

## Final Key Questions and Background

### **Extracorporeal Membrane Oxygenation (ECMO)**

#### **Background**

Extracorporeal membrane oxygenation (ECMO) is a form of life support that provides cardiopulmonary assistance outside the body. ECMO may be used to support lung function for severe respiratory failure or heart function for severe cardiac failure. An ECMO circuit can be set up as veno-venous (VV) or veno-arterial (VA). VV-ECMO provides external gas exchange, bypassing the lungs and protecting them from high tidal volumes of ventilation that would otherwise be needed to oxygenate and ventilate the patient. VV-ECMO is indicated for patients with potentially reversible respiratory failure, including those with severe acute respiratory distress syndrome (ARDS), primary graft dysfunction following lung transplant, and trauma to the lungs.

VA-ECMO provides the same external gas exchange as VV-ECMO, but also augments blood flow in settings of severe cardiac injury. VA-ECMO is indicated for patients with cardiac failure, including cardiogenic shock unresponsive to typical intensive care medicines and cardiac arrest that does not respond to cardiopulmonary resuscitation (CPR). VA-ECMO may also be used for patients following heart surgery or as a bridge to heart transplantation. Both VA- and VV-ECMO may be used intraoperatively as a planned alternative to traditional cardiopulmonary bypass in selected patient populations (e.g., lung or heart transplantation).

Other external gas exchange systems provide similar functions without the pump component of VV- or VA-ECMO. These arteriovenous extracorporeal lung assist (pECLA) devices bypass the lungs, but not the heart, and use the patient's blood pressure in order to sustain circulation of the externally oxygenated blood.<sup>1-3</sup> Because of the requirement for adequate cardiac function, these systems have more limited application.

ECMO is a well-established treatment for infants with lung and heart failure and has become a standard of care in many pediatric care centers.<sup>4</sup> In contrast, the evidence base for its use among adults is still emerging. Early studies of ECMO in adults found ECMO to be associated with poor survival rates.<sup>5,6</sup> However several developments have prompted renewed interest and wider utilization of ECMO in recent years.<sup>7</sup> First, technological advancements have improved the safety of the technique and broadened the application to include ambulating patients.<sup>15</sup> Technological improvements include heparin-coated cannulae, new oxygenators, and pumps.<sup>8</sup> Second, more recent clinical trials have shown improved survival without severe disability with ECMO compared to conventional ventilator support.<sup>9</sup> Finally, the 2009 H1N1 pandemic spurred increased demand for ECMO at rates higher than previously seen, resulting in additional evidence of a survival benefit.<sup>10,11</sup> Figure 1 on page 7 depicts major advancements in the development and implementation of ECMO over time.

**Policy Context**

Due to the expense and intensity of critical care, guidelines about how to implement life-sustaining and life-saving technologies warrant careful attention. Although consensus around when ECMO is indicated is still developing, the use of ECMO has grown in recent years and continues to rise subsequent to the H1N1 pandemic in 2009.<sup>12</sup> Because the availability of ECMO is limited and requires specialized medical care, liberalizing its use in the intensive care or operating room settings has important policy implications.

**Proposed Scope**

The Washington State Health Care Authority has commissioned ICER to conduct a systematic review of the published literature on the use of extracorporeal membrane oxygenation in 1) critically ill adult patients with severe respiratory or cardiac failure, and 2) adult patients who receive ECMO as a planned intra-operative procedure. Evidence will be culled from randomized controlled trials (RCTs), systematic reviews, and high-quality observational studies. Specific details on the proposed scope (Population, Intervention, Comparators, and Outcomes [PICO]) are detailed in the following sections.

***Population***

This review will examine the use of ECMO in adults (age $\geq$ 18 years) with severe respiratory and/or cardiac failure hospitalized in intensive care unit settings. Specifically, our review will focus on the use of ECMO in patients with severe acute respiratory distress syndrome, patients who are unable to maintain sufficient cardiac output (e.g., as a bridge therapy to heart transplantation), patients who received ECMO during advanced cardiac life support (e.g., extracorporeal CPR), or patients with other reversible etiologies. Additionally, we will include studies of patients for whom ECMO was used as a planned intra-operative procedure.

***Intervention***

The intervention of interest will be the use of ECMO in the intensive care or operating room setting as a means of supporting the circulation of oxygenated blood. Our review will focus on pump-driven veno-venous and veno-arterial ECMO but will also include pumpless extracorporeal lung assist (pECLA) systems.

***Comparators***

The primary comparator of interest in critical care settings will be conventional intensive care management with endotracheal intubation and ventilation. In the operating room setting, the primary comparator will be traditional cardiopulmonary bypass. We will also include comparisons between distinct systems of extracorporeal life support (e.g., pump-driven vs. pump-free gas exchange systems) where literature is available.

***Outcomes***

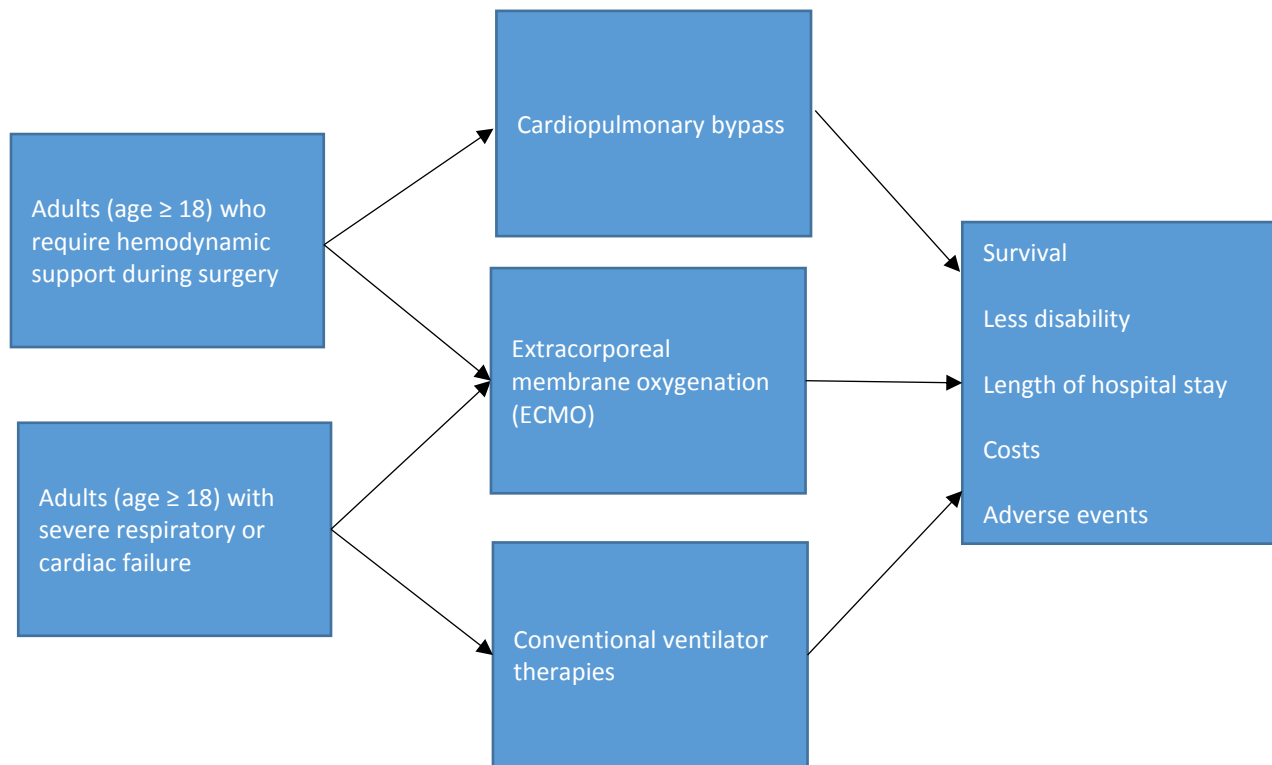
Outcomes of interest will include: 1) all-cause mortality; 2) length of hospital stay; 3) survival to discharge; 4) disability (as reported by study authors); 5) device-related complications and other adverse outcomes; 6) health-related quality of life, longer-term health status, and other measures of

well-being; and 7) costs and cost-effectiveness of ECMO. We will use available economic literature to evaluate treatment-related costs, long-term costs of care, and indirect costs (e.g., productivity loss, caregiver burden) of ECMO compared to conventional treatment. In addition, we will also analyze the budgetary impact of ECMO in a setting germane to the Washington HCA. Our budget impact analysis will focus on the direct medical costs associated with ECMO (i.e., treatment and management of complications).

**Analytic Framework**

The proposed analytic framework for this project is depicted below. It is expected that studies will vary substantially in terms of their entry criteria and technological application of ECMO. In addition, we anticipate that available RCTs may have inadequate statistical power or other quality concerns due to the difficulty of recruiting and randomizing participants, the inability to blind, high crossover rates, and potential protocol violations.

**Analytical Framework: Extracorporeal Membrane Oxygenation**



## **Methodology**

### ***Evidence Synthesis***

We propose a systematic review of all RCTs, good and fair-quality comparative cohort studies, and prior systematic reviews of the effectiveness and safety of ECMO in adults (age $\geq$ 18 years), as compared to alternative treatment approaches. Information will also be extracted from selected case series that meet specific quality criteria (e.g., consecutive sample, clearly defined entry criteria, sample retention), but will be summarized separately.

Of note, although the first report of successful ECMO in an adult patient was published in 1972, case selection, ventilation strategies, extracorporeal circuit design, and disease management have since undergone substantial changes.<sup>9,13,14,15</sup> We will therefore limit our literature search to publications since 2000, which describe ECMO with updated technologies. The full search strategy will include articles in MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and the Databases of Abstracts of Reviews of Effects (DARE) maintained by the University of York. We will supplement electronic searches with a manual review of retrieved references.

We will synthesize data on relevant outcomes quantitatively if feasible (i.e., if more than two studies are available with limited clinical heterogeneity between studies) and will generate qualitative evidence tables for each key question. As necessary, we will augment the evidence base with a non-systematic summary of evidence drawn from the literature around pediatric ECMO; while such evidence is not strictly generalizable to adult populations, it may provide useful context for the evaluation of ECMO in adults.

### ***Quality Assessment***

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories “good,” “fair,” or “poor.”<sup>16</sup> Overall strength of evidence for each key question will be described as “high,” “moderate,” or “low,” and will utilize the evidence domains employed in the AHRQ approach.<sup>17</sup> In keeping with standards set by the Washington HCA, however, assignment of strength of evidence will focus primarily on study quality, quantity of available studies, and consistency of findings.

In addition, summary ratings of the comparative clinical effectiveness and comparative value of the procedures of interest (i.e., *across* multiple key questions) will be assigned using ICER’s integrated evidence rating matrix.<sup>18</sup> The matrix has been employed in previous Washington HCA assessments of bariatric surgery, virtual colonoscopy, coronary CT angiography, proton beam therapy, and breast imaging in special populations. The matrix can be found in the Appendix to this document.

## **Key Questions**

We suggest a number of key questions as central to this review. Each question is listed below, along with the source for the evidence necessary to address it.

1. What is the comparative clinical effectiveness of ECMO versus conventional treatment strategies in adults (age $\geq$ 18 years)?

Sources: RCTs, good-quality comparative cohort studies, and good-quality systematic reviews

2. What are the rates of adverse events and other potential harms associated with ECMO compared to conventional treatment strategies?

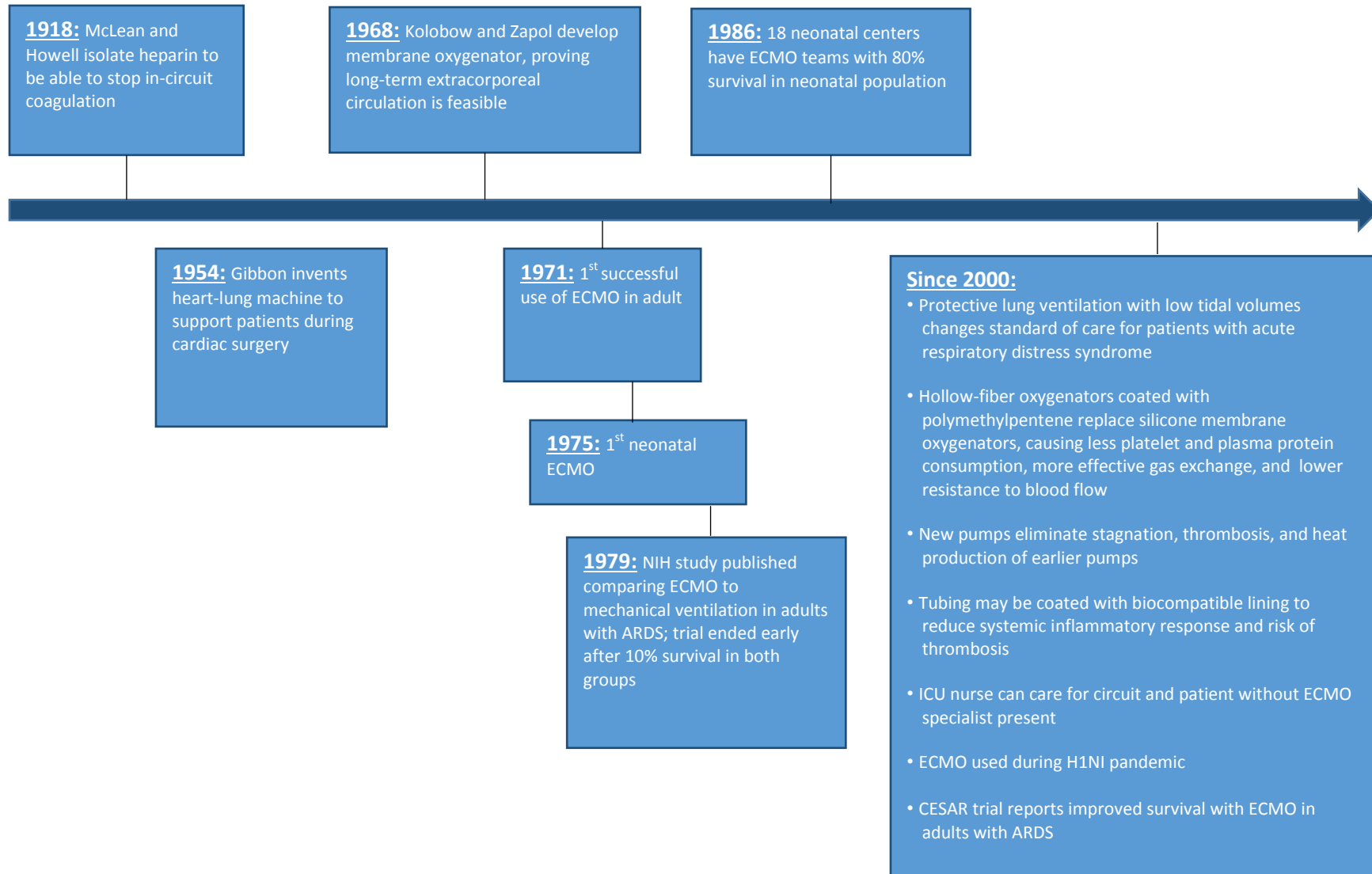
Sources: RCTs, good-quality comparative cohort studies, good-quality systematic reviews, and case series that meet specific quality criteria (i.e., consecutive sample, clearly defined entry criteria, sample retention)

3. What is the differential effectiveness and safety of ECMO according to sociodemographic factors (e.g., age, sex, race or ethnicity), severity of the condition for which ECMO is used (e.g., Murray score or APACHE score), setting in which ECMO is implemented (e.g., specialized ECMO centers), time of ECMO initiation (early vs. late), and duration of time on ECMO?

Sources: RCTs, good-quality comparative cohort studies, good-quality systematic reviews, and case series that meet specific quality criteria (i.e., consecutive sample, clearly defined entry criteria, sample retention)

4. What are the costs and potential cost-effectiveness of ECMO relative to conventional treatment strategies?

Sources: Published economic evaluations, Washington State claims data



## References

1. Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Critical care medicine*. 2006;34(5):1372-1377.
2. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO<sub>2</sub> removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive care medicine*. 2013;39(5):847-856.
3. Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. *The Lancet. Respiratory medicine*. 2014;2(2):154-164.
4. Cooper DJ, Hodgson CL. Extracorporeal Membrane Oxygenation Rescue for H1N1 Acute Respiratory Distress Syndrome. *American journal of respiratory and critical care medicine*. 2013;187(3):224-226.
5. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO<sub>2</sub> removal for adult respiratory distress syndrome. *American journal of respiratory and critical care medicine*. 1994;149(2 Pt 1):295-305.
6. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *Jama*. 1979;242(20):2193-2196.
7. Roncon-Albuquerque Jr. R, Paiva JA. Recent Advances and Novel Applications of Modern ECMO. In: Vincent J-L, ed. *Annual Update in Intensive Care and Emergency Medicine 2013* 2013:621-633.
8. Gilani FS, Farooqui S, Doddamani R, Gruberg L. Percutaneous Mechanical Support in Cardiogenic Shock: A Review. *Clinical Medicine Insights. Cardiology*. 2015;9(Suppl 2):23-28.
9. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363.
10. Davies A, Jones D, Bailey M, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *Jama*. 2009;302(17):1888-1895.
11. Gattinoni L, Carlesso E, Langer T. Clinical review: Extracorporeal membrane oxygenation. *Critical care (London, England)*. 2011;15(6):243.
12. Hubmayr RD, Farmer JC. Should we "rescue" patients with 2009 influenza A(H1N1) and lung injury from conventional mechanical ventilation? *Chest*. 2010;137(4):745-747.
13. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N Engl J Med*. 1972;286(12):629-634.
14. MacLaren G, Combes A, Bartlett RH. Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. *Intensive care medicine*. 2012;38(2):210-220.
15. Chalwin RP, Moran JL, Graham PL. The role of extracorporeal membrane oxygenation for treatment of the adult respiratory distress syndrome: review and quantitative analysis. *Anaesthesia and intensive care*. 2008;36(2):152-161.
16. Appendix VII- Criteria for Internal Validity: Assessing Individual Studies. *Procedure Manual: U.S. Preventive Services Task Force*; 2011.

17. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. 2014. <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318&pageaction=displayproduct>. Accessed March 2015.
18. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Med Care*. 2010;48(6 Suppl):S145-152.

**APPENDIX: ICER INTEGRATED EVIDENCE RATING™**

**(Compares an intervention of interest to a reference comparator)**

<i>Comparative Clinical Effectiveness</i>	Superior: A	<b>Aa</b>	<b>Ab</b>	<b>Ac</b>
	Incremental: B <sup>+</sup> /B	<b>B<sup>+</sup> a</b>	<b>B<sup>+</sup> b</b>	<b>B<sup>+</sup> c</b>
		<b>Ba</b>	<b>Bb</b>	<b>Bc</b>
	Comparable: C <sup>+</sup> /C	<b>C<sup>+</sup> a</b>	<b>C<sup>+</sup> b</b>	<b>C<sup>+</sup> c</b>
		<b>Ca</b>	<b>Cb</b>	<b>Cc</b>
	Inferior: D	<b>Da</b>	<b>Db</b>	<b>Dc</b>
Promising but Inconclusive: P/I	<b>Pa</b>	<b>Pb</b>	<b>Pc</b>	
Insufficient: I	<b>I</b>	<b>I</b>	<b>I</b>	
		<b>a</b>	<b>b</b>	<b>c</b>
		High	Reasonable/Comp	Low
		<i>Comparative Value</i>		

For additional information on [key questions and public comments](#).