Advanced REperfusion STrategies for Refractory Cardiac Arrest (The ARREST Trial)

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
8.2, 9.1, 10.1.6	**Removal of AE reporting, clarification of stopping rules per FDA, and clarity is QA/QC**	**Collection of pertinent data and clarification**
9.1	**Stopping rules and sample size clarification**	**Administrative error on getting all FDA approved language into protocol from 7.9.2019**

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
The protocol, informed consent form(s), and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Advanced R^2Eperfusion STrategies for Refractory Cardiac Arrest (ARREST Trial)

Study Description: This is a Phase II, single center (Under the Center for Resuscitation Medicine at the University of Minnesota Medical School), partially blinded, prospective, intention to treat, safety and efficacy clinical trial, randomizing adult patients (18-75 years old) with refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) out-of-hospital cardiac arrest (OHCA) who are transferred by emergency medical services (EMS) with ongoing mechanical cardiopulmonary resuscitation (CPR) or who are resuscitated to receive one of the 2 local standards of care practiced in our community:
1) **Early Extracorporeal Membrane Oxygenation (ECMO) Facilitated Resuscitation***:* Regardless of whether return of spontaneous circulation (ROSC) has been achieved and with on-going mechanical CPR, patients will enter the Cardiac Catheterization Laboratory (CCL) for expeditious VAECMO initiation, if required, followed by coronary angiography and percutaneous coronary intervention (PCI) when appropriate.
2) **Standard Advanced Cardiac Life Support (ACLS) Resuscitation***:* Patients with refractory VF/VT OHCA will be treated with ACLS resuscitation for at least 15 minutes after arrival in the emergency department (ED), or up to 60 minutes from 911 call, after which the physician (MD) can continue resuscitation efforts until ROSC is achieved or futility has been reached based on their clinical judgment. If the patient has not achieved ROSC during the times mentioned above, the ED MD can declare death when he or she believes that ACLS is futile. If ROSC is present upon arrival or has been achieved anytime during resuscitation in the ED, the patient will be taken to the cardiac catheterization laboratory (CCL) for coronary angiography and PCI, and potential VA ECMO or other circulatory support device initiation, as clinically indicated.

Objectives: The **Early ECMO Facilitated Resuscitation** Arm of the study, will expedite circulatory support, mitigate metabolic derangement, facilitate the identification and treatment of reversible coronary artery disease (CAD) and significantly improve functionally favorable survival compared with the **Standard ACLS Resuscitation** Arm.

Endpoints: **Primary study endpoint.** Survival to hospital discharge.

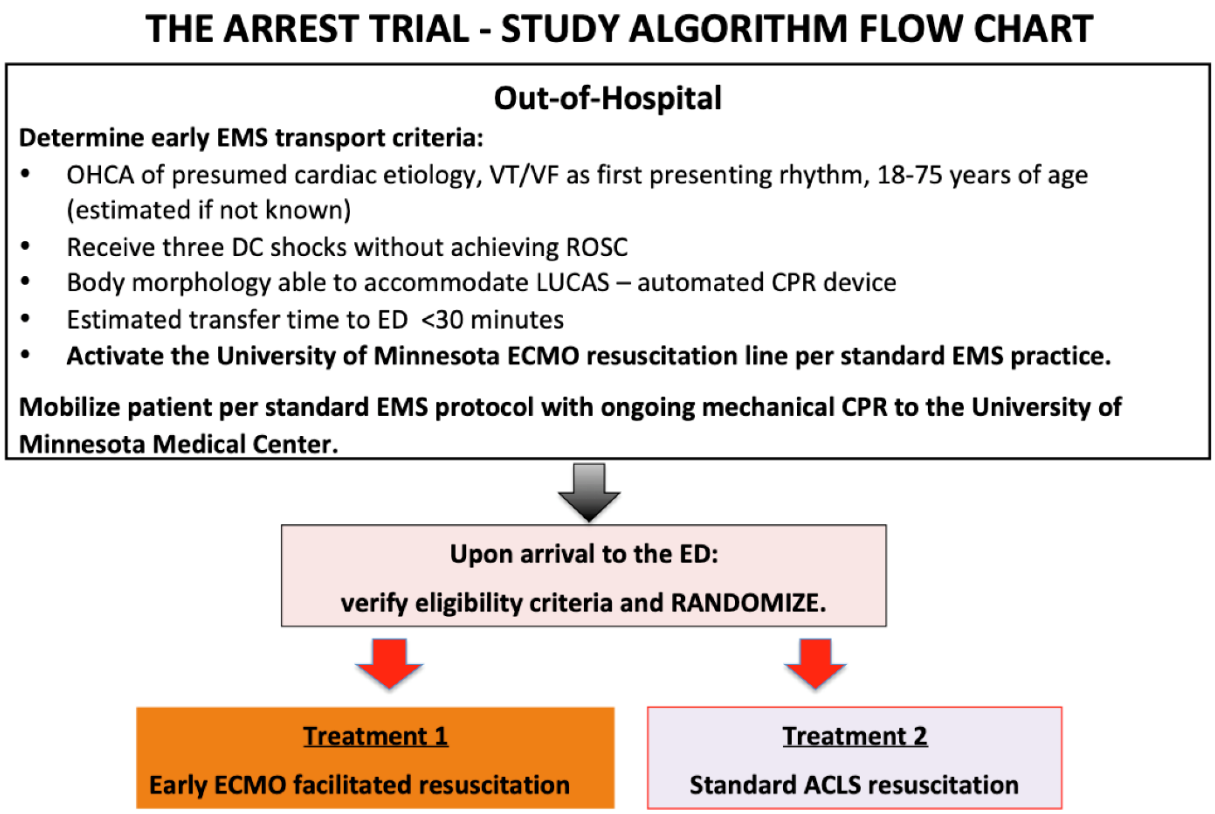
Secondary endpoints: Safety and ECMO-related complications, survival to hospital discharge with modified Rankin Scale Score (mRS) ≤ 3 along with functional status (Cerebral Performance Category [CPC]), 3- and 6-month survival and functional status (mRS score and CPC classification), cost per patient and cost per life saved.

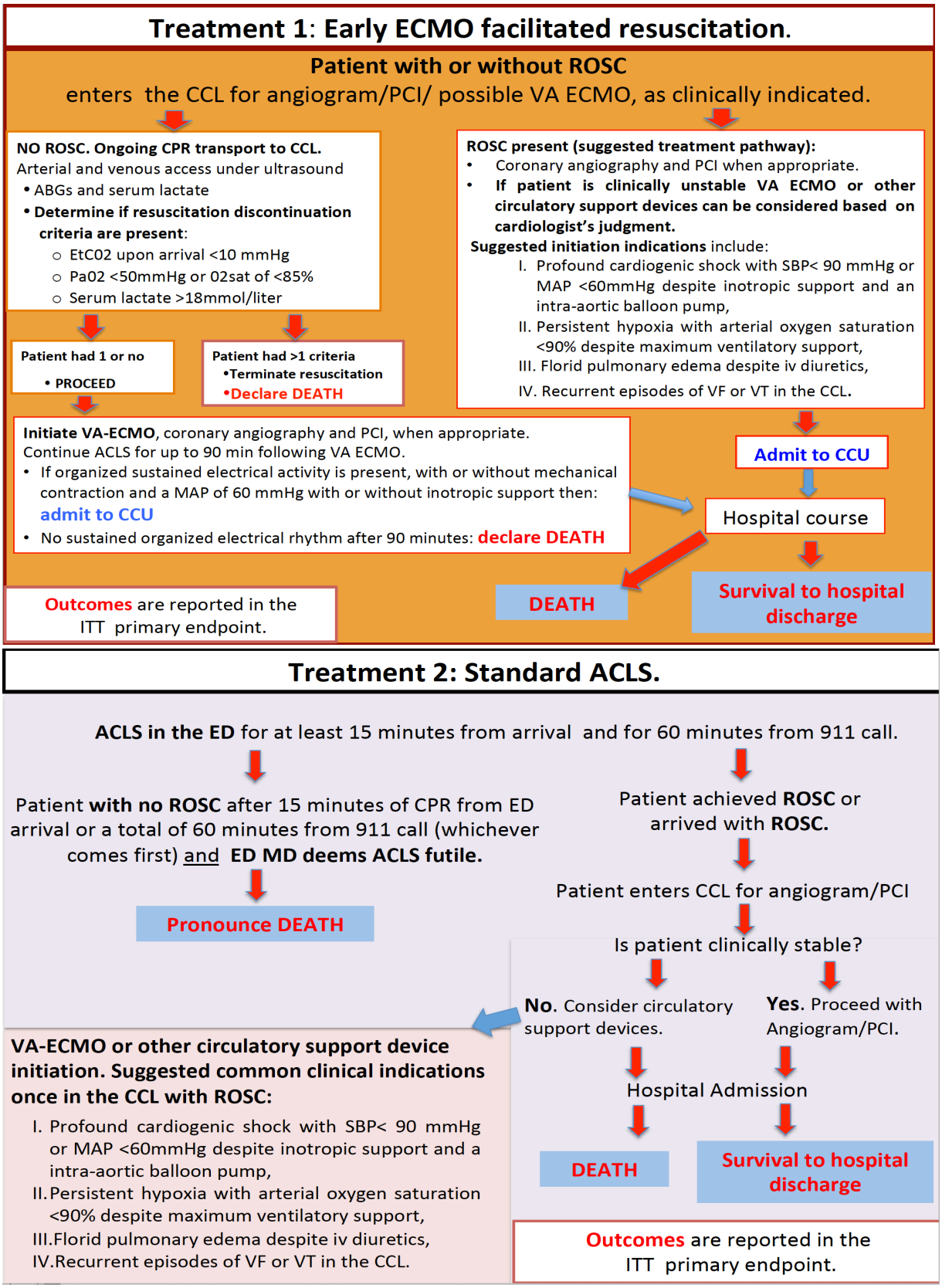
Population:

The ARREST trial population must have all the inclusion criteria below:

1) OHCA of presumed cardiac etiology
2) Shockable (VF or VT) as the first presenting rhythm
3) Presumed or known to be 18-75 years of age
4) Received 3 DC shocks without ROSC.
5) Body morphology able to accommodate a Lund University Cardiopulmonary Assist System (LUCAS™) automated CPR device.
6) Estimated transfer time from the scene to the ED or CCL < 30 minutes

1.2 SCHEMA




Treatment 1: Early ECMO facilitated resuscitation.
Patient with or without ROSC
enters the CCL for angiogram/PCI/ possible VA ECMO, as clinically indicated.
NO ROSC. Ongoing CPR transport to CCL.
Arterial and venous access under ultrasound
• ABGs and serum lactate
• Determine if resuscitation discontinuation criteria are present:
○ EtC02 upon arrival <10 mmHg
○ Pa02 <50mmHg or 02sat of <85%
○ Serum lactate >18mmol/liter
Patient had 1 or no
• PROCEED
Patient had >1 criteria
•Terminate resuscitation
•Declare DEATH
ROSC present (suggested treatment pathway):
• Coronary angiography and PCI when appropriate.
• If patient is clinically unstable VA ECMO or other circulatory support devices can be considered based on cardiologist's judgment.
Suggested initiation indications include:
I. Profound cardiogenic shock with SBP< 90 mmHg or MAP <60mmHg despite inotropic support and an intra-aortic balloon pump,
II. Persistent hypoxia with arterial oxygen saturation <90% despite maximum ventilatory support,
III. Florid pulmonary edema despite iv diuretics,
IV. Recurrent episodes of VF or VT in the CCL.
Initiate VA-ECMO, coronary angiography and PCI, when appropriate.
Continue ACLS for up to 90 min following VA ECMO.
• If organized sustained electrical activity is present, with or without mechanical contraction and a MAP of 60 mmHg with or without inotropic support then: admit to CCU
• No sustained organized electrical rhythm after 90 minutes: declare DEATH
Admit to CCU
Hospital course
Survival to hospital discharge
DEATH
Outcomes are reported in the ITT primary endpoint.
Treatment 2: Standard ACLS.
ACLS in the ED for at least 15 minutes from arrival and for 60 minutes from 911 call.
Patient with no ROSC after 15 minutes of CPR from ED arrival or a total of 60 minutes from 911 call (whichever comes first) and ED MD deems ACLS futile.
Pronounce DEATH
Patient achieved ROSC or arrived with ROSC.
Patient enters CCL for angiogram/PCI
Is patient clinically stable?
No. Consider circulatory support devices.
Yes. Proceed with Angiogram/PCI.
Hospital Admission
DEATH
Survival to hospital discharge
VA-ECMO or other circulatory support device initiation. Suggested common clinical indications once in the CCL with ROSC:
I. Profound cardiogenic shock with SBP< 90 mmHg or MAP <60mmHg despite inotropic support and a intra-aortic balloon pump,
II. Persistent hypoxia with arterial oxygen saturation <90% despite maximum ventilatory support,
III. Florid pulmonary edema despite iv diuretics,
IV. Recurrent episodes of VF or VT in the CCL.
Outcomes are reported in the ITT primary endpoint.

1.3 SCHEDULE OF ACTIVITIES (SOA)

The ARREST Trial is a pragmatic clinical trial randomizing study subjects to one of two standards of care practiced in the community. Treatment of patients in both groups is solely at the discretion of the treating clinician.

Assessment	**Hospitalization**	**Discharge from Hospital**	**3 month visit[1] (±14 Days)**	**6 month visit[1] (±30 Days)**
Inclusion/Exclusion	X			
Randomization	X			
Continued Participation Informed Consent	X			
Demographics	X			
Medical History	X			
Pre-hospital data	X			
Hospital data	X			
Data collection on procedures done during hospitalization	X			
Data collection labs done during hospitalization	X			
Blinded mRS score		X	X	X
Blinded CPC Score		X	X	X
AE/SAE reporting	X	X	X	X
UB04		X		

[1] Calculated from day of Discharge

2 INTRODUCTION

2.1 STUDY RATIONALE

More than 350,000 people in the United States die from out-of-hospital cardiac arrest (OHCA) each year.[1, 2] Although survival rates are higher in OHCA patients with a shockable rhythm, i.e., ventricular fibrillation/pulseless ventricular tachycardia (VF/VT; 21-35%) compared with those with a nonshockable rhythm (1-8%),[2-9] more than 50% of patients with VF/VT OHCA are refractory to current treatment and never achieve return of spontaneous circulation (ROSC), or die before they are admitted to the hospital.[2] Acute or chronic coronary artery disease (CAD) is present in 70-84% of patients with **refractory** VF/VT cardiac arrest,[4, 10-19] and we believe that it is the burden of significant CAD that limits the ability of conventional CPR to successfully resuscitate these patients. Coronary stenosis or occlusion can now be potentially reversed by advanced perfusion/reperfusion strategies.[11, 12, 19] Thus, although patients with refractory VF/VT represent the subgroup with the worst prognosis (85-90% mortality), the underlying cause of cardiac arrest is likely to be reversible in most of these patients. It is this subgroup that offers the greatest opportunity to impact survival and public health.

The treatment strategy for patients with refractory VF/VT cardiac arrest should clearly include achievement of adequate coronary and cerebral perfusion by using mechanical CPR devices, optimizing CPR hemodynamics, facilitating early transport, and providing ongoing treatment during transport. Compared with a strategy that provides these measures but requires ROSC before the patient can gain access to the cardiac catheterization laboratory (CCL), the addition of circulatory support using extracorporeal membrane oxygenation (ECMO), which can function as the stabilization platform to facilitate percutaneous coronary intervention (PCI) when clinically indicated, is expected to significantly improve functionally favorable survival to hospital discharge. To implement these strategies, we instituted the Refractory VF/VT clinical pathway as a standard of care in Minneapolis/St. Paul (MSP), Minnesota, through a community-wide, comprehensively integrated, collaboration called the Minnesota Resuscitation Consortium (MRC).[11, 12] During the first 12 months, 62 sequential OHCA patients entered the CCL with CPR in progress. Significant CAD was present in 84% (52/62), with an average syntax score of 29±14.[11] Overall, 45% (28/62) survived to hospital discharge, and 42% (26/62) survived to hospital discharge with good neurological function (Cerebral Performance Category [CPC] 1 or 2) and had a CPC score of 1 at 3 months.[11] The results have stayed consistent over the 30 months of operations with survival being maintained around 40-45%. Historical data for patients in the same population who received Amiodarone and standard resuscitation practice showed a survival rate of 15%, with CPC 1 or 2.[11] In our 2.5 year experience, we have treated 152 patients with average CPR duration of 61±2.1 minutes and survival with CPC 1 or 2 has remained at 40%. Our experience with this clinical protocol suggests that survival rates may be higher with routine, **early ECMO facilitated resuscitation** compared to the conventional resuscitation practice in which either ROSC is required for CCL access. Our experience to date also indicates functionally favorable survival improves following hospital discharge and continues improving up to 3-6 months. However, because widespread use of emergent ECMO initiation at short notice with field activation would require major infrastructural investments, both the

contribution and relative cost of routine, **early ECMO facilitated resuscitation** to the management and survival of this population need to be assessed in a randomized trial.

ARREST Trial hypothesis. Based on our preliminary results, we hypothesize that routine **early ECMO facilitated resuscitation** will expedite circulatory support, mitigate metabolic derangement, facilitate the identification and treatment of reversible CAD and significantly improve survival to hospital discharge compared with ED-based **standard ACLS resuscitation**.

ARREST Trial. We propose a Phase II, single center, partially blinded, intention to treat, safety and efficacy clinical trial to assess the results of routine **early ECMO facilitated resuscitation** compared with ED-based **standard ACLS resuscitation**. Both strategies represent current standards of care **in our community**. The Minnesota Resuscitation Consortium (MRC) has the patient population, experience, expertise, and infrastructure to successfully execute the proposed study. Two EMS systems currently transport patients to an ED for the **standard ACLS resuscitation**, and three EMS systems transport patients to the University of Minnesota for the routine **early ECMO facilitated resuscitation**.

Specific Aim. The primary objective is to assess the rates of survival to hospital discharge in adult patients (aged 18-75 years) with refractory VF/VT OHCA who are transported to the University of Minnesota and randomized to treatment under the **early ECMO facilitated resuscitation** arm compared with those treated under the **standard ACLS resuscitation**.

Primary Study Endpoint Survival to hospital discharge.

Secondary Endpoints Secondary efficacy endpoints include survival to hospital discharge with mRS≤3, 3- and 6-month survival overall and with mRS≤3, functional status at discharge, 3 and 6 months (mRS and Cerebral Performance Category [CPC] score), cost per patient and cost per life saved (individual patient billings). Safety endpoints include incidence of serious adverse events (overall due to cardiac arrest and prolonged resuscitation and related to advanced perfusion strategies).

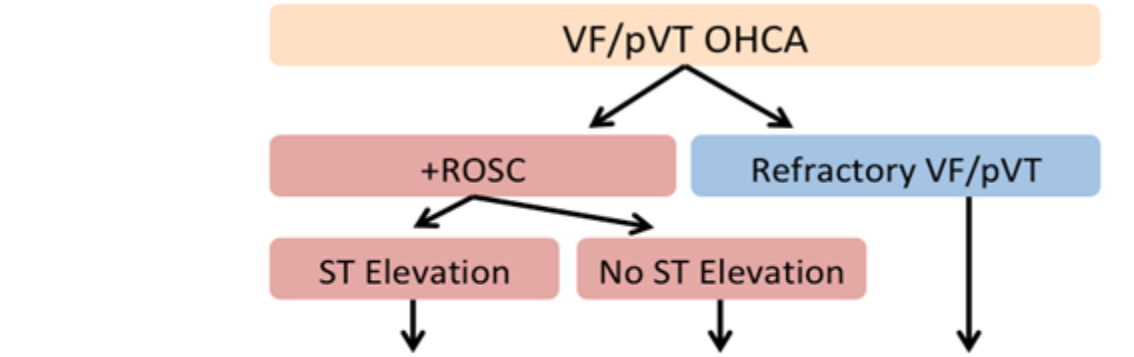
Significance. If our study results indicate potential safety and efficacy, it will provide the basis for a future multicenter clinical trial to assess definitive survival benefit and generalizability of this approach.

2.2 BACKGROUND

CLINICAL SIGNIFICANCE

The public health burden of out-of-hospital cardiac arrest (OHCA) is enormous, with approximately 395,000 cases and more than 350,000 deaths each year in the United States.[1, 2] Survival rates vary widely by area and population.[3] However, despite improvements in recent years, overall survival to hospital discharge for OHCA remains under 12% even in the best EMS systems.[2, 6] Presenting rhythm is a predictor of survival after OHCA.[8] Numerous studies show higher rates of survival to hospital discharge in patients with an initial shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia [VF/VT]) (21-35%) compared with patients with nonshockable rhythms (1-8%).[2-9] Although only 20-35%

of EMS-treated patients with OHCA have VF/VT,[2-6, 20-22] and the incidence of VF/VT among patients with cardiac arrest has decreased in recent years,[23] these patients still make up 70-80% of all cardiac arrest survivors with favorable neurological function (modified Rankin Scale score [mRS] ≤3).[4, 24, 25] Nevertheless, more than 50% of patients with VF/VT OHCA are refractory to current treatment and never achieve return of spontaneous circulation (ROSC) or die before they are admitted to the hospital.[2] A large number of patients with VF/VT OHCA have acute or chronic coronary artery disease (CAD).[11, 19] The incidence of clinically significant coronary stenosis is greater than 60% in patients resuscitated from VF/VT cardiac arrest[13-15, 26-30] and even higher—70-84%—in patients with refractory VF/VT cardiac arrest.[4, 10-19] We believe that it is the burden of significant CAD that limits the ability of conventional CPR to allow for successful resuscitation. (Figure 1) *This observation is a critical insight. Without addressing the root cause and mitigating coronary ischemia with revascularization, conventional CPR efforts alone can offer little advantage, as currently low survival rates suggest.*



	STE	No STE	Refractory
Significant CAD	70-95%	25-50%	75-85%
Acute Lesions	70-80%	25-35%	60-65%

Figure 1. The breakdown of shockable rhythms based on the presence or absence of return of spontaneous return of circulation and the presence or absence of ST elevation on the 12-lead ECG. Corresponding % of coronary artery disease (>70% stenosis) and acute (thrombotic) lesions are presented. VF/pVT: Ventricular fibrillation/pulseless ventricular tachycardia; ROSC: return of spontaneous circulation. **Yannopoulos et al**. The Evolving Role of the Cardiac Catheterization Laboratory in the Management of Out-of-Hospital Cardiac Arrest Patients: **A Scientific Statement from the American Heart Association**. Circulation 2019. In press.

Coronary stenosis or occlusion can be potentially reversed by advanced perfusion/reperfusion strategies.[11, 12, 19] Thus, the underlying cause of cardiac arrest is likely to be reversible in most patients with refractory VF/VT OHCA. However, these patients currently have a poor prognosis because they require early identification of the potentially reversible coronary cause in order to have any significant chance to be resuscitated, but they are too unstable to be considered for coronary angiography and PCI by most cardiology practices. Therefore, ROSC is generally required before the patient can gain access to the cardiac catheterization laboratory (CCL).[31-33] This can potentially be addressed by early initiation of extracorporeal CPR (ECPR), a method of extracorporeal life support (ECLS) using a device for

extracorporeal membrane oxygenation (ECMO). ECMO can expedite circulatory support, alleviate the ischemic burden of prolonged resuscitation, ameliorate metabolic degradation and—most importantly—provide the hemodynamic stability needed to expand the opportunity for CCL-based diagnostic and therapeutic interventions.[34]

The treatment strategy for patients with refractory VF/VT cardiac arrest should clearly include achievement of adequate coronary and cerebral perfusion by using mechanical CPR devices, optimizing hemodynamics, facilitating early transport, and providing ongoing treatment during transport. Compared with a strategy that provides these measures but requires ROSC before the patient can gain access to the CCL, the addition of early circulatory support by expediting ECMO initiation, can be used as the stabilization platform to facilitate PCI when clinically indicate. That approach is expected to significantly improve survival to hospital discharge and functionally favorable survival by 3-6 months post hospital discharge. However, emergent ECMO initiation at short notice with field activation carries significant human and infrastructural costs in addition to the technical, procedural, and management challenges that arise after the patient is hospitalized. Therefore, before major infrastructural investments can be made, both the contribution of **early ECMO facilitated resuscitation** to the management and survival of this population and the relative cost of such a strategy need to be assessed in a randomized clinical trial.

SUPPORTING SCIENCE – ANIMAL STUDIES:

IMPORTANCE OF CORONARY REVASCULARIZATION IN PORCINE MODEL OF REFRACTORY ISCHEMIC VF.

Our group developed a pig model in which occlusion of the left anterior descending (LAD) coronary artery was induced via balloon inflation.[35] After 5 min, VF was induced by delivering intracardiac current and left untreated for 8 min. CPR was performed for 3 min, and advanced cardiac life support (ACLS) was performed until ROSC was achieved or the pig had received 15 min of CPR. Of 27 pigs, 21 had ROSC within 15 min; 6 pigs did not have ROSC within 15 min and were classified as having refractory VF. If ROSC was not achieved in these pigs within 45 min of continued ACLS, reperfusion was attempted via LAD balloon deflation and removal with continued CPR until ROSC or another 10 min of resuscitation. **Results**: *ROSC was achieved in 4 of 6 animals, but only after reperfusion.* **Conclusions**: *In animals with refractory VF, reperfusion was necessary to achieve ROSC.* **Relevance:** In refractory ischemic VF arrest that does not respond to standard ACLS, coronary revascularization/reperfusion appears to be necessary for ROSC. Because patients with refractory VF have a very high rate of acute and chronic CAD, PCI may be their only option for successful resuscitation.

ECMO-FACILITATED PCI AND SHORT-TERM SURVIVAL IN A PORCINE ISCHEMIC LAD MODEL OF REFRACTORY VF ARREST.

Our team reported the results of ischemic refractory VF in 33 intubated and anesthetized female pigs (44±3 kg).[34] VF was induced by endovascular balloon occlusion of the ostial LAD. After 5 min of untreated VF and 10 min of CPR, pigs were randomized to LAD reperfusion at min 45 with ongoing CPR without ECMO (16 pigs) vs venoarterial ECMO cannulation at minute 45 of CPR (17 pigs) and subsequent

LAD reperfusion. Resuscitation continued until ROSC was achieved or 60 min of CPR had elapsed. Animals without ROSC at 60 min were declared dead. Resuscitated animals were maintained for 4 hours. The primary endpoint was 4-h survival. **Results**: 4-h survival was significantly improved in pigs with ECMO (82%) compared to those without ECMO (31%), *p*=0.003. After 4h, 9 pigs with ECMO were suitable for decannulation. **Conclusions**: ECMO-facilitated coronary reperfusion significantly improved 4-hour survival compared with reperfusion facilitated by CPR alone. ECMO support enabled cardiac recovery and hemodynamic stability within 4 hours. **Relevance**: These results support the idea that, although coronary reperfusion is a necessary condition for achieving ROSC, *after prolonged (45 min) CPR the metabolic ischemic substrate requires circulatory support to improve outcomes*.

SUPPORTING SCIENCE – HUMAN CLINICAL STUDIES (TABLE 1)

Table 1. Survival in patients with refractory OHCA treated with advanced perfusion techniques (ECMO and PCI)

			Number of patients		Survival rates		
	Enrollment years	ECMO cannulation	OHCA n	VF/VT n (%)	All OHCA n (%)	CPC 1-2 n (%)	VF/VT n (%)
Kagawa et al 2012	7.5	ED	42	23 (55)	7 (17)[a]	6 (14)[a]	17/46 (37)[c]
Avali et al 2012	5	ED/CU/CCL	18	16 (89)	1 (5.5)[a]	1 (5.5)[a]	-
Haneya et al 2012	5	ED	26	12 (46.2)	4 (15)[b]	27/85 (32)[c]	-
Leick et al 2013	2	CCL	28	8 (28.6)	11 (39)[a]	8 (28.5)[a]	-
Maekawa et al 2013	4.5	ED	53	32 (60.4)	17 (32.1)[b]	8 (15.1)[b]	-
Wang et al 2014	5.5	ED	31	15 (48.4)	12 (38.7)[b]	8 (25.8)[b]	-
Johnson et al 2014	7	ED	15	11/26 (42)[a]	1 (6.6)[b]	3/26 (11.5)[bc]	-
Sakamoto et al 2014	3	ED	234	234 (100)	68 (29)[ad]	32 (13.7)[ad]	68 (29)[ad]
Kim et al 2014	7.5	ED	55	31 (56.4)	9 (16.4)[b]	8 (14.5)[b]	-
Stub et al 2015	3	ED	11	11 (100)	5 (45)[b]	5 (45)[b]	5 (45)[b]
Pozzi et al 2016	4	ED	68	19 (28)	6 (8.8)[b]	3 (15.8)[b]	6 (31.5)[b]
Lee et al 2016	4	ED	23	20 (87)	10 (43.5)[a]	7 (30.4)[a]	8 (40)[a]
Fjølner et al 2017	3.5	CCL	21	9 (43)	7 (33)[b]	7 (33)[b]	5 (55.6)[b]
Lamhaut et al 2017	4	Field vs ED	156	81 (58)[e]	21 (13.5)[b]	21 (13.5)[b]	21 (25.9)[b]
Schober et al 2017	10	ED	7	4/7 (57)	1 (14)[f]	-	-
Yannopoulos et al 2017	**1**	**CCL**	**62**	**62 (100)**	**28 (45)[b]**	**26 (42)[b]**	**28 (45)[b]**

ECMO = extracorporeal membrane oxygenation; OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention. [a]30-day survival. [b]Survival to hospital discharge. [c] Percentage includes OHCA + IHCA. [d] This is per protocol analysis. Intention-treat-analysis was 32/260 (12.3%). [e] 139 patients with available data. [f]6-month survival.

According to the 2016 Extracorporeal Life Support Organization (ELSO), survival to discharge following ECPR for cardiac arrest that is refractory to conventional CPR was 29% in their registry database of 2885 adults.[36] Published studies have reported widely varying results. Most of the experience is from non-US cohorts, mainly in Asia.[16, 17, 25, 37-39]

Several studies of patients unresponsive to CPR who received ECMO (and PCI when indicated) found worse outcomes with OHCA vs in-hospital cardiac arrest (IHCA). Kagawa et al[37] analyzed data for 86 patients with OHCA or IHCA unresponsive to CPR who received ECMO (and PCI when indicated). Survival to day 30 was 29% overall, 17% (7/42) for OHCA vs 41% (18/44) for IHCA, and 37% (17/46) for patients presenting with VF/VT vs 20% (8/40) for patients with non-shockable rhythms. Compared with patients who did not survive to day 30, survivors had a significantly shorter time interval from collapse to initiation of ECMO (54 minutes [34–74 minutes] vs 40 [25–51] minutes, p=0.002) and a higher rate of intra-arrest PCI (70% vs 88%; p=0.04). Wang et al[16] retrospectively described a cohort of 230 patients who had received ECPR during a period of 5 years (31 patients with OHCA and 199 with IHCA). No

significant differences were observed between OHCA and IHCA in rate of survival to discharge (38.7% vs 31.2%, p>0.05) or functionally favorable outcome (25.8% vs 25.1%, p>0.05). Duration of ischemia (collapse to ECPR) was a key issue for survival. The authors attributed the high survival rate in patients with OHCA compared to previous studies[37, 38, 40, 41] to a well-organized and rapid-response EMT system, efficiency in handling patient transportation and resuscitation, and an equipped cart in the emergency room rather than in the ICU, shortening the duration of ischemia. In Australia, Stub et al[10] treated 26 patients with refractory prolonged cardiac arrest with the CHEER protocol (mechanical **C**PR, **H**ypothermia, **E**CMO and **E**arly **R**eperfusion) during a period of 32 months. Of 15 patients with IHCA, all had ROSC with ECMO, and 9 (60%) survived. In 11 patients with OHCA (all with VF), ROSC was achieved in 2 patients before ECMO was initiated and in 8 of 9 patients placed on ECMO. A total of 5 OHCA patients (45%) survived, including 3 of 9 patients who were placed on ECMO. Avali et al[40] reported their experience with ECMO support in patients with refractory cardiac arrest (IHCA, n=24; OHCA, n=18). Survival to discharge from intensive care was 46% (11/24) for IHCA and 5% (1/18) for OHCA (p<0.05). At 6 months, survival rates with good neurological outcome were 38% (9/24) for IHCA and 5% (1/18). Haneya et al[41] analyzed a total of 85 consecutive adult patients treated with ECLS. Thirty-day survival was 42% (25/59) in patients with IHCA and 15% (4/26) in patients with OHCA (p<0.02). Duration of CPR was independent risk factor for mortality. In the United States, Johnson et al[42] reported 26 cases who received ECMO (and reperfusion when indicated) over a 7-year period, of whom 11 (42%) presented with VF/VT. Of 15 patients with OHCA, 1 patient (6.6%) who presented with VF/VT survived to discharge and made a full neurologic recovery. Survival to discharge was 27.3% (3/11) for IHCA.

Inconsistent results were found in studies comparing extracorporeal CPR vs conventional CPR in OHCA. In South Korea, Kim et al[39] found similar rates of survival to hospital discharge in OHCA patients with prolonged conventional cardiopulmonary resuscitation (CCPR) compared with patients who received extracorporeal cardiopulmonary resuscitation (ECPR) (19.4% [86/444] vs 16.4 [9/55]). However, propensity score matching of patients with ≥ 21 minutes of CPR duration showed neurological outcome at 3 months to be more favorable with ECPR than with CCPR (14.5 vs 8.1%). Maekawa et al[38] analyzed data from 162 adult Japanese patients with witnessed OHCA of cardiac origin who had undergone cardiopulmonary resuscitation for longer than 20 minutes. Survival to discharge was 32.1% (17/53) with ECPR and 6.4% (7/109) with conventional CPR. Matched propensity analysis showed significantly higher neurologically intact survival at 3 months with ECPR vs conventional CPR (29.2% vs 8.3%; p=0.018). In the SAVE-J trial, a prospective observational study of OHCA patients with VF/VT performed in Japan over 3 years, Sakamoto et al[17] compared patients admitted to 26 hospitals providing ECPR vs those admitted to 20 hospitals that did not provide ECPR. Per the protocol analysis, overall 1-month survival was 29% (68/234) with ECPR vs 6% (9/159) in the non-ECPR group**.** Cerebral Performance Category (CPC) scores of 1 or 2 were achieved at 1 month in 13.7% (32/234) of patients who received ECPR vs 1.9% (3/159) of those without ECPR (p<0.0001), and at 6 months in 12.4% (29/234) vs 3.1% (5/159) (p=0.002). In Austria, Schober et al[43] found that survival to discharge in good neurological condition was 14% (1/11) with ECPR and 6% (13/232) with conventional CPR.

Several studies compared patients with refractory VF/VT vs those with nonshockable rhythms. Leick et al[44] found 30-day survival was 37.5% (3/8) in patients presenting with VF/VT, and 35% (6/17) in patients

presenting with nonshockable rhythms. The door-to-ECLS implantation time was the only significant and independent predictor of 30-day mortality. In Denmark, Fjølner et al[24] found that of 21 patients adult patients admitted with witnessed, refractory, normothermic OHCA treated with ECPR, 7 (33%) survived to hospital discharge, all with a CPC score of 1 or 2. Survival to hospital discharge was 55.6% (5/9) in patients with VF/VT as the initial rhythm and 16.7% (2/12) in patients presenting with pulseless electric activity or asystole. In patients with refractory OHCA who received ECPR In Lyon, France, Pozzi et al[18] found survival to discharge was 31.5% (6/19) for VF/VT and 0% (0/49) for nonshockable rhythms (p=0.00). In patients who received ECMO for refractory OHCA in South Korea, Lee et al[25] found 30-day survival of 40% (8/20) for patients with VF/VT, and 67% (2/3) for patients with nonshockable rhythms. In a study in Paris by Lamhaut et al,[45] although overall survival in patients with refractory OHCA and ECPR was 13.5% (21/156), early field application of ECMO within 60 minutes from a 911 call and careful selection of patients improved survival from 8% to 29%. Absence of coronary angiography was the strongest predictor of mortality (OR 7.1), and only patients presenting with VF/VT were among the survivors.

In 62 consecutive adult patients treated with the Minnesota Refractory VF/VT clinical Protocol (described in detail below), Yannopoulos et al[11] reported 45% (28/62) patients were discharged alive and 42% (26/62) were discharged from the hospital with favorable neurological function (CPC 1 or 2).

Clinical Equipoise for a Randomized Trial. Kim et al[46] performed a meta-analysis of studies published through 2015 and concluded that, although rates of survival and good neurologic outcome at 3-6 months after cardiac arrest tended to be higher with ECPR than with conventional CPR in overall analyses, the effects of ECPR were not clear in patients with OHCA. According to the 2015 American Heart Association guidelines,[31] "there is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest." In studies published since 2015, survival ranged from 8.8% to 43.5% for ECPR in patients with OHCA (**Table 1**),[11, 18, 24, 25, 43, 45] and up to 55.6% in patients with VF/VT OHCA.[24] Although these results are encouraging, most reports were retrospective, and all studies were observational, with inherent selection bias that no statistical adjustment can eliminate completely. No randomized clinical trials have been performed. Wide variation in results stem from heterogeneous study populations, varying bystander intervention, differences in pre-hospital EMS organizations, the lack of a standardized protocol for ECPR with ECMO in refractory cardiac arrest, differences in in-hospital care, and differences in outcome criteria have resulted in widely varying findings in published study results.

Refractory VF/VT is a spectrum of timing of return of spontaneous circulation (pulses) in response to standard ACLS treatment ranging from return of pusles shortly after the third failed shock (as defined in this protocol) to never. In any individual case, it is impossible to determine where along this continuum the patient may ultimately fall. For patients who will never obtain a pulse, science supports the contention that the sooner ECMO is initiated the potentially better the outcome. [11, 37, 40, 41, 44, 59, 60] In order to achieve early administration of ECMO from OHCA, it is necessary to begin mobilization from the scene to the hospital immediately following the third failed shock.[39] At the same time, for those patients who obtain a pulse in response to standard ACLS treatment later along this continuum may avoid the need for ECMO and it's attendant complications and cost. Early administration of ECMO precludes

knowing who may have obtained pulses with continued standard ACLS treatment without the need for ECMO intervention. Studies to date[10, 24, 42, 43] and experience with the Minnesota Resuscitaton Consortium Refractory VF/VT protocol[11. 59, 60] indicate there is potential benefit for initiation of ECMO following out-of-hospital cardiac arrest of up to 90 minutes from 911 call.

Given this state of our collective understanding, clinical equipoise exists. Only a randomized clinical trial can show whether and to what extent early routine ECPR deployment can improve survival in patients with refractory VF/VT OHCA. The proposed ARREST trial at the University of Minnesota will randomize patients with refractory VF/VT OHCA to receive either 1) **Early ECMO Facilitated Resuscitation Arm,** or 2) **Standard ACLS Resuscitation Arm** to provide cardiorespiratory support**.** Both groups will receive angiography, and PCI when necessary.

Contribution to Public Health In view of the current low survival rates in OHCA, the knowledge gained from the proposed ARREST trial will make an important contribution to our ability to avoid a substantial number of deaths, with significant potential impact on national public health by returning neurologically intact patient's to their communities. In the past, very few hospitals had access to emergent ECMO. However, according to the Extracorporeal Life Support Organization registry,[36] the number of patients receiving ECPR has increased exponentially in the past 10 years, and the use of ECPR in refractory cardiac arrest represents the most rapidly growing segment.[47] The ARREST trial will not only generate safety/effectiveness data but also shed light on the comparative costs associated with ECPR, thus providing an informed basis to justify broader implementation and a definitive Phase III clinical trial.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Refractory cardiac arrest has a very grim prognosis. Survival from refractory VF/VT drops to <1% after 35 minutes of conventional CPR and resuscitation. Prolonged CPR is encountered universally in these patients and leads to multiple traumatic injuries that are unavoidable. Risks associated with chest compressions include traumatic injuries such as pneumothorax, hemopericardium, rib fractures, and solid organ injuries.

Standardized, mechanical CPR will be employed as the usual practice for all out-of-hospital cardiac arrest victims (randomized or not) with the included EMS agencies as an adjunct to manual cardiopulmonary resuscitation (CPR) when effective manual CPR is not possible (e.g., during patient transport, or extended CPR when fatigue may prohibit the delivery of effective/consistent compressions to the victim, or when insufficient personnel are available to provide effective CPR).

Risks associated with ECPR include mechanical failure, hemorrhagic, neurologic, renal, cardiovascular, pulmonary, metabolic, infections and ischemic complications. ECMO initiation will be attempted for all patients meeting criteria for the **Early ECMO Facilitated Resuscitation Protocol** and the **Standard ACLS Resuscitation Protocol** as currently and routinely practiced in the Minneapolis St. Paul area. Patient

presenting with ROSC may still be placed on ECMO when the clinical team deems it necessary for circulatory support when cardiogenic and or vasoplegic shock is present.

All patients with ROSC and pulses after VF/pVT OHCA enrolled in the ARREST trial will gain access to the CCL per standard of care. As such, those patients, in both groups will go to the CCL regardless of arm allocation.

Potential VA ECMO or other circulatory support device initiation in those patients is based on the interventional cardiologist's clinical judgment. In general, evidence of the following are considered common indications in all CCL patients:

i) Profound cardiogenic shock with SBP< 90 mmHg or MAP <60mmHg despite inotropic support and an intra-aortic balloon pump,
ii) Persistent hypoxia with arterial oxygen saturation <90% despite maximum ventilatory support,
iii) Florid pulmonary edema despite IV diuretics,
iv) Recurrent episodes of VF or VT in the CCL,

In general <10% of the patient achieve ROSC before arrival to the CCL or in the ED.

Patient's allocation in a study group has no association with presence of ROSC. If patients have ROSC upon arrival or shortly after arrival they will follow the intention to treat allocation.

Since CPR and ECMO facilitated resuscitation are only recommended in patients with cardiac arrest, only patients who otherwise would be considered clinically dead are exposed to these risks. Such risks are reasonable when compared to the alternative.

Risk related to confidentiality of health information. All study personnel involved in data collection and analysis have taken the local IRBs required research training. In addition, subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location and backed up remotely.

2.3.2 KNOWN POTENTIAL BENEFITS

ECLS with VA ECMO initiation in the CCL has become the regional/local standard of care in 3 EMS systems in our community and is practiced by all paramedics under the medical direction of the EMS directors. Therefore, the University of Minnesota protocol is one of the local standards of care that will be tested in the ARREST trial.[12, 34, 61, 62, 63] The other local standard of care or Standard ACLS does not offer ECMO to patients that are not resuscitated and as such is not investigational. We have removed that part from the ARREST trial based on DSMB and FDA input.

In addition, VA ECMO or other circulatory support devices can be initiated in both groups for patients arriving in the CCL with ROSC and who subsequently become hemodynamically unstable as defined by

common clinical practice norms. At that point interventional cardiologists can consider VA ECMO or other circulatory assist devices to support the patients as per standard of care.

Below we provide data that support the notion that direct benefit can be seen in both groups. First we provide animal data and then human data.

Animal data

- **Evidence that coronary revascularization is an important factor to achieve ROSC in an ischemic LAD occlusion porcine model of refractory arrest. Data from: Sideris et al. Resuscitation. 2014.[35]**

Survival after out-of-hospital cardiac arrest (OHCA) remains poor. Acute coronary obstruction is a major cause of OHCA. We hypothesize that early coronary reperfusion will improve 24h-survival and neurological outcomes. **Methods** Total occlusion of the mid LAD was induced by balloon inflation in 27 pigs. After 5 minutes, VF was induced and left untreated for 8 minutes. If return of spontaneous circulation (ROSC) was achieved within 15 minutes (21/27 animals) of cardiopulmonary resuscitation (CPR), animals were randomized to a total of either 45 minutes (group A) or 4 hours (group B) of LAD occlusion. Animals without ROSC after 15 minutes of CPR were classified as refractory VF (group C). In those pigs, CPR was continued up to 45 minutes of total LAD occlusion at which point reperfusion was achieved. CPR was continued until ROSC or another 10 minutes of CPR had been performed. Primary endpoints for groups A and B were 24-hour survival and cerebral performance category (CPC). Primary endpoint for group C was ROSC before or after reperfusion. **Results** Early compared to late reperfusion improved survival (10/11 versus 4/10, *p*= 0.02), mean CPC (1.4±0.7 versus 2.5±0.6, *p*= 0.017), LVEF (43±13 versus 32±9%, *p*=0.01), troponin I (37±28 versus 99±12, *p*=0,005) and CK-MB (11 ±4 versus 20.1±5, *p*=0.031) at 24-hr after ROSC. ROSC was achieved in 4/6 animals **only after** reperfusion in group C. **Conclusions** Early reperfusion after ischemic cardiac arrest improved 24h survival rate and neurological function. In animals with refractory VF, reperfusion was necessary to achieve ROSC.

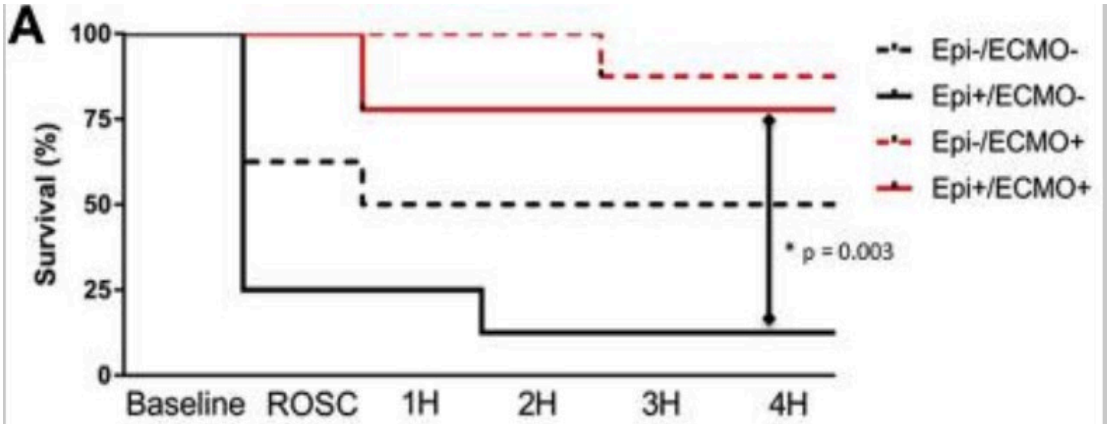
Relevance: These data suggest that patients in both groups in the ARREST could have a direct benefit from early revascularization when coronary artery disease is the potential cause of the cardiac arrest. Early access to the CCL, in order to identify the potential causes of the arrest and reverse them, is offered in both groups.

- **Evidence for Early ECMO facilitated resuscitation arm potential direct benefit**. The potential direct benefit of the early ECMO arm is based on animal studies and human experience.

ECMO-facilitated PCI and short-term survival in a porcine ischemic LAD model of refractory VF arrest.[34] Our team reported the results of ischemic refractory VF in 33 intubated and anesthetized female pigs (44±3 kg). VF was induced by endovascular balloon occlusion of the ostial LAD. After 5 min of untreated VF and 10 min of CPR, pigs were randomized to LAD reperfusion at min 45 with ongoing CPR without ECMO (16 pigs) vs venoarterial ECMO cannulation at minute 45 of CPR (17 pigs) and subsequent LAD reperfusion. Resuscitation continued until ROSC was achieved or 60 min of CPR had elapsed. Animals without ROSC at 60 min were declared dead. Resuscitated animals were maintained for 4 hours. The primary endpoint was 4-h survival. **Results**: 4-h survival was significantly improved in pigs with ECMO (82%) compared to those without ECMO (31%), *p*=0.003. After 4h, 9 pigs with ECMO were suitable for decannulation. **Conclusions**: ECMO-facilitated coronary reperfusion significantly improved 4-hour survival compared with reperfusion facilitated by CPR alone. ECMO support enabled cardiac recovery and hemodynamic stability within 4 hours.

Relevance: These results support the idea that, although coronary reperfusion is a necessary condition for achieving ROSC, ***after prolonged (45 min) CPR the metabolic ischemic substrate requires circulatory support to improve outcomes*.**

The main figure of the publication is seen below



B

Epinephrine Effect	Epi-	Epi +
	p = 0.47	
Alive	11 (69%)	8 (47%)
Dead	5 (31%)	9 (53%)
Total	16	17

C

ECMO Effect	ECMO-	ECMO +
		p = 0.003
Alive	5 (31%)	14 (82%)
Dead	11 (69%)	3 (18%)
Total	16	17

(A) Kaplan-Meier survival curves demonstrating survival at each time point noted. Survival tables showing alive and dead animals at 4 h based on the presence or absence of **(B)** Epi or **(C)** ECMO. The p values are noted. There was no interaction between Epi and ECMO treatments (p = 0.77).[34] **Data are from Bartos, JA et al.** JACC Basic Transl Sci.. **2017;2(3)244-53** **PMID: 29152600**

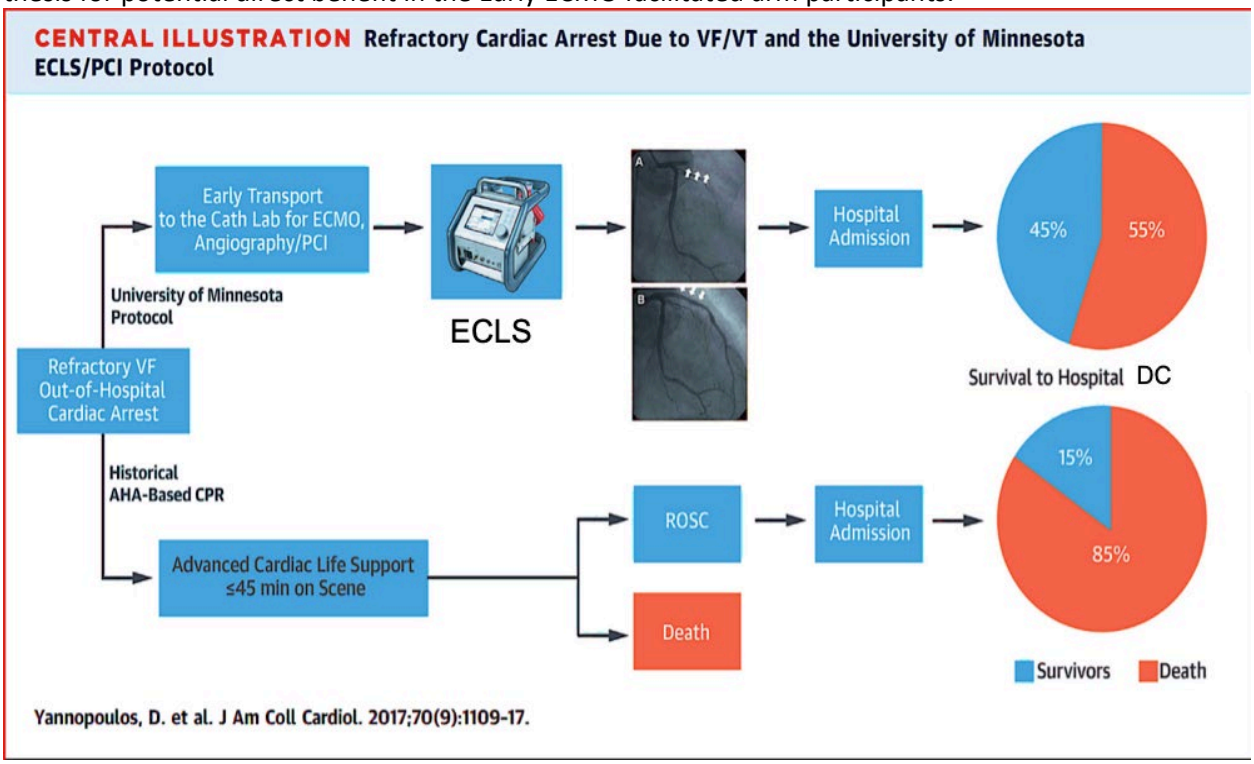
Human data

Our experience at the University of Minnesota suggests that ECMO facilitated resuscitation can significantly enhance the chances for survival compared to any other national or regional standard of care for the treatment of patients with refractory VF/pVT.

An extensive review of all the published series on ECLS (VA ECMO for Resuscitation) is given by the AHA scientific statement by Yannopoulos et al.[61] The summary table is available in the ARREST protocol.

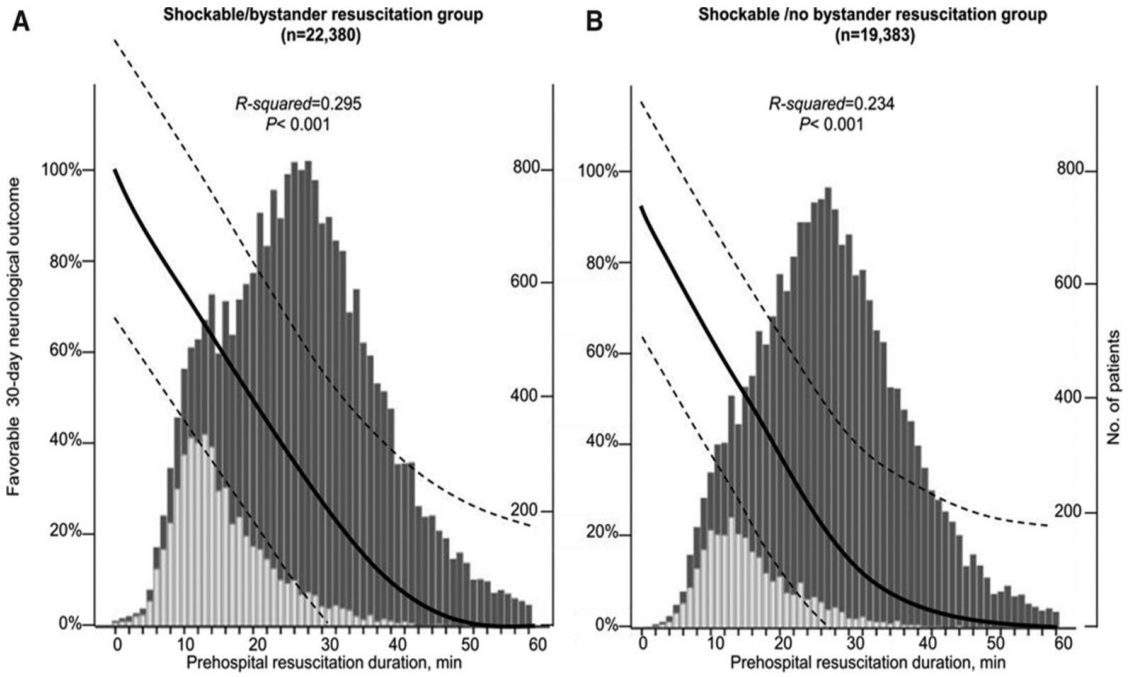
- **Potential for direct benefit for patients enrolled under the Early ECMO facilitated resuscitation arm of the ARREST trial.**

Below is the summary figure of the first year of our protocol initiation that supports the backbone to the thesis for potential direct benefit in the Early ECMO facilitated arm participants:



Legend: Utilizing the proposed ARREST trial early ECMO facilitated resuscitation arm approach, the University of Minnesota protocol has shown a significant potential for increasing survival after OHCA from refractory shockable rhythms. The overall neurological intact survival was 42% in the same cohort. **Average age was 53 yo and the average CPR duration was 55 minutes.**[12]
Data from: **Yannopoulos et al.** J Am Coll Cardiol. 2017 Aug 29;70(9):1109-1117. PMID:28838358

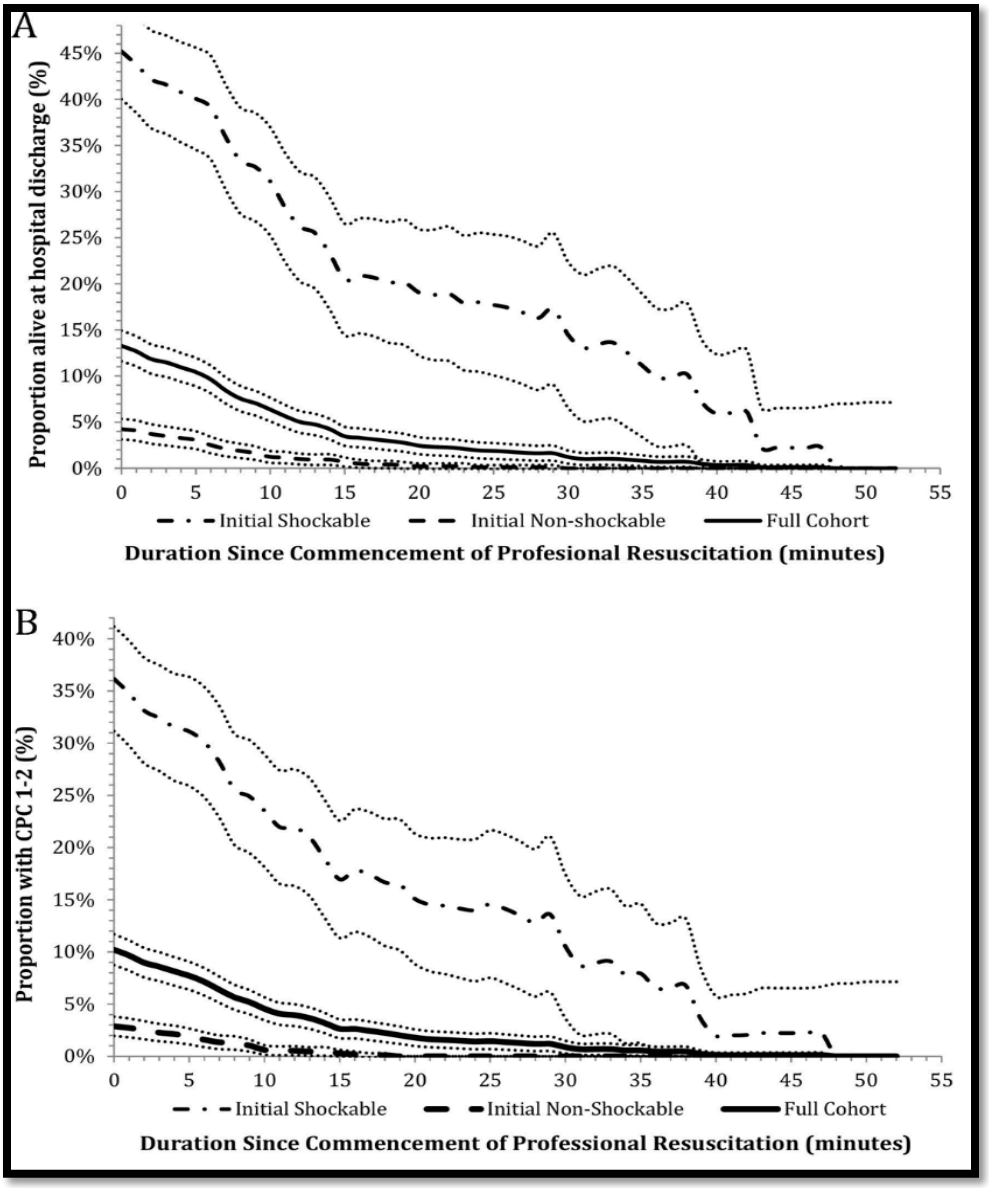
Our data strongly suggest a potential for direct benefit when compared to the data published by many investigators over the last few years reporting the chance to survive based on duration of CPR. Below are the data of the largest cohort reported by Professor Nagao from Japan.[64]



Legend: The relationship between prehospital resuscitation duration and favorable 30-day neurological outcome. The curve estimation in quadratic model of the shockable/bystander resuscitation group (**A**), the shockable/no bystander resuscitation group (**B**), the nonshockable/bystander resuscitation group. Each solid curve with dotted lines shows predicted values with 95% confidence intervals for favorable 30-day neurological outcome. Each light gray box represents the actual number of cases achieving favorable 30-day neurological outcome, and each deep gray box represents the actual number of cases not achieving favorable 30-day neurological outcome. Data from: Nagao et al. Circulation. 2016 Apr 5;133(14):1386-96. PMID: 26920493.

Nagao's data suggest that with the current CPR practice after 35-40 minutes of resuscitation the chances for survival are extremely poor but the margins of error suggest that efforts up to 60 minutes could yield a few survivors.

Grunau et al (Resuscitation. 2016) showed the same futility **after 40 minutes** of professional resuscitation in patients with refractory VF in Canada. There was a baseline absolute 10% difference for survival without good neurological intact survival even within the first 10 minutes of CPR.[65] See next page.



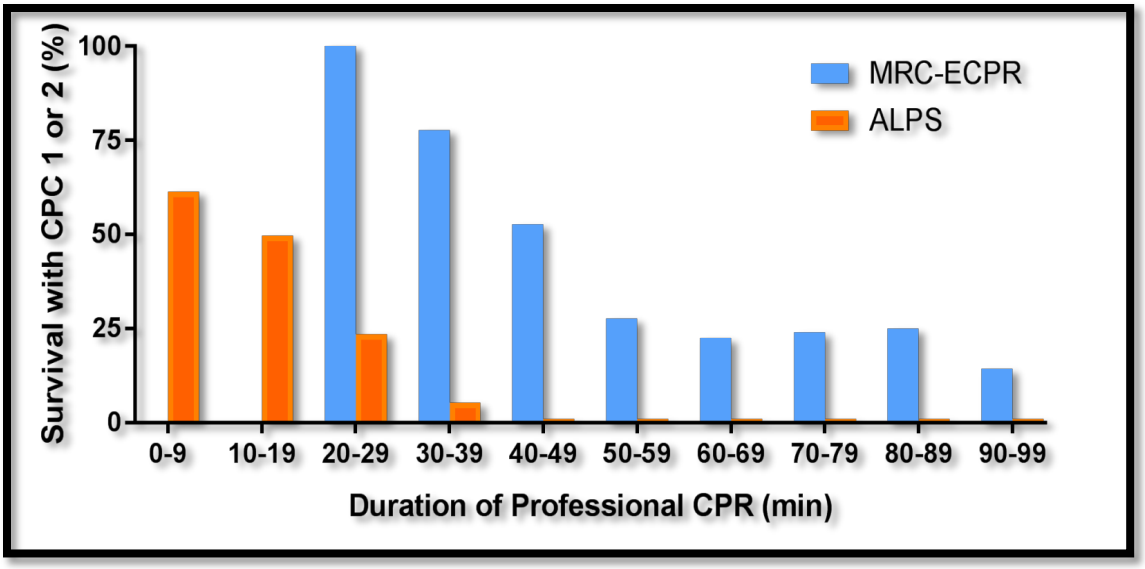
Legend: Probability of survival to hospital discharge (A), and favorable neurologic outcome at hospital discharge (B), among those with refractory cardiac arrest at increasing increments since commencement of professional resuscitation (with 95% confidence intervals).[65]

- **The temporal effect of ECMO on potential survival.[66]**

We recently compared the probability of survival with CPC of 1or 2 based on time of CPR before ECPR initiation **at the University of Minnesota** and the survival with CPC of 1 or 2 from the **ALPS trial**[48] database for patients with the ARREST inclusion criteria. This paper is under review in JACC. As the data show, ECMO initiation appears to offer a higher chance of survival compared to standard ACLS.

Below we show the main figure of our manuscript submitted to the Journal of American College of Cardiology that describes the effect of the duration of CPR with and without the availability of ECPR (VA ECMO based resuscitation).

Relationship of CPR Duration and Survival



Time (min)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	Total
MRC-ECPR	0	0	7	9	19	29	31	25	16	7	143
ALPS	70	151	102	95	99	69	29	11	3	7	636

Legend: Survival with Cerebral Performance Category of 1 or 2 with the Minnesota Resuscitation Consortium protocol (University of Minnesota and ARREST trial early ECMO arm) compared to the ALPS trial patient population with similar inclusion criteria of age. Of the 218 patients that received CPR longer than 40 minutes in the ALPS trial no one survived. On the contrary the survival probability in the University of Minnesota ECPR protocol showed 100% neurologically intact survival for patients receiving professional CPR for 20-29 minutes prior to initiation of ECMO. However, even with ECPR, survival declines over time with an increase in mortality of 24% with every 10 minutes of delay beyond 29 minutes. Despite this time dependence, in the setting of ECPR, survival remains possible even with very long CPR durations as the University of Minnesota cohort demonstrates a stable survival rate of approximately 20% with CPR extending between 60 and 89 minutes. The table below the figure shows the number of patients at risk in 10-minute increments of CPR duration of the two cohorts. As of note, the **average duration of CPR** in the ALPS cohort was 34±5 minutes and for our University of Minnesota cohort 61±7 minutes almost double. Data from **Bartos JA et al JACC 2019; under review**

Based on these data, there is evidence for potential direct benefit for patients enrolled under the ARREST trial's Early ECMO facilitated resuscitation arm.

- **Potential for direct benefit for patients enrolled under the Standard ACLS resuscitation arm of the ARREST trial.**

The second arm is also locally practiced standard in the state of MN. Patients with refractory VF are moved with on-going CPR (using the LUCAS mechanical CPR device) after three unsuccessful shocks to the Emergency Department. It is standard of care in all the EMS systems that participate in the Minnesota Resuscitation Consortium to never declare death in the field for patients presenting with shockable

rhythms. In the Emergency department, patients receive continued resuscitation until they either achieve ROSC or they are declared dead. This practice is reflected in the second arm of the ARREST trial. The contact PI (Yannopoulos) is the Medical Director of the Center for Resuscitation Medicine at the University of Minnesota Medical School and has access to the state database for all cardiac arrests. As such we have access to all the outcomes for all the types of cardiac arrests.

Over the last three years, there were 162 patients, age 18-75, with presumed cardiac etiology OHCA due to a shockable rhythm that were transferred with on-going CPR **without ROSC in the field** (no pulses) to other hospitals in the Minneapolis St Paul area (Not to the University of Minnesota).

Patients were moved with mechanical CPR after 3 shocks per standard EMS protocols. There were only 11/162 survivors all with good neurological function or 6.7%. None of these patients were placed on ECMO. Data were extracted from the CARES state database. This group represents the **second regional standard of care of the ARREST trial.**

- **The potential for direct benefit in the standard ACLS arm due to early CCL access and VA ECMO.**

The investigators of the ARREST TRIAL offer access to the CCL for angiogram and potentially **VA ECMO** for cardiorespiratory instability in patients with ROSC in both groups. Many patients that achieve ROSC tend to rearrest or end up in futile cardiorespiratory failure early after achieving ROSC.[67] In addition, the majority of patients that receive prolonged (>20 minutes) CPR, are prone to multi-organ failure that leads to death in the CCU.[68]

In our recent experience at the University of Minnesota, patients with stable or intermittent ROSC **had a 67 % (22/33) survival rate** (CPC 1 and 2 also 22/33 or 67%) when they were supported with VA ECMO in the CCL for standard indications. Those indications are described in broad clinical terms further down in the document and have been added to the protocol and flow chart as recommended by the FDA. That potential benefit from ECMO support to stabilize those patients is offered in both arm and treatment strategies. **For comparison**, patients who presented with shockable rhythms OHCA (and were treated by the same three EMS systems that deliver patients to the University of Minnesota for refractory VF) **achieved ROSC within 3 shocks** (healthier substrate than those of the ARREST trial) and were **transferred to the closest hospital** -rather than the University of Minnesota- had an overall survival of **54% (222/411)** over the last 3 years.

The potential for direct benefit due longer duration of ACLS and CPR efforts. Patients enrolled in the standard ACLS resuscitation arm will receive at least an additional 15 minutes of CPR from the arrival in the ED or at least up to 60 minutes of ACLS from 911 before the MD can declare futility and death. In this case patients will be given the best available chance to survive based on the current standard of care.

Based on these data, we believe that by participating in the ARREST trial all patients have a potential for benefit regardless the arm allocation and a higher chance to survival.

3 OBJECTIVES AND ENDPOINTS

Primary Objective.

The Minneapolis/St. Paul community has established 2 standards of care for adult patients with refractory VF/VT OHCA, incorporating early emergency medical services (EMS) transport of patients to a higher level of care, both of which may include implementation of ECMO if available. The overall objective of this study is to assess the rate of survival to hospital discharge in adult patients (18-75 years) with refractory VF/VT OHCA treated with one of these two local standards of care: 1) ***Early ECMO Facilitated Resuscitation:*** early ECMO access for circulatory support and PCI, when needed, or 2) ***Standard ACLS Resuscitation:*** continued ED-based ACLS resuscitation until achievement of ROSC or Death declaration.

In both arms, patients with ROSC will be taken to the cardiac catheterization laboratory (CCL) for angiography and percutaneous coronary intervention (PCI), as clinically indicated. VA ECMO can be initiated in some of those patients for clinical indications for cardiorespiratory failure based on the judgment of the interventional cardiologist and will be reported on an intention-to-treat manner. As an important secondary endpoint, functional status (Modified Rankin Scale score of 3 or less [mRS ≤ 3] and CPC ≤ 2) will be determined at hospital discharge, 3, and 6 months in both patient groups.

Primary Efficacy Endpoint:

- Survival to hospital discharge

Justification: Survival is the most widely accepted endpoint in CPR and OHCA trials. Our trial is designed to evaluate the effect of expediting normalization of circulation with artificial means (ECMO initiation) in order to facilitate survival.

Secondary Objective.

Longer Term Outcome: We will assess the rates of survival to hospital discharge with mRS ≤3, 3- and 6-month survival, survival to 3 and 6 months with mRS ≤3, and functional status at discharge, 3 and 6 months (mRS and Cerebral Performance Category [CPC] scores).
Safety: We will assess the frequency of serious adverse events (SAEs) and frequency of ECMO-related complications in the two groups.
Cost: The cost per patient and cost per life saved in the two groups will be determined based on billing charges assessed by the UB-04 form.

Secondary Efficacy Endpoints:

- Survival to hospital discharge with mRS ≤3
- Survival to 3 and 6 months,
- Survival to 3 and 6 months with mRS ≤3,

- Functional status at discharge, 3 and 6 months (mRS score; Cerebral Performance Category [CPC] score).
- Cost per patient (based on billing charges)
- Cost per life saved (based on billing charges)

Justification: Many patients that survive from the OHCA and are discharged continue to improve over 3-6 months. As such, we need to assess their status at a later time to fully capture the potential for improvement in this population.
ECMO-based resuscitation protocols are also very expensive and resource and personnel intensive. As such, we need to understand the costs involved with these strategies.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Primary Hypothesis.
Based on the promising preliminary experience, we hypothesize that the Early ECMO Facilitated Resuscitation Arm will facilitate the identification and treatment of reversible CAD and significantly improve survival to hospital discharge compared with the Standard ACLS Resuscitation Arm.

Phase of the trial.
This is a Phase II, single center, partially blinded, prospective, intention to treat, safety and efficacy clinical trial.

Measures to Minimize Bias.

- Initial patients will be randomly allocated to one of the 2 regional standards of care in a 1:1 ratio. According to the University of Minnesota Refractory VF/VT Protocol, EMS providers always use a central telephone number to notify that a refractory VF/VT patient is being transported. The research team will use this standard EMS call to mobilize and be present at the ED for the patient's arrival. Immediately following hospital arrival, the research team will evaluate study entry criteria and, if eligible, randomize and enter the patient in the study, transferring the patient to the ED or CCL. In this way, the study will remain completely transparent to EMS providers, eliminating potential bias in EMS treatment pre arrival. It is impossible to blind treatment assignment in the CCL, but the study has been designed to eliminate bias in the out-of-hospital setting. Emergency department and CCL personnel will be aware of group assignment, but treatments will follow the current clinical standards of care. Post CCL care providers for patients admitted to the coronary intensive care unit (CICU), from both arms, will be instructed to not seek information about group assignment unless, in their judgment, a medical situation of critical clinical importance requires it.
- All patients will be treated with the same established CICU post-arrest protocols established by the Center for Resuscitation Medicine.
- Patients in the Early ECMO Facilitated Resuscitation Protocol Arm can also be held for a few minutes in the ED until the CCL team arrives during which time they will receive continued ACLS. That fact makes the distinction between arms by hospital providers very difficult when patients are admitted.
- Both arms can have patients that are admitted to the ICU **without ECMO** (if ROSC has been achieved and hemodynamically stable) and **on ECMO** based on the clinical needs. This fact also makes the distinction between arms by hospital providers very difficult when patients are admitted.
- Patient on both groups may have ROSC prior to arrival or immediately after randomization. They will follow the intention to treat arm allocation. Patients with initial ROSC in both groups may still get ECMO support as determined by the treating ECMO/Cardiology team.

- VA ECMO or other circulatory support device initiation in patients entering the CCL with ROSC is based on the interventional cardiologist's clinical judgment and cannot be not prespecified by protocol. In general, evidence of the following are common indications for VA ECMO initiation in all CCL patients:
    - Profound cardiogenic shock with SBP< 90 mmHg or MAP <60mmHg despite inotropic support and an intra-aortic balloon pump,
    - Persistent hypoxia with arterial oxygen saturation <90% despite maximum ventilatory support,
    - Florid pulmonary edema despite iv diuretics,
    - Recurrent episodes of VF or VT in the CCL

The number of study groups/arms and study intervention duration

There will be two arms as mentioned above. Enrollment and follow up will continue for 3 1/2 years.

4.2 SUBGROUP ANALYSES

The primary study endpoint will be compared between: 1) males versus females, 2) study subjects < 55 versus ≥55 years old, 3) presence versus absence of coronary artery disease (>70% stenosis), and 4) 911 call to ECMO initiation <50 versus ≥50 minutes. It should be noted, however, that *a priori,* the power to detect significant treatment effects in these subgroups, which are substantially smaller than the trial's entire cohort, will be low.

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Primary Hypothesis. Based on the promising preliminary experience, we hypothesize that the **Early ECMO Resuscitation Arm**, with early ECMO access for circulatory support and PCI, when needed, will facilitate cardiorespiratory stabilization as well as identification and treatment of reversible CAD and significantly improve survival to hospital discharge compared with the **Standard ACLS Resuscitation Arm.** Many patients that survive from the OHCA and are discharged continue to improve over 3-6 months. As such, we will assess their functional status at hospital discharge, 3 and 6 months to fully capture the potential for improvement in this population.

Early identification of reversible causes of refractory VF arrest and circulatory support appears to provide a benefit, but without randomization it is impossible to determine if the patients that survive would have survived in the absence of early ECMO initiation or they could have achieved ROSC without early ECMO initiation.

4.4 END OF STUDY DEFINITION

Study will end either upon death of the patient or after completion of the 6-month assessment in the survivors.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- Adults (presumed or known to be aged 18-75 years, inclusive),
- An initial documented OHCA rhythm of VF/VT,
- No ROSC following 3 defibrillation shocks,
- Body morphology able to accommodate a Lund University Cardiac Arrest System (LUCAS™) automated CPR device, and
- Estimated transfer time from the scene to the ED or CCL of < 30 minutes.

5.2 EXCLUSION CRITERIA

- Age < 18 years old or > 75 years old;
- Non-shockable initial OHCA rhythm (pulseless electrical activity [PEA] or asystole);
- Valid do-not-attempt-resuscitation orders (DNAR);
- Blunt, penetrating, or burn-related injury, drowning, electrocution or known overdose;
- Known prisoners;
- Known pregnancy;
- Nursing home residents;
- Unavailability of the cardiac catheterization laboratory.
- Severe concomitant illness that drastically shortens life expectancy or increases risk of the procedure;
- Absolute contraindications to emergent coronary angiography
    - Known anaphylactic reaction to angiographic contrast media
    - Active gastrointestinal or internal bleeding

5.3 SCREEN FAILURES

Eligibility and exclusion criteria for ARREST are described in section 5.1 and 5.2 of this Protocol. Some of the criteria will not be ascertainable immediately following hospital arrival. These potentially include the age (18-75) in some cases, valid do-not-attempt-resuscitation (DNAR) orders, known pregnancy, absolute contraindications to emergent coronary angiography, and severe concomitant illnesses such as end-stage renal disease, end-stage liver disease, or stage IV cancer. Thus, some patients may be randomized and later found ineligible for the clinical trial. Their exclusion will be based on objective factors that are not related to the group to which they were randomized. We will record all required

information on such patients up to the point that their ineligibility is determined. Exclusion of these patients from the trial is unavoidable because some of the procedures to determine eligibility cannot be carried out immediately following hospital arrival. The intention-to-treat population will not include such screen failures. However we will retain all the information collected for such patients, including, especially, the reason(s) for exclusion, and will report on this population in tables presented to the Data and Safety Monitoring Board and in annual reports to NHLBI.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Enrollment is based on patients with refractory VF/VT out-of-hospital cardiac arrest treated by the EMS systems participating in the ongoing MRC Refractory VF/VT Protocol and transported to the University of Minnesota Medical Center, Fairview, where, immediately following hospital arrival, they will be evaluated by the research team for study inclusion and exclusion criteria and, if eligible, randomized and entered in the study.

Because the ARREST Trial will remain transparent to EMS providers, all patients receive the same CPR quality and treatment by the same EMS systems using ACLS guidelines and automated CPR (LUCAS™2), thus limiting potential confounders of differences in resuscitation care and CPR performance. Resuscitation interventions will be performed consistent with local practice and American Heart Association standards.[31] If the patient has an initial cardiac arrest rhythm of VF/VT and continues to have VF/VT, antiarrhythmics may be administered per standard policy and procedure. If the patient does not develop ROSC after the first 3 defibrillation attempts and meets criteria for the University of Minnesota Refractory VF/VT Protocol (identical to the inclusion criteria for the ARREST Trial, but limited ARREST Trial exclusion criteria), paramedics call a central telephone number/dispatch per their standard practice. The research team will use the standard EMS call to mobilize and be present at the ED for the patient's arrival. MRC Refractory VF/VT Protocol patients are placed on LUCAS and are transferred to the University of Minnesota Medical Center, Fairview Hospital, with ongoing mechanical CPR per standard of care. Immediately following hospital arrival, the research team will evaluate the ARREST Trial inclusion and exclusion criteria and, if eligible, randomize and enter the patient in the study. Thus, paramedics are blinded to the study and out-of-hospital care is implemented using standard ACLS guidelines and automated CPR (LUCAS™2) for both groups.

The clinical CCL/ECMO team is always activated by the initial call and if not already in the hospital, it has a response time of 20 minutes from notification that happens at the time of EMS notification.

All entered study subjects or their legally authorized representative will have signed informed consent for continued participation in the trial and agreed to follow up assessment at 3 and 6 months. Contact information of the study subject, their significant other, and relevant additional contacts will be acquired prior to hospital discharge. Three and 6-month evaluations will occur by telephone or in-person during clinic appointments.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The ARREST study is a pragmatic clinical trial. Other than randomization to one of two arms [**Early ECMO Facilitated Resuscitation Arm** versus **Standard ACLS Resuscitation Arm**] there are no specified study interventions. All surviving patients will have their mRS and CPC score at hospital discharge determined; survival, mRS score, and CPC classification determined at 3 months post hospital discharge; and survival, mRS, and CPC classification determined at 6 months post hospital discharge. Cost per patient, cost per life saved (based on billing charges), safety and ECMO-related complications for the two treatment groups will also be determined.

Screening and Randomization.
There is no recruitment for this study as it is not possible to prospectively identify victims of out-of-hospital cardiac arrest. The subjects will be enrolled under exception from informed consent, 21 CRF 50.24.

EMS providers will deliver standard resuscitation procedures according to their standard practice. If the patient does not have ROSC following 3 defibrillations, EMS providers will call a central dispatch number per standard clinical practice, providing the research team with notification of a potentially eligible ARREST Trial study subject. At the same time the CCL/ECMO team is notified and activated. Immediately following hospital arrival, the research team will evaluate the ARREST Trial inclusion and exclusion criteria and, if eligible, randomize and enter the patient in the study, transferring the patient to the ED or CCL according to group allocation.

No Study Treatment; The following are suggested clinical practices that may or may not occur based on the judgment of the treating physician.

Early ECMO facilitated Resuscitation Arm. Following the standard EMS call to a central telephone number, if the research team determines the possible study subject would be randomized to the Early ECMO Facilitated Resuscitation Arm if entered in the study, they will begin mobilization of the CCL/ECMO team. EMS providers transport the patient to the University of Minnesota Medical Center, Fairview Hospital using the LUCAS device for CPR. Resuscitation interventions, including intravenous epinephrine, antiarrhythmics, defibrillation, and other appropriate treatments, occur prior to and during transport per EMS policy and procedure. Immediately following hospital arrival, the research team will evaluate the ARREST Trial inclusion and exclusion criteria and, if eligible, randomize and enter the patient in the study, directing the patient's hospital-based disposition. If the CCL/ECMO team is not in-house and has not yet arrived, resuscitation continues in the ED resuscitation area until arrival of the CCL/ECMO team. In this circumstance, given that average EMS transport times are 15± 5 minutes, it is expected that resuscitation will continue following arrival in the ED for about 10-15 minutes until CCL

personnel arrive. If the CCL is available the patient is directly transported to the CCL. Regardless of the presence of ROSC, ST-elevation myocardial infarction (STEMI) or acute ischemic changes on a 12 lead ECG, or VF/VT, PEA, or asystole cardiac arrest while in the ED, upon mobilization of CCL personnel, the patient is immediately transported to the CCL for coronary angiography and interventions, as appropriate. After arrival in the CCL, ongoing mechanical CPR continues, if required. The patient is immediately assessed on CCL arrival for resuscitation discontinuation criteria: 1) EtC02 upon arrival <10 mmHg, 2) PaO2 < 50mmHg or O2sat < 85%, and 3) serum lactate > 18mmol/liter. If the patient has > 1 criteria, resuscitation is terminated and the patient is declared dead. If the patient has 1 or no criteria, resuscitation efforts are continued. Emergency cannulation of the femoral vessels with a 15 or 17 french (Fr) arterial cannula based on size and gender and a 25 Fr venous cannula is performed with percutaneous technique and ultrasound (US) guidance. If there is difficulty in obtaining access or if the US suggests severe peripheral arterial disease, a descending aortic angiogram will be obtained to assess the ability of the femoral vessels to accommodate the size of the ECMO cannulas. In cases where the femoral vasculature cannot accommodate the ECMO cannulas, additional hemodynamic support is achieved by placement of an intra-aortic balloon pump (IABP) triggered by the aortic pressure generated by the LUCAS device. ECMO candidates are connected to the pre-primed CARDIOHELP circuit consisting of a centrifugal pump (Maquet Rotaflo; Maquet Cardiovascular; Wayne, NJ). Interventional cardiologists place all devices. Once hemodynamic/perfusion support is achieved, coronary angiography is performed and revascularization accomplished based on the clinical judgment of the interventional cardiologist.

Standard ACLS Resuscitation. If the patient is randomized to this protocol, research personnel will notify the ED MD about the randomization. Patients who have not achieved ROSC continue on ACLS resuscitation after arrival in the ED. Patients receive continued ACLS treatment in the ED for at least 15 minutes following ED arrival or at least 60 minutes from 911 call. If ROSC is achieved in the ED, the CCL team is mobilized and the patient transferred to the CCL per standard University of Minnesota clinical practice. If the patient has ROSC in the ED, but continues to re-arrest, the CCL team will not be mobilized until the patient demonstrates ROSC (as determined by the treating clinician, consistent with current clinical practice). If the ED MDs deem the ACLS effort futile at any point after 15 minutes of CPR from ED arrival or 60 minutes after the 911 if known, they can declare death.

Patients presenting or achieving ROSC in both group arms.

All patients with ROSC and pulses after VF/pVT OHCA gain access to the CCL per standard of care at the University of Minnesota. As such, those patients, in both groups will go to the CCL **regardless of arm allocation.**

VA ECMO or other circulatory support device initiation in those patients is based on the interventional cardiologist's clinical judgment. In general, evidence of the following are common indications for VA ECMO initiation in all CCL patients:

i) Profound cardiogenic shock with SBP< 90 mmHg or MAP <60mmHg despite inotropic support and an intra-aortic balloon pump,
ii) Persistent hypoxia with arterial oxygen saturation <90% despite maximum ventilatory support,

iii) Florid pulmonary edema despite IV diuretics,
iv) Recurrent episodes of VF or VT in the CCL.

Post-resuscitation Critical Care Recommended Pathway

Standard critical care measures follow guideline statements for post-cardiac arrest care[13,17,18] and ECMO management[19] with the following additional measures. All patients receive non-contrast computerized tomography (CT) scans of the head, chest, abdomen, and pelvis on CICU admission, assessing for cerebral anoxic injury, trauma, or bleeding. All patients receive therapeutic hypothermia (TH) for 24 hours. Goal temperature is 34° C, but is increased to 35-36° C if significant bleeding has occurred. Patients are maintained in 30-degree reverse trendelenburg with the head midline. Continuous electroencephalogram and near infrared spectroscopy (NIRS; Equanox; Nonin, Plymouth, MN) are initiated within 24 hours. NIRS measures cerebral oximetry and monitors brain perfusion while the patient is on ECMO. Hemodynamics are maintained with mechanical, inotrope, pressor, and vasodilator support to sustain a mean arterial pressure (MAP) between 65 and 100 mmHg. Fluid boluses provide euvolemic fluid status to prevent ECMO circuit chugging. ECMO flow is maximized until pressors are discontinued, then reduced, as tolerated, promoting native cardiac function. ECMO decannulation readiness is assessed daily with short durations of reduced ECMO flow and simultaneous echocardiography. On ECMO, ventilators are kept on rest settings with 7-10 cmH2O positive end-expiratory pressure at 12 breaths per minute, and a tidal volume of 6-8 mL/kg ideal body weight. Plateau pressures are maintained below 30 cmH2O. Settings are adjusted after ECMO decannulation. Continuous veno-venous hemodialysis is provided when needed. Potassium is replaced up to 3.0 mmol/L during TH and 4.0 mmol/L once rewarmed. Enteral nutrition is provided via oral-gastric (OG) or nasal-gastric (NG) access once rewarmed. All patients receive five days of empiric, broad-spectrum antibiotics with narrowed coverage thereafter, as necessary. Daily surveillance blood cultures are performed while on ECMO. Blood products are provided with a goal hemoglobin > 8 g/dL, platelets > 100,000 per µL, and fibrinogen > 200 mg/dL. Heparin maintains an activated clotting time (ACT) of 180-200 sec while on ECMO. For life-threatening bleeding, the ACT goal is reduced as low as 140-160 sec. All PCI patients received aspirin 81mg and ticagrelor by NG or OG tube.[59]

ECMO Exposure. Patients in both groups receiving ECMO are anticipated to require ECMO support for a longer duration than 6 hours and are expected to be in the range of 3 - 5 days or longer.

The expected duration of ECMO support is based on the investigators' experience implementing the MRC Refractory VF/VT Protocol (J Am Coll Cardiol. 2017 Aug 29;70(9):1109-1117). From December 1st, 2015 through February 29th, 2017, 62 patients met MRC Refractory VF/VT Protocol criteria for EMS transport. Left ventricular function was severely compromised for the first 48 hours in all patients admitted to the intensive care unit (ICU), but significant recovery was observed within 5 days. An intra-aortic balloon pump was inserted in 25 (45%) of 55 patients. The mean left ventricular ejection fraction in survivors was 18 ± 19% at 24 hours, 34 ± 19% at 48 hours, 43% ± 16% at 5 days, and 48% ± 11% at hospital discharge. After CCL treatment, extracorporeal life support (ECLS) was continued for 3.0 ± 2.0 days.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

All ECMO devices (Cardiohelp, Maquet Rotaflo; Maquet Cardiovascular; Wayne, NJ) will be stored by the perfusionists per standard clinical practice.

6.2.2 PRODUCT STORAGE AND STABILITY

At all times one device will be pre-primed and placed in the CCL to be available for use. The University of Minnesota initiates ~200 ECMOs per year for resuscitation and other indications and the average time from pre-priming to use is 2-3 days.

6.2.3 PREPARATION

Perfusionists perform daily rounds to verify the status of available devices in the CCL as part of their daily workflow. These are not experimental devices and will be managed per standard protocol. Maintenance is based on contractual agreements by the hospital cardiorespiratory division and the company.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients eligible for this study will be VT/VF OHCA patients refractory to standard treatment as defined by the ARREST Trial inclusion and exclusion criteria. Initially patients will be randomly allocated in a 1:1 ratio immediately following hospital arrival. As noted in the Statistical Considerations section, this trial has a Bayesian Adaptive Design, which means that the treatment allocation ratio may be changed later to reduce the probability of assignment to an inferior treatment arm. See Section 9 below. The study has been designed to minimize treatment bias as far as possible. EMS providers will be blinded to the study. University of Minnesota Refractory VF/VT Protocol patients are placed on LUCAS and transferred to the University of Minnesota with ongoing mechanical CPR per standard of care. All out-of-hospital care, including CPR, ACLS, and resuscitation efforts, will be implemented using ACLS guidelines and automated CPR (LUCAS™2) and treatment will be unchanged. Patients will be randomized and entered in the study by research personnel only after hospital arrival and assessment of ARREST Trial inclusion and exclusion criteria. Emergency department personnel will be aware of group assignment. However, ED treatment of all patients follows protocol and standard of care. CCL personnel also will be aware of group assignment, but treatment is similarly protocolized. Post-CCL care in the CICU will be blinded to group assignment. Patients in both groups could have received identical treatment. Patients from both groups will be treated with the same established CICU post arrest protocol by the same critical care team. The PIs will not be involved in any end-of-life decision making. The **Figure** below shows the phases of care in which providers are blinded to group allocation (in light blue).

Thus, we expect patients in both groups to similarly reflect the gender, ethnic diversity, severity or duration of cardiac arrest, and receive the same therapy except early ECMO facilitated resuscitation versus standard ACLS resuscitation.

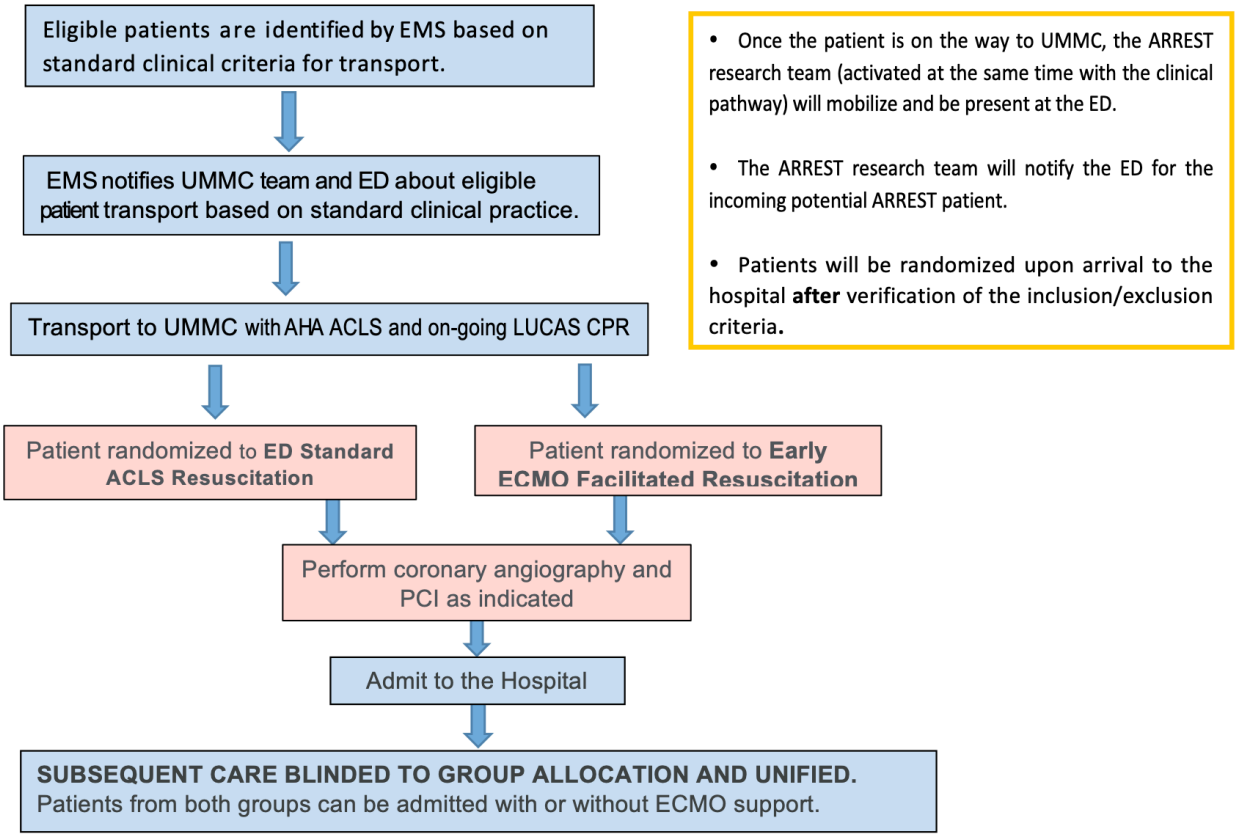


Figure: Patient flow chart showing blinding.

The secondary endpoints (mRS scores and CPC classifications) at hospital discharge, 3 months, and 6 months will be blinded assessments. These will be acquired by someone who is certified in the completion of the mRS and trained and competent to also assess CPC classification (although no certification exists for CPC classification).

Blinded assessment of the mRS and CPC study endpoints will be accomplished as follows:
At hospital discharge, 3 months, and 6 months, a blinded evaluator will determine the mRS and CPC in-person or by telephone. If the patient cannot be evaluated prior to hospital discharge, a blinded evaluator will acquire the mRS score and CPC classification within 2 weeks of hospital discharge by telephone or in-person during a follow up clinic visit.

6.4 STUDY INTERVENTION COMPLIANCE

This is a pragmatic clinical trial comparing two standards of care in the Minneapolis/St Paul metropolitan area. Other than randomization to one of two standards of care, there are no specified study procedures. Investigators will monitor delivery of the protocol arm to which each patient is randomized and immediately remediate if it is not delivered.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

This is a pragmatic clinical trial comparing two standards of care in the Minneapolis/St Paul metropolitan area. Other than randomization to one of two standards of care, there are no specified study procedures. Discontinuation of life-sustaining efforts in either study arm will be based on the expressed wishes of the patient, legally authorized representative and/or family in consultation with the treating clinician.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects/LARs have the right to withdraw from research at any time (45 CFR 46 [A] [8]). If the subject/LAR decides to withdraw from all components of the research study, investigators will discontinue interacting or intervening with the subject in order to obtain data about him/her for the research study. All data collected prior to withdrawal will be used for study analysis. Discontinuation or withdrawal of a subject may also occur because of study closure due to DSMB review.

7.3 LOST TO FOLLOW-UP

The ARREST sample size estimates allowed for up to 15% loss to follow-up. Every effort will be made to keep such losses to a minimum. In general, occurrences of serious adverse effects which require terminating exposure to the investigational device or procedure will be counted as treatment failures.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The Modified Rankin Scale Score (mRS) will be assessed by mRS-certified research personnel blinded to study subject randomized group assignment. The mRS will be assessed by telephone or in-person interview at hospital discharge, 3 and 6 months. See section 6.3 for a description of the methods of accomplishing blinded assessments.

Criteria for choosing an instrument to measure neurological status include prior data about reliability and validity, availability of instruments suitable for a multicenter trial, and application to prior cardiac arrest survivors. The **Modified Rankin Scale (MRS)** has face validity and can be determined in person or over the telephone. MRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.(Hop, Rinkel et al. 2001; Weimar, Kurth et al. 2002) Use of a structured interview in a recent study of stroke patients improved the weighted kappa from 0.71 to 0.91 (Wilson, Hareendran et al. 2005). The only previous published applications of mRS to survivors of cardiac arrest evaluated a cohort of neurosurgical patients with in-hospital cardiac arrest (Rabinstein, McClelland et al. 2004) and a cohort of survivors of out-of-hospital cardiac arrest.(van Alem, de Vos et al. 2004)

The Cerebral Performance Category [CPC] score will also be assessed by research personnel trained and capable in CPC acquisition blinded to study subject randomized group assignment. The CPC classification will be assessed by telephone or in-person interview at hospital discharge, 3 and 6 months.

Consensus statements recommend use of the **Cerebral Performance Category (CPC)** to assess functional outcomes after resuscitation from cardiac arrest. (Cummins, Chamberlain et al. 1991; Jacobs, Nadkarni et al. 2004) CPC is a five-point scale that was adapted from the Glasgow Outcome Scale (Jennett and Bond 1975; The Brain Resuscitation Clinical Trial II Study Group 1991). CPC has limited discrimination between mild and moderate brain injury. A small study with incomplete follow-up of survivor's demonstrated only moderate correlation with other measures of health-related quality of life (Hsu, Callaham et al. 1996). However, CPC at discharge predicts long-term survival. (Herlitz, Ekstrom et al. 1995)

The gross, billing charges per patient will be collected utilizing UB04 data for research purposes. The costs in each group will be averaged. Charges collected will include care in the emergency department (ED), CCL and inpatient care. The costs will be compared between groups and presented both as cost per patient and cost per patient per life saved.

8.2 SAFETY AND OTHER ASSESSMENTS

Important safety outcomes include the incidence of serious adverse events common in the two groups, serious adverse events attributable to advanced reperfusion strategies, and ECMO device-related adverse events. The parameters that will be used to monitor the safety of the study treatment, their definition, and their classification are as follows.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- *Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse event. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event (e.g., for a preexisting condition not associated with a new adverse event or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse event.

Unexpected adverse event. Any adverse event, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

Unanticipated adverse device event. Any serious adverse event on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that event, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse event. Any adverse event that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the event as it occurred (i.e., does not include an adverse event that, had it actually occurred in a more severe form, might have caused death).

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All serious adverse events (SAEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Adverse Events Common to Both Treatment Arms due to CPR and prolonged ischemic times

1. Infection/sepsis (Infection: any infection requiring intervention by the treating clinicians; Sepsis: systemic inflammatory response syndrome in response to an infectious process (confirmed by the treating clinicians)

2. Acute kidney injury (AKI) (Confirmed by the treating clinicians). (Increase in serum creatinine ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours, or increase in serum creatinine ≥1.5 times baseline, or Urine volume < 0.5 ml/kg/h for 6 hours, or Urine volume < 0.5 ml/kg/h for 6 hours)

3. Liver failure/injury (Rapid development of hepatocellular dysfunction in a patient without known prior liver disease (confirmed by the treating clinicians)

4. Cardiogenic shock (Intervention required to maintain adequate hemodynamics (confirmed by the treating clinicians)

5. Multiple organ dysfunction syndrome (MODS) Two or more organs in which homeostasis cannot be maintained without intervention (confirmed by the treating clinicians)

6. Seizure activity (Documented by EEG or clinical assessment and confirmed by the treating clinicians)

7. Brain death (***Brain Death (****The Canadian Neurocritical Care Guideline) defined brain death as the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions, including the capacity to breathe. Brain death is equivalent to death of the individual, even though the heart continues to beat and spinal cord functions may persist (Citation in Data Definitions)* ***Neurological determination of death (NDD)*** *is the process and procedure for determining brain death. The Canadian medical standard for NDD is reported in and is described for children.* ***Ancillary Tests:*** *The demonstration of the absence of intracerebral blood flow is considered the standard as an ancillary test for brain death. Currently validated imaging techniques are cerebral angiography (1) and radionuclide angiography (2.* ***Apnea Test on ECMO:*** *The patient should be placed on continuous positive airway pressure (CPAP) while the sweep gas flow rate is set to a maximum of 1.0 liter/minute. If the PaCO2 does not rise above 60 mmHg or change by 20 mmHg, the sweep flow can be incrementally lowered to as low as 0.1 liter/minute while still maintaining adequate oxygenation in most circumstances.)*

8. Recurrent cardiac arrest

9. Survival to hospital discharge with mRS >3

10. Critical illness myopathy and neuropathy

11. Rib fractures

12. Sternal Fractures

13. Spleen and liver lacerations

14. Aspiration pneumonitis

15. Pneumothorax/hemothorax

16. Retrosternal hematomas

17. Cardiac Contusions

Adverse Events Potentially Related to Reperfusion Strategies

1. Acute myocardial infarction (caused by advanced reperfusion strategies)
2. Acute stroke (caused by advanced reperfusion strategies)
3. Injury to the canalized artery (caused by advanced reperfusion strategies)
4. Pericardial effusion or tamponade (caused by advanced reperfusion strategies)
5. Bleeding requiring transfusion (caused by advanced reperfusion strategies)
6. Acute renal failure (caused by contrast dye)
7. Deep venous or arterial thrombosis/embolism (caused by advanced reperfusion strategies)
8. Pulmonary edema (caused by advanced reperfusion strategies)
9. Hemolysis, acquired von Willebrand factor deficiency, or thrombocytopenia (caused by ECMO)
10. Lower limb ischemia (caused by advanced reperfusion strategies)
11. Mechanical failure of the ECMO device
12. Death (as a direct complication of advanced reperfusion strategies)

ECMO Device-Related Adverse Event

1. Mechanical: Oxygenator failure (*Requiring change due to clot formation or gas exchange failure or blood leak)*
2. Mechanical: Raceway rupture ((*In a roller pump rupture of the raceway tubing))*
3. Mechanical: Other tubing rupture (*Rupture of ECLS tubing)*
4. Mechanical: Pump Failure (*Requiring hand cranking or pump exchange*)
5. Mechanical: Heat exchanger malfunction (*Malfunction of heat exchanger leading to unintentional hypothermia <35C or hyperthermia >39)*
6. Mechanical: Clots: oxygenator (*Requiring change due to clot formation or gas exchange failure or blood leak)*
7. Mechanical: Clots: bridge *(Requiring change due to clot formation or mechanical failure)*
8. Mechanical: Clots: bladder *(Requiring change due to clot formation or mechanical failure)*

9. Mechanical: Clots: hemofilter (*Clots in hemofilter causing hemofilter to need to be changed or to fail)*

10. Mechanical: Clots: other *(Requiring change due to clot formation or mechanical failure)*

11. Mechanical: Clots: Circuit Component Clots (*Circuit component [e.g. pigtails, connectors, bridge, arterial or venous tubing] requiring change due to clot formation or mechanical failure)*

12. Mechanical: Air in circuit (*Requiring circuit intervention or circuit clamping for bubble detector alarm, visualized air, air entry into patient)*

13. Mechanical: Cracks in pigtail connectors *(Crack in pigtail connector requiring change or mechanical failure)*

14. Mechanical: Cannula problems (*Requiring intervention [reposition or exchange] for misplacement, dislodgement, replacement due to clots/fibrin, mechanical failure or inappropriate position)*

15. Mechanical: Circuit change (*Entire circuit (with exception of cannulae) changed due to clot formation or mechanical failure)*

16. Mechanical: Clots and Air Emboli (*Requiring circuit intervention or circuit clamping for bubble detector alarm, visualized air, air entry into patient)*

17. Mechanical: Thrombosis/Clots: circuit component (*Circuit component (e.g. pigtails, connectors, bridge, arterial or venous tubing) requiring change due to clot formation or mechanical failure)*

18. Hemorrhagic: GI hemorrhage (*Upper or lower GI hemorrhage requiring PRBC transfusion >3U PRBCS/24 hrs in adults), and/or, endoscopic intervention, and/or hemostatic agent deployment)*

19. Hemorrhagic: Cannulation site bleeding (*Peripheral cannulation site bleeding requiring PRBC transfusion (>3U PRBCS/24 hrs in adults) and/or, surgical intervention (includes intravascular hemostatic agent deployment). A reperfusion cannula is a type of peripheral cannulation) site.*

20. Hemorrhagic: Mediastinal cannulation site bleeding (*Mediastinal cannulations are also referred to as central cannulations and are placed via their mediastinum. Mediastinal cannulation site bleeding requiring PRBC transfusion (>3U PRBCS/24 hrs in adults, and/or surgical intervention.)*

21. Hemorrhagic: Hemolysis (hgb > 50 mg/dl) *(Confirmed by the treating clinicians)*

22. Hemorrhagic: Disseminated intravascular coagulation (DIC) *(Confirmed by the treating clinicians)*

23. Neurologic: Brain death (***Brain Death (****The Canadian Neurocritical Care Guideline) defined brain death as the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions, including the capacity to breathe. Brain death is equivalent to death of the individual, even though the heart continues to beat and spinal cord functions may persist (Citation in Data Definitions)* ***Neurological determination of death (NDD)*** *is the process and*

procedure for determining brain death. The Canadian medical standard for NDD is reported in and is described for children. ***Ancillary Tests:*** *The demonstration of the absence of intracerebral blood flow is considered the standard as an ancillary test for brain death. Currently validated imaging techniques are cerebral angiography (1) and radionuclide angiography (2.* ***Apnea Test on ECMO:*** *The patient should be placed on continuous positive airway pressure (CPAP) while the sweep gas flow rate is set to a maximum of 1.0 liter/minute. If the PaCO2 does not rise above 60 mmHg or change by 20 mmHg, the sweep flow can be incrementally lowered to as low as 0.1 liter/minute while still maintaining adequate oxygenation in most circumstances.)*

24. Neurologic: Seizures: clinically determined (*Clinically determined by assessment)*
25. Neurologic: Seizures Confirmed by EEG (*Confirmed by Electroencephalograph)*
26. Neurologic: CNS Infarction (*CT or US or MRI demonstrating localized ischemic change*
27. Neurologic: CNS hemorrhage (by US or CT or MRI)
28. Neurologic: Intraventricular CNS hemorrhage *(US or CT or MRI ≥ Grade 2 IVH on US, CT or MRI)*
29. Neurologic: Intra/extra parenchymal CNS Hemorrhage *(US or CT or MRI; May be intraparenchymal, subdural or subarachnoid)*
30. Neurologic: CNS diffuse ischemia *(CT or MRI demonstrating diffuse ischemic changes)*
31. Neurologic: Neurosurgical intervention performed (*Neurosurgical procedure performed during ECLS run (e.g. intracranial pressure monitor, external*
32. Renal: Creatinine 1.5 - 3.0 (*After ECMO start time, patient newly acquires a creatinine serum measurement of 1.5- 3.0)*
33. Renal: Creatinine > 3.0 (*After ECMO start time, patient newly acquires a creatinine serum measurement of >3.0)*
34. Renal: Dialysis required (*Peritoneal Dialysis [PD] or Hemodialysis [HD])*
35. Renal: Hemofiltration required (*Continuous Venovenous Hemodiafiltration (CVVHD), Continuous Venovenous Hemofiltration (CVVHF) or Continuous Venovenous Hemodiafiltration (CVVHDF)*
36. Renal: CAVHD required *(Continuous Arteriovenous Dialysis)*
37. Renal: Renal Replacement Therapy Required (*Peritoneal Dialysis (PD), Continuous Venovenous Hemodiafiltration (CVVHD), Continuous Venovenous Hemofiltration (CVVHF) or Continuous Venovenous Hemodiafiltration (CVVHDF) or Hemodialysis (HD) based on the patient's ultimate mode of therapy*
38. Cardiovascular: Inotropes on ECLS (Dobutamine. Dopexamine. Epinephrine (adrenaline) Isoprenaline (isoproterenol) Norepinephrine (noradrenaline)

39. Cardiovascular: CPR required (*Chest compressions and cardiopulmonary resuscitation required during ECLS run)*
40. Cardiovascular: Myocardial stun by echo *(Confirmed by the treating clinicians)*
41. Cardiovascular: Cardiac arrhythmia *(Requiring antiarrhythmic medication infusion, overdrive pacing, cardioversion or defibrillation)*
42. Cardiovascular: Hypertension requiring vasodilators *(Confirmed by the treating clinicians)*
43. Cardiovascular: Tamponade (blood): (*Tamponade during ECLS run requiring pericardial drain or mediastinal washout)*
44. Cardiovascular: Tamponade: air *(Confirmed by the treating clinicians)*
45. Cardiovascular: Tamponade (not blood): (*Tamponade during ECLS run requiring pericardial drain or mediastinal washout)*
46. Pulmonary: Pneumothorax requiring treatment (*Requiring insertion of chest drain)*
47. Pulmonary: Pulmonary hemorrhage (*Requiring pRBC transfusion(>3U PRBCS/24 hrs in adults)*
48. Infectious: Culture proven infection *(Confirmed by the treating clinicians)*
49. Infectious: WBC < 1,500
50. Metabolic: Glucose < 40
51. Metabolic: Glucose > 240
52. Metabolic: pH < 7.20
53. Metabolic: pH > 7.60
54. Metabolic: Hyperbilirubinemia (*total bilirubin >170umol/L (> 10mg/dL) or conjugated bilirubin >51umol/L (>3mg/dL), or need for extracorporeal purification for elevated bilirubin)*
55. Metabolic: Moderate hemolysis (*Peak plasma hemoglobin 50-100 mg/dL or 500-1000 mg/L occurring at least once during ECLS run. Sustained for at least 2 consecutive days)*
56. Metabolic: Severe hemolysis (*Peak plasma hemoglobin > 100mg/dL or >1000 mg/L occurring at least once during ECLS run. Sustained for at least 2 consecutive days)*
57. Limb: Ischemia (*Post peripheral cannulation, requiring addition of limb reperfusion cannula >=6 hrs post cannulation)*
58. Limb: Compartment Syndrome *(Requiring fasciotomy)*

59. Limb: Fasciotomy (*Fasciotomy performed secondary to compartment syndrome from ECLS cannulation [fasciotomy performed during ECLS hospitalization])*

60. Limb: Amputation (*Limb amputation secondary to complications from ECLS run (amputation performed during ECLS hospitalization)*

8.3.4 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 resuscitation, hospitalization, study visits and interviews, or upon review by a study monitor. 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.

The PI or designated research staff will record all reportable events with start dates occurring any time after enrollment at the last day of study participation all adverse event will be marked as resolved or continued with or without sequelae. At each study follow up visit, the investigator will inquire about the occurrence of SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

This very critically ill study population is recognized and expected to experience initial and repeated life threatening events throughout resuscitation and hospitalization. Accordingly, following consultation with the Food and Drug Administration, investigators will not track or report adverse events, expected to be nearly continuous in all patients.

Serious adverse events will be tracked and reported as described below. Investigators will further track the frequency of serious adverse events, compare the study frequency with patients treated similarly previous to and outside the study, and report any significant increased frequency based on investigator clinical judgment and experience.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The investigator should report all SAEs as soon as possible but no later than 7 calendar days from the day study personnel became aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

8.3.7 REPORTING OF PREGNANCY

Pregnancy, although possible, is unlikely. In case pregnancy is identified after resuscitation and intervention, the OB/GYN teams will be contacted to consult and manage related issues.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated adverse device effect (UADE) means 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 (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. The study investigator shall complete an Unanticipated Adverse Device event (UADE) Form and submit to the study sponsor The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device event and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs (per local IRB policy) and participating investigators within 10 working days after the sponsor first receives notice of the event. Thereafter, the sponsor shall submit such additional reports concerning the event as FDA requests.

8.4.2 UNANTICIPATED PROBLEM REPORTING

All UADEs will be reported to the sponsor within 72 hours from when the research team became aware of the event.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary endpoint in the ARREST clinical trial is survival to hospital discharge.

The primary study hypotheses are

$$H_0: p_E = p_C \quad \text{versus} \quad H_A: p_E \neq p_C$$

where p_E denotes the probability of response in the target population under Early ECMO Facilitated Resuscitation and and p_C the probability of response under Standard ACLS Resuscitation with response defined by surviving to hospital discharge. The study will reject the null hypothesis H_0 when there is a suitably large posterior probability that either $p_E > p_c$, i.e. ECMO is superior, or $p_E < p_C$, i.e. ECMO is inferior. The threshold has been chosen to ensure type I error rate control at the nominal 0.05 level using computer simulation. The posterior probabilities will be based on a Bayesian Beta-Binomial model described below. The study sample size has been selected to provide 90% power for rejecting the null hypothesis under the targeted alternative scenario with $p_E = 0.37$ versus $p_C = 0.12$.

The primary null hypothesis that will be tested in this trial is there is no difference in the probability of a favorable outcome between the group randomized in the field to **Early ECMO Facilitated Resuscitation** and the group randomized to **Standard ACLS Resuscitation**.

The primary alternative hypothesis is that success rates in the **Early ECMO Facilitated Resuscitation** group will be 37%, while those in the **Standard ACLS Resuscitation** group will be 12%.

The primary endpoint is dichotomous. The most appropriate analysis given the Bayesian design (see below) is based on a beta-binomial model for the posterior distributions.

Bayesian Adaptive Design and Monitoring

This trial has a Bayesian adaptive design. What this means is that there will be periodic evaluation of the primary outcomes in the two groups. At such evaluations, if there is a difference in success rates between the two groups, the ratio of patients randomized will be weighted toward the better of the two groups.

Probability Model

Let Y_i indicate whether the i^{th} participant survives to hospital discharge which we assume follows a Bernoulli distribution with probability of response p_a when this participant is assigned to group a = E or C. We specify independent Uniform(0,1) ≡ Beta(1,1) prior distributions for p_E and p_C. Let N_a denote the number of participants assigned to group a and X_a the number of responses. It follows that the posterior distribution for p_a is Beta(X_a+1, N_a - X_a + 1) and

$$\text{Prob}(p_E > p_C \mid \text{Data}) = \int_0^1 [1 - F(y \mid X_E + 1, N_E - X_E + 1)]\, f(y \mid X_C + 1, N_C - X_C + 1)\, dy$$

where F(y | a, b) and f(y | a, b) respectively denote the Beta(a,b) cumulative distribution and probability density functions. Note that Prob($p_E < p_C$ | Data) = 1 - Prob($p_E > p_C$ | Data). We calculate Prob($p_E > p_C$ | Data) in R v3.5.1 using adaptive quadrature via the integrate() function.

Group Sequential Adaptive Design

We will calculate Prob($p_E > p_C$ | Data) each time we ascertain an evaluable outcome on 30 participants, and stop the trial for superiority when Prob($p_E > p_C$ | Data) ≥ 0.986, or for inferiority when Prob($p_E < p_C$ | Data) ≥ 0.986. If the trial does not stop, the next group of enrollees will be randomized to ECMO with probability equal to the current value of Prob($p_E > p_C$ | Data) subject to the restriction that the randomization ratio may not exceed 3:1 in either direction. The initial cohort of patients will be randomized 1:1. Upon ascertaining evaluable outcomes on 150 participants, if neither posterior probability threshold for superiority or inferiority is exceeded the trial will be stopped with a failure to reject the null. This maximum sample size was chosen to provide 90% power for the targeted alternative scenario of with $p_E = 0.37$ versus $p_C = 0.12$ as evidenced by the computer simulation study reported below.

Operating Characteristics

We carried out a computer simulation study to assess the operating characteristics of the proposed adaptive design. To this end, we simulated 10,000 trials following the proposed adaptive design by generating outcome data under a null scenario with $p_E = p_C = 0.12$ and the targeted alternative scenario with $p_E = 0.37$ versus $p_C = 0.12$. When aiming to obtain up to n = 150 evaluable outcomes, Table 1 indicates the proposed adaptive design controls the type I error rate at the nominal 0.05 level and provides 90% power for the targeted alternative benefit. While the adaptive design is unlikely to stop early under the null scenario with an average sample size of 148.5, it is likely to stop early under the targeted alternative scenario with an average sample size of 81.6. Breaking these figures out by the average number assigned to each group shows that under the null, on average, the adaptive design with randomize about 74 people to each group, whereas under the targeted alternative, on average, only 29 participants are randomized to the inferior standard group and 52.5 to ECMO group.

Table 1: Simulated operating characteristics of the adaptive trial design based on 10,000 trials with n = 150 under the two key scenarios. Posterior probability threshold is 0.986 throughout the trial. Null scenario assumes 0.12 response probability in both groups, alternative assumes 0.37 versus 0.12.

Scenario	Proportion of Trials Rejecting Null Hypothesis	Average Trial Sample Size	Average Number Assigned to ECMO Group	Average Number Assigned to Standard Group
Null	0.048	148.5	74.2	74.3
Alternative	0.905	81.6	52.5	29.2

To account for up to 15% withdrawal, we will aim to enroll up to 175 participants and thereby ensure up to 150 participants with evaluable outcomes for the primary hypothesis test assessment.

Stopping Criteria

We will allow early stopping for superiority or inferiority of ECMO, i.e. symmetric bounds. That is, we plan to stop the study when either posterior Prob($p_E > p_C$ | Data) ≥ 0.986 or posterior Prob($p_E < p_C$ | Data) ≥ 0.986. In the former situation, we will declare ECMO superior, and in the latter, we will declare ECMO inferior. These assessments will be carried out a pre-planned sample sizes throughout the study, not continuously. In particular, we will assess these posterior probabilities each time we complete follow-up on 30 participants. If the trial does not stop for either superiority or inferiority, the randomization ratio will be modified for the next group of 30 participants as described previously.

Secondary outcomes will include the occurrence of ECMO-related complications, survival to hospital discharge with mRS ≤3, survival to 3 and 6 months, survival to 3 and 6 months with mRS ≤3, functional status at discharge, 3 and 6 months (mRS score; Cerebral Performance Category [CPC] score), cost per patient (based on billing charges), and cost per life saved (based on billing charges).

9.2 SAMPLE SIZE DETERMINATION

The primary outcome is binary, with success defined as survival to hospital discharge. The appropriate analysis, given the Bayesian design, is computed using the posterior beta-binomial distribution. We hypothesize a treatment effect of 12% success in the **Standard ACLS Resuscitation** group and 37% success in the **Early ECMO Facilitated Resuscitation** group. Assuming success rates of 12% vs. 37% in the 2 groups and 90% power and a type 1 error rate of 0.05, the required sample size is N = 148 evaluated patients. We inflated this figure to account for 15% rate of withdrawal prior to hospital discharge and for false positive activation and randomizations (which may occur due to the emergent nature of the randomization) to obtain a target sample size for randomization of N = 174.

9.3 POPULATIONS FOR ANALYSES

The primary population for analysis is the set of patients who are randomized immediately following hospital arrival and are not excluded afterward by conditions that cannot be determined emergently. The patients that are found to meet prespecified exclusion criteria for the ARREST trial post randomization will be excluded. These are the only patients excluded from the ITT population.

It may happen in rare cases that a patient randomized to **early ECMO facilitated resuscitation** does not receive ECMO, or conversely that a patient randomized to **standard ACLS resuscitation** does receive ECMO because they became clinically unstable after they entered the CCL with ROSC. These cases, if they are found to meet eligibility and exclusion criteria, will be analyzed according to the ITT principle: 1) those randomized to receive **early ECMO facilitated resuscitation** will be classified in the early ECMO

facilitated resuscitation group irrespective of whether or not they received ECMO, and 2) those randomized to receive **standard ACLS resuscitation** will be classified in the standard ACLS resuscitation group irrespective of whether or not they received ECMO.

The secondary 'as-treated' population will be comprised of two groups of patients: (1) those who receive ECMO, regardless of treatment assignment, and (2) those who do not receive ECMO (again regardless of treatment assignment).

As specified elsewhere in this Protocol, there are pre-specified subpopulations of interest. These are defined by: 1) gender, 2) age group (< 55 years old versus ≥ 55 years old), 3) presence versus absence of coronary artery disease (> 70% stenosis), and 4) 911 call to CCL arrival (< 50 minutes vs. ≥ 50 minutes). These will be treated as strata in Mantel-Haenszel analyses and in multivariable logistic analyses of the data. Such analyses will include terms for interaction of the randomized treatment group assignment with the stratifying factors.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The measurements that will form the basis for evaluating the primary and secondary outcomes of the study include survival to hospital discharge, survival to hospital discharge with mRS ≤ 3, survival, mRS score, and CPC classification determined at 3 months post hospital discharge, and survival, mRS, and CPC classification determined at 6 months post hospital discharge. Cost per patient and cost per life saved (based on billing charges) for the two treatment groups will be determined.

This Phase II, prospective, single-center, safety and efficacy clinical trial, randomizing refractory VF/VT patients to receive 1 of 2 standard treatments in our community directly addresses a national healthcare need. These data will be evaluated to determine the safety of CCL-based ECMO initiation as a means to provide circulatory support and emergently treat the reversible causes of VF/VT out-of-hospital cardiac arrest. The data will further inform the resuscitation community regarding efficacy to improve survival and cost per life saved. The results of these data will provide the basis for making a decision to implement a multicenter clinical trial to assess generalizability of this approach.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The analysis of the primary end point—survival to hospital discharge will be based on a 2 x 2 table where the test statistic is computed from the posterior beta-binomial distribution. The primary analysis is based on intention to treat. The difference between the two treatment arms will be considered significant of the posterior probability that one arm is superior is 0.986 or larger.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary efficacy analyses will include survival to hospital discharge with mRS ≤ 3, survival at 3 and 6 months, survival at 3 and 6 months with mRS ≤ 3, functional status at discharge, 3 and 6 months (mRS

score and Cerebral Performance Category [CPC] score), cost per patient (based on billing charges), and cost per life saved (based on billing charges). These analyses will be performed both on an intention-to-treat and an as-treated basis. Categorical outcomes will be analyzed using Fisher's Exact Test or the logistic model. Quantitative outcomes (cost per patient and cost per life saved) will be analyzed using t-tests (with log transformation for skewed distributions as appropriate) and analysis of variance.

9.4.4 SAFETY ANALYSES

The incidence of AEs will be recorded for all patients in the safety population and presented by treatment arm to the DSMB for review during the study, as well as summarized and compared across treatment arms in the final report of study results. AEs attributable to advanced reperfusion strategies will be reported separately. The statistical significance of differences in safety signal incidence between the 2 treatment groups will be reported. Emphasis will be placed on the presentation of primary study results, with statistical tests provided for guidance on the precision of estimates as indicated. The DSMB must weigh risks against benefits. Thus, interim presentations to the DSMB will include between-group comparisons of the relation of severe adverse events (including deaths) to favorable outcomes. Similar considerations apply to publication of study results when the trial is completed. The specific adverse events listed that potentially reflect the safety of the Early ECMO Facilitated Resuscitation may or may not affect survival to hospital discharge or longer term functional outcome.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The following will be reported as baseline descriptive statistics in the two groups:

- Age
- Gender
- Race/ethnicity
- Location of cardiac arrest
- Cardiac arrest witnessed
- Bystander CPR performed
- Time from 911 call to EMS arrival at patient, minutes
- Time from 911 call to arrival at CCL/MED, minutes
- Time from 911 call to ECLS application, minutes
- Time from CCL entry to ECLS, minutes
- CCL entry to balloon time, minutes
- Incidence of Return of Spontaneous Circulation (ROSC)

- Resuscitation therapies administered
    - Drugs and doses administered
    - Number of shocks
    - Type and success of advanced airway
    - Therapeutic hypothermia

9.4.6 PLANNED INTERIM ANALYSES

An independent DSMB will be appointed in order to ensure the safety of the subjects by monitoring adverse outcomes throughout the trial and by reviewing outcome data for both efficacy and possible harm. At least one bioethicist will be included in the DSMB membership. In addition, the Board will review the results of interim analyses. The DSMB must review and approve the protocol before the study can commence. The DSMB will evaluate the rate of adverse events between the treatment and control arms at 6-month intervals. As noted above, the DSMB will be notified whenever the randomization allocation ratio is changed. The DSMB will be required to conduct a formal vote on a recommendation to stop the study if the posterior probability that one group is superior to the other exceeds 0.986. The DSMB will also monitor secondary study outcomes success rates between the treatment and control groups, and rates of adverse events.

9.4.7 SUB-GROUP ANALYSES

The primary study endpoint will be compared between: 1) males versus females, 2) study subjects < 55 versus ≥55 years old, 3) presence versus absence of coronary artery disease (>70% stenosis), and 4) 911 call to ECMO initiation <50 versus ≥50 minutes. It should be noted, however, that *a priori,* the power to detect significant treatment effects in these subgroups, which are substantially smaller than the trial's entire cohort, will be low. These are exploratory. The sample sizes of these defined subgroups are such that the power to test hypotheses in these subgroups is substantially smaller than that for the main hypothesis.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Patients in this trial will have complex clinical courses prior to hospital discharge. They will experience a wide variety of adverse events, many of them serious, some of them known complications of ECMO treatment. The Statistical and Data Coordinating Center will maintain detailed histories, by hospital course day, of adverse events and treatments. Tables comprised of such detailed histories will be available for examination by members of the DSMB. DSMB summary tables will classify the nature and frequency of adverse events essentially by collapsing such histories across treatment groups and other strata of interest.

All data in SDCC files, reports, or tables will be de-identified.

9.4.9 EXPLORATORY ANALYSES

In addition to the primary and secondary analyses described above, the SDCC will carry out non-pre-specified analyses in certain subgroups. This will include time of day of the event, laboratory findings, and treatments administered during the hospital stay. Such analyses may be carried out on emergent factors which were not anticipated or described at the beginning of the trial. As such, any hypothesis testing (p-values) arising from such analyses must be regarded as exploratory. They will need to be noted and reported to the DSMB and in publications emanating from the trial, but they will also need to be confirmed by future studies and will be clearly described as exploratory.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Enrollment is initiated under an exception from informed consent as the patient is unconscious and 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, and script for objection to research.

10.1.1.1 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 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.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. 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.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product 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 the 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 the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Minnesota SDCC. 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 University of Minnesota SDCC 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 University of Minnesota SDCC.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data records for the ACCESS trial will be stored at the SDCC for at least 10 years after completion of the study. All data are anonymized, with records indexed by alphanumeric IDs; no names, SSNs, hospital record numbers, phone numbers, addresses or other identifiers will be stored at the SDCC.

10.1.4 SAFETY OVERSIGHT

The independent DSMB will ensure the safety of the subjects by monitoring adverse outcomes throughout the trial and by reviewing outcome data for both efficacy and possible harm. In addition, the Board will review the results of interim analyses. The DSMB will review and approve the protocol before the study can commence. The DSMB will evaluate the rate of adverse events between the treatment and control arms at 6-month intervals. The DSMB will also monitor primary and secondary study outcomes between the two groups. The SDCC will forward DSMB recommendations to study investigators, the Institutional Review Boards, the FDA, and the NIH in accordance with federal regulations 45 CFR Part 46 Subpart A, 21 CFR 312, and the investigational device exemption (IDE) regulations. The DSMB will be given password-protected access to the database of deaths and occurrences of survival to hospital discharge with mRS ≤ 3 and occurrences of severe adverse events attributable to advanced reperfusion strategies. These data will be updated on an expedited basis. Members of the DSMB and/or statistical staff at the SDCC may request a conference call of the group at any time.

10.1.5 CLINICAL MONITORING

The sponsor-investigator will permit direct access for the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

Independent monitoring of the clinical study for clinical protocol and IDE application compliance will be conducted by University of Minnesota's Clinical and Translational Science Institute (CTSI) clinical trial monitoring service.

The CTSI monitors will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities (FDA, IRB, local and State regulations).

A Clinical Events Committee (CEC) will include Cardiac Surgery Professor and ECMO surgical director Ranjit John MD PhD, and Associate Professor of Surgery and Critical Care Medicine Mellissa Brunsvold MD, who is the medical ECMO director at the University of Minnesota and Professor Robert Wilson MD (interventional Cardiology)**.** They will review and adjudicate serious and unexpected adverse events independently from the PI and co investigators.

Frequency of monitoring visits will occur:

- After IRB approval
- As soon as possible after the first subject is enrolled
- During the study data collection phase
- After the last subject has completed his/her participation in the study

This monitoring schedule may be revised based on the following considerations:

- Accrual rate
- Protocol deviations or non-compliance with regulatory authorities
- Magnitude of data corrections required
- Study stage (e.g. start-up or follow-up)
- Complexity of the trial
- Request (IRB, Investigator, other etc.)
- DSMB recommendation

Monitoring visits will be performed annually, at a minimum. The sponsor-investigator will permit direct access to the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of these data.

Primary responsibilities of the monitors will include verifying the following:

- Investigator qualifications
- Facilities and equipment
- Storage, dispensing and disposition of investigational products
- Protocol compliance
- Informed consent
- Training and delegation of authority
- Subject eligibility
- Recruitment, screening and enrollment
- Verification of data and data clarification
- Adverse event reporting
- FDA correspondence
- Deviations

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

The data management system includes daily off-site backup of all files. Data analyses will be carried out using SAS (version 9.3 or later) or R (version 3.2 or later).

Data quality monitoring will include daily consistency checks to cover issues that cannot be addressed upon data entry. Corresponding query reports will be made available on the internal study website for clinical staff to review and follow-up. Privacy will be maintained by password access to the REDCap system, with timed sessions that close automatically if no activity is detected. All staff with access to clinical records are required to have training in the areas of Good Clinical Practice (GCP), Health Insurance Portability and Accountability Act (HIPAA), responsible conduct of research, and conflict of interest (https://about.citiprogram.org). A staff roster will be maintained in a separate REDCap project to track the status and training of all study personnel. Clinical staff who require database access will have individual login credentials, which are made available only as needed during their time on the study.

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The investigator-sponsor will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted Form FDA 3500 A, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s)
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators;
- Curriculum vitae (investigator-sponsor and clinical protocol sub-investigators);
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for investigator-sponsor and listed sub-investigators;
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol;
- Laboratory certification information;
- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Decoding procedures for blinded trials;
- Master randomization list;
- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by investigator-sponsor;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of investigator-sponsor correspondence to sub-investigators, including notifications of adverse effect information;

- Subject screening and enrollment logs;
- Subject identification code list;
- Investigational drug accountability records, including documentation of device disposal;
- Interim data analysis report(s)*;* and the
- Final clinical study report.

Data in ARREST are entered using the REDCap data entry system and stored in secure files at the Statistical and Data Coordinating Center (SDCC). Patients are identified ONLY by an anonymized alphanumeric patient ID (PID): an example would be mu40238. The SDCC does not receive or store any participant names, SSNs, hospital numbers, or other identifying information. No directly identifiable regarding participants will appear in any reports, publications, presentations, or other disclosures of clinical study outcomes in the ARREST trial. Access to any participant data stored in SDCC.

The University of Minnesota Data Coordinating Center (SDCC) will provide web-based HTML forms, implemented using REDCap (Research Electronic Data Capture) software, to collect necessary information from the participating study sites. Web entry forms will have dynamic features such as immediate checks on data and relationships within a form and between forms. Details and clarification about data items will be provided using pop-up windows and links to appropriate sections of the on-line version of the Manual of Operations. Data encryption and authentication methods will be used. The SDCC will build additional features into the web entry forms including: forms transmission history, access to past forms, tracking of data corrections, and the capability to save and re-load incomplete forms. The central data management system will be ORACLE, which has been used by studies at the Coordinating Centers for Biometric Research (CCBR) for over 30 years. CCBR staff have developed methods for importing data from REDCap into ORACLE, with capability for sophisticated, comprehensive edits using utilities developed at the CCBR. The ORACLE Database Management System (DBMS) includes daily off-site backup of all files. Access to the database will be password-protected and permissions granted only to ARREST data coordinating center staff. Data analyses will be carried out using SAS (version 9.3 or later) or R (version 3.2 or later).

All data files are backed up to a remote location on a daily basis, and can be restored by designated data management personnel in case of system failures or power outages. Access to our system by unauthorized entities is closely monitored. The REDCap system automatically includes a data dictionary and complete specifications with regard to data type (e.g., numeric, character, dates, ICD-10 codes, other).

The investigator-sponsor will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IDE have been discontinued and the FDA so notified.

Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

10.1.6.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (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 study intervention. 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.

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH 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 GCP:

- 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 investigator to use continuous vigilance to identify and report deviations depending on the classification of the deviation within the required number of days. All deviations that *may affect* the subject's rights, safety, or welfare, and/or the completeness, accuracy and integrity of the study data must be addressed in study source documents, and reported to the NHLBI Program Official and Data Coordinating Center. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.8 PUBLICATION AND DATA SHARING POLICY

The dataset will be prepared in accordance with requirements for National Heart, Lung, and Blood Institute (NHLBI) data repository datasets and associated documentation for submission to the Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) and the NHLBI Policy for Data Sharing from Clinical Trials and Epidemiological Studies, and in accordance with the Guidelines for NHLBI Data Set Preparation. Diagnostic information on adverse events and deaths will be efficiently classified per ICD10-CM (International Classification of Diseases, 10th Revision, Clinical

Modification; https://www.cdc.gov/nchs/icd/icd10cm.htm) via REDCap's internal link to the BioPortal (https://bioportal.bioontology.org/) maintained by the National Center for Biomedical Ontology (NCBO). The REDCap interface, storage, and export formats facilitate adherence to the Study Data Tabulation Model (SDTM; https://www.cdisc.org/standards/foundational/sdtm), as prescribed by the Clinical Data Interchange Standards Consortium (CDISC; https://www.cdisc.org/). The set of REDCap data projects involved in the trial, including metadata such as data dictionaries and uploaded documents/files to support the study (for example, ECGs), will be assembled and exported from REDCap in XML (Extensible Markup Language) format, consistent with guidelines on file structure prescribed by CDISC/SDTM.

10.1.9 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, 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 design and conduct of this 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.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

ACLS	advanced cardiac life support
AE	Adverse Event
AED	automated external defibrillator
AKI	Acute Kidney Injury
CABG	Coronary bypass grafting
CCL	cardiac catheterization laboratory
CFR	Code of Federal Regulations
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
CRF	case Report Form
DNAR	Do not attempt resuscitation
ED	emergency department
DSMB	Data safety monitoring board
ECG/EKG	Electrocardiography
ECPR	extracorporeal cardiopulmonary resuscitation
ECMO	extracorporeal cardiopulmonary mechanical oxygenation
ELSO	extracorporeal life support organization

EMS	emergency medical service
EMT	emergency medical technician
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IABP	Intra-aortic balloon pump
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive care unit
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
JAMA	Journal of the American Medical Association
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary of Regulatory Activities
MODS	Multiple organ dysfunction syndrome
MOP	Manual of Procedures
MRC	Minnesota Resuscitation Consortium
mRS	modified Rankin Scale score
N	Number (typically refers to subjects)
NCT	National Clinical Trial
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, HHS
NIH	National Institutes of Health
N-STEMI	no ST-segment elevation myocardial infarction on 12-lead ECG
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, HHS
OHCA	out-of-hospital cardiac arrest
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PCI	percutaneous coronary intervention
PEA	pulseless electrical activity
PI	Principal Investigator
QA	Quality Assurance
ROSC	return of spontaneous circulation
SAE	Serious Adverse Event

SMC	Safety Monitoring Committee
SDCC	Statistical and Data Coordinating Center
UP	Unanticipated Problems
US	United States
VF	ventricular fibrillation
VT	ventricular tachycardia
WHO	World Health Organization

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.3	04/02/19	Remove AE collection	We will collect all SAEs which have established clinical interventions that support trial out-comes.
1.3	04/02/19	Added “posterior” probability	Adds Clarity around stopping rules
1.3	04/02/19	Updated section 10.1.6	Clarity and accuracy

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APPENDIX A: EFIC PLAN

Advanced **R²E**perfusion **ST**rategies for Refractory Cardiac Arrest (The **ARREST** Trial)

Waiver of Informed Consent Requirements in certain Emergency Research

Plan for fulfillment of the requirements of 21 CFR 50.24

INTRODUCTION

The goal of this document is to provide a logistical outline for the implementation of the additional protections associated with 21 CFR 50.24, Waiver from Informed Consent Requirements for Emergency Research as related to the ARREST study. The implementation of this plan is the first phase of conducting the proposed trial and the data acquired from the planned activities will be presented to the IRB to assist in the deliberations regarding the approval process for the study to take place. Additional resources may be requested to assist in review of this plan and are available from the Principal Investigator, Demetris Yannopoulos MD.

Refractory VF/VT is a spectrum of timing of return of spontaneous circulation (pulses) in response to standard ACLS treatment ranging from return of pusles shortly after the third failed shock (as defined in this protocol) to never. In any individual case, it is impossible to determine where along this continuum the patient may ultimately fall. For patients who will never obtain a pulse, science supports the contention that the sooner ECMO is initiated the potentially better the outcome. [11, 37, 40, 41, 44, 59, 60] In order to achieve early administration of ECMO from OHCA, it is necessary to begin mobilization from the scene to the hospital immediately following the third failed shock and enter the patient in the study immediately after determination of eligibility and randomziation following hospital arrival.[39] Accordingly, science supports the defintion of a therapeutic window for this study as initiation of the study intervention (e.g. implementation of one of two standards of care) as soon as possible. [11, 37, 39, 40, 41, 44, 59, 60] For patients who will never obtain a pulse, even several minutes delay may make the difference between an outcome of life or death.

At the same time, for those patients who might obtain a pulse in response to standard ACLS treatment later along this continuum may avoid the need for ECMO and it's attendant complications and cost. Early administration of ECMO precludes knowing who may have obtained pulses with continued standard ACLS treatment without the need for ECMO intervention. Studies to date[10, 24, 42, 43] and experience with the Minnesota Resuscitaton Consortium Refractory VF/VT protocol[11. 59, 60] indicate that

for patients who obtain a pulse but require ECMO, the sooner ECMO is initiated the potentially better the outcome and that there is potential benefit for initiation of ECMO following out-of-hospital cardiac arrest of up to 90 minutes from 911 call.[10,11,24,42,43,59,60]

Research involving cardiac arrest patients presents an ethical dilemma. Protecting patient autonomy through the informed consent process is one of the cornerstones of ethical research. Because the ARREST cardiac arrest patients will be unconscious throughout the time needed to be randomized with ongoing CPR, they will be *unable to provide informed consent*. Refractory cardiac arrest represents one of the most desperate and urgent medical conditions possible. Because the therapeutic window for this study is absent, defined as implementing the study intervention (e.g. implementation of one of two standards of care) as soon as possible, acquisition of informed consent will not be possible. Further, any delay to initiation of the study intervention for either group constitutes a direct risk to potential patient survival. Therefore, the patient will be randomized under FDA regulation 21 CFR 50.24, exception from informed consent under emergency circumstances. Attempts to contact an LAR in this circumstance will be documented. Researchers will have a brief notification script approved by the IRB and will attempt to notify the LAR/family members when feasible.

APPLICABILITY OF WAIVER (21 CFR 50.24) TO THE ARREST TRIAL

The ARREST trial is going to be under the auspices of the FDA and therefore, ARREST falls under the Waiver guidelines.

> ***1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions***

The proposed trial randomizes patients with refractory VT/VF cardiac arrest that arrive at the University of Minnesota Emergency Department to receive either: 1) early ECMO-facilitated resuscitation and CCL access for ECMO, diagnostic angiogram and possible PCI, or 2) standard ACLS resuscitation at least 15 minutes of emergency department-based resuscitation, followed by CCL access for ECMO, diagnostic angiogram and possible PCI if ROSC has been achieved or death is declared. Observational data implies an approximate 80 % incidence of acute coronary occlusion and ischemic heart disease in cardiac arrest patients with refractory VT/VF cardiac arrest. Therefore, there may be significant potential survival benefit with immediate CCL admission with ECMO, mitigating the need for ROSC to identify and treat the potential reversible cause of the refractory arrest. However, observational results are subject to selection bias and other unmeasured confounders. No definitive randomized trial has ever been performed. We propose a single center randomized trial focused on evaluation of these two standards of care in the refractory VT/VF cardiac arrest population, with sufficient statistical power to detect differences in functionally favorable survival.

> *2****. Obtaining informed consent is not feasible because; the subjects will not be able to give their informed consent as a result of their medical condition; the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.***

This study qualifies for exception from informed consent required for emergency research as outlined in FDA regulation 21 CFR 50.24. Treatment of refractory cardiac arrest must begin immediately if there is any hope for survival. In this setting, by definition, the patient will be unconscious and/or unable to participate in the informed consent process. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available, nor is it likely possible for the hospital provider to explain the study and acquire informed consent while caring for the patient, any delay of which could directly compromise patient care and outcome. Since we are studying patients with refractory cardiac arrest, which is frequently the first manifestation of cardiovascular disease, there is no way to prospectively identify individuals who are likely to become eligible for this trial. Taken together, these issues provide sufficient support for an exception from consent in order to evaluate an intervention that holds potential benefit to this patient population.

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

Both strategies in this trial offer potential direct benefit for the patients by providing the prospect of early reversibility of acute or severe chronic coronary artery disease. Identification and reversibility of the cause of the arrest holds potential to provide better outcomes.

4. Subjects are facing a life-threatening situation that necessitates Intervention.

As defined, patients with refractory cardiac arrest are facing an immediately life-threatening situation that requires emergency intervention.

5. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

Both treatment strategies evaluated in this study are associated with potential risks and potential benefits and are well -established practices in Minneapolis/St Paul. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal and the currently dismal outcome for patients with refractory out-of-hospital cardiac arrest.

6. The clinical investigation could not practicably be carried out without the waiver.

Treatment for refractory cardiac arrest must begin immediately if there is any hope for survival. In this setting, the patient is most often unconscious and unable to provide consent for study enrollment. Legal next-of-kin are often not available during emergency department stabilization, treatment, and disposition. Since we are studying out-of-hospital cardiac arrest, which is frequently the first manifestation of cardiovascular disease, there is no way to prospectively identify individuals who are likely to become eligible for this trial.

7. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

For patients who will never obtain a pulse, science supports the contention that the sooner ECMO is initiated the potentially better the outcome. [11, 37, 40, 41, 44, 59, 60] In order to achieve early administration of ECMO from OHCA, it is necessary to begin mobilization from the scene to the hospital immediately following the third failed shock and enter the patient in the study immediately after determination of eligibility and randomziation following hospital arrival.[39] Accordingly, science supports the defintion of a therapeutic window for this study as initiation of the study intervention as soon as possible. [11, 37, 39, 40, 41, 44, 59, 60] For patients who will never obtain a pulse, even several minutes delay to initation of ECMO may make the difference between an outcome of life or death.

At the same time, for those patients who might obtain a pulse in response to standard ACLS treatment later along this continuum may avoid the need for ECMO and it's attendant complications and cost. Early administration of ECMO precludes knowing who may have obtained pulses with continued standard ACLS treatment without the need for ECMO intervention. Studies to date[10, 24, 42, 43] and experience with the Minnesota Resuscitaton Consortium Refractory VF/VT protocol[11. 59, 60] indicate that for patients who obtain a pulse but require ECMO, the sooner ECMO is initiated the potentially better the outcome and that there is potential benefit for initiation of ECMO following out-of-hospital cardiac arrest of up to 90 minutes from 911 call.[10,11,24,42,43,59,60]

Thus, we expect it will not be feasible to attempt to obtain informed consent during the absent, initial therapeutic window. Nonetheless, whenever feasible, we will attempt to contact the LAR or family member within the therapeutic window and ask whether he or she objects to the subject's participation in the investigation. We will make every effort to contact legal representatives after completion of their randomized treatment to notify them that the patient was enrolled in a randomized trial. Research personnel will attempt to contact the subject's LAR as soon as feasible and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period then he/she will be approached by research personnel for notification of enrollment.

ADDITIONAL PROTECTIONS

The 5 additional protections associated with conducting a trial under 21 CFR 50.24 (and 45 CFR 46) are the following:

1. Community Consultation
2. Public Disclosure before the trial – including methods by which patients can "opt-out" or refuse participation in the trial
3. Public Disclosure after the trial
4. Plan for contact of Legally Authorized Representatives (LAR) or family members to seek informed consent for the patient's participation in the trial prior to randomization, if feasible, or after enrollment as soon as possible when feasible.
5. Formation of a Data Safety Monitoring Board to oversee the trial

The plan for each of these activities will be discussed in detail. The regulatory language is included for convenience and reference as well as some text taken from the FDA Guidance document (April 2013) that offers an interpretation of the regulations to assist investigators, sponsors, and IRBs.

COMMUNITY CONSULTATION

The federal regulations for community consultation state:

> *Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) Consultation (including where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.*

The goals of community consultation are the following:

1. To ensure that all relevant communities have the opportunity for input into the IRB's decision-making process before initiation of the study.
2. To present information so that community members understand the proposed investigation, its risks & benefits, and to discuss that the investigation will take place without informed consent.

Community consultation is not community consent for the trial to take place. If community consultations were viewed as community consent, this would imply that the information came from a large proportion or essentially all the members of the community as opposed to individuals who are thought to be representative 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 the information obtained from the community consultation. For the purposes of waiver (and EFIC), the definition of communities are "the community in which research will take place," which includes the geographic area where the hospital or study site is located, and the "community from which subjects will be drawn," which includes the group of patients who share particular characteristics (i.e. patients with the disease of interest or those "at-risk" for the disease or condition of interest).

The **content** of community consultation will inform the communities that informed consent will not be obtained for most (or all) research subjects. Specifically, the goal will be to:

- Inform the communities about all relevant aspects of the study including its risks and expected benefits
- Hear the perspective of the communities 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 community (ies) 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 community (ies), the languages spoken within those communities, the targeted research population and its heterogeneity

Description of the ARREST Network

ARREST will be conducted at the University of Minnesota Medical Center.

The clinical coordinating center for this trial is the University of Minnesota (U of M); patients will be enrolled at the U of M. The University of Minnesota has a long history of successful engagement in acute resuscitation research and is also well versed in application of the Waiver of Informed Consent Requirements that will be needed for the ARREST trial.

We are seeking to conduct ARREST under 21 CFR 50.24 and will include patients who present with refractory ventricular fibrillation (VF) out-of-hospital cardiac arrest and subsequently are transported to the University of Minnesota based on established protocols

Development of study presentation materials

Templates for materials for community consultation (e.g. focus group script, interview, surveys, and other educational materials) and public notification will be developed by the ARREST study team, which has significant prior experience conducting community consultation and public disclosure activities. Material presented for community consultations will include: a) background information on cardiac arrest, b) current lack of effectiveness in the treatment for cardiac arrest, c) profile of typical cardiac arrest patients, d) protocol description, e) experimental intervention rationale, f) randomization definition, g) potential study risks, h) potential study benefits, i) differences between research and treatment, j) rationale for waiver of from informed consent, and k) the ethical constructs of Waiver of informed consent. The PI or a research team designee will be available at all community consultation activities to answer questions and hear concerns regarding the project.

The requirements of Waiver also include informing the community that a research project will be done that may impact members of the local population. This public disclosure will be made prior to the initiation of the project and after the project is completed. The content of the public disclosure messages will include a) the nature of the trial and that it involves victims of cardiac arrest; b) the trial involves waiver of informed consent under emergency circumstances; c) the trial involves specific potential risks and benefits; and d) contact information on where to receive answers to concerns or questions as well as further information. The types of public disclosure and their content will be determined by the PI's at each site and local IRBs; the suggestions listed here are consistent with the public notification content suggested by the FDA's 2013 guidance document.

If a local IRB determines the need for unique community Waiver activities, the ARREST team will assist the local institutions' site investigators in developing appropriate materials and processes.

Methods and Activities

Community consultation will occur prior to study commencement. Various methods of consultation will be used. Consultation will include participants who represent potential study patients (the Targeted Population) and others who represent the Geographic Population where the study is to occur. Options and processes for Community Consultation are described;

TARGETED FOCUS GROUPS

To represent the targeted study population, we will conduct focus groups with approximately 10-15 participants in each group. All groups will consist of patients or family members of patients who have had myocardial infarctions, cardiac arrests, or are at significant risks of a cardiac arrest. We will approach these individuals in the emergency department, cardiology clinics, at events sponsored by the local patient advocacy groups and survivor support groups to offer them the opportunity to participate in one of the proposed focus groups. Participants will be compensated for parking fees and childcare, if needed. Focus groups may be developed within the context of pre-existing meetings (such as survivor support groups) or from a broader solicitation of participation (for example, through ads on support group websites or clinic/ ED recruitment). Focus groups will be conducted until thematic saturation of concerns / questions is achieved; in general, this occurs after 5 groups of 8-12 members. Regardless, at least three focus groups of the targeted population will be conducted.

We will also conduct focus groups for health care providers to determine their knowledge and any concerns related to studies using Waiver, and in particular, the ARREST study. One focus group will be comprised of paramedics. Other focus groups will be comprised of (but not limited to) cardiology and emergency clinicians. These focus groups will likely occur at pre-existing meetings, such as faculty or staff meetings, and the number of participants will not be capped.

We will obtain written consent from the participants who participate in the focus groups and collect information about their basic demographics. In addition, if audiotaping is to be conducted, focus group facilitators will ask for verbal consent to audio- tape the focus group session prior to starting the discussion. This portion of the consent process will include a description of the confidentiality protections associated with the focus group discussion; each participant will receive up to $20 in compensation to cover the costs of travel, parking, and childcare in order to attend the focus group session. Light refreshments may be provided at each focus group session.

The presentations at the focus groups will be loosely scripted to allow for a fluid discussion, but will include information about research in general, Waiver, and ARREST, as described above. After the opportunity to discuss each of the research concepts, participants will be asked their opinions about clinical research scenarios. These are designed to explore attitudes related to emergency research in general and emergency research without consent.

Each focus group will meet for approximately 1 to 2 hours. An IRB member will be invited to observe the focus group discussions. Participants will be asked to complete an evaluation form at the end of the focus group discussion. A study packet containing basic information about cardiac arrest and Waiver will be distributed to all participants, and they will be given information about how they may “opt-out” of participating in the trial should they present to the Emergency Department with a refractory cardiac arrest during the study period. Results of the focus group will be summarized and presented to the IRB upon completion of this activity.

GEOGRAPHIC COMMUNITY CONSULTATION

Representatives of the geographic community will also be invited to attend community meetings that may include focus groups or more general gatherings of pre-existing representative groups, such as local community meetings, church groups, school functions, and club meetings. These 1 to 2 hour community meetings/focus groups will aim to include: a) community leaders, b) representatives of community organizations, and c) the general public. A variety of community organizations and individuals will be invited to participate in these community consultation activities, with participation solicited through the

existing group communications. In order to ensure an adequate number of participants, but not so many as to hamper the two- way exchange of information, community and group leaders will be enlisted to assist in populating the community consultation activities. Organizations will be selected to match, as closely as possible, cardiac arrest subject demographics, including race, age and gender. They will represent stakeholders in the issue of cardiac arrest and will have substantially different backgrounds, expertise and interest in the topic.

SURVEY METHODS OF COMMUNITY CONSULTATION

Based on our experience with EFIC trials, we believe that a well-crafted structured survey is an effective method of community consultation if the survey mimics an interview, if the interviewer has sufficient knowledge and background to answer specific protocol - and research -related questions, and the research leadership team is available for consultation as needed. Our experience has taught us that respondents are better able to understand complex research concepts (such as randomization and placebo) and consenting mechanisms (surrogates, EFIC), when very specific examples are given. We will use our previous experience and the results of the focus groups to fashion a survey that will be used to solicit community consultation about ARREST.

Potential methods to include surveys in community consultation include;

A. Face to face interviews/surveys at Cardiology clinics – community at risk

We will ask patients in the cardiology clinic waiting rooms and their family members to participate in our survey. They will be asked to identify themselves as a cardiac patient or another high-risk group (for example, congestive heart patients) .We will obtain verbal consent for survey participation. We will ensure that survey participation does not interfere with patient care. Each survey will take approximately 10-15 minutes to complete and will be delivered by a trained research associate (RA) under the supervision of the study team.

B. On line surveys of Advocacy Groups – community at risk

The Minnesota Chapter of the American Heart Association will be approached to solicit assistance to link our ARREST/Waiver survey with their website and will collaborate with them to help recruit participants for a focus group meeting and to complete surveys. The website will include a survey hotline, where community members can contact ARREST researchers for additional information or clarification of survey questions or the study.

C. Face to face interviews/surveys in the Emergency Department – geographic population, ethnic minorities, and at- risk populations

We will approach stable patients in the ED and their families. We will not interfere with the patients' medical care. Members of the study team will identify potential survey participants from the ED electronic patient tracking board. A study team member or research associate will approach the patient or family member to see if they are willing to complete the survey. If the patient/family member agrees, the study team member or RA will obtain verbal informed consent and proceed with conducting the interview. Each survey will take approximately 10-15 minutes to complete. Because we will conduct these surveys during the patients' ED visit, we will not provide compensation for any expenses incurred. We will perform this survey at various times of the day and on different days of the week to ensure that this sample is representative of the community of individuals that utilize the study hospital ED. We will also include targeted surveys of ethnic minorities. Our experience with other studies has shown that larger broad venues (i.e., the Minnesota State Fair), while representative of the overall state population, include few respondents who are minorities and who are members of lower socioeconomic

groups. To reduce this bias we will include as many emergency department and clinic patients as possible from public and county hospitals and clinics, who traditionally fall into lower socioeconomic groups and who disproportionately represent racial and ethnic minorities.

Opt-Out

During each community consultation event, and in public disclosure efforts, instructions will be given on how to inform the study team of the desire to opt-out of the ARREST trial. Community members who can be identified as having opted-out will not be enrolled in the study. They will be given an opt-out bracelet to indicate their preference not to be enrolled.

IRB ACTIVITES AND REVIEW

The IRB may choose to appoint an IRB member to oversee community consultation activities. This IRB liaison will be invited to attend the focus group sessions and all other community consultation activities, and may provide an in-depth review of the results obtained. An example of proposed community consultation activities that could be performed are described in Table One.

Table 1. Summary of potential community consultation planned activities

Group	Description	Materials
Individuals with the condition of interest or at risk individuals	At least three **Focus groups** of at-risk persons (i.e., cardiac patients) each with approximately 10-15 participants will meet at the institution or other public forums within the context of support groups -At the University of Minnesota, the groups will be drawn from the following options: other participating sites may elect to use information from these groups or to conduct their own community consultation activities and target different community representatives. MN Sudden Cardiac Arrest Survivors Network ANW Women's Heart Group Mercy Cardiac Rehab White Bear Lake Heart Safe - MN State Advocacy Group - AHA Cardiovascular Health Alliance Group - MN Dept of Health MN Resuscitation Consortium (MRC)Bystander Committee MRC Advisory Committee (professionals) Additional professional health care provider **focus groups** 50-100 **surveys** will be conducted at the cardiology clinics	Power point presentations, Verbal and written informed consent script audio (or video) tape and recorder, feedback forms, information on Opt Out Option Surveys after one on one discussion about the ARREST and Waiver of Informed Consent

Individuals in the geographic area	Existing group meetings PTA, church groups Etc. 50-100 **surveys** to be conducted in the HCMC ED	Power point presentations, Verbal and written informed consent script audio (or video) tape and recorder, feedback forms, information on Opt surveys after one on one discussion about the ARREST and Waiver of Informed Consent

PUBLIC DISCLOSURE BEFORE AND AFTER THE TRIAL

Objectives of Public Disclosure– applies to both before and after the trial

The requirements of 21 CFR 50.24 include informing the community of the performance of a research study that may impact members of the local population. Public disclosure will be done prior to the initiation of the project and after the project is completed. The content of the public disclosure messages will be derived in conjunction with the local IRBs and implemented following IRBs' approval of the public disclosure plan.

Public Disclosure requirements state:

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 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 most subjects

- Information about the interventions 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

Development of study presentation materials

Methods of announcing information about the trial and the development of advertising and other materials about the trial will take place both locally and at the other parent sites. Standard materials for use in public disclosure activities will be developed by the U of M coordinating center and local study team members and approved by the local IRB. The local study team will coordinate local public disclosure efforts with local public relations office as appropriate. Public service announcements, press releases, paid print and broadcast advertising, community access cable TV, postings in existing hospital and community publications and mailings, social media, and other modalities will be considered as well.

CONTENT OF PUBLIC DISCLOSURE
It is impossible for a single public announcement or disclosure method to include all information that is found in the informed consent documents, the investigator's brochure, and the research protocol. We propose that the following are the most important issues for community understanding: a) the nature of the trial and that it involves victims of cardiac arrest; b) the trial involves exception to informed consent under emergency circumstances; c) the trial involves specific potential risks and benefits; and d) contact information on where to receive answers to concerns or questions as well as further information. The types of public disclosure and their content will be determined by the PI's at each site and local IRBs.

DOCUMENTATION AND IRB REPORTING
Investigators will document all inquiries from the public or interested parties on an Initial Public Notification Feedback Form. E-mail questions, comments, and feedback will also be documented. Investigators will collate and report results to the IRB before the start date of the study.

Methods and Activities – Public Disclosure (Table 2: examples of Public Disclosure activities)

COMMUNITY AND IN-HOSPITAL ACTIVITIES
Prior to the start of the trial, the site Principal Investigator or designee will present the proposed study to Cardiology, Internal Medicine, Critical Care and Emergency Medicine residents, faculty, and staff as appropriate.

If allowed by these various entities, brochures, posters, and flyers, will be displayed in the Emergency Department, the Cardiology Clinic and the General Internal Medicine Clinic before and during the trial. These materials will provide a description of study, local contact numbers, study website address, and opt-out information. It will indicate that the study will be conducted with Waiver. All materials will be reviewed by the IRB for approval prior to dissemination.

Pending approval by the Public Relations Department of each institution, an announcement will be made on the institutional intranet informing hospital staff of the proposed trial. Contact information for the site Principal Investigator and study personnel will be provided in the announcement. An email announcement of the trial will also be made to the faculty and staff of relevant clinical departments.

The site Principal Investigator and Study Coordinator will provide study training sessions for the emergency clinicians who will be identifying potential patients in the ED. The investigators will also train the Attending/Fellow physicians and nurses who treat cardiac patients within each institution. Study updates will periodically be provided to these providers by email or in person.

KEY COMMUNITY CONTACTS
The investigators will work with the local chapters of the American Heart Association to develop information for public notification aimed at the general public about ARREST and Waiver, and will ask permission to post this information on their website as part of a public disclosure method. Many institutions sponsor support groups for survivors of cardiac arrest or other cardiac pathologies. These meetings present a great opportunity for distribution of public disclosure materials.

Information about cardiac arrest, the ARREST study and Waiver will be distributed to those who choose not to participate in interviews/surveys.

MEDIA ANNOUCEMENTS
With the assistance of their PR offices, investigators will develop and publish public media announcements in local outlets with broad reach. The content of these announcements will mirror those items listed above and will appear before and intermittently during the duration of the trial. The content of media announcements will be first approved by the IRB.

Table 2. Summary of Potential Public Disclosure Activities

Activity	Description	Content	Date/Time/Frequency information (if applicable)
Posters, brochures, flyers	Posters displayed in EDs and Clinics(if permitted) Brochures and flyers available in ED and Clinics	• Description of study • Local contact numbers • Website addresses • Opt-out information	Available prior to start of trial and throughout trial Flyers available after trial to disclose study results
Internal Announcements	Presentation to cards /CCU and ICU/ ED faculty and staff Announcement on hospital intranet Email announcements to hospital personnel	• Description of study • Local contact numbers • Website addresses	Announcements made prior to start of trial, throughout trial, and after trial (to disclose results)
Websites	National and local websites (for patients and physicians)	• Description of study • Local contact numbers • Opt-out information	Available immediately after IRB approval and continuing throughout duration of trial

Key Community Contacts	Website announcements through Minnesota AHA Public notification at staff meetings	• Description of study • Local Contact numbers • Website addresses • Opt-out information	Prior to start of trial

Timeline for Community Consultation and Public Disclosure Activities

The community consultation activities will be conducted over the course of approximately 3 months. Public disclosure will be initiated prior to the start of the trial, will continue during enrollment, and will conclude with dissemination of study results after the trial is completed. The investigators plan to initiate public disclosure activities at least 4 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, which is anticipated to be within a 3 to 5 year timeframe.

Reporting of community consultation results will be provided by the study team to the IRB. Summaries of the data will be made available to the IRBs, and the U of M coordinating center.

The 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

All group discussions will be reviewed by the study team, and general themes will be summarized. The results of all local community consultation efforts will be summarized and submitted to IRBs. If appointed and if present at community consultation activities, an IRB liaison will provide an in-depth review of the discussions and additional feedback to the IRB as needed. Summaries of responses from 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 subjects who learn of the trial through public disclosure efforts or other means, and who would not want to participate to communicate that decision to treating physicians without causing any delay in treatment. This will be indicated by Opt-Out medic alert bracelets available from the study team that will say “ARREST declined.”

Contact of an LAR or family member

The federal regulations for contact of a Legally Authorized Representative (45 CFR 46 and 21 CFR 50.24) state:

21 CFR 50.24

(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.

Refractory cardiac arrest represents one of the most desperate and urgent medical conditions possible. For both patient groups, science supports the defintion of a therapeutic window for this study as initiation of the study intervention as soon as possible. [11, 37, 39, 40, 41, 44, 59, 60] Since the patient is in a refractory and immediately life-threatening situation, care must not be interrupted or compromised, and the study intervention must be initiated as soon as possible if there is any chance for survival. Thus, it will not be feasible to attempt to obtain informed consent prior to randomization. Nonetheless, whenever feasible, we will attempt to contact the LAR or family member within the therapeutic window and ask whether he or she objects to the subject's participation in the investigation. We will make every effort to contact legal representatives after completion of their randomized treatment to notify them that the patient was enrolled in a randomized trial. Research personnel will attempt to contact the subject's LAR as soon as feasible and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period then he/she will be approached by research personnel for notification of enrollment.

Post enrollment disclosures

POST ENROLLMENT NOTIFICATION
If the subject is unable to comprehend a request for continued participation after Waiver enrollment, or the subject dies after enrollment, the investigator must attempt to inform the family members and or a legally authorized representative (LAR). Since survival to hospital discharge following cardiac arrest is <20%, investigators anticipate the majority of their efforts will be attempting to contact family members or LARs.

For enrolled subjects who die in the ED or the hospital, investigators will first attempt to notify a legally authorized representative of the subject. If such a representative is not reasonably available, a family member will be notified of the subject's inclusion, the details and other pertinent information regarding the study. Notification will occur either by attempting up to two phone calls to the subject's family or sending two letters to the subject's address (as listed on the EMS run report form, hospital chart information or telephone directory). Research team members will document all efforts to contact patients and their family members and maintain records according to the same process followed for all other record keeping during the study. Telephone discussions and letters will fully inform the subject's representatives of the nature of the research project, the goals and objectives, the study protocols, the details of the Waiver regulations, and the information on the community consultation and public notification that occurred. Subject notification in each case will be documented and will become a permanent part of the study record.

For subjects who appear to have no relatives or persons responsible (e.g., homeless), investigators will make every reasonable effort, including working with the County Medical Examiner, law enforcement and hospital personnel to help identify a next-of-kin for unidentified deceased subjects so that they may be notified.

POST STUDY DISCLOSURE OF RESULTS
Disclosure of study results will be made both locally and nationally. The study results will be announced on local websites and Health System website, in emails, letters to hospital personnel, community physicians, the AHA. Press releases will be coordinated by the coordinating center at U of M. The study results will also be disclosed through peer-reviewed journals and presentations at national meetings.

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. The investigators will include this information on the brochures and posters for public disclosure. The coordinating center will provide medical alert bracelets or tags with the words "ARREST declined" to those individuals who decide to refuse participation in the trial once admitted to the hospital.