

Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest (EROCA) IDE

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CC	Coordinating Center
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LSMEAN	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UM	University of Michigan
UP	Unanticipated Problem
US	United States

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NHLBI Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Robert W. Neumar, MD, PhD

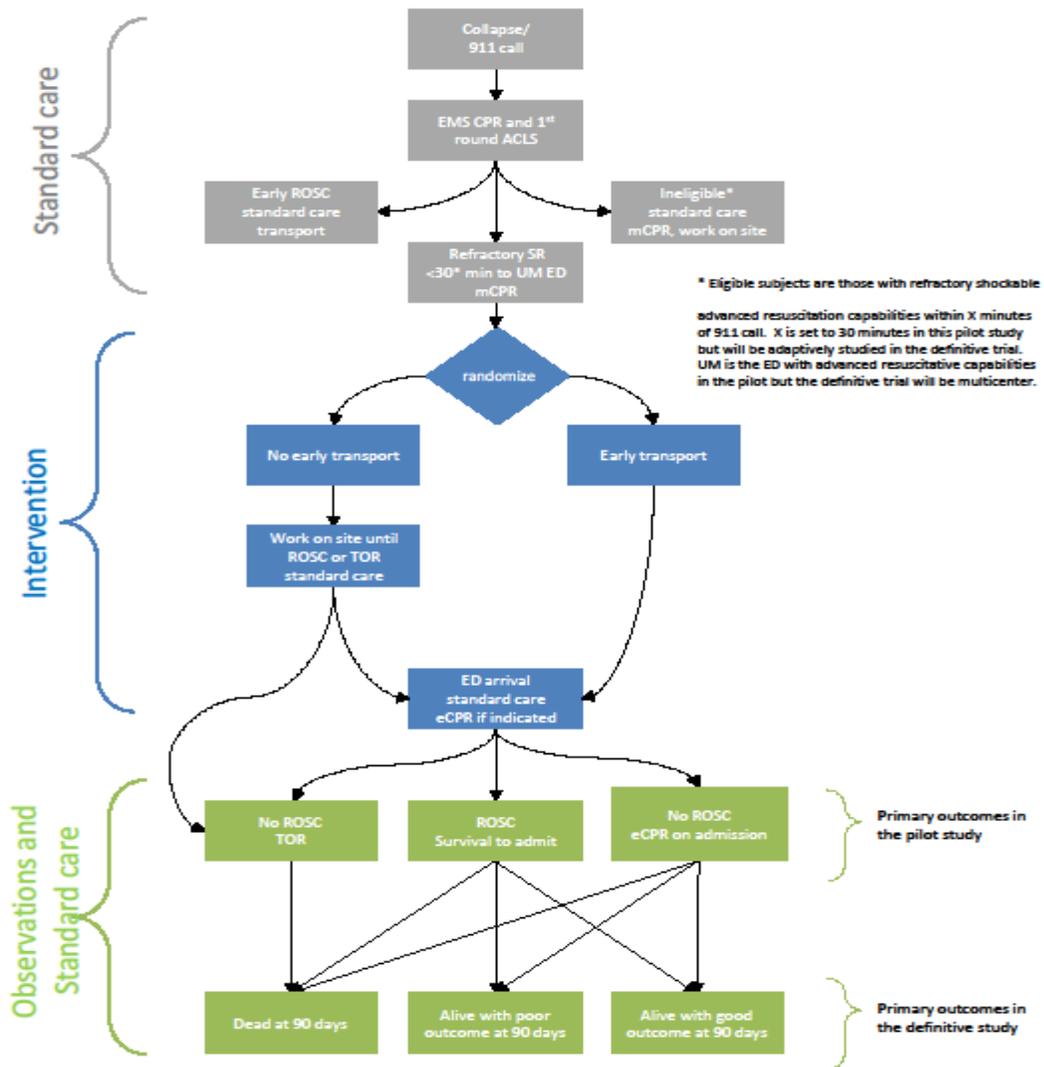
Signed: _____ Date: _____
Signature

PROTOCOL SUMMARY

Title:	Extracorporeal CPR for refractory out-of-hospital cardiac arrest (EROCA)
Précis:	EROCA is a prospective, randomized, open-label, clinical endpoint study comparing standard prehospital care to expedited transport of patients with refractory out-of-hospital cardiac arrest (OHCA) to a qualified emergency department capable of performing advanced resuscitation including extracorporeal cardiopulmonary resuscitation (ECPR). A maximum total of 30 patients will be randomized in the prehospital setting. The primary objectives are to determine the proportion of qualifying OHCA patients arriving to a qualified ED within 30 minutes of the initial 911 call and what proportion of patients can have ECPR initiated within 30 minutes of ED arrival. Patients arriving at the qualified ED will be treated under a standard institutional guideline and will be followed in the hospital for adverse events. In addition, patients will have follow up visits at 90 days to determine functional and neuro-cognitive outcomes.
Objectives:	<p>Co-Primary: Determine what proportion of patients with refractory OHCA can be reliably delivered to an ECPR-capable ED within 30 min of either the 911 call or prehospital provider witnessed first cardiac arrest (qualifying OHCA event).</p> <p>Co-Primary: Determine what proportion of patients with ongoing refractory cardiac arrest that have ECPR initiated within 30 minutes of ED arrival.</p> <p>Safety: To estimate frequency of adverse events associated with study interventions.</p> <p>Exploratory: Demonstrate the feasibility of field randomization of patients with refractory OHCA based on estimated time from 911 call or EMS witnessed arrest to qualified ED arrival</p> <p>Exploratory: To provide preliminary estimates regarding neurological outcomes following this treatment.</p>
Endpoints	<p>Co-Primary : Time interval from 911 call or prehospital provider witnessed first cardiac arrest to qualified ED arrival in minutes</p> <p>Co-Primary : Time interval from qualified ED arrival to ECPR initiation in minutes</p> <p>Safety: Composite of major hemorrhage (requiring transfusion of over 4 units packed red blood cells per incident), arterial thrombosis (stroke, renal infarction, limb ischemia), venous thrombosis (pulmonary embolism or deep venous thrombosis), hemopericardium (requiring pericardiocentesis), pneumothorax(requiring thoracostomy tube placement), or vascular injury (causing complete occlusion and/or requiring vascular</p>

	procedure).
	Exploratory: Utility weighted modified Rankin Scale at 90 days
	Exploratory: Neuropsychological and cognitive testing using NIH toolbox
	Exploratory: Time to vascular access and time to ECPR cannulation
Population:	Out-of-hospital cardiac arrest patients who do not have return of spontaneous circulation after initial rhythm analysis by first- responders who can potentially arrive at a qualified ED in persistent cardiac arrest within 30 minutes of initial 911 call or EMS witnessed first cardiac arrest.
Phase:	2
Number of Sites	
enrolling participants:	1
Description of Study Interventions :	Patients in the field will be randomized to either early transport to the hospital versus standard care (continued attempts at advanced cardiac life support in the field). Standard clinical procedures in the hospital will be followed for refractory cardiac arrest patients.
Study Duration:	30 months
Participant Duration:	Three months

SCHEMATIC OF STUDY DESIGN



EMS = emergency medical services, CPR = cardiopulmonary resuscitation, mCPR = mechanical CPR, eCPR = extracorporeal CPR, ACLS = advanced cardiac life support, ROSC = return of spontaneous circulation, TOR = termination of resuscitation, SR = shockable rhythms, ED = emergency department, UM = University of Michigan

***Return Of Spontaneous Circulation**

****Expedited transfer** refers to immediately transferring a patient to the hospital while CPR is in progress, using mechanical chest compressions.

KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

2.1.1 CLINICAL SIGNIFICANCE

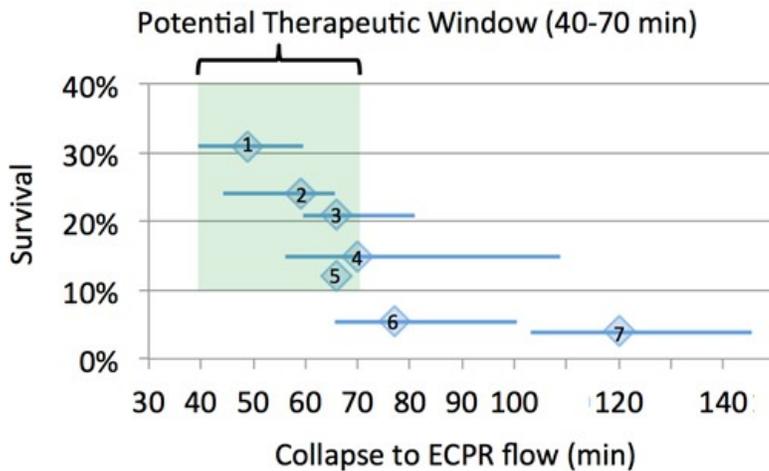
Approximately 200,000 people are treated for out-of-hospital cardiac arrest (OHCA) each year in the United States. The modest improvement in survival rates over the past decade have been primarily attributed to better implementation of cardiopulmonary resuscitation (CPR), advanced cardiac life support (ACLS), and post-cardiac arrest care. However, no new therapies have been proven effective in more than a decade. The result is a plateauing of overall survival rates at approximately 10% [Mozaffarian 2015]. Extracorporeal cardiopulmonary resuscitation (ECPR) using percutaneous veno-arterial extracorporeal circulation (VA-ECMO) is emerging as a feasible and potentially effective resuscitation strategy for non-traumatic OHCA patients who fail standard therapy. In published case series, survival rates range from 4-33%, and organ donation as a secondary outcome occurs in 5-15% of patients. Despite the promise of this emerging therapy, a fundamental barrier to widespread implementation is the fact that efficacy of ECPR for OHCA has yet to be proven in a prospective randomized clinical trial. In October of 2015, the International Liaison Committee on Resuscitation (ILCOR) Consensus on Science and Treatment Recommendation made the following treatment recommendation: *We suggest ECPR is a reasonable rescue therapy for selected patients with cardiac arrest when initial conventional CPR is failing in settings where this can be implemented (weak recommendation, very-low-quality evidence)* [Callaway 2015]. The primary knowledge gap listed was: *Controlled clinical trials are needed to assess the effect of ECPR versus traditional CPR on clinical outcomes in patients with cardiac arrest.* The new AHA guidelines for CPR and Emergency Cardiovascular Care published in October 2015 state: *There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of*

mechanical cardiorespiratory support (Class IIb, LOE C-LD) [Link 2015]. Thus, the most recent consensus of the world's experts in the field is a call for more evidence in the form of a prospective randomized clinical trial.

2.1.2 RELEVANT CLINICAL RESEARCH

Almost all published case series of successful ECPR for OHCA initiate ECPR in the emergency department [Chen 2008, Kagawa 2010, Nagao 2000 and 2010, LeGuen 2011, Morimura 2011, Avali 2012, Bellezzo 2012, Johnson 2014, Sakamoto 2014, Stub 2014]. The reason for this strategy is that the shorter the interval from cardiac arrest onset to initiation of ECPR, the better the chance for a favorable outcome. Figure 3 illustrates this relationship in recent OHCA studies (published after 2010) that specifically reported the collapse to ECPR interval and survival with good neurologic function for the entire study population. These and similar reports are the basis for our initial targeting of a 911 call to ECPR interval <60 min in the EROCA trial. In many countries where ECPR is used to treat OHCA, the ED is routinely staffed by physician specialists in anesthesia or cardiology with more formal training and experience in ECMO than emergency medicine physicians in the U.S. Institutions in the U.S. that perform ECPR for OHCA typically rely on cardiac surgery or cardiology consultants to come to the ED to place ECMO catheters and initiate ECPR [Johnson 2014]. However, the model has many logistical limitations that make it challenging to initiate ECPR within the therapeutic window, and if maintained will be a persistent barrier to widespread implementation.

One example of a program that has incorporated emergency medicine physicians into the ECPR team that includes cardiologist and cardiothoracic surgeons Sharp Memorial Hospital in San Diego [Bellezzo 2012]. In their published case series, 8 out of 18 OHCA patients that met inclusion/exclusion had ECPR successfully initiated in the ED, and 3/18 had spontaneous ROSC before ECPR could be initiation. Of the 8 patients successfully treated with ECPR, 5 survived with good neurologic function (63%). However ECPR catheters could not be placed in 4 patients, and two other patients were reported to have fatal complications of catheter placement (aortic dissection and bifemoral vein cannulation). Although these results demonstrate feasibility in a US ED, they also emphasize the importance of validated training and maintenance of competency for both clinical trial participation and widespread implementation.



Relationship between collapse to ECPR interval and survival with good neurologic function in refractory OHCA cardiac arrest 1) Maekawa 2013; 2) Kagawa 2012; 3) Fagnoul 2013; 4) Haneya 2012; 5) Nagao 2010; 6) Avali 2012; 7) Le Guen 2011. Diamonds represent median intervals from collapse to ECPR and lines represents range. (Adapted from Fagnoul 2014 table 2.)

2.2 RATIONALE

Currently available evidence suggests that ECPR for OHCA should be initiated within 60 minutes of cardiac arrest onset to maximize the potential therapeutic benefit. Therefore, in addition to delivering patients to the ED within 30 minutes, it is essential that our system of care is able to initiate ECPR within ≤ 30 minutes of ED arrival. In a recently published study of ED-initiated ECPR, the median time from ECPR team arrival to initiation of ECPR was 20 minutes [IQR 15-30 minutes] [Stub 2014]. The goal is to achieve < 30 -minute arrival to cannulation for all patients meeting inclusion/exclusion criteria for ECPR therapy.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Risks of mechanical or traditional CPR: bruising and soreness of the chest is common after mechanical or traditional CPR. Pneumothorax and hemo-pericardium are also possible risks. Rib fractures and solid organ injuries (liver and spleen) are additional potential risks.

Risk of EMS (early transport): motor vehicle crash during transport to the hospital.

Alternatives to early transport with mechanical CPR: Continued BLS and ACLS at the scene with manual or mechanical CPR until ROSC is achieved or resuscitation efforts are terminated (current practice).

Risks of ECPR (standard care procedure in hospital): vascular injury, limb ischemia, major hemorrhage, venous thromboembolism, stroke, renal failure, and infection.

Alternatives to ECPR for refractory cardiac arrest: An option is to transport patients to the interventional cardiology laboratory with ongoing CPR for coronary angiography and PCI if indicated. The rationale for this approach is that an acute coronary occlusion is the cause of the cardiac arrest and treating that occlusion could result in ROSC. At this time there is less evidence to support this approach compared to ED-initiated ECPR followed by coronary angiography and PCI following initiation of ECPR if indicated.

Risks of research: improper disclosure or release of personal or medical information.

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefit of the research to the research subjects is an improved chance of survival with good neurologic function. The current practice for patients with refractory OHCA is for EMS providers to cease resuscitation efforts in the field and pronounce the patients dead. Early transport to an ED capable of advanced resuscitation strategies and ECPR has been reported to result in 4-33% survival with good neurologic function. The potential benefit to society is an improved system of care of OHCA that could double overall survival rates and with widespread implementation save thousands of lives each year in the United States. Reported risks for ECPR include hemorrhage, renal replacement therapy for acute kidney injury, vascular damage, thromboembolism, stroke, and infection. Relative to the potential benefit of survival with good neurologic function, these risks seem reasonable.

3 OBJECTIVES AND PURPOSE

Co-Primary: To determine what proportion of patients with refractory OHCA can be delivered to an ECPR-capable ED within 30 min of the 911 call or prehospital provider witnessed first cardiac arrest (qualifying OHCA event). This is to establish the feasibility of the early transport protocol.

Co-Primary: To determine what proportion of patients can have ECPR initiated within 30 minutes of ED arrival for patients with ongoing refractory OHCA. This is to establish the feasibility of the ED advanced resuscitation protocol in situations where prenotification of the team has occurred by qualified prehospital providers.

Safety: To estimate frequency of adverse events associated with study interventions. This early phase trial is not adequately sized to provide meaningful comparative estimates. The

population of OHCA survivors is at high risk for death and adverse experiences under routine clinical care.

Exploratory: Demonstrate the feasibility of field randomization of patients with refractory OHCA. This study is using a novel procedure to determine eligibility based on timing and location.

Exploratory: We will collect ECPR process measures including time to confirmed vascular access and confirmed ECPR cannulation. These measures are collected as part of routine clinical care on all patients undergoing ECPR for cardiac arrest at the qualified emergency department(s).

Exploratory: To provide preliminary estimates regarding neurological outcomes following this treatment. This study is not adequately sized to provide meaningful comparative data on neurological outcomes. This aim will provide insight into the proportion of patients with excellent outcomes, along with the proportion of patients with neurologically unsatisfactory outcomes.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

4.2.1 Primary Endpoints

Co-Primary Endpoint: Time interval from 911 call or prehospital witnessed first cardiac arrest (qualifying OHCA event) to ED arrival in minutes.

The primary endpoint was selected because the goal of the study is to demonstrate the feasibility of transporting patients with refractory OHCA to an ECPR-capable ED within 30 minutes of the 911 call or EMS witnessed arrest.

Co-Primary Endpoint: Time interval from ED arrival to ECPR initiation in minutes

This time interval was chosen because the apparent therapeutic window for OHCA ECPR is 60 minutes and time from ED arrival to ECPR flow is estimated to be 30 minutes.

4.2.2 SAFETY ENDPOINTS

Composite safety endpoint of hemorrhage requiring blood transfusion, pneumothorax requiring thoracostomy, hemopericardium requiring pericardiocentesis.

Composite safety endpoint of, hemorrhage requiring blood transfusion (greater than 4 units packed red blood cells per incident), vessel damage requiring vascular procedure or leading to occlusion, venous/arterial thromboembolism, stroke, renal failure and infection

4.2.3 EXPLORATORY ENDPOINTS

Additional safety outcomes: Splenic injury, liver injury, and all individual components of the composite endpoints listed in 4.2.2

All participants: Utility weighted modified Rankin Scale and cerebral performance category at hospital discharge and 90 days.

Randomization feasibility: Number of attempted uses of randomization app versus successful enrollments

Patient reported outcomes: Neuro-QOL

Cognitive functioning outcomes: NIH-Toolbox

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

All adult out-of-hospital cardiac arrest patients, receiving emergency treatment by local Fire Department First Responders capable of using mechanical chest compression devices and Huron Valley Ambulance (HVA) paramedics will be evaluated for this study. This may include ethnic minorities, disabled, and economically challenged populations.

5.1.1 PATIENT LEVEL INCLUSION

- Present with out-of-hospital cardiac arrest, presumed non-traumatic etiology, requiring CPR
- Age presumed or known to be 18 through 70 years old (prior to 71st birthday)
- Predicted arrival time at ECPR-capable hospital within timeframe specified
- Initial shockable rhythm (ventricular tachycardia or ventricular fibrillation) or witnessed pulseless electrical activity or asystole
- Persistent cardiac arrest after initial cardiac rhythm analysis and shock (if shock is indicated)

Participants will be enrolled in the study if they meet initial inclusion criteria at the time of their cardiac arrest.

5.1.2 INCLUDED EMS AGENCIES / REGIONS / HOSPITALS

- Local Fire Department First Responders using mechanical chest compression devices including:
 - Ann Arbor Fire Department First Responders
 - Ann Arbor Township Fire Department First Responders
 - Saline Area Fire Department
 - Scio Township Fire Department First Responders
 - Huron Valley Ambulance Paramedics
 - Michigan Medicine, University of Michigan

5.2 PARTICIPANT EXCLUSION CRITERIA

Exclusion criteria include:

- Sustained return of spontaneous circulation (ROSC)
- DNAR or DNI advanced directive
- Preexisting evidence of opting out of study
- Prisoner
- Pregnant (obvious or known)
- ECPR capable ED is not at the destination hospital as determined by EMS
- LAR/Family member aware of study and refuses study participation at the scene

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

There is no participant “recruitment” for this study as it is not possible to prospectively identify victims of out-of-hospital sudden cardiac arrest and obtain informed consent. Participants will be included in the study if they meet enrollment criteria at the time of their cardiac arrest. Based on historical data, we anticipate randomizing 30 refractory OHCA patients over 18 months. This clinical trial will be conducted under exception from informed consent (further details in Section 13).

Patients will be screened and assigned a randomization group at the time of dispatch. Study eligibility and randomization will be further determined with the aid of an algorithm or expected time to eligible hospital map where a 911 dispatch operator will input eligibility data points and receive one of 3 responses. This is pre-enrollment treatment group assignment. Despite assignment to one of these three groups, the patient will not be considered randomized until they have met the inclusion criteria (including the refractory nature of the cardiac arrest.)

1. Not eligible continue usual resuscitative care (stay in place until ROSC or resuscitation

meets termination criteria)

2. Eligible, randomized to usual care (operationally same as 1 for paramedics)
3. Eligible, randomized to early transport

After an initial rhythm assessment and shock delivery (if indicated), patients who do not have ROSC will be considered randomized. Based on the assignment given at the time the prehospital providers were dispatched, they will either continue usual care (stay in place until ROSC) if assigned to that group (control), or undergo expedited transport with mechanical CPR device in place (experimental group). Patients who do not meet inclusion criteria or have exclusion criteria will not be considered randomized or enrolled, since no experimental procedures will occur to them (standard procedure is for patients to be transported after ROSC). If ROSC is achieved during transport or in the emergency department (experimental group), they will be included in the primary analysis of the expedited transport group. All patients will be followed for clinical outcomes.

All Emergency Medical Services (EMS) personnel (engaged sites) will be trained by a member of the study team to the study protocol including randomization, eligibility, study procedures, exception from informed consent, and opting-out mechanisms. Training records will be maintained with the site coordinator.

In accordance with the FDA's Regulations, the investigator must attempt to notify all participants that they have been enrolled in a study. If the participant is unable to comprehend this due to loss of consciousness or dies, the investigator must attempt to notify their legally authorized representative.

Study participants who die in the field or the hospital emergency department, attempts will be made to notify their family/LAR, by using EMS and hospital records contact information. Initial contact will be made by a letter requiring a signature/receipt for receipt confirmation. With respect for the grieving process, a letter will be sent 2-4 weeks after the death of the patient. These records will also be reviewed and data abstracted, in addition to reviewing for any potential adverse events. Letters returned to sender or knowledge initial letter was not received, a telephone call will be made, up to 2 times for notification. This will be done by a trained research team member, experienced with discussing sensitive topics such as the death of a loved one. A communication tracking log will be kept.

Study Participants who survive to hospital admission or their LAR/family member will be approached to notify them of being in the research study and invited to continue study participation, as soon as feasible after hospital admission. The person obtaining consent will first discuss the study with the participant's physician or nurse to assess their condition and best timing for discussion with them or their LAR/family member. Once signed, a copy of this form is provided to the participant/LAR, in the medical record, and the original will be placed

in their research record.

We will conduct education and training of engaged agencies and hospitals to maximize recruitment. Screening logs will be reviewed regularly with engaged agencies.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

A study participant has the right to withdraw from the study at any time without consequence. Reasons for withdrawal may include not wanting to complete the 90-day follow-up visit, becoming tired with the follow-up surveys and requesting to stop, or deciding to no longer participate.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

FDA regulations require investigators to prepare and maintain adequate study files recording all observations and other pertinent information relative to the clinical trial and when a participant or LAR/family member withdraws further participation, the data already collected, remains with the study database.

If a study participant or LAR/family member declines further study participation, then no further data collection will occur. Since this is an observational study after randomization, the participant can safely withdraw and will not be at risk of injury.

In the case of participant withdrawal, data about their death is contained in public vital statistics records and will be queried. Access to public records is not subject to restriction under 21CFR or other FDA regulations.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, the IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the sponsor, IRB and/or FDA.

6 STUDY INTERVENTION

This study is a comparison of two treatment strategies for refractory out-of-hospital cardiac arrest (OHCA): continued standard care in the field (control) versus expedited transport with ongoing mechanical CPR to a hospital capable of initiating extracorporeal cardiopulmonary resuscitation (ECPR) in the emergency department (experimental). ECPR is defined as percutaneous veno-arterial extracorporeal membrane oxygenation (ECMO) initiated during cardiac arrest. The duration of ECPR is typically 72 hours to allow the patient's heart function to recover prior to weaning. Many devices make up an ECMO circuit (cannulas, conduit, reservoir, pump, oxygenator, heat exchanger, monitors, sweep gas controller, bubble traps, blood filters, positive and negative pressure monitors and controls). The devices used for ECMO are FDA-approved for up to 6 hours for the indication of cardiopulmonary bypass. However, ECPR for the treatment of refractory cardiac arrest is not a FDA approved or cleared indication for ECMO devices, and thus is considered investigational in this study. Current American Heart Association Guidelines state that *"In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support (Class IIb, LOE C-LD)"*. ECPR is currently performed in the University of Michigan University Hospital ED for selected patients with refractory cardiac arrest as part of our standard practice. Examples of local guidelines for EMS and ED care are given as appendices B and C.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 Study specific procedures

Consent Process

Participants or their legally authorized representative (LAR) or family member will be approached within a reasonable timeframe and will be requested for consent to continue in the study. The availability and emotional state of LAR/family members will be taken into account, and anticipate a longer timeframe in these situations. The progress of obtaining written informed consent will be documented in the medical record. For participants who do not survive to hospital admission, a letter will be sent as notification.

Review of Medical Records

FDA's regulations require clinical investigators to prepare and maintain adequate and accurate case histories (21 CFR 312.62(b) and 812.140(a)). In general, the investigator should arrange to have access to all records that are generated and maintained from enrollment until discharge or death, unless the participant or their LAR/family member discontinues the participant's participation in the study. Medical records will be reviewed by a member of the research team up until this time and if the participant or LAR or family member discontinues participation, the data already collected will remain with the study.

Prehospital Medical Records

BLS and ACLS run reports will be reviewed on all study participants by the study team and study specific data abstracted. Run reports become part of the medical record when patients are brought to the emergency department and for cardiac arrests pronounced dead in the field, will be sent to the study team securely (i.e. by fax).

The following scales will be performed by a member of the research team at hospital discharge and Day 90, in participants who survive.

Modified Rankin Scale (mRS)

The mRS is commonly used for measuring the degree of disability or dependence in the daily activities of people who have suffered a neurological disability. mRS score is widely used in stroke research.

Cerebral Performance Categories Scale (CPC)

CPC score is widely used in cardiac arrest research to assess neurologic outcome.

NIH Toolbox

The NIH toolbox includes several cognitive, motor, and psychological tests. It can be administered via an iPad.

7.1.2 STANDARD CARE STUDY PROCEDURES

Standard care for the treatment of OHCA will include cardiac defibrillators, mechanical CPR, intravenous (IV) therapy, arterial blood pressure monitoring, central line monitoring, intubation, mechanical ventilation, heart monitoring, cardiac catheterization, hypothermic

targeted temperature management, and continuous EEG monitoring. Standard procedures for engaged prehospital providers/agencies and qualified emergency departments will be followed. Examples of prehospital and in-hospital standard care protocols are given as appendices B and C.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

No biological materials, including blood samples, will be obtained as part of this study protocol.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening (Day 0, Field Baseline)

Screening will be done by prehospital providers in all out-of-hospital cardiac arrests in the engaged agencies area. All out-of-hospital cardiac arrests, meeting inclusion criteria will be considered for the study.

Pre Enrollment – Treatment Group Assignment / Randomization

At the time of dispatch of EMS, the dispatcher will enter the address of the arrest, age of the patient, and time of 911 call into a web form. The form will use an application to determine whether the patient is within the travel distance to arrive at the hospital within the pre-specified interval. They will immediately receive one of the following messages:

- 1) Not eligible, continue usual resuscitative care (patient may be out of geographic time area, may be over 71 years old)
- 2) Eligible, randomized to usual care
- 3) Eligible, randomized to early transport.

If the dispatcher is unable to access the assignment/randomization website, there will be a study team member, with access rights to the website available by telephone at all times.

7.3.2 ENROLLMENT/BASELINE

Pre-hospital run sheet(s) will be reviewed for study eligibility and enrollment criteria. The emergency department and hospital electronic medical record will be reviewed for continued inclusion criteria, including time intervals from 911 call to randomization and 911 call to

emergency department admission, if applicable. Until hospital discharge, all data collected will come from previously collected medical records.

Initial Enrollment/Field Baseline (Day 0)

Patients will be enrolled and randomized if they meet the inclusion criteria, namely, the presence of refractory cardiac arrest (defined as no ROSC after initial rhythm analysis and shock if indicated). The treatment group was pre-assigned during the screening phase, but patients with immediate ROSC are considered screened out of the study as no experimental intervention will occur to them.

Patients with persistent cardiac arrest in the field who are randomized will be followed for clinical outcomes per the protocol whether or not they have ECPR.

Due to the sudden and urgent nature of cardiac arrest, treatment must occur immediately. Enrollment will occur at the time of randomization by the prehospital providers at the scene of the out-of-hospital cardiac arrest. Patients will be enrolled under the exception from informed consent (EFIC) process.

Prehospital Medical Records

Prehospital run reports is where Basic Life Support (BLS) and Advanced Life Support (ALS) document the events of the 911 call and often become part of the medical record when patients are brought to the emergency department. Any run reports not found in the medical record and for participants who dies prior to the emergency department will be collected directly from the agencies.

EMS medical records will be reviewed and the following data abstracted:

- Date and time of 911 call
- Time of index cardiac arrest
- Status of witnessed arrest
- Status of Bystander CPR
- Time of collapse
- Time CPR initiated
- Duration of EMS CPR
- Initial recorded cardiac arrest rhythm
- Use of Impedance-threshold device
- Use and type of advanced airway
- Location of cardiac arrest (home, public place, parking lot, street, etc.)
- Date and time of ED arrival

Index Cardiac Arrest/Emergency Department (Day 0)

Emergency Department (ED) medical records will be reviewed and the following data abstracted:

- Date and time of ED arrival
- Status and timing of ROSC
- Demographic information
- Physician progress note(s)
- Past medical history; known comorbidities
- Nurses notes
- Tests performed and their results
- Procedures performed and their outcome
- Status of ECPR procedure
 - Time of confirmed placement of arterial and venous ECMO catheters
 - Time of initiation of ECPR
- ED Discharge diagnosis
- ED disposition

Survival to Hospital Admission (Day 0- Hospital Discharge or Death)

Attempt to notify the participant, LAR, or family member of study participation and seek permission to continue in the study, using the written IRB approved informed consent form.

Hospital medical records will be reviewed and the following data abstracted:

- Date and time of Hospital admission
- Status of ROSC
- Use of therapeutic hypothermia
- Neurologic status
- Physician progress note(s)
- Nurses notes
- Tests performed and their results
- Procedures performed and their outcome
- Assess for serious adverse events

Hospital Discharge

Hospital medical records will be reviewed and the following data abstracted:

- Date and time of Hospital discharge
- Survival status
- Assess for serious adverse events
- Discharge disposition

The following assessments will be performed by a member of the study team:

- CPC
- mRS
- NIH Toolbox Cognitive Testing

Assess for Serious Adverse Events (SAE's)

Prehospital and hospital records will be reviewed for serious adverse events.

7.3.3 FOLLOW-UP

Follow-up Visit (Day 90 +/- 15 days)

The following assessments will be performed by a member of the study team:

- CPC
- mRS
- NIH Toolbox Cognitive Testing
- Quality of Life Survey

7.3.4 FINAL STUDY VISIT

Final study visit is the Day 90 visit described above in section 7.3.3. The study participant will be contacted by telephone to set up a follow up appointment. Reasonable costs such as parking, bus fare, or mileage will be covered by the study.

7.3.5 EARLY TERMINATION VISIT

Prehospital patients in cardiac arrest will not have the ability to notify prehospital providers of their choice to participate or not. If a LAR/family member is aware of the study and objects to their participation, prehospital providers will not enroll the patient.

If the participant survives to hospital admission, a member of the study team will attempt to contact the participant or LAR/family member to notify them of study participation and obtain informed consent for continued participation in the study. The participant or LAR or family member has the right to decline study participation at any time before or after informed consent is obtained. A participant, however may not withdraw use of the data already collected. At the point of termination, the medical record will no longer be reviewed. However, data about a participant's death is contained in public vital statistics records. Access to public records is not subject to restriction under 21 CFR 50.24 or other FDA regulations.

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Index Cardiac Arrest (Field)	Emergency Department	Survival to Hospital Admission	Hospital Course	Hospital Discharge	End of Study/Day 90
Screening	X					
Enrollment	X					
Randomization	X					
ROSC	X	X				
Survival Status	X	X	X	X	X	X
Review of pre-hospital medical	X					
Review of medical record	X	X	X	X	X	X
Informed Consent Process		X				X
CPC					X	X
mRS					X	X
NIH Toolbox					X	X
Quality of Life Survey						X
Monitor Serious Adverse Events	X	X	X	X	X	X

ROSC – Return of Spontaneous Circulation

CPC – Cerebral Performance Category

mRS – Modified Rankin Scale

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Clinical care is at the discretion of the clinical team. No concomitant medications, treatments or procedures are required or prohibited by the research protocol.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Predefined safety clinical events are outlined in the endpoints sections 4.2.2 and 4.2.3. Since the study intervention is early transport versus continued resuscitation in the field, and all interventions occurring after this intervention represent standard care, safety endpoints will provide a qualitative assessment of the strategies given the limited sample size. Summaries of

events by group will be provided to all relevant monitoring bodies. Given the severity of cardiac arrest, most patients will experience one or more SAEs as part of routine clinical care.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is an AE that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, requires intervention to prevent permanent impairment or damage, or any event that the treating clinician or internal medical monitor judges to be a significant hazard, contraindication, side effect, or precaution. Reporting serious adverse events (SAEs) are based on the guidelines of the International Conference on Harmonization (ICH).

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other

unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

‘Severity’ is not the same as ‘serious.’ Serious is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or health. The term ‘severe’ is often used to describe the intensity (severity) of a specific event (as in mild, moderate, severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. Most AEs include clinical criteria that describe patient/event outcomes or indicated interventions to more clearly substantiate seriousness.

All adverse events occurring within 24 hours of study enrollment and all serious adverse events occurring during study participation will be documented on the AE case report form. Adverse events will be documented using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE). The CTCAE provides descriptive terminology that will be used for recording and reporting adverse events that occur in the EROCA trial. The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v 3.0) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Grade 1:	Mild AE
Grade 2:	Moderate AE
Grade 3:	Severe AE
Grade 4:	Life-Threatening or Disabling AE
Grade 5:	Death related to AE

Note: Severity is not equivalent to seriousness. A serious adverse event (SAE) would be any event in category 4 or 5, and any event in category 3 that required or prolonged hospitalization.

Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade Selection i.e., Grade 5 (Death) is not appropriate for some AEs and therefore is not an option. A version of the CTCAE is available in the MoP

8.2.2 RELATIONSHIP TO STUDY AGENT

The site principal investigator is responsible for designating, at the time an AE is reported, how likely it is that the AE is caused by the study intervention. This determination requires clinical judgement, but for purposes of this study an algorithm is used to help the investigator provide reporting that is as objective as possible and consistent with reporting across the trial.

Modified for EROCA, based upon: Adverse Events Reporting Requirements SOP. NIH-NIAID. <http://www.niaid.nih.gov/ncn/sop/adverseevents.htm> , accessed 11-30-04.

Not related: The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely: May have reasonable or only tenuous temporal relationship to intervention. Must meet both of the following conditions:

- Could readily have been produced by the subject's clinical state, or environmental or other interventions.
- Does not follow known pattern of response to intervention.

Possibly: Must meet any 2 of the 3 following conditions

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or environmental or other interventions.
- Follows a known pattern of response to intervention.

Probably: Must meet all 3 of the following conditions

- Has a reasonable temporal relationship to intervention.
- Could not *readily* have been produced by the subject's clinical state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.

Definitely: Must meet all 3 of the following conditions

- Has a reasonable temporal relationship to intervention.
- Could not *possibly* have been produced by the subject's clinical state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.

8.2.3 EXPECTEDNESS

The site principal investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI or designated research staff will record all reportable events with start dates occurring any time after study enrollment until 24 hours (for non-serious AEs) or 90 days or last day of study participation (for SAE's). At each study visit, the investigator or study coordinator will inquire about the occurrence of SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

A serious adverse event (SAE) is an AE that is fatal or life threatening, is permanently or substantially disabling, requires or prolongs hospitalization, results in a congenital anomaly, requires intervention to prevent permanent impairment or damage, or any event that the treating clinician or internal medical monitor judges to be a significant hazard, contraindication, side effect, or precaution. Reporting serious adverse events (SAEs) are based on the guidelines of the International Conference on Harmonization (ICH).

8.4.1 ADVERSE EVENT REPORTING

All AEs occurring within 24 hours of study participation and all serious adverse events (SAEs) occurring up until 90 days or last day of study participation are recorded on the online AE case report form (CRF) through the study database. The Site PI or Study Coordinator or designee is responsible for entering any and all AEs and SAEs into the database as soon as he/she becomes aware of the event and updating the information (e.g., date of resolution, action taken) in a timely manner. All non-serious AEs must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. (All non-serious AEs during hospitalization must be entered within 5 days of discharge or end of study for that subject.) For SAEs, the data entry must take place within 24 hours of discovery of the event.

The Site PI is responsible for the monitoring and follow-up of AEs until resolution (or end of study for that subject) and appropriate documentation in the subject research record. In addition to performing protocol-specified follow up, the participating PI must review all previously reported ongoing AEs to evaluate the current status. If an AE that was previously reported on the Adverse Event CRF fully resolves and then recurs at a later date, the second occurrence is considered a new AE and a new Adverse Event CRF must be completed. Likewise, if an SAE that was previously reported and subsequently fully resolved later recurs at a level requiring expedited reporting, the SAE must be reported as a new SAE on the Adverse Event CRF.

Upon completion of the study protocol by the subject, premature withdrawal from the study by the subject, or subject's death, all information regarding each AE must be completed, if not done so earlier.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete a SAE Form within the following timelines:

All Serious Adverse Events (SAEs) occurring during a subject's study participation will be recorded up until 90 days or last day of study participation. All SAEs must be entered into the database system within 24 hours of first

knowledge of the SAE. Additionally, all current study data for that particular subject must be entered to allow for timely review.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the event.

Any other UP will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IR's receipt of the report of the problem from the investigator.

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device

effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.4 EVENTS OF SPECIAL INTEREST

Not applicable

8.4.5 REPORTING OF PREGNANCY

Patients who are obviously pregnant will not be enrolled. If pregnancy is discovered, the team will request permission to follow pregnant women to pregnancy outcome. As the intervention (early transport with mechanical CPR) occurs prior to laboratory testing, no additional treatment is possible under this protocol after the discovery of pregnancy and patients are only on the protocol for the collection of outcomes.

8.5 STUDY HALTING RULES

No formal quantitative stopping rules are in place for EROCA. The study may be modified or discontinued at any time by the IRB, the NHLBI, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an independent DSMB composed of individuals with the appropriate expertise, including emergency medicine. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NIH. We will provide tables providing all SAEs by group, along with clinical outcomes, and a listing of SAEs by individual enrolled (given the small sample size of EROCA), as part of reporting to DSMB.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Designated study staff not involved with the enrollment will conduct monitoring. This will occur throughout the study, and will involve targeted or review of certain data (primary

endpoints, safety endpoints, consent forms). Monitoring reports will be distributed to the PI or site PIs if applicable.

- Independent audits will not be conducted.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. As necessary, individualized quality management plans will be developed to describe a site's quality management.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

This is a pilot trial, designed to demonstrate proof of feasibility prior to a larger scale trial that will be powered to improve patient outcomes. The primary endpoints target process measures, namely the delivery of randomized patients to the qualified ED within 30 minutes of qualifying event.

10.2 STATISTICAL HYPOTHESES

- Co-Primary Endpoint(s): Arrival to qualified ED within 30 minutes

We hypothesize that the proportion of patients randomized to early transport arriving at the hospital within 30 minutes will be greater than the historical proportion of 38.7%.

- Co-Primary Endpoint(s): Initiation of ECPR within 30 minutes of ED arrival

We hypothesize that greater than or equal to 80% of patients will have ECPR (qualifying ED standard care process) initiated within 30 minutes of ED arrival.

10.3 ANALYSIS DATASETS

The analytic datasets will use a modified per-protocol population. Patients who are assigned to early transport and do not have ROSC after initial rhythm analysis (and shock if indicated) and have the early transport initiated will be considered the primary analytic population for the ED arrival endpoint. Patients who are randomized to early transport and remain in cardiac arrest for at least 10 minutes after ED arrival and have the institutional standard care ECPR process initiated are considered the primary analytic population for the ECPR initiation endpoint. Exploratory clinical and safety endpoints will be collected on the entire population of refractory OHCA patients enrolled/randomized to either early transport or usual care.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

The primary goal of this study is to establish that a high proportion of patients with refractory OHCA can be expeditiously transported to the hospital for initiation of advanced resuscitation. Randomization is not intended to create comparable groups, but instead is being used to demonstrate the feasibility of using a position sensitive randomization procedure in the field. Randomization in this protocol includes two currently used approaches to OHCA: expedited transport to the hospital after initial attempts at resuscitation versus continued resuscitation efforts in the field until ROSC.

Descriptive statistics for study groups will be presented as medians, and interquartile ranges for continuous data; categorical data will be reported as proportions.

Patients randomized to the test arm and achieve ROSC prior to initiation of ECPR will be included in the primary analysis of the expedited transport group.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Co-Primary Endpoint(s): Arrival to qualified ED within 30 minutes

The proportion of qualifying episodes to arrive at the ED within 30 minutes will be compared to our historical data point estimate of 38.7% using a one sample exact test of binomial proportions at the 0.05 two-sided significance level.

Co-Primary Endpoint(s): Initiation of ECPR within 30 minutes of ED arrival

Using the modified intention to treat population with ongoing cardiac arrest in the qualified ED, we will declare the analysis of this objective successful if 80% or more of patients have ECPR (qualifying ED standard care process) initiated within 30 minutes of ED arrival. No formal hypothesis test will be conducted.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

This study does not have any powered secondary endpoints. All clinical and other process endpoints are exploratory.

10.4.4 SAFETY ANALYSES

This is a small clinical trial. We will summarize SAEs by study group (early transport versus usual care) and provide a listing of all SAEs for each of the patients in the intent to treat population.

10.4.5 ADHERENCE AND RETENTION ANALYSES

We will qualitatively summarize the reasons that patients were randomized but that the assigned early transport or usual care pathways were not followed. We will qualitatively summarize reasons for participant withdrawal.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

We will provide descriptive statistics including demographic variables by study group (early transport versus usual care). As the patients are randomized in the field, no baseline laboratory variables are available. No hypothesis testing will be used to compare the groups due to the small sample size.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

The DSMB will review safety data as per their charter. The main listed safety endpoints will be reviewed. No formal statistical boundaries will be used to determine stopping for safety concerns.

10.4.7.2 EFFICACY REVIEW

We will not employ formal stopping rules for efficacy or futility given the small sample size of the study

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

We will pre-specify subgroup analyses of the primary endpoints by gender, age (less than 50 versus 51-70), diabetes, prior cardiac disease, and race/ethnicity. These subgroup analyses will be presented graphically and in tables. Given the small sample size formal hypothesis testing will not be performed. In addition, we will also categorize the defined safety endpoints by each of the subgroups mentioned above, graphically and in tables.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

We are employing two primary endpoints, but no adjustment for multiplicity will be performed as the process endpoint is a threshold.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual participant data for the primary endpoints will be summarized in tabular form. We will also include exploratory endpoint data (mRS and CPC) in these tables.

10.4.11 EXPLORATORY ANALYSES

Each of the exploratory endpoints will be summarized using appropriate techniques based on the distribution (for continuous variables) or event rates (for categorical variables). Group (early transport versus usual care) comparisons will be presented in graphical, or tabular form for the exploratory endpoints. Formal hypothesis testing will be avoided given the small sample size.

10.5 SAMPLE SIZE

Based on 2014 data, we expect approximately 20 unique visits in one year to qualify, thus in 18 months we expect 30 patients to qualify with the protocol used on at least 24 (80%) of these. With 24 patients, if we find that 19/24 (79.2%) of cases meet time limit we have 98% power to find that the proportion of patients arriving at the ED within 30 minutes is significantly different than in 2014. The protocol will be deemed optimal if $\geq 19/24$ patients are transported to the ED within 30 minutes (95% CI lower bound 62.6%).

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

The website will be used to randomize subjects. As different dispatchers will likely be attending to the care of subsequent cardiac arrest patients, we believe that there is limited chance that they will be able to predict the next treatment assignment, and as such, the risk of bias is low.

Randomization will occur in blocks of 5. We will use an urn method. Randomization will not be stratified by any clinical variable or by enrolling prehospital provider. The blocking is intended to maintain balance. The randomization ratio is 4:1 with the expedited transport group favored. Since the main study goals involve the expedited transport of patients to the hospital and since randomization has been introduced mainly to evaluate the effectiveness of the randomization procedure we believe the 4:1 ratio is justified. In addition, expedited versus delayed transport are both currently used treatment strategies for OHCA across North America and there is equipoise about assignment into either of these groups. In situations where the dispatcher uses the website and gives a treatment group assignment, but the patient is not enrolled/randomized in the study because they did not have refractory cardiac arrest, that treatment group assignment will be returned to the urn.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

This study is unblinded.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The entire study will be conducted using an electronic data acquisition method where all clinical data on enrolled subjects will be data entered (single-keyed) by the site personnel into a web-based data management system. In order to provide user-friendly and easy-to-navigate interfaces, the data capture screens are designed based upon individual CRFs. Prior to study start, the system is validated to ensure the data entry screens mirror the CRFs and that the pre-programmed data rules appropriately detect incorrect data. The data will be managed after data entry via data queries from the Coordinating Center at UM.

The latest version of each CRF will be available for use as worksheets and source documents by study personnel. This process facilitates version control of these study related documents, particularly since documents may evolve over the course of the study. This user friendly web-based database system, developed by the coordinating center, will be used for data entry, data validation, project progress monitoring, subject tracking, tracking, user customizable report generation and secure data transfer.

12 QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD AND JUSTIFICATION FOR EXCEPTION FROM INFORMED CONSENT

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6. Additional details regarding EFIC are provided in appendix A . Below when referring to the participant or individual, it is highly likely that the legally

authorized representative for the subject will be providing consent as the patients will likely remain comatose in the early emergency department care.

1. Subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention.
 - a. Cardio-pulmonary resuscitation (CPR) is the first line of treatment for a cardiac arrest, a life-threatening situation, and must be initiated immediately. This study will enroll patients not responding to standard basic life support (BLS) and advanced cardiovascular life support (ACLS) and no other alternative treatments are proven effective when the arrest is refractory to standard therapy.
 - b. The vast majority of people who suffer an out of hospital cardiac arrest (OHCA) die, despite the expertise of highly-trained emergency medical service (EMS) providers. It is unknown whether standard CPR can be improved.
 - c. Based on the CARES registry data for Washtenaw/Livingston Medical Control Authority (MCA), 408 OHCA patients were treated in 2014, 133 (33%) achieved sustained return of spontaneous circulation and only 30 survived to hospital discharge (7.4%) with only 24 (5.9%) having good neurologic function at hospital discharge. This is well below the national survival rate of 8-10%.
 - d. Clinical trials are needed. No prospective, randomized clinical trial has compared standard CPR to ECPR. Almost all published case series of successful ECPR from OHCA initiate ECPR in the emergency department [Chen 2008, Kagawa 2010, Nagao 2000 and 2010, LeGuen 2011, Morimura 2011, Avali 2012, Bellezzo 2012, Johnson 2014, Sakamoto 2014, Stub 2014]. The reason for this strategy is that the shorter the interval from cardiac arrest onset to initiation of ECPR is. The better the chance for a favorable outcome. Scientific evaluation is necessary in order to further test the efficacy of the proposed intervention, transport to an ED for higher level of care and ECPR.
2. Obtaining informed consent is not feasible because:
 - a. Patients who are in cardiac arrest are unresponsive and unable to communicate. It is unreasonable and impractical for first responders to identify, verify, and obtain consent from a legally authorized representative.
 - b. The optimal therapeutic window for initiating interventions and ECPR is within 60 minutes of the cardiac arrest onset.

- c. OHCA patients cannot be identified prospectively
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
- a. Patients are in a life-threatening situation
 - b. Published case series where initiating ECPR in the emergency department have reported survival rates with good neurologic function ranging from 4-33%
 - c. Potential risk of complications of transport with mechanical CPR (rib fractures, pneumothorax, internal organ laceration or motor vehicle crash) or ED initiated ECPR (hemorrhage, vascular injury, deep venous thrombosis, pulmonary embolism, stroke, limb ischemia, infection) are balanced by the anticipated benefit of survival with good neurologic function.
4. The clinical investigation could not be practicably be carried out without the waiver
- a. Time to treatment for cardiac arrest needs to begin immediately. Since these patients are unable to consent for themselves and there is not time to identify, inform, and consent a legally authorized representative, all patients must be enrolled under EFIC. Additionally, informed consent requires the LAR to have time to understand the consent material, be able to ask questions, and decipher what the patient would want. This is not possible to do in a few minutes and during such a stressful time. Inability to obtain informed consent can limit the ability to discover new treatments for such a critical and life-threatening event like sudden cardiac arrest.
5. Length of the potential therapeutic window and contact a legally authorized representative.
- a. The optimal therapeutic window is immediate or non-existent. Randomization into the study must be done immediately, at the time of initiating CPR.

Every effort will be made to identify, inform, and determine consent to continue in the study from a legally authorized representative, in a reasonable amount of time.

Participants who regain good neurologic function and are able, will be informed and consent will be attempted.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the

consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Initial enrollment is initiated under an exception from informed consent as the patient is unconscious in cardiac arrest. Enrollments will not occur until after EFIC plan and protocol approval by the relevant IRB(s).

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to continuing study procedures. The following consent materials are submitted with this protocol: informed consent to continue participation, notification letters.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the participant or the individual's legally authorized representative agreeing to continue to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of continued participation will be provided to the participants and their families along with a description of what has occurred so far given initial enrollment under EFIC. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to continue to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Coordinating Center at University of Michigan. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Coordinating Center.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Intended Use: Samples and data collected under this protocol may be used to study cardiac arrest. No genetic testing will be performed.

Storage: Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at the Coordinating Center (UM). After the study is completed, the de-identified, archived data will be transmitted to and stored at the institutional or NHLBI determined data repository, under the supervision of UM

and/or NHLBI, for use by other researchers including those outside of the study. Permission to transmit data to the UM institutional data repository will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the UM institutional data repository.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs) and expected adverse reactions data) and clinical laboratory data will be entered into, a 21 CFR Part 11-compliant data capture system provided by the UM. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as clinicaltrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable

registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee

recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman, the PI of the Coordinating Center, representatives of NHLBI, the PI of the clinical sites, and the project manager. The Steering Committee will meet in person at least annually.

16 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDICES

APPENDIX A: Original EFIC PLAN

Please see revised Community Consultation and Public Disclosure activities planned for the Saline, MI area expansion of the study, provided as a separate document.

EROCA Trial

Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest

Exception From Informed Consent (EFIC) Plan

Public Disclosure Sites: Ann Arbor, MI, Washtenaw County Plan Date Prepared: May 04, 2016

Plan Revised Date 02/02/17

Date of IRB approval: 9/22/16

Introduction

Learning how to provide better emergency care for patients with life-threatening conditions requires clinical research conducted in the earliest minutes and hours of treatment. Clinical trials of interventions for emergencies like cardiac arrest involve patients who are unresponsive and unable to communicate, and treatments that must be given so rapidly that it is impractical to identify and obtain consent on behalf of the patient from a surrogate decision maker (legally authorized representative). Such trials are therefore performed with an exception from informed consent (EFIC) for emergency research, and are governed by a special set of research regulations defined at 21 § CFR 50.24. We propose a clinical research project, EROCA, to be conducted using EFIC. This document will explain why the project qualifies for EFIC, and how the investigators propose to meet the Community Consultation and Public Disclosure requirements for EFIC.

Research involving OHCA patients presents an ethical dilemma. The resulting delay in obtaining consent can significantly affect the efficacy of an intervention and limits patient eligibility for inclusion in such a time-critical study. Despite this difficulty, clinical trials to determine the best treatment for OHCA must be done. Failing to conduct research on potentially beneficial treatment for this population also poses harm.

Applicability of EFIC to the EROCA Trial and Compliance with FDA Requirement, 21 CFR 50.24

Listed below are the FDA regulations that qualify use of the EFIC process in clinical research, followed by an explanation of how this study meets these requirements.

1. Subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention.

- a. Cardiopulmonary resuscitation (CPR) is the first line of treatment for a cardiac arrest, a life-threatening situation, and must be initiated immediately. This study will enroll patients not responding to standard basic life support (BLS) and advanced cardiovascular life support (ACLS) and no other alternative treatments are proven effective when the arrest is refractory to standard therapy.
- b. The vast majority of people who suffer an out of hospital cardiac arrest (OHCA) die, despite the expertise of highly-trained emergency medical service (EMS) providers. It is unknown whether standard CPR can be improved.
- c. Based on the CARES registry data for Washtenaw/Livingston Medical Control Authority (MCA), 408 OHCA patients were treated in 2014, 133 (33%) achieved sustained return of spontaneous circulation and only 30 survived to hospital discharge (7.4%) with only 24 (5.9%) having good neurologic function at hospital discharge. This is well below the national survival rate of 8-10%.
- d. Clinical trials are needed. No prospective, randomized clinical trial has compared standard CPR to ECPR. Almost all published case series of successful ECPR from OHCA initiate ECPR in the emergency department [insert references]. The reason for this strategy is that the shorter the interval from cardiac arrest onset to initiation of ECPR is. The better the chance for a favorable outcome. Scientific evaluation is necessary in order to further test the efficacy of the proposed intervention, transport to an ED for higher level of care and ECPR.

2. Obtaining informed consent is not feasible because:

- a. Patients who are in cardiac arrest are unresponsive and unable to communicate. It is unreasonable and impractical for first responders to identify, verify, and obtain consent from a legally authorized representative.
- b. The optimal therapeutic window for initiating interventions and ECPR is within 60 minutes of the cardiac arrest onset.
- c. OHCA patients cannot be identified prospectively

3. Participation in the research holds out the prospect of direct benefit to the subjects because:

- a. Patients are in a life-threatening situation
- b. Published case series where initiating ECPR in the emergency department have reported survival rates with good neurologic function ranging from 4-33%
- c. Potential risk of complications of transport with mechanical CPR (rib fractures, pneumothorax, internal organ laceration or motor vehicle crash) or ED initiated ECPR (hemorrhage, vascular injury, deep venous thrombosis, pulmonary embolism, stroke, limb ischemia, infection) are balanced by the anticipated benefit of survival with good neurologic function.

4. The clinical investigation could not be practicably be carried out without the waiver
- a. Time to treatment for cardiac arrest needs to begin immediately. Since these patients are unable to consent for themselves and there is not time to identify, inform, and consent a legally authorized representative, all patients must be enrolled under EFIC. Additionally, informed consent requires the LAR to have time to understand the consent material, be able to ask questions, and decipher what the patient would want. This is not possible to do in a few minutes and during such a stressful time. Inability to obtain informed consent can limit the ability to discover new treatments for such a critical and life-threatening event like sudden cardiac arrest.
5. Length of the potential therapeutic window and contact a legally authorized representative.

The optimal therapeutic window is immediate or non-existent. Randomization into the study must be done immediately, at the time of initiating CPR.

Every effort will be made to identify, inform, and determine consent to continue in the study from a legally authorized representative, in a reasonable amount of time.

Participants who regain good neurologic function and are able, will be informed and consent will be attempted.

Additional Protections

Additional protections of the rights and welfare of the participants will be provided, including:

1. Community Consultation
2. Public Disclosure before the study starts, including opt-out and decline participation options
3. Public Disclosure following completion of the study; providing sufficient information, including demographic characteristics and study results.
4. Establishment of an independent Data Safety Monitoring Board (DSMB) to exercise oversight of the study.
5. Plan to contact the legally authorized representative (LAR) or family member to seek informed consent for the patient's participation in the study within the therapeutic window if feasible or after enrollment as soon as possible when feasible. If a patient dies prior to hospital admission, all attempts will be made to notify their LAR or family member of the study

and patient's participation, if feasible. If a patient regains consciousness and is capable, informed consent will be attempted as soon as feasible.

Community Consultation

The federal requirements of 21 § CFR 50.24 include consulting with the community of patients that could potentially be enrolled in the proposed research project, and public disclosure that a research project will be done that will involve members of the local population.

If community consultation were viewed as community consent, this would imply that the input came from a large proportion or essentially all the members of the community as opposed to representatives of the community. The process is meant to solicit input from the community regarding the study. The IRB makes the final determination as to study approval based on information obtained from the community consultation. For the purposes of EFIC, the definition of community includes "the community in which research will take place" and the "community from which subjects will be drawn." In other words the community includes the geographical area from which patients will be drawn and the group of patients with, or at risk for, the disease of interest.

The **content** of community consultation will inform the community participants that informed consent will not be obtained for any research subjects prior to enrollment. Specifically, the goal will be to:

- Inform the community about relevant aspects of the study including its risks and expected benefits
- Hear the perspective of the community on the proposed research
- Provide information about ways in which individuals wishing to be excluded may indicate this preference

The **type and frequency** of community consultation will:

- Provide opportunities for broad community discussion
- Ensure that representatives from the communities involved in the research participate in the consultation process
- Use the most appropriate ways to provide for effective community consultation
- Be based on numerous factors, including the size of the communities, the languages spoken within those communities, the targeted research population and the heterogeneity of the population

Based on our interpretation of the regulations and their proposed ethical basis, we have prepared a list of recommendations for implementation of the commonly used methods for community consultation.

A schedule of community consultation activities will be prepared and communicated to the IRB at the outset of the process. Representatives of the IRB are invited and encouraged to attend any of the activities. Any additions, cancellations, or changes to the schedule will be communicated to the IRB. At community consultation activities, investigators will describe the need for EFIC and why prospective consent is not possible, inform the community about the relevant aspects of the study, including its risks and benefits.

Questions and concerns will be solicited from the community participants and documented. Participants will also be given the opportunity to answer a survey to share their views. Our goals for community consultation are to learn about the values and feelings of participants as they apply to the proposed research, rather than to have the community deliberate or vote on the project per se. People are experts on themselves rather than on research, so we primarily ask people to tell us about themselves and how they feel about what they have heard.

Community Consultation Activities

The consultation will encompass the following three major forms:

1. Visits to existing community groups at regularly scheduled meetings. Anticipate attending 3-5 meetings, depending on response from committee chairs.

We feel that the best way to show respect for the community is to go out and meet people where they are already gathering. It also minimizes the risk of low turn-out at meetings scheduled de novo and increases the investigators' exposure to a variety of comments.

In this method of community consultation, members of the study team, sometimes accompanied by representatives of their participating Institutional Review Boards, ask to present and discuss the study at a regularly scheduled meeting of a relevant community group.

For each group, we propose the following:

- A study team member will be present to answer questions from the community.
- Presentation will be clear, use of video/handouts depending on the venue, and be brief
- If a presentation is longer than 15 minutes, it will be interactive.
- We will consider who the best person is to present to each group.

- Study team will be available for at least 30 minutes depending on how much time we are allocated (10 minutes to present, 15 minutes for discussion, and 5 minutes to hand-out and get back evaluation surveys).
- Study team will probe for discussion using open-end questions.
- Study team will ensure that the discussion includes feedback from the participants on EFIC.
- No monetary incentive to participants will be offered

A survey for group participants to indicate their thoughts, feelings, and opinions about the EFIC regulations and the study, anonymously, will be handed out and collected back at the end of the event. Study staff should allow at least five minutes at the end of the event for attendees to complete the

We propose to contact the following groups by telephone and/or mail about presenting at their meetings, with the goal of holding 3-5 events total:

- Ann Arbor Community Foundation
- Ann Arbor City Council
- Business groups
- Ann Arbor Police Officers
- Ann Arbor YMCA
- Faith-based organizations
- Neighborhood Residential Associations
- Retiree groups
- UMHS Groups/Programs
 - Support group meeting for patients and families at the Frankel Cardiovascular Center
 - Patient and Family Centered Care (PFCC)

2. Survey Methods

Based on our experience with other EFIC research studies, we believe an interview style, two-way dialogue discussion and address any questions, followed by a well-designed structured survey is an effective method of communication. Our experience revealed that respondents are more apt to understand complex research concepts, such as randomization, informed consent, EFIC, surrogate, etc, when specific examples are given. We also believe this method can be used to reach large numbers and a wide variety of respondents including, individuals at risk of cardiac arrest.

A member of the research team will provide ample information to the survey respondent, and the survey will provide detailed information about EFIC regulation and the EROCA study. We anticipate conducting 50-75 surveys.

We propose visiting the following:

A. Cardiology Clinic – community at risk

We will approach adult patients and family members in the UMHS clinic to participate in our survey. If the participant agrees, verbal consent will be obtained and proceed with the interview. We will ensure that their participation does not interfere with patient care. Each survey will be take approximately 7-10 minutes to complete and will be initiated by a trained clinical research coordinator (CRC) delegated by the PI.

B. Emergency Department – community at risk, geographic location, at risk population. Adult stable patients in the UMHS emergency department and their family members will be approached.

Completing a survey will suffice as implied consent. We will ensure that their participation does not interfere with patient care. Each survey will be take approximately 7-10 minutes to complete and will be initiated by a trained clinical research coordinator (CRC) delegated by the PI. Members of the study team will identify potential participants from the ED electronic tracking board. A study team member or research coordinator will approach the patient and/or family member for their willingness to complete the survey. If the participant agrees, verbal consent will be obtained and proceed with the interview.

C. *Set up EFIC/EROCA table if feasible at one or more events in Ann Arbor so community members can learn about the study and complete a survey if they choose. Examples of events include:*

- a. *Health Fairs*
- b. *Sporting events*
- c. *Concerts and performing arts events*
- d. *Festivals and Art Fairs*

3. Use of a study website that has capacity to solicit and receive comments

Included could be a streamed generic emergency research video from the NETT

<https://nett.umich.edu/patients-communities/community-videos>

4. Opt-Out Mechanism

Prior to and throughout the duration of the clinical trial, patients and their families will have various methods through which they can refuse participation in the trial. We will include this information at the community consultation meetings and on the brochures and posters for public disclosure. We will provide “File of Life” magnets, driver’s license

stickers, and cards at community events and have a link on our website to mail if requested. If a medical bracelet (wrist band) is preferred, one will be provided with instructions that it must be worn throughout the study duration.

EMS providers are accustomed to looking for medical information, typically in a “File of Life” posted to the refrigerator or the back of the door and if outside their home, their wallet is searched for identification and any medical history. We will provide “File of Life” magnets, stickers, wrist bands, and cards at community events and have a link on our website to mail if requested.

If a family member is instructed about the study and declines, the patient will not be included in the study and standard CPR protocols will be followed. This will be carefully covered in EMS training.

Community Consultation Mechanics

Once community consultation meetings are scheduled, IRB will be notified and members are encouraged to attend the meetings, if available.

All attendees, interviewees, and those who access the website will be asked to complete an attendance record, including their demographics. Only IRB approved handouts will be available to all attendees and should be in provided in an understandable language. Opt out procedures will be documented and included in the handout.

Responses from the three forms of community consultation will be compiled in one report and submitted to IRB for consideration.

Presentation Materials

All presentation materials, including scripts, survey, and educational materials presented in this plan have been developed with input from members of the Neurological Emergencies Treatment Trials (NETT) , who have quite a bit of experience conducting community consultation and public disclosure.

Reporting Community Consultation

All community consultation activities will be reported to the IRB, including the responses required written survey questions. Proposed timeframe to complete the community consultation activities is 4 months.

A summary of the community consultation will include information about: the participants, the presentation, community questions and comments, and responses to closed- and open-ended questions.

Catchment area information will be collected as per the IRB. This information will allow the research team to concentrate its consultation and announcement efforts on the appropriate communities.

PUBLIC DISCLOSURE

Public Disclosure requirement of the Exception from Informed Consent (EFIC) regulations (21 CFR 50.24) for emergency research, states:

21 CFR 50.24

(a)(7) Additional protections of the rights and welfare of subjects will be provided, including at least:

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

Public disclosure will be done prior to enrollment and continue throughout the study period and after the study has completed. The study team will provide updates prior to and during the study period, and after the study has completed. The study results will be distributed locally and nationally through peer-reviewed journals, and presentations at national meetings.

Public disclosure is defined as the “dissemination of information about the research sufficient to allow a reasonable assumption that communities are aware of the plans for the investigation, its risks and expected benefits and the fact that the study will be conducted”. It also includes “dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study’s results”.

Appropriate public disclosure includes:

- Clear statement that informed consent will not be obtained for any subjects
- Information about the study medications use including a balanced description of the risks and benefits
- Synopsis of the research protocol and study design
- How potential study subjects will be identified
- Participating sites/institutions
- Description of the attempts to contact a LAR
- Suggestions for opting out of the study

Public Disclosure Planned

Using several different channels of communication for public disclosure increases the likelihood of reaching more of the intended audiences. It also can increase repetition of the message, improving the chance that intended audiences will be exposed to it often enough to absorb it. For these reasons, we will use a combination of channels.

Our plans for implementation include:

1. In-hospital Activities

We will post brochures and posters across Michigan Medicine Clinics, to include, the Emergency Department, Cardiology Clinics, employee areas, and any other are identified as relevant, before and during the trial. We will also utilize email messaging, to include M Headlines, M Research, The University Record, etc. These materials will provide a description of the study, local contact information, study website address, and opt-out information. All materials will be reviewed by IRB prior to use.

2. Community Activities

Obtain a booth/table at various local community events and hand out brochures and/or flyers describing study with contact information and talk with members of the community. We will target groups that appear to have interest in healthcare and/or cardiac disease, such as health fairs, American Heart Association (Ann Arbor), and organized walk/runs in the area as well as any other event where community members may gather in large numbers, such as libraries, sports facilities, concerts, fairs and festivals.

3. Electronic Resources

Electronic-based education is a passive approach to disseminating information that has benefits and challenges. There is no way to accurately measure whether how much of the community is reached by these methods. Access may be limited to those segments of the population with regular computer access. Despite these problems, electronic study education is inexpensive to develop and maintain and offers continuous and anonymous input from the public.

In collaboration with UMHS Department of Communication, we propose to advertise EROCA and EFIC in local appropriate websites and via paid social media advertising.

A copy of the press release or another IRB approved document will be submitted to neighborhood associations, requesting the information be shared. There are many on-line neighborhood associations who can reach hundreds of their neighbors through electronic means.

A copy of the press release or another IRB approved document will be submitted to City of Ann Arbor Communications Director requesting it be placed in their monthly newsletter that reaches all City of AA employees and approximately 500 community members on their mailing list.

2. BROADCAST AND PRINT MEDIA

Purchased advertising in broadcast and print media ensures dissemination of accurate materials to a wide audience. We plan to advertise in the paper and electronic versions of the local news papers.

In collaboration with UMHS Department of Communication, a news release will be written and IRB approved prior to distribution to any media.

Printed materials, including advertisements for publication in newspapers and magazines, brochures, and flyers will be reviewed and approved by the IRB . Advertisements will be purchased in both English language and foreign language newspapers as appropriate. All printed advertisements will provide a general description of the study, the national and/or local website address, as well as site contact information.

We also plan to contact local radio stations, who may be interested in covering the study and EFIC. Investigator appearances on local, radio, television, or call-in talk shows can bridge the line between public disclosure and community consultation.

Any local flyers or brochures distributed will reference EROCA study website as an additional resource for patients, families, and healthcare providers to get information as well as ask questions about EROCA.

Reporting Public Disclosure

All Public Disclosure activities will be summarized into a report and submitted to IRBMED for review.

Timeline for Community Consultation and Public Disclosure Activities

We anticipate beginning community consultation and public disclosure activities as soon as possible after IRB review and approval of our EFIC plan, with a goal of completion by January, 2017. The community consultation activities will occur over the course of about 5 months. Public disclosure will begin prior to study enrollment, will continue throughout study enrollment, and conclude with dissemination of study results after the study has concluded. We plan to initiate public disclosure activities at least 2-weeks prior to the start of the proposed trial. Public disclosure will continue beyond the end of study enrollment and through disclosure of study results, and anticipate a 1-3 year timeframe.

Analysis and Presentation of Results From Community Consultation and Public Disclosure

Reporting of community consultation results will be provided by the study team to the IRB. Summaries of the data will be reported to the FDA.

Data collected regarding CC and PD will include the following elements:

- Consultation methodology used
- Community type: geographic or condition-specific
- Participants involved: number and demographics
- Duration, content, format of information presented
- Free text log of comments, questions, and responses to open-ended questions
- Log of pre-determined closed-ended survey questions and responses

The study team will review survey responses and group meetings in summary form, and general themes will be summarized. The results of all local community consultation efforts will be summarized and submitted to IRBMED for review. If appointed and if present at the focus group discussions, an IRB liaison will provide an in-depth review of the discussions and additional feedback to the IRB as needed. Summaries of public disclosure will be reported to the IRB prior to approval, and then at least annually or upon request from the IRB.

A provision of the protocol has been made to allow participants who learn of the trial through community consultation or public disclosure or other means, and who would not want to participate if treated for a cardiac arrest, to opt-out of trial prior to such an event. Opt-out forms will be available on the Huron Valley Ambulance (HVA) and all community consultation interactions.

Contacting Legally Authorized Representatives (LAR) or family members

The federal regulations for contact of a Legally Authorized Representative (21 CFR 50.24) state:

(a)(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if

feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

A procedure for prospective informed consent will be developed as is required by 21 CFR 50.24, in the unlikely event that a LAR can be identified within the presumed short therapeutic time window for the intervention and is able to provide a meaningful prospective surrogate consent for patient enrollment. However, it is highly unlikely consent will be obtained prospectively in this EROCA trial for the reasons summarized in the scientific protocol, to delay treatment of the patient in sudden cardiac arrest long enough to identify and contact either an LAR or other family members. In circumstances in which it is impossible to identify a LAR within the therapeutic time frame, EFIC will be applied.

Participants enrolled in EROCA under EFIC procedures and unable to consent, their LAR or family member(s) will be informed of the clinical investigation, including inclusion criteria at the earliest possible opportunity.

Participants enrolled in EROCA with EFIC, or their LAR/family member(s), will be informed of study enrollment in the clinical investigation at the earliest possible opportunity. Participants admitted to the hospital will be approached in person. A study team member will speak with the senior clinician to determine the stability of the participant and the appropriate time for speaking with the participant, or if not alert and capable of making informed decisions, a LAR or family member. The study team member will approach the participant(or LAR/family) to notify them about the participant's enrollment under EFIC, provide information about the study, including continued enrollment.

Participant's rights, the responsibilities of the investigators, and answer any questions about the study. At that time, the patient or the LAR will be asked to provide consent for continued participation in the study. A written informed consent document will be used to document the decision to either continue in the study or to not participate any further. A copy of this form will be provided to the participant and another copy will be placed in the research record.

Participants who do not wish to continue to participate will be excluded from all further aspects of the study except for the collection of data required by the FDA and permitted by the IRB to determine safety and efficacy. If informed consent is provided by a LAR or family member, we will approach the subject at the earliest possible opportunity to seek prospective, written informed consent for continuing participation in the study, should they become capable of doing so.

It is anticipated that the notification of participants of LAR/family member(s) will commonly take place in the hospital within 12-24 hours of their cardiac arrest. If the participant remains unable to participate in this process and family members or another legally authorized representative are not present, continued attempts will be made to contact an LAR. Attempts to notify the participant or an LAR will be repeated three times after the patient has been initially enrolled. All notification attempts will be recorded on the subject's case report form. Reports of these logs will be included in annual reports to the IRB.

If a participant is enrolled into EROCA and dies before a legally authorized representative or family member can be contacted, the investigators will send a letter with basic information about the clinical investigation, the subject's inclusion, and contact information to obtain more information or to answer questions if desired.

Due to the high mortality rate with sudden cardiac arrest, we expect many participants will die prior to coming to the hospital and a letter will be sent to their LAR and/or family member(s). If no contact members are identified in prehospital and hospital records, attempts will be made to locate one through an obituary search for a next of kin listing and if found, their contact information will be sought using on-line address sites.

For participants enrolled, who die prior to hospitalization, a letter will be sent to the participant's LAR/family member. The letter will include information about the study, their enrollment under EFIC, information collected, no further participation, contact information if they have questions.

Description of Refusal of Participation Procedures (Opt-Out)

Prior to and throughout the duration of the clinical trial, patients and their families will have various methods through which they can refuse participation in the trial. We will include this information at the community consultation meetings and on the brochures and posters for public disclosure. We will provide "File of Life" magnets, stickers, and cards at community events and have a link on our website to mail if requested.

APPENDIX B: UMHS ED ECPR GUIDELINES

Extracorporeal cardiopulmonary resuscitation (ECPR) is standard practice in the University of Michigan Hospital Emergency Department. ECPR utilizes a venous-arterial extracorporeal membrane oxygenation (VA-ECMO) circuit built from several components including. These 510K cleared devices may change based on the institutional practice of the hospital and are provided here as an example of the types of devices used.

QUADROX-iD Adult diffusion membrane Oxygenator
CentriMag Primary Console
CentriMag Back-up Console
CentriMag Motor
CardioHelp System

Inclusion/Exclusion criteria for ECPR

Inclusion Criteria:

- Age 18-70
- -Initial shockable (ventricular tachycardia or ventricular fibrillation) or witnessed pulseless electrical activity or witnessed asystole
- Anticipated interval from cardiac arrest onset (or 911 call) to establishing ECMO flow \leq 60 minutes
- Potentially reversible cause of cardiac arrest ¹

Exclusion Criteria:

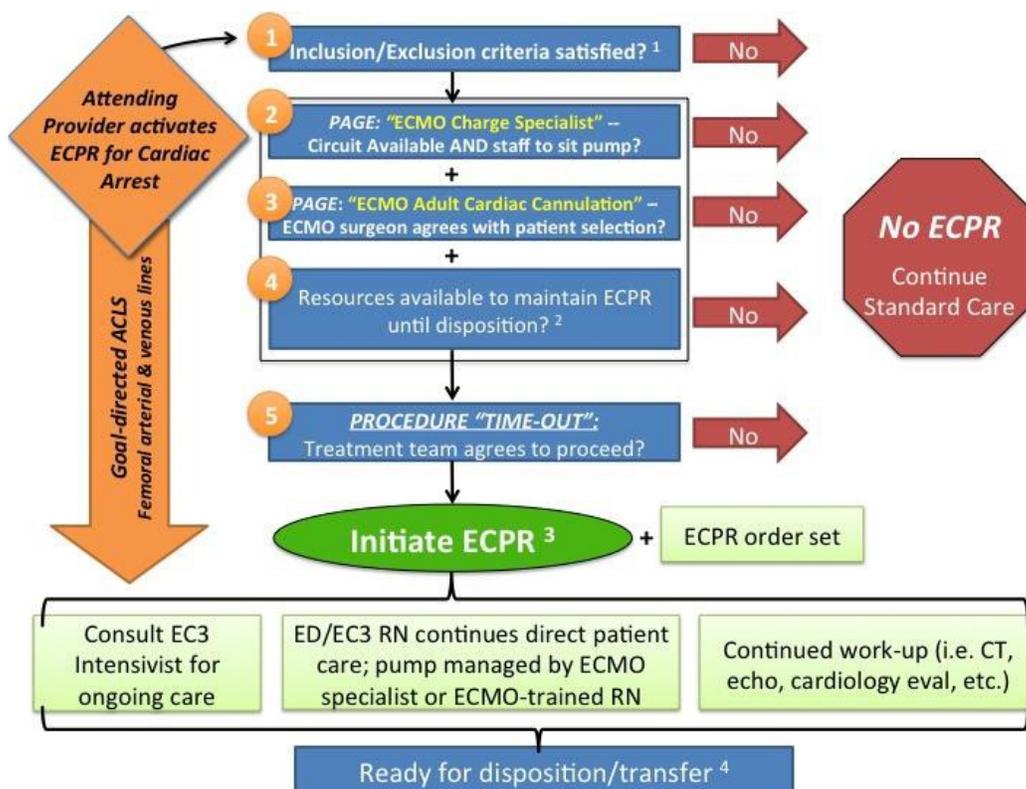
- Sustained return of spontaneous circulation (ROSC)
- DNAR or DNI advanced directive
- Goals of care exclude ECPR (DNAR/DNI, advanced directive, or family discussion)
- Contraindication to anticoagulation ²
- Estimated BMI >40
- Advanced or life-limiting comorbidity ³
- Unable to independently perform ADLs at baseline
- Treating physician and/or ECMO consultant feels that ECPR is futile ⁴

(1) Potentially reversible causes of cardiac arrest include: ACS, refractory arrhythmia, myocarditis, massive PE, severe hypothermia, drug overdose

(2) Contraindications to anticoagulation include: Suspected or known intracranial hemorrhage, traumatic arrest, significant active bleeding

- (3) Advanced or life-limiting co-morbidities include: Stroke or CNS lesion with significant neurologic or cognitive impairment, liver cirrhosis including ESLD, ESRD, advanced COPD or other chronic lung disease, advanced or metastatic malignancy
- (4) Indications of futility are subject to the gestalt of the treating physician and/or ECMO surgeon, but may include: Septic shock multiorgan failure, hypoxemic arrest, metabolic acidosis with pH <7.0, Lactate >15, ETCO₂ <10 despite optimal ACLS, poor candidate for destination LVAD, artificial heart, or transplant

UMHS AES ECPR Protocol



- (1) Inclusion/Exclusion criteria per Appendix 1
- (2) Necessary resources will be determined case-by-case, with necessary available resources including: ECMO specialist or ECMO credentialed emergency department RN dedicated to sitting pump until transfer to CVC; CVC bed to be made available ASAP; ED and EC3 staffing/volume/capacity to care for ECPR patient; Availability of EC3 Intensivist by phone or in person

- (3) Initiation of ECPR includes femoral veno-arterial cannulation by an ECMO surgeon or an emergency physician credentialed for the procedure, as well as circuit and pump management by an ECMO specialist or ECMO-credentialed emergency department RN
- (4) Potential disposition destinations include: Cardiovascular center ICU; cardiac catheterization lab; and/or EC3, if EC3 intensivist and ECMO credentialed RN available

Standard data collected on cardiac arrest patients in UMHS AES

For internal review, quality improvement, and education, the following data elements are among those routinely obtained in patients with cardiac arrest and post-cardiac arrest care delivered in AES:

1. Time intervals, including time of arrest or 911 call, transport time, time of ED arrival, down-time, duration of CPR, time of return of circulation or initiation of ECPR
2. Drugs and shocks administered
3. Method(s) and device(s) used for CPR
4. Method(s) and device(s) used for airway management
5. End-Tidal CO2 measurements
6. Vital sign trends, with attention to diastolic blood pressure measurements when obtained invasively
7. Ventilator parameters, including settings and dynamic measurements
8. Blood gas results
9. Cerebral blood flow index via "C-Flow" device
10. Method(s) of therapeutic hypothermia, when utilized
11. Initial and subsequent cardiac rhythms
12. Return of circulation ECG interpretations
13. Bedside echocardiography images and interpretations
14. Cardiac catheterization results
15. ED, ICU, and hospital length of stay
16. EEG and neuro-prognostication results, including head CT, MRI, SSEP, NSE level, Neurology consultation documentation
17. Cerebral performance category upon discharge

Cardiac Arrest – General

This protocol should be followed for all adult cardiac arrests. Medical cardiac arrest patients undergoing attempted resuscitation should not be transported unless return of spontaneous circulation (ROSC) is achieved or transport is ordered by medical control or otherwise specified in protocol.

- ☑ If an arrest is of a known traumatic origin refer to the **Dead on Scene Protocol**.
- ☑ If it is unknown whether the arrest is traumatic or medical, continue with this protocol.
- ☑ Patients displaying a Do Not Resuscitate order or bracelet – follow **DNR Protocol**.
- ☑ When an ALS unit is present, follow this general cardiac arrest protocol in conjunction with the protocol that addresses the indentified rhythm.
- ☑ Once arrest is confirmed, emphasis should be on avoiding interruptions in CPR.
- ☑ CPR should be done in accordance with current guidelines established by the American Heart Association.

Pre-Medical Control MFR/EMT/SPECIALIST

1. Confirm Arrest
 - A. Assess for signs of normal breathing.
 - B. Check a carotid pulse for not more than 10seconds.
2. Initiate CPR or continue CPR if already in progress and apply and use AED as soon as available.
3. Ensure CPR quality
 - A. Compressions at least 2” in depth for adults.
 - B. Compression rate at least 100 per minute (An FDA approved mechanical CPR device operating at the manufacturer pre-set rate meets this rate requirement).
 - C. Avoid excessive ventilation (volume and rate).
4. Continue CPR with minimal interruptions, changing the rescuer doing compressions every 2 minutes, when possible.
5. Initiate ALS response if available.
6. Establish a patent airway, maintaining C-Spine precaution if indicated, using appropriate airway adjuncts and high flow oxygen. See **Emergency Airway Procedure**.

EMT

7. Establish a patent airway with a supraglottic airway. After insertion, provide continuous CPR without pauses for ventilation. Ventilations should be

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delivered at 8-10 breaths per minute or 1 breath every 5 to 6 seconds. See **Emergency Airway Procedure**.

8. Verify CPR quality frequently and anytime the rescuer providing compressions or ventilations changes.

9. If Return of Spontaneous Circulation (ROSC) has **not** been achieved after three, two minute cycles of CPR and ALS is not available or delayed, contact medical control, initiate transport.