ECPR for OHCA in Canada:
Planning the Research Agenda

April 25-26, 2017, Ottawa, Ontario

Meeting Report

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Canadian Blood Services
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CanROC
Canadian Resuscitation Outcomes Consortium
Consortium Canadien de Recherche en Réanimation

CIHR IRSC

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This meeting (Planning Meeting to Develop an Interdisciplinary Research Network for Extracorporeal Cardiopulmonary Resuscitation (ECPR) in Canada) was supported by the Canadian Institutes of Health Research www.cihr-irsc.gc.ca .

The meeting was held in collaboration with the Canadian Resuscitation Outcomes Consortium (CanROC) who facilitated the scheduling of this meeting immediately prior to the annual CanROC Assembly in April 2017.

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Executive Summary

The use of extracorporeal membrane oxygenation (ECMO) for patients with out-of-hospital cardiac arrest (OHCA) has been termed extracorporeal cardiopulmonary resuscitation or "ECPR" and is emerging as a potential treatment option for patients that previously have had little chance of survival. Results from retrospective studies and preliminary results from several clinical studies show increased opportunity for survival with good neurological outcomes. However, the efficacy and cost-effectiveness of this intervention remain unclear and a number of logistical and ethical challenges remain to be resolved.

In order to consider ECPR for OHCA in the Canadian context, a meeting was held in Ottawa on April 25-26, 2017, subsequent to an initial meeting held in 2016[1]. The objective was to develop a collaborative multidisciplinary research consortium and a coordinated national research agenda, with participation of experts from pre-hospital care, emergency medicine, critical care, resuscitation science, neuroscience, cardiology, cardiac surgery, ECMO, bioethics, end-of-life care, patient and public engagement, and organ donation and transplantation.

Presentations were given by invited speakers to provide updates and background information:

- ECPR clinical studies in progress
- ECMO, ECPR and OHCA registries
- Patient, family and public engagement
- Building research networks

Building on this information, participants were asked to review and prioritize research questions based on importance to patient outcomes and feasibility in a Canadian setting. Through group and plenary iterative discussions, implications and sequencing in terms of preparing for a randomized control trial (RCT), pragmatic trial or linked research studies were considered. Deliberations focused on the following areas:

ECPR Clinical Trials

There are challenges in conducting RCTs in this area, including enrolling sufficient numbers of patients, developing standardized protocols and determining criteria for program/hospital participation. However, there was general consensus that planning for a Canadian trial should move forward.

[1] Brooks et al. Extracorporeal cardiopulmonary resuscitation implementation and research in Canada: Opportunities and barriers; A proceedings report from the first meeting of the Canadian ECPR Research Working Group.

Optimizing and Standardizing Processes along the ECPR Pathway

Key research questions were identified to address the areas of uncertainty associated with ECPR clinical practice and logistics. Priorities included:

- *Feasibility and effectiveness of ECPR compared to conventional CPR.* There was consensus that baseline pre-hospital care and conventional EMS and ALS practices should be optimized before initiating an ECPR program, and that ECPR should be evaluated against state-of-the-art conventional CPR, given the cost, effort and current outcomes of ECPR programs.
- *Pre-hospital inclusion and exclusion criteria that should be used to identify patients appropriate for ECPR.* It is critical for paramedics to quickly and accurately identify those patients that will most benefit from ECPR: to ensure better outcomes for those patients that can be helped, to prevent increasing harm for those that may respond to conventional CPR and to use scarce, expensive resources effectively.
- *Time limits for resuscitation attempts on scene before transportation to hospital for ECPR.* The decision to initiate the ECPR protocol must be made early, to notify and prepare the receiving hospital and to minimize arrest to flow time. However, patient outcomes may be better for certain patients if paramedics perform on-site CPR for a longer period of time before transport. Definition is needed for target times to ensure optimal outcomes.
- *Mechanical chest compression devices or manual chest compressions during transport to hospital.* Quality of resuscitation during extraction and safe transport to hospital may be significantly impaired, thereby potentially worsening patient outcomes. Research is needed to determine if the use of mechanical CPR during transport improves outcomes.
- *ECPR team, logistics and training.* The practices and infrastructure at hospitals (personnel and scheduling, floor lay-out, resources, and equipment) dictate the practical aspects of ECMO implementation. Draft protocols, best practices and checklists may help each program customize procedures for their own operations.
- *Standardized ECMO protocols.* ECMO practice has great variability as it involves a bundle of interventions that differ based on equipment used and patient condition and characteristics. Development of optimal use of ECMO for post-arrest patients may be beneficial in improving outcomes.
- *Neuroprognostication.* There are risks for anoxic brain injury after resuscitated cardiac arrest with ECPR. Neuroprognostication is a key factor in determining when ECMO can no longer be effective and is withdrawn. Investigation is required into whether the current methods for neuroprognostication after resuscitated cardiac arrest are still applicable to this patient group.
- *ECMO termination guidelines.* Consideration must be given to ECMO termination rules for those patients with poor prognosis who will not survive. Best practices for ECMO withdrawal in these situations, from both a medical and ethical perspective, would benefit patients, families and health care providers.
- *Characteristics of patients who survive and those who die.* In order to understand which patients will benefit from ECPR and for which patients ECPR is a futile and even harmful

treatment, characteristics of patients that survive and reasons to stop ECMO that lead to death must be examined.

- *Organ donation considerations.* Refractory OHCA remains a high mortality condition. Data from observational studies and interim data from the Prague study suggest that, despite the potential, organ donation remains a relatively rare secondary outcome from ECPR. Analysis is needed to determine the reasons for this, and the optimization of donation opportunities in ECPR patients who will not survive.

An ECPR Registry for Canadian Patients

In all phases of care, collection of data through a nation-wide registry was cited by meeting participants as a priority. Several existing registries could provide opportunities to house Canadian ECPR data, representing an alternative approach to the creation of a de novo Canadian ECPR registry which would require substantial new resources and buy-in from programs across the country. Assessment of existing registry options would need to include review of data elements, reporting capabilities, scope of data captured, current data sharing agreements and links to other databases.

Patient, Family and Public Engagement

Public engagement was identified as a critical input to the design of any RCT or program evaluation, and for the identification of outcomes that are most important to patients and the public. Public engagement was also seen as necessary for any ethics-related discussion around consent, access and acceptable parameters for ECPR trials.

Next Steps

The following activities were identified as next steps in the process to develop the research agenda and network.

1. ***Formalize the ECPR research network***
    - Set up a steering committee to develop formal terms of reference, investigate areas of alignment and collaboration with the other groups and explore funding options.

2. ***Plan for an ECPR RCT***
    - Work on a collective grant application that will position the network to begin an RCT in 5 years.
    - Develop study design and parameters for the trial.

3. ***Evaluate ECPR registries and databases***
    - Establish a registry working group to establish a minimal data set, and to analyze existing relevant registries and develop options and recommendations.

4. ***Conduct Environmental Scan(s) and Literature Reviews***

- Survey Canadian programs to determine current practices for pre-hospital and ECMO care and to gauge interest, capacity, capability for initiating an ECMO program.
- Conduct literature searches for ECPR for international information on the above items.

5. ***Conduct an Economic Analysis***
   An economic analysis is currently underway to determine how many people can be saved through ECPR and at what cost.

6. ***Research Surrounding Public/Patient/Family Attitudes on ECPR***
   Begin looking at community receptivity and attitudes about ECPR programs, and patient and family perceptions of ECPR as a treatment (inclusion/ exclusion criteria, consent process, rules for termination of ECMO and end-of-life decision making).

7. ***Support Programs Looking to Implement ECPR***
   Work with regional systems to develop a rational ECPR strategy, develop a system preparedness guideline/checklist, and support participation in the ECPR Research Network.

1. Background

Extracorporeal membrane oxygenation (ECMO) is a form of heart-lung bypass that oxygenates and circulates blood external to the body through cannulation of large arteries and veins. ECMO is used in major hospitals for respiratory failure, cardiac failure and, in some cases, refractory cardiac arrest. The use of ECMO has emerged as a potential treatment option for patients with out-of-hospital cardiac arrest (OHCA). The use of ECMO for patients in cardiac arrest is termed extracorporeal cardiopulmonary resuscitation or "ECPR". While the likelihood of survival among ECPR-eligible patients treated with conventional resuscitation approaches zero after 40 minutes of CPR, ECPR has been shown to yield a small number of survivors when implemented at this juncture.[2,3]

The number of centres with OHCA ECPR programs has been slowly increasing in the United States and Europe. However, the efficacy and cost-effectiveness of this intervention remains unclear. In addition, there remain many unresolved logistical issues and a lack of robust data to inform protocol specifics. Existing clinical protocols vary in exclusion and inclusion criteria, definitions of refractory cardiac arrest, and allowable time limits for duration of CPR and time to deployment of ECMO. ECPR is highly technical, logistically challenging, and resource-intensive. In addition, there are ethical issues surrounding consent, treatment and end-of-life decision making for patients treated with ECPR.

In order to consider ECPR for OHCA in the Canadian context, the Canadian ECPR Research Network was formed and an inaugural meeting was held in Toronto on May 4, 2016. This meeting was the first step towards the development of a collaborative multidisciplinary research consortium and a coordinated national research agenda to study ECPR for OHCA in Canada.[4] The objectives were to review the current knowledge and guidelines on the use of CPR for OHCA, identify knowledge gaps as they relate to the clinical process of ECPR, and to identify challenges associated with ECPR implementation and research in Canada. At the meeting, the group identified several high priority research questions and recommended that future work should include evolution of a national research collaborative, surveillance of the literature for data from ECPR clinical trials currently underway, development of a minimum data set for ECPR research in Canada, and the development of pilot studies to support future clinical trial implementation.

[2] Joshua et al. Prevalence, natural history, and time-dependent outcomes of a multi-center North American cohort of out-of-hospital cardiac arrest extracorporeal CPR candidates. Resuscitation 2017 Aug;117:24-31.

[3] Ortega-Deballon et al. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: A systematic review of international practices and outcomes Resuscitation 2016 Apr;101:12-20.

[4] Brooks et al. Extracorporeal cardiopulmonary resuscitation implementation and research in Canada: Opportunities and barriers; A proceedings report from the first meeting of the Canadian ECPR Research Working Group.

Building upon the work from the first meeting, an application was made for a CIHR meeting grant. This was approved and, along with support from Canadian Blood Services, a second meeting was held on April 25, 26, 2017 in Ottawa. This report describes the meeting, summarizes the discussions held and identifies next steps.

2. Meeting process

(Refer to *Appendix 1 Meeting Agenda*.)

This meeting brought together experts in prehospital care, emergency medicine, critical care, resuscitation science, neuroscience, cardiology, cardiac surgery, ECMO, bioethics, end-of-life care, patient and public engagement, and organ donation and transplantation to develop a research agenda for the study of ECPR for OHCA in Canada (refer to *Appendix 2: List of Participants*).

During the meeting, presentations were given by invited speakers to provide updates and information in the following areas:

- ECPR clinical studies in progress (Vancouver and Prague),
- ECMO, ECPR and OHCA registries,
- Patient, family and public engagement,
- Building research networks.

In the previous ECPR meeting held in May 2016, meeting attendees had identified knowledge gaps and high priority research questions related to ECPR in three different phases of care: (1) prehospital care, (2) emergency department care and ECMO deployment and (3) ECMO maintenance and outcomes/prognosis (refer to *Appendices 3 – 5*). Building on this information, participants were asked to review and prioritize research questions based on importance to patient outcomes and feasibility in a Canadian setting. Through group and plenary iterative discussions, implications and sequencing in terms of preparing for an RCT, pragmatic trial or linked research studies were considered. The meeting closed with a discussion on next steps in building a research network and developing a research program for ECPR in Canada.

3. Presentations

Dr. Steven Brooks (Co-Chair)

Associate Professor, Department of Emergency Medicine, Queen's University
Emergency Physician, Kingston General Hospital, Kingston, Ontario
Kingston, ON

Challenge address

Dr. Brooks discussed the growing interest in ECPR as an emerging strategy to improve outcomes for out-of-hospital cardiac arrest (OHCA) patients in Canada. There is some evidence to support that ECPR, in selected patients, can provide a bridge to therapy for patients with refractory ventricular fibrillation and significantly increase survival with good neurological outcomes. The question of whether ECPR results are superior to conventional CPR is currently being studied through observational studies and five randomized control trials registered with clinicaltrials.gov.[5]

Dr. Brooks provided updates on activities completed since the previous meeting in May 2016. An internal meeting report was distributed and a condensed manuscript was submitted to the Canadian Journal of Emergency Medicine. Findings were presented at the Canadian Critical Care Forum in Toronto (Sept 2016), the Canadian Society of Transplantation-Canadian National Transplant Research Program-Société Québécoise de Transplantation Joint Scientific Meeting (October 2016), the Australia New Zealand Intensive Care Society meeting (October 2016), the China-International Organ Donation Conference and 1st ISODP-TTS Leadership Workshop on Organ Donation & Transplantation in China (October 2016), the Whistler Canadian Critical Care Conference (March 2017), and at a Canadian Donation Physician webinar (April 2017). A meeting grant from CIHR for this meeting was applied for and received.

The objectives of the meeting were outlined by Dr. Brooks:

- Review progress of research and pioneering ECPR programs since last year,
- Develop a research plan based on prioritized questions, with an organized structure upon which to create a formal research grant proposal,
- Formalize the structure of the research network.

The goal is to have an action plan with interested volunteers who can contribute to the work moving forward.

Dr. Sam D. Shemie (Co-Chair)

Division of Critical Care, Montreal's Children Hospital
Medical Advisor, Deceased Donation, Canadian Blood Services
Professor of Pediatrics, McGill University, Montreal, QC

Dr. Shemie discussed whether a government funded, not-for-profit coordinating organ donation and transplant agency, such as Canadian Blood Services, could legitimately and ethically provide support to develop life-saving interventions that may also increase organ donation. Despite advances in conventional CPR and ECPR, the most common outcome after cardiac arrest is still death, with many patients suffering irreversible anoxic brain injury. Anoxic brain injury after resuscitated cardiac arrest has evolved to be the most common etiology of devastating brain injury leading to organ

[5] https://www.clinicaltrials.gov NCT01605409, NCT03065647, NCT01511666, NCT03101787, NCT02527031

donation in Canada.[6] ECPR and uncontrolled organ donation after circulatory death (uDCD) practices have similar interventions and patient populations but differing end goals, potentially resulting in ethical conflicts. To mitigate this, it should be made clear that ECPR and ECMO deployment first and foremost will be used to save lives and then, if unsuccessful, to save other patients through organ donation.

Given that the intersections between CPR, ECMO and organ donation are inevitable and evolving, cautious progress and collaboration between CPR, ECMO, ICU, neurosciences and organ donation communities will be required. However, if ECPR is implemented at an institution, families of non-survivors of this intervention should be offered the opportunity for organ donation and organ donation outcomes should be reported routinely as part of all ECPR studies.

Dr. Brian Grunau

Emergency Physician, St. Paul's Hospital, Providence Health Care
Scientist, Centre for Health Evaluation & Outcome Sciences
Clinical Assistant Professor, Department of Emergency Medicine, University of British Columbia
Vancouver, BC

The Vancouver experience: Update on a Canadian ECPR program

Dr. Grunau discussed the progress of the ECPR program at St. Paul's hospital. The program was started in January 2016, after several years of planning, to integrate ECPR for appropriate patients who had failed conventional resuscitation efforts, with the goal of providing a short duration, intensive therapy. The goal metric for ECPR initiation was achieving EMS arrival time at the scene of the arrest to ECMO flows for eligible candidates in < 60-75 min.

After briefly reviewing the inclusion/exclusion criteria, processes and key target times for the St Paul's program, Dr. Grunau presented results from their ECPR experience. ECMO flows were established in 10 of 14 patients, of which two survived with good neurological function. Among the eight non-survivors, two were declared brain dead, five had withdrawal of life sustaining therapy, and one had an unplanned cardiac death due to a retroperitoneal bleed. There were two organ donors, each of whom donated both kidneys and their pancreas. He noted that comparison to other published ECPR results is difficult due to variability in inclusion and exclusion criteria as well as differences in the denominator used to calculate rates (including those that would be treated with ECMO regardless). He suggested that the effectiveness (and cost-effectiveness) of ECPR needs to be a measure of incremental benefit to regional OHCA management algorithm, and the denominator cannot be ECMO-treated patients, but overall eligible OHCAs. Current evaluation is being done to

[6] Kramer, AH, Baht, R, Doig, CJ. Time trends in organ donation after neurologic determination of death: a cohort study. *CMAJ* 2017 Jan 13;5(1):E19-E27.

assess overall outcomes of ECPR-eligible patients, comparing the intervention region to the usual care. It is hoped that the outcomes of those treated with conventional resuscitation will be the same for both groups. The additional benefit for the ECPR region will be gained in ECMO survivors.

Lessons from the St. Paul's ECPR program were discussed:

- Using the program's restrictive inclusion criteria, eligible candidates were identified at rate of approximately 1 patient/month (14 patients over 16 months) within a catchment of approximately 1 million citizens
- Factors that impact volume likely include the inclusion criteria, population density of the region and age distribution of the population.
- A prehospital based protocol is essential for OHCA as paramedics are the entry point to the ECPR system. Identification of candidates early and transport at the right time are critical to achieve time metrics. St. Paul's experience has been that, with training and tools (instruction cards), paramedics have been excellent at identifying appropriate candidates.
- An important caution is to acknowledge and mitigate the risk of worsening outcomes currently yielded with conventional advanced life support. A retrospective study demonstrated that prior to ECPR implementation, 87% of those with initial shockable rhythms were survived to hospital admission. This may be mitigated by optimizing the time to initiate transport, attendance by ALS paramedics, and use of a mechanical CPR device.
- Planning, training and simulations of logistics in the emergency department (ED) are critical to ensure staff are aware of their roles and responsibilities.
- Human resources with regards to cannulation and perfusion services can be problematic given the relative rarity of these cases, and the need for emergent cannulation. A sufficient volume of experience is required to maintain competency, which is a major obstacle in assigning this role to on-shift emergency physicians. Cannulation and perfusion services in the St. Paul's system are performed by CV surgeons and perfusionists, who respond from home during off hours. Although greater than 75% of activations occur during non-business hours, target ECMO initiation durations have been achieved in the majority.
- Public relations and funding can be an issue (allocation of a resource-intensive treatment with a low likelihood of success). In British Columbia, ECMO is not a government-funded therapy, and the hospital is required to fund it from other budget items. This issue is compounded as it leads to the cancellation of cardiac surgeries, which are funded procedures and essential for the hospital budget. Human resource issues can also be challenging within existing staffing infrastructure (scheduling, extra duties for staff), however due to the rarity of patients the creation of new ECPR-specific call schedules would be cost-prohibitive. Significant attention and effort is required to ensure continued support from the public and healthcare professionals in the hospital.
- Family reluctance to withdraw life sustaining therapy in patients where treatment has become futile has been cited as a potential issue; however, there has only been one case at St. Paul's and it was resolved quickly, highlighting the ability to overcome this challenge.

Resource allocation data was also provided. Median duration of ECMO treatment has been approximately 24 hours, for survivors and non-survivors alike, achieving the goal of an intensive short-duration intervention. Hospital stay for survivors is 9.4 days. The study is in progress and will also be evaluating the additional economic benefit which is derived from organ transplantation (kidneys) which results in a major savings in dialysis treatments.

Dr. Grunau concluded by stating that ECPR, especially for OHCA, is resource intensive; however, it may be a viable option for survival among select patients with sudden unexpected cardiac arrest who have failed all conventional therapies. Evaluations of ECPR needs to take place at the system level, and needs to include impacts to prehospital, hospital, and post discharge care, as well as opportunities for organ donation.

Dr. Jan Belohlavek

Critical Care Physician, Director, Coronary Care Unit, Consultant in Cardiology and Critical Care; General Teaching Hospital
Associate Professor of Medicine, Cardiovascular Medicine, Charles University,
Prague, Czech Republic

The hyperinvasive approach to refractory OHCA "Prague OHCA study" An initial RCT experience

Dr. Belohlavek provided an update of his work in an ECPR RCT in Prague. The Prague EMS services a catchment centre of 1.25 million people with one dispatch centre. The hospital spent 2 years preparing prior to starting the trial. Key elements of its program include dispatcher-assisted bystander CPR during emergency calls, an early alert by EMS to the cardiac centre, use of mechanical chest compressions (LUCAS device), intra-arrest cooling (RhinoChill), ECMO, neuromonitoring (NIRS-INVOS), immediate invasive assessment (coronary artery angiography/percutaneous intervention) and treatment for existing conditions[7]. Inclusion criteria is age between 18 and 65, witnessed OHCA of presumed cardiac cause, minimum of 5 min ALS performed by emergency medical services (EMS) without sustained ROSC, unconscious, ECMO team and ICU bed capacity in cardiac centre available. Exclusions include unwitnessed collapse, non-cardiac cause, ROSC within 5min of ALS or conscious patient. If ALS by EMS is greater than 5 min with no ROSC, then the paramedic calls to the cardiac centre. A web-based randomization system

[7] Belohlavek et al. Hyperinvasive approach to out-of-hospital cardiac arrest using mechanical chest compression device, prehospital intraarrest cooling, extracorporeal life support and early invasive assessment compared to standard of care. A randomized parallel groups comparative study proposal. "Prague OHCA study" *Journal of Translational Medicine* 2012; 10:163 https://translational-medicine.biomedcentral.com/articles/10.1186/1479-5876-10-163

assigns patients into the two treatment arms of the study: hyperinvasive treatment vs. standard of care. Despite this, there are still some cases that "cross-over" to the hyperinvasive arm of the study.

Time goals are very tight for the entire process: 10 min for ACLS team to be on site, 10 min at site (to randomization), 20 min to hospital admission, 20 min to ECLS start, for a total time of 60 minutes from EMS on scene to ECMO cannulation start. ECMO deployment is performed in the cardiac catheterization lab under fluoroscopy with mean time from arrival to catheterization lab to start of ECMO of 14 minutes.

The study has been running for over three years and has averaged two patients per month (less than 5% of all OHCA cases). Of the 93 patients enrolled, 38 were in the standard treatment arm and 55 in the intervention (including 10 crossovers). The mean age was 55 years, average time to ECMO was 61 minutes, and time from catheterization lab arrival to ECMO was 14 min. The standard arm had ROSC in 20/38 patients with almost all survivors presenting with ventricular fibrillation (VF). The hyperinvasive treatment arm had 55 patients; 13 with ROSC during transport of which 9 had a normal recovery. Of the remaining 38 patients, 37 had successful ECMO deployment, with 10 survivors. There were 23 deaths of which 3 were offered as organ donors. **Preliminary conclusions are that the hyperinvasive approach prolongs the resuscitation time that is associated with favorable outcome in refractory OHCA.**

Dr. Belohlavek provided some observations from the trial to date:

- Web-based randomization is possible during ongoing CPR.
- A hyperinvasive approach to refractory OHCA is feasible and prolongs time for favourable outcomes, but is logistically demanding.
- This approach does not seem to increase risk of either persistent neurological damage or any other major adverse consequence of advanced interventions.
- Survival with conventional treatment of refractory OHCA is higher than expected.
- Organ donation is rare from these patients because many of them may suffer fulminant multi-organ dysfunction that precludes organ donation.
- Presuming high quality CPR is provided, termination of resuscitation efforts before 60 minutes in patients suitable for ECPR should be seriously challenged.

Logistics challenges include:

- Team availability,
- High demands on nursing staff,
- Maintaining staff competency given the low numbers of patients and large number of staff (both hospital and EMS),
- Very short decision-making time limits for ECPR eligibility,
- Who and where to cannulate.

One of the most useful predictors for outcomes was signs of life during CPR (e.g. moving, responding). Lactate and end-tidal carbon dioxide (EtCO2) levels did not appear to be helpful. Common complications are bleeding, shock gut and severe hypovolemia, lack of pulsatility, refractory multi-organ failure. Neuroprognostication is also complicated for these patients. Ethical issues still exist – uncertain risk-benefit profile and high cost, inability to obtain informed consent, grave prognosis and potential harms (failed recovery, bridge to nowhere, prolonged ICU stay) – and continue to be studied during the trial.

Dr. Scott Youngquist

Emergency Care Physician, University of Utah Medical Centre
Associate Professor, Surgery, University of Utah
Salt Lake City, US

Extracorporeal Resuscitation Consortium Registry

The Extracorporeal Resuscitation Consortium Registry collaborative was formed in 2015 by Dr. Joseph Tonna, an emergency and intensive care specialist at the University of Utah Medical Centre when it was recognized that multiple emergency departments initiating ECPR programs for OHCA would benefit from establishing a collaborative workgroup. The group was formalized with an online presence (https://www.edecmocollaborative.org/) and a prospective study registry was created. Currently 14/33 ED ECMO sites have joined the group.

The mission of the collaborative is to share best practices, conduct multi-centre research, and educate around the appropriate application of ECPR in order to improve patient outcomes. The organizational structure consists of the Director and two Committees: Data Use/Publication Committee and an Advisory Committee. The committees have rotating membership for members interested in serving.

The objectives of the registry are to:

- Improve the scientific basis for ECPR,
- Allow members to track their own outcomes,
- Allow members to share practice patterns and protocols,
- Collect prospective, observational data,
- Encourage support of ELSO,
- Provide a platform for multi-centre, interventional trials.

The registry includes adult victims of cardiac arrest (prehospital or ED location of arrest) who have undergone ECPR attempts. Data elements capture information in the following areas:

- Demographics,
- Pre-arrest comorbidities,

- Arrest characteristics,
- Cannulation technique,
- ICU management/outcome (days 1, 2, 3, 7, 28 and/or discharge),
- Complications,
- Survival/neurologic function,
- Organ donation.

Sites have access to their own data at all times and can publish freely from it (the group requests written acknowledgement of the collaborative in facilitating the work). Investigators wishing to analyze data from the entire collaborative can make a request to the publication committee and multi-site observational and interventional trials by members are encouraged.

There are data quality procedures in place to maintain the integrity of the data:

- REDCap Research Electronic Data Capture used for database,
- Used by 2,325 institutions in 108 countries,
- Hosted on secure servers at the University of Utah,
- Branching and software logic and calculated fields are used to reduce implausible entries,
- Required fields/modules and supplemental modules are available,
- Remote training session prior to site implementation,
- Manual review of outstanding outcomes fields quarterly.

Current activities include:

- Institutional Review Board (IRB) approved observational study with waiver of informed consent,
- University of Utah set up as central IRB submission for members,
- Finalization of data elements,
- Dry runs of data entry to be performed,
- Data sharing agreements with most sites.

Dr. Youngquist ended his presentation by welcoming the opportunity for further collaboration with Canadian ECPR researchers.

Dr. Ryan Barbaro

Pediatric Critical Care Physician, C.S. Mott Children's Hospital
Clinical Lecturer, Pediatrics and Communicable Diseases, Child Health Evaluation and Research Unit, University of Michigan
Pediatric Medical Director for Extracorporeal Life Support and the ELSO Registry
Ann Arbor, US

Extracorporeal Life Support Organization (ELSO) registry

Dr. Barbaro provided an overview of the ELSO registry. ELSO was started in 1989 with the purpose of supporting institutions in delivering extracorporeal life support through continuing education, guidelines development, original research and publications, and the maintenance of a comprehensive registry. Since then, the registry has grown to include over 90,000 patients (over 8,000 annually) from over 450 centres in 60 countries. ELSO has an Executive Committee, which oversees the Steering Committee and a number of standing committees. There are member centres which each have an ECLS Medical Director and ECLS Coordinator. Administratively, the groups are supported through the ELSO Offices in Ann Arbor, Michigan.

The ELSO registry was created to support clinical care, benchmark centre outcomes and facilitate research. Data elements are organized according to Pre-ECLS, ECLS Support and Outcomes. ELSO Registry Form can be found at:
https://www.elso.org/Portals/0/Files/PDF/ELSOECLSRegistryForm6.0%202019.pdf

An addendum for ECPR elements was recently added and includes data on Arrest/ Resuscitation and ECLS Care. The ECPR addendum can be found at:
https://www.elso.org/Portals/0/Files/PDF/ELSOECPRForm2.pdf

There are over 8,000 ECPR cases (both in and out of hospital cardiac arrests) in the registry with 3,430 patients in the ECPR addendum. Eight Canadian centres currently report ECPR data into ELSO and are generally in-hospital cases. Members of ELSO sign a data use agreement and can request data for research, patient care, presentations, or quality review. In closing Dr. Barbaro noted the opportunity to collaborate with ELSO and indicated the organization's willingness to work with Canadian researchers to modify the addendum to collect needed data.

Dr. Jim Christenson

Emergency Care Physician, St. Paul's Hospital, Providence Health Care
Co-PI, Canadian Resuscitation Outcomes Consortium
Professor and Head of the Academic Department of Emergency Medicine, University of British Columbia
Vancouver, BC

The Canadian Resuscitation Outcomes Consortium (CanROC) registry

Dr. Christenson provided an overview of CanROC and its registry. CanROC developed as an offshoot of the North American Resuscitation Outcomes Consortium in October 2015. Its vision is to establish a consortium of Canadian scientists, care providers, educators and the public who will engage as a

community to improve outcomes from cardiac arrest and major trauma across the country. Strategic objectives include:

- Establishing a national OHCA and Trauma Registry (CanROC Registry) which can be used for public health surveillance, EMS quality improvement, and a data depository for large observational trials,
- Leveraging this national registry to conduct rigorous interventional studies to answer major questions with regard to treatment and systems of care for OHCA and major trauma,
- Training and mentoring the next generation of resuscitation investigators,
- Developing a purposeful framework for engaging community stakeholders including all health care professionals, survivors, family of cardiac arrest and major trauma victims, and other interested community members.

A Steering Committee provides oversight to the group, with subcommittees established for Cardiac Arrest, Trauma, EMS, Public Engagement, Publications, and Graduate Students. A database has been created at St. Michael's Hospital (direct case entry or electronic transfer):

- Minimum cardiac arrest dataset established,
- Minimum trauma dataset almost completed,
- New Sites have been engaged: working through data collection and entry,
- Original sites still producing papers on local data,
- 2 major grants submitted.

CanROC collects data on all cases of out of hospital cardiac arrest assessed by EMS. Data includes patient demographics and prehospital characteristics, treatments administered and outcome at hospital discharge. Of most interest cases that have received treatment for OHCA (any CPR by professionals or any defibrillator applied).

Common reporting is in development. National benchmarks and data sharing agreements with sites are underway. There is a formal process to analyze and publish observational data from the combined set through the Publications Committee. Although there is no current mechanism for capturing ECPR-treated patients nor a specific dataset outlined, the CanROC database could be an option for tracking ECPR cases within Canada, to further understand implementation and impact of local ECPR Programs. It would have the distinct advantage of a known denominator of all OHCA's upon which incremental benefit could be determined.

Katie N. Dainty, Ph.D.

Scientist, RESCU & the Li Ka Shing Knowledge Institute, St. Michael's Hospital
Assistant Professor, Institute of Health Policy, Management & Evaluation
University of Toronto
Toronto, ON

Patient engagement in ECPR research: What does it mean?

Patient engagement in research is defined by CIHR's Strategy for Patient-Oriented Research (SPOR) as the meaningful and active collaboration between researchers and patients and families in governance, priority setting, conducting of research and knowledge translation.[8] Depending on the context, patient-oriented research may also engage people who bring the collective voice of specific, affected communities.

Patient engagement has been identified as a priority in the UK since 1996. Other countries have since established their own organizations for working with patients in research, e.g., James Lind Alliance (2004), Patient-Centered Outcomes Research Institute (PCORI) (2010), and CIHR SPOR (2014).

The desired outcomes for any patient engagement strategy include: inclusive mechanisms and processes created, respectful collaboration, experiential knowledge valued as evidence, research is informed and co-directed by patients and quality/robustness of research is improved.

Patients can participate in research through many roles:

- As research committee members: planning, designing and guiding the project as it progresses,
- As competent patient engagement researchers: they may acquire a certain amount of research knowledge and skill and know how to engage other patients,
- As research contributors: identifying the right research question, study outcomes, study design, recruitment, data collection, and analysis of findings,
- Improving access to other patients via peer networks and accessing difficult-to-reach patients and groups.

It can be challenging to identify patient and family partners and provide them with the knowledge base necessary to ensure meaningful participation. There can be funding issues and time constraints, and researchers must accept that patient partners may have different priorities than clinicians. These challenges can be overcome, however, through several mechanisms:

- Inclusiveness: Patient engagement in research integrates a diversity of patient perspectives and research is reflective of their contribution.
- Support: Adequate support and flexibility are provided to patient participants to ensure that they can contribute fully to discussions. This implies creating safe environments that promote honest interactions, cultural competence, training, and education. Support also implies financial compensation for their involvement.

[8] http://www.cihr-irsc.gc.ca/e/48413.html#a4

- Mutual Respect: Researchers, practitioners and patients acknowledge and value each other's expertise and experiential knowledge.
- Build: Patients, researchers and practitioners work together from the beginning to identify problems and gaps, set priorities for research and work together to produce and implement solutions.

Patient engagement has been limited in emergency medicine research. However, there are some emerging examples in the development of a patient reported outcome measures for discharged ED patients (three previous ED patients on the research team) and in the SOONER Trial which actively involved community participants in design of the intervention and evaluation. CanROC now has a Public Engagement Committee, and includes a patient, public or family member on every study.

Dr. Dainty concluded by saying patient participation would be a valuable and timely addition to the ECPR research program in order to build mechanisms and processes required.

Dr. Laurie J. Morrison

Professor, Clinician Scientist, Division of Emergency Medicine, Department of Medicine, University of Toronto and Li Ka Shing Knowledge Institute, St Michael's Hospital
Toronto, ON

How to build a research consortium

Dr. Morrison shared her experiences working with many research networks and provided a list of critical success factors to consider when establishing the ECPR research network.

- Select collaborators carefully. It is important who you put around the table to guide and collaborate with. You need like-minded collaborators with who can get along well with people. "Park your ego" – those whose main concern is their own importance or personal objectives will negatively affect the culture of the network.

- Select those who are passionate about the topic. Given the amount of time and effort required in starting a new research collaborative, passion is a necessary ingredient.

- Be inclusive and include:
    - Broad healthcare representation with a multi-disciplinary focus,
    - Provincial and geographical representation,
    - End users of the system who will eventually have to implement any ECPR programs/trials.

- Be dedicated to capacity building; provide opportunity for young researchers and clinicians to bring their own ideas to the table regardless of seniority. Embrace MSc, PhDs, clinician and non-clinician scientists to ensure a diversity of experience and ideas.

Some specific skill sets that are needed for the network include:

- Those with strong background in methodology,
- Strong project coordinator/executive leader – not necessarily a clinician but someone who will drive the work forward and keep things organized and aligned,
- Privacy and data sharing agreement experience – consider a data access committee with expertise that understands data, registries and privacy legislation.

One of the first activities is to develop a terms of reference/engagement or memorandum of understanding so that everyone agrees to and can share common vision and goals. Dr. Morrison also noted that working on a publication policy and a registry were good activities to help consolidate the team and that once these were set-up, then the research protocol could be developed.

4. ECPR Research Areas

ECPR Clinical Trial

Participants discussed the question of whether Canadian investigators should be conducting well designed clinical trials for ECPR or focus on observational study designs and incremental innovations (for example, investigating optimizing ECMO process/outcomes, economic analysis, etc.) to further the understanding of ECPR for OHCA.

There was general consensus from the group that there has been enough work and experiences from others such that an effort to begin planning for a Canadian trial should move forward:

- There have been several observational studies published suggest this therapy may be beneficial for a specific cohort of patients, with acknowledgment of the variability in reported outcomes.
- There are centres in Canada that have already implemented ECPR for OHCA, in spite of funding and logistic challenges. Other centres are planning implementation and could contribute to a future RCT.

It was acknowledged that there are challenges in conducting RCTs in this area.

- ***Enrolling sufficient numbers of patients***
  There are a low number of patients in any one given area making it difficult to achieve the necessary data in a timely manner. An RCT would likely need to be multi-centre and perhaps include international collaborations. Discussion would also be needed on whether broadening inclusion criteria in order to increase the numbers of patients (for data acquisition) is acceptable vs. maximizing positive outcomes by restricting enrolment to

those patients who may be most likely to benefit. Consideration should be given to the fact that institutional and community support may suffer if survival/positive outcomes are low. The study design would need to ensure that implementation of ECPR does not lead to increased harm for patients. It was suggested that it may be more appropriate to begin with more restrictive inclusion criteria, and then expand after outcomes and experience are evaluated.

- ***Developing the protocol***
  ECPR intervention consists of a bundle of treatment that will collectively impact patient outcomes. How do you determine which procedures are included in the bundle? Which make a difference? Assessing the impact of the individual elements of the bundle would require a large study with many patients, which may not be feasible. As well, centres may have different processes, prehospital models and practices, and ECMO equipment and procedures. Standardizing and optimizing treatment would be necessary to evaluate consistently, comparing similar processes and reducing variability. This would be especially critical for screening and inclusion/exclusion criteria.

- ***Determining the centres that could be included in an RCT***
  It is currently unknown how many centres in Canada have implemented or are planning to implement ECPR, and how many other centres may have the capacity to offer this treatment. Some factors that may affect site selection include:
  - Current performance with conventional resuscitation,
  - Availability of mechanical chest compression devices,
  - EMS set-up: level of providers, prehospital treatments, hospital transport practices,
  - Population density and demographics,
  - Financial resources,
  - Current ECMO program and 24/7 access,
  - Staffing expertise and capacity (perfusionists, intensivists, interventional cardiologists, etc.),
  - Community and hospital administration support and interest.

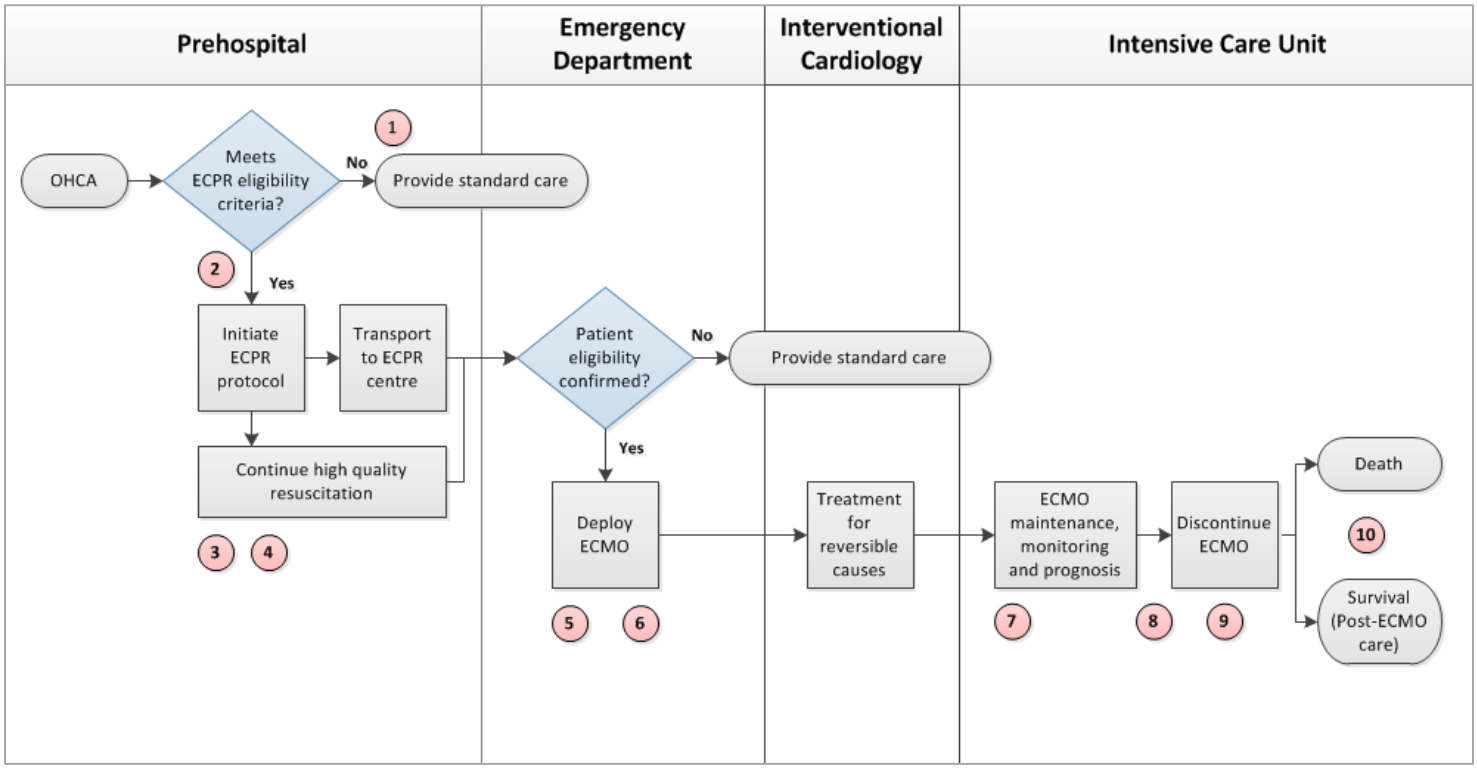
  Including many centres in the trial may make it more challenging to design and adhere to standardized protocols but may be necessary to obtain the required sample size.

Participants acknowledged that there are a number of pre-requisites prior to starting a clinical trial. It is critical to clearly establish the comparison group and the denominator population/patient group when calculating rates to determine success.

Key Research Questions: Optimizing / Standardizing Processes along the ECPR Pathway

In reviewing the key research questions by phase of care (prehospital, emergency department and ICU) participants identified the processes or areas that needed to be researched and standardized in order to prepare protocols in preparation for future clinical trials. The key questions related to these are listed below.

Figure 1: ECPR Pathway



1. **Optimized Conventional CPR (CCPR) Care**
   What is the feasibility and effectiveness of ECPR compared to CCPR?

   Questions still remain on the effectiveness of ECPR/ECMO compared to optimized prehospital CPR/ALS programs. There was consensus that baseline prehospital care and conventional EMS and ALS practices should be optimized before initiating an ECPR program, and that ECPR should be evaluated against state of the art conventional CPR and not what current practices may be, given the cost, effort and current outcomes of ECPR programs.

There are practices from Prague – including bystander CPR with telephone assistance from the hospital/EMS – that could further increase the success of CCPR and perhaps effort should be focused in this area, especially by those hospitals that do not meet the pre-requisites to initiate an ECPR program. Consideration should be given to the development of metrics of performance in conventional resuscitative techniques (e.g. chest compression fraction, proportion receiving ALS care, etc.) and systems of care (e.g. EMS response times, overall survival) before adding a resource-intensive ECPR programs.

2. Eligibility criteria

What are the prehospital inclusion and exclusion criteria that should be used to identify patients appropriate for ECPR?

It is critical for paramedics to identify those patients that will most benefit from ECPR quickly and accurately: to ensure better outcomes for those patients that can be helped, to prevent increasing harm for those that may respond to CCPR and to use scarce, expensive resources effectively. Though there have been many observational studies and some RCTs (in progress), there are still unanswered questions about inclusion/exclusion criteria and patient outcomes on ECMO.

- Should unwitnessed ventricular fibrillation rhythms be included or excluded?
- Should non-shockable rhythms (asystole, pulseless electrical activity) be included?
- Should age criteria be strictly enforced or is “healthy” vs. “unhealthy” better criteria when making decisions related to ECMO?
- How should bystander CPR or dispatcher directed CPR be taken into consideration?

When considering an RCT, it was suggested that it may be more appropriate to begin with more restrictive inclusion criteria, and then expand after outcomes and experience are evaluated. This strategy may assist in initial program success, however may limit volume thus impeding a site’s experience and proficiency.

3. Time limits for paramedic-provided on-scene CPR

How long should resuscitation attempts be made on scene before transportation to hospital for ECPR candidates identified in the prehospital setting? Are outcomes related to the duration of resuscitation provided on scene?

Are patient outcomes better if paramedics perform CPR for a longer period of time on-site before transporting (“stay and play”) vs. spending less time at the site in an effort to get the patient to the hospital and on ECMO in the fastest time possible (“scoop and run”)? Could patients be harmed if transported early for ECPR if CPR during transport is suboptimal compared with a strategy focusing on high-quality CPR and ACLS care on scene for a longer duration?

Evidence indicates that increasing resuscitation times are proportional to higher risk of futility of treatment. The Vancouver and Prague programs both target for a time under 60 minutes from witnessed CA to ECMO. Longer times result in a significant decline in survival; however, differences in patient outcomes may be dependent on several factors: whether there are shockable rhythms, patient characteristics such as age, etc. There is some association between the no flow time and outcomes, but variable results have been reported in literature. Information from the Prague trial may help inform this.

In order to achieve the 60 min or under target, optimizing logistics is critical. The decision to initiate the ECPR protocol must be made early, to notify and prepare the ECMO hospital and to minimize arrest to flow time. Definition is needed for target/optimal times for:

- Initial time juncture = time of EMS dispatch (for witnessed arrests)
- Witnessed OHCA to bystander CPR and/or EMS arrival +
- EMS arrival to hospital arrival +
- Hospital arrival to cannulation (door to flow) =
- Total time (EMS-dispatch to flow): ≤ 60 min

There may be instances where the ECPR protocol is triggered in the field but once the patient is assessed at the hospital, it is determined that they are not a candidate for ECMO. False activation results in potential harm to patients due to difficult resuscitation performance during transport and inefficient use of resources. What is an acceptable false activation rate? Future research should look at establishing candidacy for ECMO based on correlation to patient outcomes.

4. Manual or mechanical chest compressions

Should mechanical chest compression devices or manual chest compressions be used for patients selected for ECPR during transport to hospital?

Quality of resuscitation during extraction and transport may be significantly impaired, thereby potentially worsening patient outcomes. This may be dependent on many factors: cardiac arrest location characteristics; use of manual CPR vs. mechanical CPR devices; training of paramedics; number of paramedics available during transport; geographic location and distance from hospital. It is unclear if the use of mechanical CPR during transport of patients bound for ECPR therapies at hospital improves outcomes, however this is plausible given the evidence demonstrating impaired CPR quality during extrication, and the evidence supporting the benefit of CPR quality.[9]

[9] Christenson J, Andruskiek D, Everson-Stewart S, et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. *Circulation* 2009; 120(13):1241–1247.

5. ECMO team, logistics and training

The practices and infrastructure at hospitals (including personnel and scheduling, floor lay-out, resources, and equipment) dictate the practical aspects of ECMO implementation. Considerations in developing an ECPR program include:

- Who should be responsible for cannulation and initiating flow? How do they maintain skills/competency, given the low number of patients expected through an ECPR program?
- Do you implement on-site or on-call model for specialists involved in ECMO that facilitates emergent ECPR deployment?
- How do you train emergency physicians and nurses and maintain competency?
- Where should cannulation take place? ED, angiography suite, OR. How can these locations best accommodate 24/7 initiation?
- How should the room be set up? When should equipment prep be started?

Given the wide variability in infrastructure and staffing among hospitals, protocols and checklists from other centres may help but each program will need to customize for their own operations.

6. Standardized ECMO protocol

How would you review and develop standard of care for ECMO management in ECPR?

- *Circuit management*
- *ECMO and patient management including centre specific variables (volume, experience, organizational, system)*
- *Equipment, anticoagulation, flows, targets, lung rest, transfusion*
- *Titration to perfusion targets*
- *Targeted temperature management*

ECMO practice has great variability as it involves a bundle of interventions that differ based on equipment used and patient condition and characteristics. A single centre trial may be consistent across patients thus maintaining internal consistency but reproducibility and comparison to other studies may be difficult. To achieve sufficient numbers to be statistically significant, multi-centre trials would be needed in Canada. To prepare for a multi-centre trial, a standard protocol would need to be developed to address practice variation between programs.

An environmental scan and a systematic literature review would be useful to determine if there is any evidence or consensus on optimal treatments for ECPR ECMO management. For example, the CESAR trial (Conventional ventilatory support vs. extracorporeal membrane oxygenation for severe adult respiratory failure) and other existing protocols may provide information on impact of centre variables, anticoagulation factors, etc. There may also be treatment that may not

improve patient care per se but may improve organ viability in the event of organ donation that should be considered.

7. Neuroprognostication

Are there any reasons to change our current neuroprognostication processes for resuscitated cardiac arrest for OHCA/ECPR patients? Do our tools (clinical, imaging, electricity) for neuroprognostication still apply to this patient group?

Neuroprognostication is a key factor in determining when ECMO is withdrawn. Given the criticality of this, investigation is required into whether the current methods for neuroprognostication are still applicable to this patient group. What is the optimal waiting period and testing required for neurological evaluation?

An environmental scan of current practices (ECMO for OHCA vs. non-OHCA patients) would be helpful, including time points in the neuroprognostication decision making (i.e., early vs. late). Registry data may also help in evaluating neuroprognostic tools (predictor and scoring tools) including EEG, evoked potential and neuroimaging.

8. ECMO termination guidelines

In addition to determining the best way to wean survivors off ECMO, there must be consideration given to ECMO termination rules for those patients with poor prognosis who will not survive. These are difficult situations for families, the health care team and for patients when there may be neurological recovery without myocardial recovery. Best practices for ECMO termination, from both a medical and ethical perspective, would be beneficial for all involved.

9. Organ Donation Considerations

Data from observational studies and interim data from the Prague study suggest that, despite the potential, organ donation remains a relatively rare secondary outcome from ECPR. At St. Paul's Hospital in Vancouver, four out of 12 ECPR patients were potential donors and of those, only two became organ donors. Initial data from the Prague trial indicate that multi-organ failure is more common than brain-death in ECPR patients, resulting in a short duration on ECMO of less than 24 hours.

a. Determination of death on ECMO: What are the criteria for the determination of death by neurological criteria in patients on ECMO? What are the criteria for determination of death by circulatory criteria in patients after discontinuation of ECMO? Are there differences in the way death is determined by neurological criteria on or off ECMO? Neurological assessments for the cessation of brain function may be complicated by temperature management, clearance of sedation/analgesics, apnea testing and the potential for ancillary brain blood flow testing.

b. Under what conditions can controlled donation after circulatory death be an option for patients with anoxic brain injury who will die after ECPR but do not fulfill criteria for brain death?

10. Characteristics of patients that survive and patients that die

What are the characteristics of ECPR patients that survive? What are the characteristics of those that die?

Outcomes for ECPR patients vary considerably with significant consequences and with a relatively low success rate. Patients that survive may have myocardial recovery with or without brain recovery. Some patients may recover neurologically, but not with myocardial function, with potential option for advanced heart failure therapies such as transplant or durable ventricular assist device (ECMO as a bridge to advanced therapy) or not (bridge to nowhere).

In order to understand which patients will benefit from ECPR and for which patients ECPR is a futile and even harmful treatment, reasons to stop ECMO that lead to death must be examined (multi-organ failure, anoxic brain injury, ECMO complications such as uncontrolled bleeding or cannula/circuit catastrophe, etc.) as well as the characteristics of patients that survive (to discharge and to 6 months). Time intervals (e.g., amount of time on ECMO, time from discontinuation of ECMO to death) should also be considered. A registry of ECPR should include data pertaining to organ donation (e.g., type of organ donation, organ viability, graft utilization and recipient outcomes).

It would be useful to understand what data hospitals are currently collecting. Once outcomes are clearly defined, existing databases and case studies can be analyzed to see if this information is available for retrospective analysis. In parallel, these definitions can be added to capture outcomes data prospectively for new cases.

Considering an ECPR Registry of Canadian ECPR Cases

In all phases of care, collection of data through a nation-wide registry was cited by meeting participants as a priority. The group considered creation of a de novo Canadian ECPR database or collaborating with an existing ECMO, ECPR or cardiac arrest database as an alternative approach. There was debate among the group on the best approach to accomplish our objectives of measuring current ECPR practice in Canada, informing practice with observational analysis using Canadian data and informing the design of future randomized controlled trials.

The group recognized that several existing registries could provide opportunities to house Canadian ECPR data, representing an alternative approach to the creation of a de novo Canadian ECPR registry

which would require substantial new resources and buy-in from institutions across the country. The group recognized there were important advantages associated with joining an established registry:

- Infrastructure and maintenance has already been established resulting in reduced costs for development and ongoing maintenance,
- Collaborations with other registries provide a wider set of data and more opportunities for knowledge sharing,
- Much of the work has already been done for data elements identification and definitions,
- Some centres may already be providing data to an existing registry,
- Data sharing agreements may already be in place, which would significantly decrease time required to implement and start collecting data.

The following would need to be assessed in selecting a pre-existing data registry:

- Review of data elements to determine whether they were appropriate for the Canadian context, and if not, ability to custom/ make changes or add fields,
- Review of data elements to ensure they would provide the granularity required to answer the research questions (research database vs. a patient care database),
- Ability to request or pull sub-sets of data from the database,
- The amount and quality of the data captured:
    - What other groups are entering data into the registry? Mandatory fields vs. supplemental or voluntary fields,
    - Data validation practices in place
- Review of scope of data captured: does it capture all phases of care, from pre-hospital to outcomes? Does it capture all OHCA or just those that deploy ECMO?
- Consider where Canadian centres are already entering data to avoid duplicate entry, as well as data sharing agreements may already be covered,
- Cost associated in joining an established registry,
- Links, exports and interfaces that registries have with other potentially useful databases, e.g., UNOS (United Network for Organ Sharing) and SRTR (Scientific Registry of Transplant Recipients).

The group considered important differences in the types of analyses that would be possible when working with an ECPR or ECMO-based registry as compared with a cardiac arrest registry. Whereas cardiac arrest registries would support comparative analyses involving cardiac arrest patients not treated with ECPR, use of the ECMO-based registries would not. Conversely, the ECMO-based registries have the advantage of collecting detailed ECMO-specific data on ECPR cases, whereas this would need to be developed in cardiac arrest databases such as CanROC.

A first step would be to review the data elements from CanROC, ELSO and ERECT and from RCT datasets and develop a minimum dataset for ECPR for Canada. Once financial and privacy (data

sharing implications) issues are managed, research questions can be prioritized. Collaborations with these existing registries could then be sought with these research questions in mind.

Patient, Family and Public Engagement

Public engagement was identified as a critical input to the design of any RCT or program evaluation, and for the identification of outcomes that are most important to patients and the public. Public engagement was also seen as necessary for any ethics-related discussion around consent, access and acceptable parameters for ECPR RCTs.

Key research areas that would need to be explored prior to embarking on clinical trials include:

- ***Community preparedness***
  A critical success factor for any ECPR program is community awareness and support. The community will assess through different perspectives, e.g., as potential patients or as taxpayers assessing opportunity costs for their hospital. How will different access to ECPR due to location/distance from hospital be perceived? What is required, realistic and appropriate when considering community engagement? What opportunities should be given for community response and feedback? Given informed consent will be waived, what information needs to be provided and to whom? To what degree is community engagement required and necessary compared to community notification? What form might this community engagement take (public service/media announcements, social media, focus groups, and information sessions)?

- ***Ethics issues***
  High mortality interventions and informed consent
  - Informed consent by patient and/or by families is most often not feasible; therefore, how does one obtain general consensus from the community where ECPR may be implemented? Is the public supportive of a resuscitation practice that is highly invasive/high risk with high mortality and potential for survivors with poor neurological outcomes? Is the public supportive of a time-limited ECMO trial in ECPR candidates?

  Practices surrounding ECMO termination for patients with poor prognosis
  - There is a risk of families wanting to continue ECMO in the face of futility of further treatment. How would the public respond to firm ECMO termination rules, and how does this play out at the bedside? What is the clinical experience – have there been conflicts reported so far? How much certainty of prognosis required?
  - How should patient with full neurologic recovery but no myocardial recovery and no other therapy options be treated (the “bridge to nowhere situation”)? There needs

to be recommendations on how to address these infrequent but very challenging and disturbing situations.

Organ donation and ECPR

- Saving the patient is the primary desired outcome for ECPR but organ donation is a justifiable secondary outcome of failed ECPR. Given the high mortality rate and invasiveness of the interventions, what are health care providers and the public perceptions of organ donation as an outcome? Are there perceived conflicts of interest? Are families likely to consent under these conditions?
- What about ethical considerations related to extension of time on ECMO to successfully recover organs?

Impacts on families and survivors

- It was recognized that experience of survivors and families would inform research in all phases of ECPR care. This information would also drive improvement to programs that provide support to families and patients in ECPR who have unique needs. This would cover consistency of information provided, family understanding and acceptance of the patient's condition, consent, dealing with family conflict or impasse and end-of-life decision-making.

Public, patient and ethicist discussions are needed to ensure that there is a strong moral foundation before proceeding with broad implementation of ECPR. Participants agreed that it was necessary to bring representatives to this research group and to build mechanisms to support them in an ongoing basis. Questions emerged on selection of patient representatives (academic background patients vs. lay people; public vs. patients vs. family members), compensation for participations, roles and processes for integration and education.

5. Next Steps

At the end of the meeting, the Chairs summarized next steps and committed to engaging participants in an ongoing way to execute these steps:

1. ***Formalize the ECPR research network***
    - Set up a steering committee to work on formal terms of reference.
        - Add patient/family/public representative
        - Ensure regional/provincial representation if possible
        - Add someone with data registries and privacy expertise

    - Include diversity of members, i.e., various disciplines, young investigators as well as experienced physicians
- Initiate further discussions with CanROC on continued support and alignment (potentially through CanROC meetings).
- Investigate areas of alignment and collaboration with the Canadian ECMO group
- Explore options for funding for the network structure, the registries and the research studies through a research program grant proposal (e.g., CIHR, Laerdal grant, ECMO industry)
- Begin holding conference calls every second month.

2. Plan for an ECPR RCT

- Work on a collective grant application that will position the network to begin an RCT in 5 years.
- Identify methodological/statistical support to assist in the development of the RCT design and analytics.
- Develop parameters for the trial
    - RCT vs. prospective non-randomized comparative clinical studies
    - Sample size, criteria for site participation, number of sites and their location
    - Separate Canadian trial or part of an international trial
    - Choice of primary and secondary outcomes
    - Standardized inclusion/exclusion criteria
    - Standardized protocols and most effective intervention ensemble / bundle of care
    - Determination of variables to be collected
    - Phased approach (phase 1 – phase 3 trials and evaluations)

3. Evaluate ECPR registries and databases

- Establish a Registries Working Group
- Analyze existing cardiac arrest and ECMO/ECPR registries (CanROC, ELSO, ERECT) and existing datasets (Vancouver St. Paul's group, Prague study)
- Establish scope of data and minimal data set
    - Identify questions and parameters that are critical for evaluating ECPR (including patient outcomes)
    - Identify phases of care to be included – prehospital, ED, ICU, post-hospital care?
    - Inclusion criteria
    - Develop draft data elements and definitions
- Develop options and recommendation for registry (including costs, collaboration opportunities and funding options)

- Gather a group of national and international experts (including Canadian ECMO group, ILCOR, existing registries representatives) to standardize/validate a minimum ECPR data set.

4. ***Conduct Environmental Scan(s) and Literature Reviews***
    - Survey Canadian EMS services to determine current practices for prehospital care:
        - Screening criteria
        - "Stay and play" vs. "load and go"
        - Basic vs. advanced paramedics
        - Mechanical vs. manual CPR
        - Staffing and dispatch models for EMS
        - Systematic barriers/enablers to ECPR implementation
    - Collaborate with the Canadian ECMO group and survey Canadian hospitals to determine current practices for ECMO care and/or gauge interest, capacity, capability:
        - Who's doing it? Who's ready to do it? Who is capable of doing it? Who is interested in doing it?
        - Do they have ECMO programs? For which group of patients?
        - What are their inclusion/exclusion criteria for ECMO?
        - What are their current care protocols?
        - What neuroprognostication tools do they use?
        - Do they contribute their data to any registries?
        - Are they planning to establish an ECMO or ECPR program in the next 2 years? Do they have the capacity and prerequisites required?
    - Conduct literature searches for ECPR for international information on the above items.

    Once information is gathered, expert consensus conferences can be organized on various topics to establish standard criteria and protocols for future trials.

5. ***Conduct an Economic Analysis***
    An economic analysis is currently underway (Drs. John Gill, Brian Grunau, Scott Klarenbach, Anson Cheung, Ruth MacRedmond, Sam Shemie, Steven Brooks) to determine how many people can be saved through ECPR (including survivors, potential organ donors and transplant recipients) with what outcomes and at what cost.

6. ***Begin Research Surrounding Public/Patient/Family Attitudes on ECPR***
    Begin work in those areas that would provide foundational information for future clinical grants. This includes looking at community receptivity and attitudes about for ECPR programs (costs, benefits, risks of, and access to high mortality interventions, optics of ECPR as life-saving or organ-preserving) and patient and family perceptions of ECPR as a treatment (inclusion/

exclusion criteria, consent process, rules for termination of ECMO and end-of-life decision making).

- Obtain information from existing studies that may relate to ECPR/ECMO patients and families and could be leveraged to answer some questions in ECPR:
    - Prague study (public opinion, family and patient experiences)
    - Qualitative study of the experiences of survivors and families in ICU (Drs. John Gill, Brian Grunau)
    - Families and pre-mortem interventions for organ donation (Lindsey McKay)
- Design and conduct a workshop with a group of patients, families and public (James Lind Alliance style) to collect qualitative data while working through the complex issues that inform people's "opinions" on ECPR.

7. Support Programs Looking to Implement ECPR

- Work with regional systems to develop a rational ECPR strategy
    - Provide input and context to clinical leaders and administrators
- Develop a system preparedness guideline/checklist which would include:
    - EMS pre-requisite standards (service metrics, personnel training)
    - ED/Cath lab/ICU/ECMO requirements
- Support participation in the ECPR Research Network
    - Evaluation and quality assurance initiatives, and registry/database inclusion
    - Enlist newly recruited individuals and ECPR centres to advance current and new Research Network initiatives

Appendix 1: Meeting Agenda

DAY 1

Time	Agenda Item
8.00 – 8.45	**Breakfast**
8.45 – 9.30	***Meeting opening/Challenge address*** • Dr. Steve Brooks (Co-Chair), Associate Professor, Department of Emergency Medicine, Queen's University; Emergency Physician, Kingston General Hospital • Dr. Sam D. Shemie (Co-Chair), Division of Critical Care, Montreal's Children Hospital; Medical Advisor, Deceased Donation, Canadian Blood Services; Professor of Pediatrics, McGill University
9.30 – 10.00	***The Vancouver experience: Update on a Canadian ECPR program*** • Dr. Brian Grunau, Emergency Physician, St. Paul's Hospital, Vancouver
10.00 – 10.40	***The Prague ECPR RCT experience*** • Dr. Jan Belohlavek, Director, Coronary Care Unit, Consultant in Cardiology and Critical Care; Associate Professor of Medicine, Cardiovascular Medicine, General Teaching Hospital, Charles University, Prague
10.40- 11.00	**Break**
11.00 – 12.00	***Plenary discussion*** • ECPR updates from participants • Taking the "temperature" of the group: Should Canadian investigators be conducting well designed clinical trials for ECPR or focus on implementation, observational study designs and incremental innovations (optimizing ECMO process/outcomes, economic analysis etc.) to further our understanding of ECPR for cardiac arrest?
12.00 – 12.40	**Lunch**
12.40 – 2.30	***Break-out groups: Prioritization of ECPR research questions***
2.30 – 2.50	**Break**
2.50 – 3.50	***ECMO/ECPR Registries:*** ***Extracorporeal Resuscitation Consortium registry*** • Dr. Scott Youngquist, Emergency Physician, Prehospital Medicine Specialist, University of Utah Medical Centre ***Extracorporeal Life Support Organization registry*** • Dr. Ryan Barbaro, Clinical Lecturer, Pediatrics and Communicable Diseases, Child Health Evaluation and Research Unit, Critical Care Medicine, University of Michigan

	CanRoc registry ● Dr. Jim Christenson, Head, Professor, Department of Emergency Medicine, University of British Columbia ***Panel Q&A***
3.50 – 5.00	***Break-out groups:*** ● What should the registry strategy be for Canadian ECPR data? ***Plenary review***
5.00 – 6.30	**Reception – Mackenzie Room**

DAY 2

Time	Agenda Item
7.15 – 8.00	**Breakfast**
8.00 – 8.30	***Recap of Day 1 and introduction to Day 2***
8.30 – 9.00	***Patient, family and public engagement and participation in research*** ● Dr. Katie Dainty, Scientist, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto
9.00 – 10.15	***Break-out groups: Transitioning from ideas to action*** ● Development of research projects and proposals
10.15 – 10.30	**Break**
10.30 – 12.00	***Break-out groups: Transitioning from ideas to action (cont'd)*** ● Development of research projects and proposals
12.00	**Working Lunch**
12.15 – 1.15	***How to build a research consortium*** ● Dr. Laurie J. Morrison, Professor, Clinician Scientist, Division of Emergency Medicine, Department of Medicine, University of Toronto and Li Ka Shing Knowledge Institute, St Michael's Hospital
1.15 – 1.30	**Meeting wrap-up**

Appendix 2: List of Participants

Planning Committee

Steven C. Brooks, MD, MHSc **Co-Chair**	Emergency Care Physician, Kingston General Hospital Clinician Scientist, Kingston General Hospital Research Institute Assistant Professor, Queen's University Kingston ON Associate Scientist, Li Ka Shing Knowledge Institute at St. Michael's Hospital Toronto, ON
Sam D. Shemie, MD **Co-Chair**	Critical Care Physician, Montreal Children's Hospital, McGill University Health Centre and Research Institute Professor of Pediatrics, McGill University Medical Advisor, Deceased Donation, Canadian Blood Services Montreal, QC
Katie N. Dainty, PhD	Scientist, RESCU & the Li Ka Shing Knowledge Institute, St. Michael's Hospital Assistant Professor, Institute of Health Policy, Management & Evaluation University of Toronto Toronto, ON
Clay Gillrie, RN	Program Manager, Deceased Donation Canadian Blood Services Vancouver, BC
Brian Grunau, MD, MHSc	Emergency Physician, St. Paul's Hospital, Providence Health Care Scientist, Centre for Health Evaluation & Outcome Sciences Clinical Assistant Professor, Department of Emergency Medicine, Faculty of Medicine Vancouver, BC
Laura Hornby, MSc	Research Consultant Clinical Research Consultant, Deceased Donation, Canadian Blood Services Lead Project Manager, DePPaRT Study, Pediatric Critical Care Children's Hospital of Eastern Ontario Research Institute Montreal, QC
Dave Nagpal, MD	Cardiac Surgeon and Critical Care Physician, Surgical Director, Heart Transplant and Mechanical Circulatory Support Program, London Health Sciences Centre Assistant Professor in Cardiac Surgery and Critical Care Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario London, ON
Sylvia Torrance, BSc	Associate Director, Policy Research and Leading Practices Centre for Innovation, Canadian Blood Services Ottawa, ON

Advisory Committee

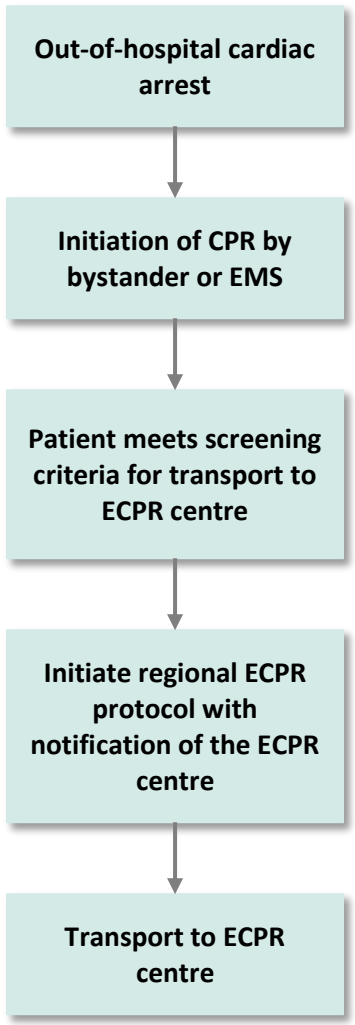
Andrew J. Baker, MD	Critical Care Physician, Chief, Critical Care Department, Medical Director, Trauma and Neurosurgery Program, St Michael's Hospital Scientist, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital Professor, Departments of Anesthesia and Surgery, University of Toronto Toronto, ON
Jim Christenson, MD	Emergency Care Physician, St. Paul's Hospital, Providence Health Care Professor and Head of the Academic Department of Emergency Medicine, University of British Columbia Vancouver, BC
John Gill, MD	Nephrologist, St. Paul's Hospital, Providence Health Care Associate Professor, Division of Nephrology Department of Medicine, University of British Columbia Co-Chair, Canadian Renal Transplant Study Group (CRTS) Vancouver, BC
Laurie Morrison, MD, MSc	Emergency Care Physician, St. Michael's Hospital Professor, Clinical Scientist, Division of Emergency Medicine, Department of Medicine, University of Toronto and Li Ka Shing Knowledge Institute, St. Michael's Hospital Director, RESCU, St. Michael's Hospital Toronto, ON

Participants

Neill Adhikari, MD	Critical Care Physician, Sunnybrook Health Sciences Centre Associate Scientist, Evaluative Clinical Sciences, Trauma, Emergency & Critical Care Research Program, Sunnybrook Research Institute Toronto, ON
Amber Appleby, RN	Associate Director, Deceased Donation Canadian Blood Services Vancouver, BC
Ryan Barbaro, MD	Pediatric Critical Care Physician, C.S. Mott Children's Hospital Clinical Lecturer, Pediatrics and Communicable Diseases, Child Health Evaluation and Research Unit, University of Michigan; Pediatric Medical Director for Extracorporeal Life Support and the ELSO Registry Ann Arbour, MI, USA
Jan Belohlavek, MD, PhD	Critical Care Physician, Director, Coronary Care Unit, Consultant in Cardiology and Critical Care; General Teaching Hospital Associate Professor of Medicine, Cardiovascular Medicine, Charles University Prague, Czech Republic
Gordon J. Boyd, MD, PhD	Critical Care Physician, Neurologist, Kingston General Hospital Clinical Scientist; Assistant Professor, Queen's University Kingston, ON

Tanya Campbell, RN	Clinical Nurse Leader, Emergency Department, St. Paul's Hospital, Providence Health Care Vancouver, BC
Frederick D'Aragon, MD, PhD	Critical Care Physician, Centre hospitalier universitaire de Sherbrooke Professor, Department of Anesthesiology Faculty of Medicine and Health Sciences University of Sherbrooke Sherbrooke, QC
Ian Drennan, PhD	Advanced Care Paramedic, St Michael's Hospital Researcher, RESCU (Emergency Health) St. Michael's Hospital Toronto, ON
Blair Henry B.Sc., MTS	Ethicist, The Ethics Centre, Sunnybrook Hospital Lecturer, Department of Family and Community Medicine, University of Toronto Co-Founder, Ethical Affairs Toronto, ON
Mike Hickey, MD	Emergency and Critical Care Physician, Eastern Health St. John's, NL
Noam S. Katz, MD, MSc	Emergency Care Physician, Department of Emergency Medicine, The Ottawa Hospital, Civic Campus, University of Ottawa Ottawa, ON
Nick Kuzak, MD	Emergency Care Physician, Kelowna General Hospital, Department of Emergency Medicine University of British Columbia Kelowna, BC
Lindsey McKay, PhD	Postdoctoral Fellow, Adjunct Professor, Department of Sociology, Brock University Hamilton, ON
William E. Stansfield, MD	Cardiac Surgeon, Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network Affiliate Scientist, Toronto General Hospital Research Institute Surgeon Scientist and Assistant Professor, Division of Cardiac Surgery, University of Toronto Toronto, ON
Kimberly Young, RN	Director, Donation and Transplantation Canadian Blood Services Edmonton, AB
Scott T. Youngquist, MD, MSc	Emergency Care Physician University of Utah Medical Centre Associate Professor, Surgery, University of Utah Salt Lake City, UT

Appendix 3: Prehospital Care Flow Chart and Research Questions



Identifying ECPR candidates in the prehospital setting

1. What are the inclusion and exclusion criteria that should be used by prehospital to identify patients appropriate for ECPR?
2. Given a set of validated or agreed upon inclusion and exclusion criteria, can paramedics reliably and accurately identify candidates for ECPR in the prehospital setting?

Prehospital ECPR

3. What is the feasibility and effectiveness of ECPR implemented in the prehospital setting as compared with no ECPR or ECPR initiated in the hospital after rapid transport for patients with OHCA? Does the feasibility of prehospital ECPR initiation demonstrated in other countries (e.g. France, Spain) apply to the Canadian setting?

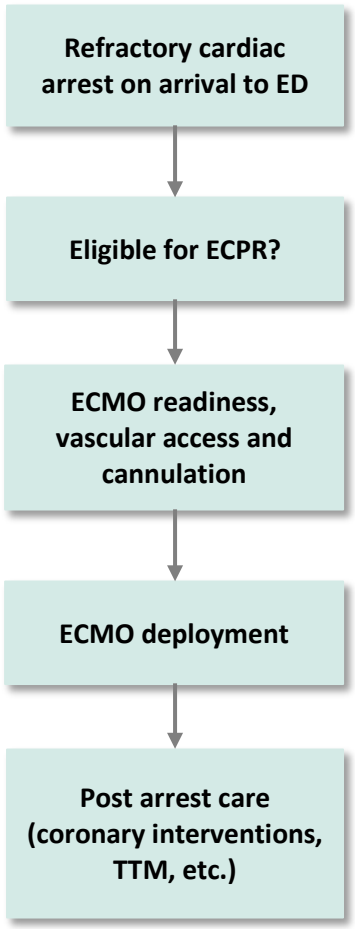
Optimizing outcomes and patient safety

4. Should mechanical chest compression devices or manual chest compressions be used for patients selected for ECPR during transport to hospital?
5. How long should resuscitation attempts be made on scene before transportation to hospital for ECPR candidates identified in the prehospital setting? Are outcomes related to the duration of resuscitation provided on scene? In other words, could patients be harmed if transported early for ECPR with suboptimal CPR compared with a strategy focusing on high-quality CPR and ACLS care on scene for a longer duration?
6. What is risk to OHCA patients related to bypassing closer hospitals without ECPR? What factors should go into this bypass decision (Estimated time to hospital? Estimated time to cannulation? Patient factors?)
7. Should indicators of the quality of CPR delivery be routinely assessed as part of ECPR trials? What metrics of performance in conventional resuscitative techniques (e.g. chest compression fraction, proportion receiving ALS care, etc.) and systems of care (e.g. EMS response times, overall survival) should be achieved prior to consideration of adding resource-intensive ECPR programs?
8. Is the quality of CPR provided by prehospital personnel prior to the initiation of ECPR associated with outcomes?

Provider safety

9. What are the risks to paramedics and public safety associated with rapid transport for patients selected for ECPR in the hospital?

Appendix 4: Emergency Department Flow Chart and Research Questions



Inclusion and exclusion criteria for ECPR

1. What are the inclusion and exclusion criteria for OHCA patients who arrive in the emergency department which identify patients most likely to benefit from ECPR? What co-morbidities are acceptable and should not be considered exclusion criteria?
2. Should patients with refractory shock post cardiac arrest be considered for ECPR on arrival to the emergency room?
3. What is the definition of "refractory" cardiac arrest? How long should conventional CPR be continued before considering ECPR?
4. Are there types of patients in which conventional CPR is less effective that could benefit from a primary strategy of ECPR as opposed to using ECPR as a salvage strategy after failed conventional advance life support measures, e.g. morbidly obese patients?

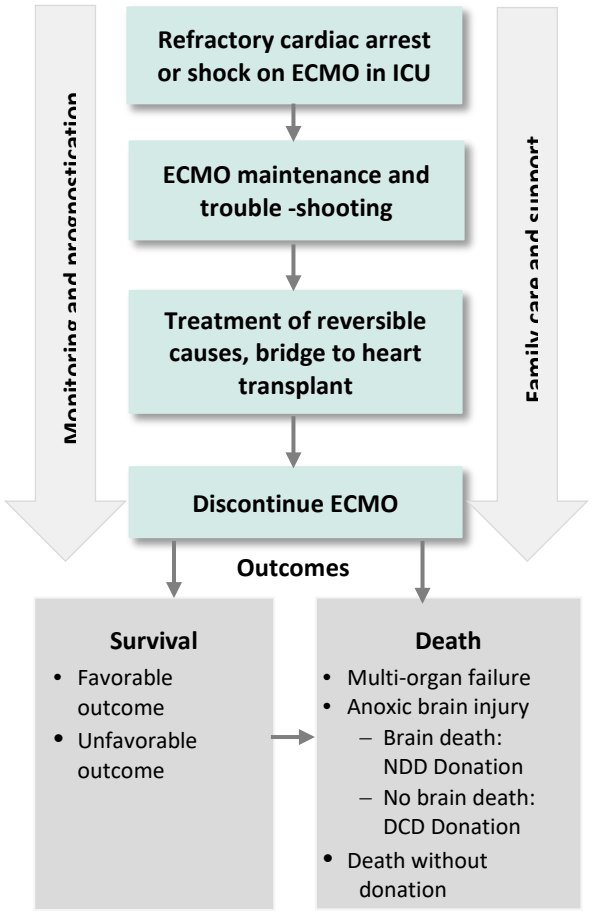
ECMO readiness

5. Where and how should ECPR equipment be stored? Is it important to keep the equipment in the emergency department to minimize delay to ECPR initiation?
6. How can the ECMO circuit be kept primed in the most efficient manner as not to waste primed circuits that expire? Should the circuits be kept primed at all times or only when receiving a pre-alert from the prehospital setting?
7. How should resuscitation rooms be set up for ECPR to ensure maximum efficiency and delivery of services?
8. What is the relative feasibility and health economics of a 24-7 ECPR program compared with a program offered during more restrictive hours (e.g. business hours)?

Personnel organization and training

9. Who can be trained to cannulate? Can emergency physicians accomplish safe and efficient cannulation for ECPR? Should this practice be limited to other specialists like surgeons or intensivists?
10. What frequency of cannulation over time is required to maintain competency in the skill? What are the response times of these various types of cannulators and how does that impact on time to ECPR delay and outcomes?
11. Who should be the resuscitation leader when ECPR is being implemented? How best to organize the resuscitation team when ECPR is involved?
12. Who will be managing the ECMO circuit during the initial set up and maintenance in the emergency department? What is the role of the perfusionist for ECPR patients in the emergency department? Are there other professionals who could be trained to manage the ECMO circuit so that a perfusionist is not required at the bedside at all times?
13. Should all emergency department staff (nurses, physicians, allied health) be trained in ECPR or rather a subset? Does the creation of an on call ECPR team improve service delivery? What is the best method for scheduling the human resources necessary for ECPR in the emergency department? What is the effect of off-site versus on-site ECPR team members on time to ECPR initiation?
14. What is the nature of training & re-training required to maintain competency amongst ECPR team members?

Appendix 5: Intensive Care Flow Chart and Research Questions



Post-arrest care

1. What are the approaches to nutrition, hemodynamic support, ventilation management, anticoagulation, sedation, and left ventricle decompression, etc., for the ECPR patient?
2. What are the indications for coronary angiography among patients treated with ECPR?
3. What is the role of targeted temperature management in patients treated with ECPR? What is the optimal target temperature management (TTM) for patients being treated with ECPR? How long should ECPR patients be treated with TTM? Does TTM during ECPR increase complication rates of ECMO (e.g. severe bleeding) or interfere with neuroprognostication?
4. What are optimal flow rates for patients treated with ECPR? How should flow rates be titrated?

Outcomes

5. What are the most important outcomes for patients treated with ECPR and at what time points should these outcomes be measured?
6. What neurologic measure should be used to indicate the level of neurologic recovery?
7. Should quality of life tools also be standardly used?
8. Should outcomes for ECPR include organ donation and transplantation?
9. What outcomes are the most important to patients, their families and society at large?

Neuroprognostication and end-of-life (EOL) decision-making

10. How should neuroprognostication be done for patients treated with ECPR?
    a. What is the role of clinical evaluation, electrophysiology (EEG, SSEP) measures, neuroimaging, and brain blood flow and brain biomarkers with respect to neuroprognostication for patients being treated with ECPR?
    b. How should confounding factors such temperature and pharmacologic agents be integrated into neuroprognostication for patients treated with ECPR?
    c. What is the neuroprognostic value of having immediate return of myocardial function after ECPR initiation?
    d. When should neuroprognostication happen in relation to implementation of ECPR, targeted temperature management or other therapies such as sedation to maximize accuracy for predicting outcomes?
11. In patients with return of cardiac function, are there clinical indicators (e.g. hemodynamics, neurologic function) that can identify patients suitable for safe discontinuation of ECMO? Are ECMO weaning trials necessary to optimize outcomes?
12. What are the criteria for the determination of death by neurological criteria in patients on ECMO? What are the criteria for determination of death by circulatory criteria in patients after discontinuation of ECMO?
13. For those patients with confirmed brain death or failure of cardiovascular recovery, what is the best way to manage EOL decision-making and withdrawal of ECMO in the palliative setting? This may include considerations around discontinuation of ECMO in the setting of medical futility and family refusal for withdrawal of life-sustaining therapy.