified systematic reviews: 5 • Systematic review 5[11-15]	Size/scope of review Relevant Studies Identified: 42 • Cohort study with CCPR comparator-7[19-25] • Cohort study ECPR only-35[26-60] Clinicaltrials.gov-Recruiting: 3 • https://clinicaltrials.gov/ct2/show/NCT02832752?intr=ECPR&rank=1 • https://clinicaltrials.gov/ct2/show/NCT03101787?intr=ECPR&rank=2 • https://clinicaltrials.gov/ct2/show/NCT03065647?intr=ECPR&rank=5

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; ARDS=acute respiratory distress syndrome; CCPR=conventional cardiopulmonary resuscitation; ECMO=extracorporeal membrane oxygenation; ECPR=extracorporeal pulmonary resuscitation; ICU=intensive care unit; PARDS=pediatric acute respiratory distress syndrome;

Value

The potential for value is moderate. The nominator plans to develop guidelines using the AHRQ systematic review. They plan a collaborative effort, including American College of Chest Physicians, American Thoracic Society, American College of Emergency Physicians, Society of

Trauma Surgeons, Society of Critical Care Medicine, and others. The process for guideline development and their use of evidence reviews however is not described in publicly available information for ELSO.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be partly duplicative of an existing product. There is a planned update of an existing systematic review for KQ 2 (ECMO for adults with ARDS). While we identified reviews relevant to KQ 4, they did not evaluate the patient and intervention characteristics of interest to the nominator.
- Impact: A new systematic review has moderate potential.
- Feasibility: A new review is feasible. The evidence base is likely small. Most of the studies lacked a comparator group, and provided descriptive statistics about individuals who had received the intervention.
- Value: The potential for value is moderate. The nominator plans to develop two clinical practice guidelines, and plans to include a number of relevant professional societies in the guideline-development process.

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Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Cross-sectional studies demonstrate that patients with ARDS represent approximately 5% of hospitalized, mechanically ventilated patients.[1] Hospital mortality ranges from 34.9% to 46.1%[2] In a multicenter study involving children hospitalized in pediatric intensive care units (PICUs) in North America, 1-4% of children undergoing mechanical ventilation had ARDS.[4] A systematic review found that mortality was 24%.[5] Out-of-hospital cardiac arrest ranges from 20 to 140 per 100 000 people, and survival ranges from 2% to 11%. In the US over 500 000 children and adults experience a cardiac arrest, and <15% survive.[6]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. Delivery of ECMO and ECPR is a high-cost endeavor.
2c. Represents important uncertainty for decision makers	Yes
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new review would partially duplicate existing products. • We identified no reviews relevant to KQ 1 and 3. • We identified 4 reviews relevant to KQ 2 ECMO for ARDS in adults. One was a Cochrane review and another is a planned update of a review by Munshi et al that will include results from a recent study. • We identified three systematic reviews relevant to KQ 4. However they did not evaluate outcomes in relation to the patient and intervention characteristics of interest to the nominator.

Selection Criteria	Assessment
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Available guidance does not appear to definitively recommend ECMO and ECPR. Recommendations are the most encouraging for the use of ECMO for children with PARDS.[3, 10, 76]
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	There is practice variation likely related to the clinical uncertainty.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	The size of a new review would be limited to small. • KQ1: 8 studies • KQ 3: 13 studies • KQ 4: 42 studies • ClinicalTrials.gov. 3 studies related to KQ 4. Most studies lack a comparison group, and participants ranged from 3 to over 1000. Many are retrospective descriptive analyses of cases at a single or group of institutions.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, ELSO plans to develop two guidelines using the AHRQ systematic review. They plan to engage representation across a number of relevant specialties. Information about their guideline development process is not available.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ARDS=acute respiratory distress syndrome; ECMO=Extracorporeal membranous oxygenation; ECPR=extracorporeal cardiopulmonary resuscitation; ELSO=Extracorporeal Life Support Organization; KQ=Key Question; PARDS=pediatric acute respiratory distress syndrome;

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: March 2015 to March 2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
Systematic Reviews (Journal) : protocols and reviews http://systematicreviewsjournal.biomedcentral.com/

Appendix C. Search Strategy & Results (Feasibility)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2014 to Daily Update

Date Searched: March 21, 2018; Searched by: Robin Paynter, MLIS

1	Extracorporeal Membrane Oxygenation/	2664
2	ECMO.tw,kf.	2667
3	or/1-2	3911
4	respiratory distress syndrome, newborn/ or hyaline membrane disease/ or "transient tachypnea of the newborn"/	1409
5	((adolescen* or child* or infant* or newborn* or neonat* or pediatr* or pre-school* or preschool or school* or teenage* or toddler*) adj10 ("respiratory failure" or "respiratory distress syndrome")).tw,kf.	1834
6	or/4-5	2734
7	3 and 6 **KQ1 Overall Results**	**136**
8	limit 7 to (clinical trial, all or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) **KQ1 RCTs, SRs, MAs**	**18**
9	Respiratory Distress Syndrome, Adult/	2799
10	((adult* or aged or men or middle-aged or women or senior* or "very old") adj10 ("respiratory failure" or "respiratory distress syndrome")).tw,kf.	834
11	and/3,9 **KQ2 Overall Results**	**378**
12	limit 11 to (clinical trial, all or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) **KQ2 RCTs, SRs, MAs**	**44**
13	("extracorporeal cardiopulmonary resuscitation" or ECPR).tw,kf.	242
14	Cardiopulmonary resuscitation/ or ("cardiopulmonary resuscitation*" or CPR).tw,kf.	7255
15	and/13-14 **KQ 3-4 Overall Results**	**230**

16	limit 15 to (clinical trial, all or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) **KQ 3-4 RCTs, SRs, MAs**	**32**

Clinical Trials searches

KQ 1 https://clinicaltrials.gov/ct2/results?intr=extracorporeal+membranous+oxygenation&age=0

KQ2
https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&age=1&age=2&gndr=&intr=extracorporeal+membranous+oxygenation&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=

KQ 3 and 4
https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=ECPR&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=