

# Protocol

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Protocol for: Stiell IG, Nichol G, Leroux BG, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med* 2011;365:787-97.



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# **Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance valve and Early vs Delayed analysis (ROC PRIMED) Trial**

**Title: A Factorial Design of An Active  
Impedance Threshold Valve versus Sham  
Valve and  
Analyze Later versus Analyze Early**

Abbreviations commonly used in this protocol:

ACLS	advanced cardiac life support
AED	automated external defibrillator
CPR	cardiopulmonary resuscitation
DCC	data coordinating center
ED	emergency department
EMS	emergency medical services
EMT	emergency medical technicians
ICU	intensive care unit
PEA	pulseless electrical activity
RCC	regional coordinating center
ROC	Resuscitation Outcomes Consortium
ROSC	resumption of spontaneous circulation
VF	ventricular fibrillation

## Table of Contents

1. Factorial Study Summary.....	3
2. Impedance Threshold Device Trial .....	6
Study Summary.....	6
Specific Aims.....	7
Background and Significance.....	7
Conceptual Framework for ITD .....	7
Preliminary Studies .....	8
Choice of Intervention .....	11
Summary of Rationale.....	11
Research Design and Methods.....	11
Experimental Design .....	11
Study Episodes .....	11
Study Population .....	11
Inclusion Criteria.....	11
Exclusion Criteria .....	12
Primary Comparison Population.....	12
Intervention .....	13
Random Allocation .....	13
Intervention–Compliance .....	14
Outcome Measures.....	14
Primary .....	14
Secondary .....	14
In-Hospital Morbidity.....	14
Prespecified Subgroup Analyses .....	14
Expected Adverse Events .....	14
Analyses.....	16
Sample Size and Study Duration .....	19
Human Subjects.....	22
Risks to Subjects.....	22
Inclusion of Women or Minorities .....	22
Inclusion of Children.....	22
3. Analyze Later versus Analyze Early.....	23
Study Summary.....	23
Specific Aims.....	24
Background and Significance.....	24
Conceptual Framework for Analyze Later.....	24
Summary of Rationale.....	27
Research Design and Methods.....	28
Study Design Overview .....	28
Study Population .....	28
Inclusion Criteria.....	28
Exclusion Criteria .....	28
Primary Comparison Populations.....	28
Random Allocation .....	29
Intervention .....	30
Adherence to Protocol.....	30
Outcome Measures .....	31
Primary .....	31
Secondary Outcomes.....	31

In-Hospital Morbidity.....	31
Sample Size, and Study Duration .....	34
Effect of Clustering and Crossover Upon Required Sample Size .....	36
4. Factorial Implementation of Both Protocols .....	38
Summary.....	38
Study Population.....	39
Except for some specific situations, the inclusion and exclusion criteria for both ITD and Analyze Later protocols will be the same.....	39
Inclusion Criteria.....	39
Common Exclusion Criteria.....	39
Resuscitation Guidelines.....	39
Monitoring of CPR Process.....	39
Outcome Measures.....	41
Primary.....	41
Secondary .....	41
In-Hospital Morbidity.....	43
Other Outcomes.....	43
Data Collection.....	43
Data Forms .....	43
Source of Data Collection .....	43
Data Entry .....	44
Database Management.....	45
Training .....	45
Overview .....	45
<i>Optimal CPR Performance</i> .....	45
<i>Scientific Basis for ITD and Analyze Later Protocols</i> .....	45
<i>Study Protocols</i> .....	45
<i>Protocol Practicum</i> .....	47
<i>Cognitive post-test</i> .....	47
<i>Run-in Phase</i> .....	47
DSMB and Monitoring Strategy.....	47
Human Subjects.....	48
Protection Against Risks .....	48
Recruitment and Informed Consent .....	48
References.....	54

## 1. Factorial Study Summary

### Background

Little is known about how to optimize resuscitation for patients with out-of-hospital cardiac arrest. This is evident from the very low survival rates that are currently reported. The advent of automatic external defibrillators (AEDs) and their potential for wide-spread use by less highly trained emergency medical service (EMS) providers and lay persons has not resulted in the substantial increased survival rates anticipated. This has led to speculation that more and sooner circulation of oxygenated blood to the brain and heart may be important. Resuscitation Outcomes Consortium (ROC) Investigators propose a large clinical trial, using a factorial design, to test two strategies to increase blood flow. One strategy involves the impedance threshold device (ITD), which enhances venous return and cardiac output by increasing the degree of negative intrathoracic pressure during decompression. The second involves initiating resuscitation with a period of manual compressions and ventilations (Analyze Later), rather than attempting defibrillation immediately (Analyze Early).

### Rationale

The rationale for the factorial design is based on several arguments.

- Most importantly, both interventions are worthy of study in their own right. Both interventions were proposed by several of the participating ROC sites in their initial applications.
- A number of ROC EMS agencies currently use cardiopulmonary resuscitation (CPR) first (i.e., Analyze Later) as their standard protocol, whereas others analyze the rhythm and shock as required before initiating CPR (i.e. Analyze Early.) Thus, if the ITD intervention were to be studied alone, we would be faced with an uncontrolled heterogeneity of practice, possibly changing during the course of the trial. This would necessitate, at a minimum, stratifying by the EMS protocol.
- We anticipate no substantial interactive effect between these two interventions. One relates to when assisted circulation takes place, compared with when the defibrillatory attempt takes place. The other has to do with the quantity of flow during assisted circulation. Both include some blood flow prior to any defibrillation attempt.
- The infrastructures to conduct the two trials are virtually identical, thus assuring substantial efficiencies in costs, and virtually cutting in half the number of patients and the time needed to study the two interventions sequentially, providing there are no interactions between the interventions.

### Challenges

The factorial design poses three challenges:

- Implementation of two interventions may be difficult for the persons who must conduct these interventions; the emergency medical technicians and paramedics, who must perform their efforts under the duress of life-threatening emergent conditions. This potential challenge has been mitigated by adopting cluster randomization for the Analyze Later protocol, whereby each cluster will be randomized to either always doing CPR first (Analyze Later) or always doing rhythm analysis first (Analyze Early). These clusters will consist of geographic areas or monitor/defibrillators within the EMS agencies. EMS personnel will place an active or sham ITD on all patients meeting criteria. Hence, EMS

providers will always follow the same procedures: a) place an active or sham ITD on all patients, and b) analyze the rhythm either early or later consistently according to cluster randomization. No on-the-spot decisions regarding randomization will be required for use of either intervention.

- The cluster randomization will require that all out-of-hospital cardiac arrest events be accounted for. This requirement is actually beneficial, in that it provides additional motivation for the implementation of a comprehensive epidemiologic database of all life-threatening out-of-hospital events (what we have termed the ROC Registry). Whether the trial benefits from the Registry or the Registry benefits from the trial is unclear at this point and will depend in part upon the timing of various funding mechanisms.
- When a factorial design is used, there is an almost irresistible temptation to test for an interactive effect (i.e., risk difference for one factor depends on the level of the other factor). While a factorial design is the only reasonably efficient way of testing for an interaction between several interventions, to power the trial for the specific interaction effect generally requires a substantially increased sample size. As noted previously, we do not anticipate any substantial interaction between these two therapies. Nonetheless, potential interactions will be assessed by the DSMB at interim analyses and the sample size adjusted accordingly.

### **Potential Advantage**

It should be noted that the intervention of Analyze Later probably cannot be appropriately compared by randomizing individual episodes. The issues with compliance caused by the confusion of having an EMS provider alternate between the basic concept of aggressively doing CPR initially versus assiduously assessing rhythm and defibrillating initially can be easily appreciated. The choice of the cluster will vary depending upon the realities of training and the fluidity of personnel within an agency. All clusters will be encouraged, and large clusters will be required, to switch from Analyze Later to Analyze Early or vice versa at midpoint, or more often through the trial, thus serving as their own control.

### **Outcomes**

The trials share a common primary outcome, namely survival to hospital discharge with modified Rankin score  $\leq 3$ , and common secondary outcomes, namely survival to discharge as well as functional status at discharge and at 1, 3 and 6 months after discharge as well as depression at 3 and 6 months.

### **Design**

The trial will be factorial with one intervention based on a double-blind randomization of individuals through the use of an active versus a sham ITD (identical to the user), and the other intervention based on non-blinded randomized clusters.

### **Setting**

The trial will be conducted in all EMS agencies participating in the Resuscitation Outcomes Consortium.

### **Sample Size and Analysis**

Since we are not testing for an interaction, sample size for each intervention will be based on the traditional significance levels of .05 for two-sided and .025 for one-sided and a power of 0.9. Each will require approximately 16-18 months of enrollment. The

specific inclusion criteria, sample size, and analytic techniques are defined with each of the specific interventions.

### **CPR Performance**

Critical to understanding both interventions is the monitoring of CPR performance. All sites will implement procedures to attempt to collect 100% of data sources needed to assess CPR performance. Three performance measures will be abstracted: the ventilation rate, the compression rate, and the CPR fraction as defined in Appendix 2. It is known, based on the longstanding effort in Seattle, as well as more recent efforts in Chicago and Norway, that the data sources will be missing or incomplete in approximately 25% of episodes. Details for the CPR performance monitoring are dealt with in Section 4, since the process is applicable to both interventions.

### **Run-in Phase**

After personnel have been trained in use of the ITD and the methods for Analyze Later vs. Analyze Early according to their cluster randomization, they will initiate a run-in phase. Evidence of compliance with the protocol and completion and submission of the data will be required before the site can enroll in the active phase of the trial.

### **Anticipated Clinical Impact**

If the ITD demonstrates the hypothesized improvement in survival, we estimate that the premature death of approximately 2,700 victims of cardiac arrest<sup>1</sup> per year would be averted in North America compared to standard CPR. If the Analyze Later approach demonstrates the hypothesized improvement in survival, we estimate approximately 4,000 lives will be saved per year in North America. By implementing a factorial study design, these benefits to clinical practice can be achieved more efficiently and faster than otherwise would be the case.

### **Remainder of This Protocol**

The remainder of this protocol is split into three parts. The second section contains the materials specific to the ITD intervention. The third section contains the materials specific to the Analyze Later intervention. The fourth section contains materials common to both interventions and/or specific to the factorial design of the study.

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<sup>1</sup> Number of treatable cardiac arrests X Proportion of cases with non VF initial rhythm or VF that does not respond to initial shock X Absolute difference in survival i.e. (US population 295,483,056 X 0.53 per 1000 population (52) + Canadian population 31,127,234 X 0.57 per 1000 population (53)) X Absolute difference

## 2. Impedance Threshold Device Trial

### Comparison of Standard CPR Plus Active Impedance Threshold Device Versus Standard CPR Plus Sham Impedance Threshold Device In Patients With Out-Of-Hospital Cardiac Arrest

#### Study Summary

**Background:** Most patients with out-of-hospital cardiac arrest do not survive to hospital discharge. Survival after cardiac arrest is correlated with the time from its onset to the circulation of oxygenated blood to the brain and heart. Compression of the chest during cardiopulmonary resuscitation (CPR) increases intrathoracic pressure and compresses the heart. Decompression of the chest results in negative intrathoracic pressure, which enhances venous return and cardiac output. Collectively these actions circulate blood to the brain and heart. The impedance threshold device (ITD) is a novel respiratory device intended to increase the degree of negative intrathoracic pressure during decompression. Studies in animal models of cardiac arrest or small randomized trials in humans demonstrate that the ITD improves hemodynamics and short-term outcomes but it remains unclear whether ITD improves survival to discharge or neurological outcome. Therefore we propose a large clinical trial to test whether standard CPR supplemented by active ITD is effective compared to standard CPR supplemented by sham ITD.

**Aims:** The primary aim of the trial is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  between standard CPR plus active ITD versus standard CPR plus sham ITD in patients with out-of-hospital cardiac arrest. The secondary aims of the trial are to compare survival to discharge, functional status at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months.

**Hypotheses:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest. The secondary null hypotheses are that survival to discharge, functional status at discharge and at 1, 3 and 6 months after discharge as well as depression at 3 and 6 months will be identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest.

**Design:** Double-blind randomized controlled trial.

**Population:** Patients with non-traumatic out-of-hospital cardiac arrest, presumed to be local age of consent or greater and treated by EMS providers.

**Setting:** EMS systems participating in the Resuscitation Outcomes Consortium.

**Sample Size:** Based on a one-sided significance level of 0.025, power = 0.90, a survival with modified Rankin score  $\leq 3$  to discharge rate of 5.32% with standard CPR and sham ITD, and two interim analyses, a maximum of 14,742 evaluable patients are needed to detect a 6.68% absolute survival with modified Rankin score  $\leq 3$  to discharge with standard CPR and active ITD.

**Anticipated Clinical Impact:** If this trial demonstrates a significant improvement in survival with use of the ITD, we estimate that the premature deaths of approximately 2,700 victims of cardiac arrest per year would be averted annually in North America alone.



## Specific Aims

**Primary Aim:** The primary aim of the trial is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  between standard CPR plus active ITD versus standard CPR plus sham ITD in patients with out-of-hospital cardiac arrest.

**Hypothesis:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest.

**Secondary Aims:** The secondary aims of this trial are to compare survival to discharge, functional status scores at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months between standard CPR plus active ITD versus standard CPR plus sham ITD in patients with out-of-hospital cardiac arrest.

**Hypotheses:** The null hypotheses are that survival to discharge, functional status scores at discharge and at 1, 3 and 6 months as well as depression score at 3 and 6 months are identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest.

**Prespecified Subgroup Analyses:** These include assessment of treatment effect by:

- a) First recorded cardiac arrest rhythm before application of the ITD.
- b) Observational status of an arrest (e.g., witnessed versus unwitnessed).
- c) EMS response time interval of  $<10$  minutes and  $\geq 10$  minutes from 911 call to initiation of CPR by EMS.

## Background and Significance

### Conceptual Framework for ITD

Despite the widespread availability of basic and advanced life support for patients with out-of-hospital cardiac arrest, few survive to hospital discharge.(1-3) In the most efficient EMS systems, less than 15% of all patients with out-of-hospital cardiac arrest are discharged from the hospital with intact neurological function.(1-3) Furthermore, the median published survival to hospital discharge after out-of-hospital cardiac arrest is only 6.4%.(4)

While there are many variables that impact on the potential for a patient in cardiac arrest to survive, the timely circulation of oxygenated blood to the heart and brain is considered critical.(2) An airway device such as a facemask or an endotracheal tube is commonly used to assist in oxygenating and ventilating the patient. However, the inherent mechanical inefficiencies of standard CPR limit the ability to circulate blood by even the most highly skilled rescuers.(5)

The purpose of CPR is to pump blood from the chest to the vital organs. Blood flow to the vital organs is highly dependent on the amount of blood return to the chest after each compression phase.(6, 7) During standard CPR, chest compression results in an elevation of intrathoracic pressure and direct cardiac compression. Both of these mechanisms result in forward blood flow out of the chest to perfuse the brain and other vital organs. When the chest recoils, intrathoracic pressures decrease relative to extrathoracic pressures, enhancing venous return to the right heart. Blood flow back to the chest is highly dependent on the degree of chest wall recoil.(8)

Blood flows through the coronary arteries predominantly during the chest decompression phase. The pressure gradient generated between the aorta and the right atrium during the

decompression phase of CPR has been termed the coronary perfusion pressure.(9) The pressure gradient between the aorta and left ventricular cavity is also a fundamental determinant of blood flow to the heart during CPR. During standard CPR, the coronary perfusion pressures are only marginally adequate, resulting in inadequate venous return during the chest wall recoil phase.(10, 11)

Since the description of standard CPR by Kouwenhoven and colleagues in 1960,(12) several new CPR techniques have been described. These include circumferential vest CPR,(13, 14) interposed abdominal counterpulsation CPR, (15-19) and phased abdominal counterpulsation CPR.(20) These techniques are not widely applied as they have not been shown to significantly improve survival to discharge or other long-term outcomes compared with standard CPR in patients with out-of-hospital cardiac arrest.

This trial is focused on evaluating the ITD (see Appendix 1 for detailed information regarding the ITD). This novel device is designed to increase the coronary perfusion pressure during the decompression phase of CPR, thereby enhancing delivery of oxygenated blood to the heart. The concept of the ITD was discovered while evaluating the mechanism of another new method of CPR termed active compression decompression (ACD) CPR.(21) ACD CPR is performed with a hand-held suction device. When measuring intrathoracic pressures in patients undergoing ACD CPR, investigators realized that if the endotracheal tube was transiently occluded during the active decompression phase, intrathoracic pressures became markedly more negative. This led to the concept of impeding inspiratory gas exchange during the chest wall decompression phase of CPR to create a greater pressure differential between the thorax and the rest of the body, thereby enhancing venous return to the heart. As such, the impedance valve harnesses the kinetic energy of the chest wall recoil, thereby augmenting the “bellows-like” action of the chest with each compression-decompression cycle.(22)

The ITD is based on the principle that this impedance leads to a greater negative intrathoracic pressure, creating a small vacuum within the thorax relative to the rest of the body, leading to increased venous blood return to the heart and increased cardiac output. This concept has been evaluated in animals undergoing standard CPR (22) or active compression decompression (ACD) CPR,(6) as well as in human patients with prolonged cardiac arrest undergoing standard manual CPR (23-25) and ACD CPR.(7)

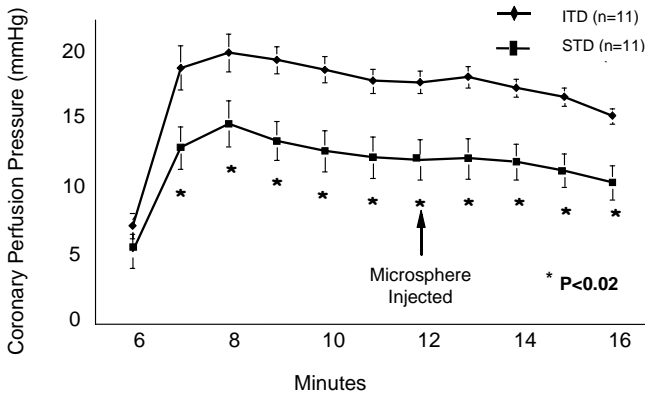
### **Preliminary Studies**

Initial studies to test the impedance valve concept were performed in a pig model of cardiac arrest.(6) Two positive end expiratory valves (PEEP) were coupled together and placed in reverse in the respiratory circuit. These were designed to prevent respiratory gases from entering the lungs during the chest decompression phase of CPR. The pigs were ventilated by overcoming the 40 cm H<sub>2</sub>O resistance of the PEEP valves. After four minutes of cardiac arrest, the combination of this impedance valve combined with ACD CPR significantly improved vital organ blood flow compared with ACD CPR alone ( $p < 0.05$ ). Brain blood flow increased to greater than baseline values (normal = 0.35 ml/min/gm) ( $p < 0.05$ ) and blood flow to the heart increased to greater than 50% of baseline values (normal = 1.2ml/min/gm) ( $p < 0.05$ ).<sup>(6)</sup> This enhanced myocardial perfusion was associated with lower energy requirements to defibrillate the animals at the end of that study. Use of the active ITD resulted in a marked improvement in coronary perfusion pressures compared to sham valve. These studies led to the development of the current ITD.

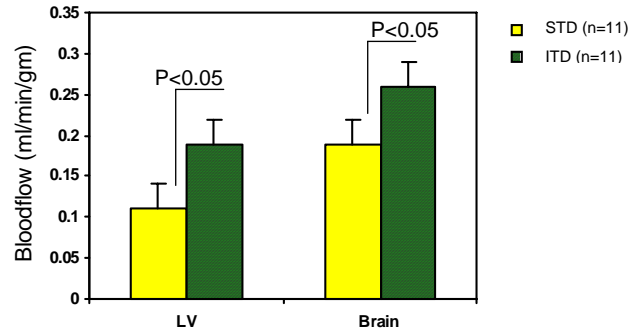
The first controlled animal studies of the ITD with standard CPR utilized a four-minute period of cardiac arrest followed by standard CPR with an automated compression device.(22) Standard CPR was performed with and without the ITD in an alternating fashion. Each time the ITD was removed from the respiratory circuit, the coronary perfusion pressures and vital organ perfusion decreased; and each time the ITD was added back, perfusion pressures stabilized or increased. A similar study evaluated active ITD versus sham ITD for 11 minutes after a six-

minute period of cardiac arrest without CPR.(5) A sham ITD was used in the control group and an active ITD in the other.

After 6 minutes of cardiac arrest and 6 minutes of standard CPR, radiolabeled microspheres were injected to measure vital organ blood flow. The active ITD increased left ventricular flow by 100%, and nearly normalized blood flow to the brain compared to the sham ITD (Figures 1 and 2).



**Figure 1**



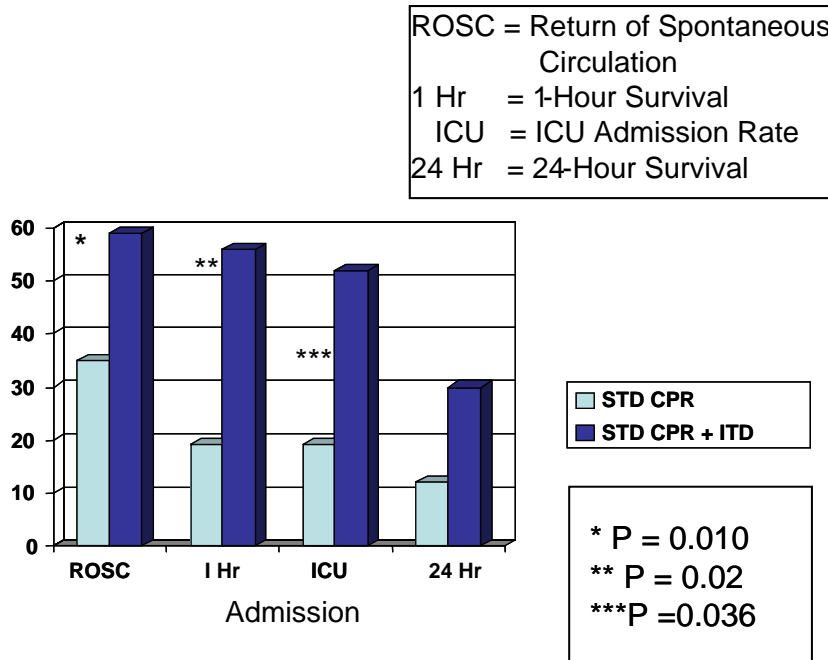
**Figure 2**

After a total of 17 minutes of ventricular fibrillation and 11 minutes of CPR, 3/11 pigs in the sham ITD group and 6/11 pigs in the active ITD group were resuscitated by direct current shock. In many ways, this six-minute arrest time prior to start of CPR more closely resembles clinical field experience where the time from arrest to the start of CPR in the United States ranges between 4-8 minutes in cities with highly efficient emergency medical services systems.

The Milwaukee ROC investigators recently randomized 230 adults who had protected airways after out-of-hospital cardiac arrest to receive standard CPR and sham ITD versus standard CPR and active ITD.(23, 24) The primary outcome of this study was admittance to ICU. Femoral arterial blood pressures were also evaluated by the research team during standard CPR at the scene of cardiac arrest in 22 other patients using the same protocol.

ICU admissions for all patients were not significantly different with use of the active ITD versus sham ITD (25% vs. 17%, respectively, P=NS). However, there was significantly increased ICU admissions in patients presenting in pulseless electrical activity (PEA) with use of active ITD, 19% (5 of 26) vs. 52% (14 of 27) (P = 0.02; not significant when corrected for comparisons in three rhythm groups-.05/3=.017) (Figure 3). In the hemodynamic study, systolic blood pressure was significantly increased with the active ITD versus the sham ITD: 85.1 ± 28.9 mmHg (n = 10) versus 42.9 ± 15.1 mmHg (n = 12), respectively; P < 0.001. Collectively these findings imply that by increasing venous return, and thus cardiac output, the ITD provides a novel means to increase circulation during standard CPR and cardiac arrest.

**Figure 3: Outcomes Presenting in Patients with PEA**



In a secondary analysis of the same study, the Milwaukee ROC investigators found that paramedics and EMTs ventilated patients in cardiac arrest an average of  $30 \pm 3$  breaths per minute, nearly twice that recommended by the American Heart Association.(26) Subsequent studies in pigs demonstrated that excessive ventilation rates (similar to that observed in the clinical setting) significantly decreased coronary perfusion pressures and survival rates.(26) Two other studies demonstrated excessive ventilation rates delivered by healthcare professionals during in-hospital cardiac arrest.(27, 28) However a recent study demonstrated ventilation at the recommended rate during resuscitation by paramedics or nurse anesthetists in a different out-of-hospital setting.(29) Most chest compressions were too shallow and nearly half the time, chest compressions were not delivered at all.

In another analysis of the Milwaukee pilot study, rescuers were observed to maintain some residual and continuous pressure on the chest wall during the decompression phase of CPR, preventing full chest wall recoil.(8) Airway pressures were consistently positive during those periods. When this incomplete chest wall decompression was reproduced in a porcine model of ventricular fibrillation cardiac arrest, it was associated with significantly increased intrathoracic pressure and significantly decreased coronary and cerebral perfusion pressures. When monitoring CPR performance of professional EMS rescuers using a recording manikin, only 16.3% of decompressions were associated with complete recoil. A slight modification in the technique of manual CPR increased the frequency of complete chest recoil to 95.0% (OR: 129.0; CI: 43.4-382.0,  $P < 0.0001$ ). (8)

The ITD in combination with conventional manual CPR was evaluated in a case-control study in large EMS system in Staffordshire, England. Survival to emergency department admittance was significantly greater among patients with any initial rhythm who received the ITD (61/181 [34%]) compared with historical controls (180/808 [22%]) ( $p < 0.01$ ). No device-related adverse effects were observed.(25)

In summary, these studies demonstrate that the ITD improves hemodynamics and short-term outcomes but may be associated with poor performance of other components of CPR. In-field monitoring facilitates identification of such poor performance and provides opportunities for corrective feedback to EMS personnel.

### **Choice of Intervention**

The investigators chose to evaluate the ITD alone rather than in combination with ACD CPR for several reasons. While the results with simultaneous use of ACD CPR and the ITD are promising,(6, 7, 30) use of the ACD CPR device requires more energy than standard CPR to perform it correctly.(6, 7, 30) Also, the sample size required to assess the effect of ACD CPR, ITD, combined therapy or standard CPR upon survival to discharge is impractical. Furthermore, a double-blind trial of ACD-CPR with or without ITD is not feasible, so the treatment effect from such a trial would be susceptible to bias. Therefore we propose a large clinical trial to assess the effect of standard CPR plus active ITD versus standard CPR plus sham ITD.

### **Summary of Rationale**

Survival after out-of-hospital cardiac arrest is poor. Studies in animal models of cardiac arrest demonstrate enhanced myocardial perfusion and vital organ blood flow when using the ITD. Studies in humans with out-of-hospital cardiac arrest demonstrated that the ITD increased systolic blood pressure and tended to improve short-term clinical outcomes without any adverse effects. A large trial is required to demonstrate whether ITD significantly improves survival and functional status. Evaluation of the effect of ITD requires monitoring whether CPR process is consistent with currently recommended methods of resuscitation.

## **Research Design and Methods**

### **Experimental Design**

This randomized trial will evaluate manual CPR with either an active or sham ITD in adult patients with out-of-hospital cardiac arrest. Randomization will occur through use of a study ITD that is constructed such that the sham and active valves are indistinguishable. The intervention will be implemented by the first qualified provider to arrive at the scene of cardiac arrest and continued by subsequent providers in all ROC sites. The first qualified providers will most often be EMT-certified responders but will also include responders able to mechanically ventilate the patient using either a bag-mask or an advanced airway. Ventilation rates will be consistent with AHA guidelines.

### **Study Episodes**

Episodes attended by EMS will be included if a study device was taken from its sealed container. All such episodes will be followed for purposes of safety evaluation.

### **Study Population**

#### **Inclusion Criteria**

Persons aged 18 years or more (or local age of consent) who suffer non-traumatic cardiopulmonary arrest outside of the hospital in the study communities who receive defibrillation and/or chest compressions by EMS providers dispatched to the scene and do not meet any of the exclusion criteria below. Note: The etiology will be presumed to be non-traumatic in origin unless the apparent cause is due to trauma, drowning, strangulation, electrocution, or exsanguination.

## **Exclusion Criteria**

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy;
- Tracheostomy present;
- CPR performed with the mechanical compression “Autopulse” device.
- Non-ROC EMS agency/provider.

## **Primary Comparison Population**

The ITD is conjectured to provide an improvement in the rate of neurologically intact ( $MRS \leq 3$ ) survival to hospital discharge in those patients experiencing OOHCA of cardiac origin and treated by EMS within 15 minutes of initial call to 911. There is, however, no contraindication to the use of the ITD in the relatively few patients whom experience OOHCA due to such noncardiac events as strangulation, drowning, or electrocution. In the emergency setting, unnecessarily introducing a need for EMS providers to evaluate eligibility criteria could potentially delay the institution of appropriate life saving treatments. Furthermore, if the ITD is proven effective and adopted widely, the eventual use of the device may include patients for whom the cardiac origin of OOHCA could not be accurately determined. Hence, this study protocol allows for the evaluation of the safety of the ITD device in some patients for whom the indication of the ITD could not be firmly established in the emergency setting. On the other hand, efficacy of the device will be analyzed in only those patients who are determined to meet the criteria defining the pre-hospital conditions for which the use of ITD is conjectured to be of benefit.

*Efficacy Population:* Analysis of primary and secondary efficacy outcomes will be conducted on a modified intent-to-treat basis. In order to be included in the efficacy analyses, patients must meet the inclusion/exclusion criteria for the ITD/sham device intervention. Furthermore, they must also meet the following criteria

- Not have experienced cardiac arrest secondary to drowning, electrocution, or strangulation;
- Have a response time (time from 911 call to time of arrival of EMS providers at scene) less than 15 minutes, and
- Have the device actually applied.

With the exception of the criterion regarding actual application of the device, determination of whether patients meet these criteria or not will be made on the basis of data available prior to randomization (i.e., available prior to opening of the bag containing the device). In every case, the determination of whether a patient belongs in the efficacy population will be made in a blinded fashion (without knowledge of whether the device bag opened was an active ITD or a sham device). Within the efficacy population, analyses will be conducted on an intent-to-treat basis. Hence in the rare event that first and second responders in a tiered response system might both open a bag containing a device, the patient will be analyzed according to the treatment arm corresponding to the first arriving vehicle.

In the event that the Analyze Late vs Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the efficacy population for the ITD/sham device comparison will be restricted to those subjects treated under the rhythm analysis strategy found to be superior. The number of subjects accrued to the study will be increased to achieve the planned maximal sample size in the superior rhythm analysis strategy arm.

Safety Population: Evaluation of the safety of the ITD will be made using all data from patients who were treated with a device, regardless of whether they are a member of the efficacy population or not.

In the event that the Analyze Late vs Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the safety of the ITD will also be evaluated separately in subgroups defined by the rhythm analysis strategy arm (AL or AE).

## **Intervention**

Upon arrival of EMS providers at a patient with cardiac arrest, CPR will be initiated. Defibrillation will be performed consistent with local practice and cluster assignment. For subjects who are being ventilated with bag-mask or advanced airway (e.g., Combitube, laryngeal mask airway [LMA], or endotracheal tube) and receiving chest compressions, EMS providers will insert a study valve between the bag and the mask/airway, whichever is available. Training will target use of the ITD with initial management of the airway to assure the earliest placement of the ITD during CPR. To assure correct ventilation rate, the rescuers will turn on the ventilation timing assist lights on the device once an advanced airway has been established. The providers will be instructed to immediately remove the valve if the patient has return of spontaneous circulation or is breathing spontaneously, to facilitate rapid elimination of inspiratory impedance in a resuscitated patient. (The ITD has a safety check valve that opens if the pressure in the airway is <16 cm H<sub>2</sub>O in the event the rescuer does not recognize that the patient is able to breathe on their own). The providers will be instructed to immediately reapply the mask if such a patient ceases to have spontaneous circulation or to breath spontaneously (i.e., has recurrent cardiac arrest).

The EMS providers will be instructed to remove the ITD from the advanced airway if the valve fills with fluid; removing this fluid by forcing air through the device with the ventilation bag, suctioning the patient, and reapplying the ITD. If the device fills with fluid a second time, EMS personnel will be instructed to remove the ITD completely and continue resuscitative efforts without use of the device.

Use of the ITD will be discontinued on arrival to the hospital.

All other resuscitative measures will follow common guidelines (Appendix 3).

## **Random Allocation**

Study devices will be randomly allocated in a proportion of 1:1 active vs. sham, with distribution determined by the CTC based on permuted blocks of concealed size within strata defined by participating site and within site by participating agency or subagency. Devices will be packaged with a flexible connector to facilitate adjunct equipment such as CO<sub>2</sub> monitoring. A mask will also be provided to facilitate achievement of a good seal between the patient's face and the ventilatory circuit so as to maintain the intrathoracic pressure. These will be placed at each base station where they can be retrieved by the medic. One device will be kept on each EMS vehicle. Study site personnel will keep inventory records for each EMS site and conduct EMS site visits to confirm inventory status. When a base station has less than three ITDs remaining, an additional set will be distributed. Each ITD package will have several stickers denoting its number. These will be placed on the medic report and emergency care record. Each site must establish a notification process with their EMS system and emergency department to notify study personnel of patient enrollment. In this manner, the subjects, investigators, study coordinators and all persons caring for the patient will be blinded to the treatment assignment. Note that active and sham devices will not be distinguishable visually even when removed from the opaque packaging. Patients will be considered to have been

randomized as soon as the ITD package has been opened. In the event that two bags are opened for the same patient during the same arrest episode, the patient will be assigned to the treatment group of the device used by the first-arriving vehicle.

### **Intervention–Compliance**

The location and number of devices supplied to each EMS rig and station for appropriate distribution will vary with the structure of the system. When an ITD is used, ambulance personnel will document the unique number of the device on their run report by using pull-off labels located within the packaging of the device. Following use, EMS providers will be encouraged to place the used device at a predetermined location and replace the used device with a new valve. After each use, the research team will be notified and will replace the used device. The coordinating center will maintain a record of where each device is distributed, and track their use.

### **Outcome Measures**

#### **Primary**

The primary outcome is survival to hospital discharge with MRS  $\leq$  3. Patients who are transferred to another acute care facility (e.g., to undergo ICD placement) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

#### **Secondary**

The secondary outcomes are survival to discharge; MRS at 3 and 6 months following hospital discharge; Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) at 1, 3 and 6 months;(31, 32) as well as Health Utilities Index III (HUI3) score(33) and Geriatric Depression Scale (T-GDS)(34) score at 3 and 6 months (details in Section 4 and Appendix 4).

#### **Exploratory**

Cerebral Performance Category (CPC) will be assessed at discharge, 3 and 6 months following hospital discharge.

#### **In-Hospital Morbidity**

Number of hospital days and time interval from 911 call to patient death will be described for all hospitalized patients as measures of morbidity after resuscitation.

#### **Prespecified Subgroup Analyses**

- a) First recorded cardiac arrest rhythm prior to valve application (VF/VT vs. PEA vs. asystole vs. not obtained before device implementation);
- b) Observational status of arrest (Witnessed by EMS vs. witnessed by bystanders vs. unwitnessed);
- c) In witnessed cardiac arrests, response time interval from call to initiation of CPR by EMS (<10 vs.  $\geq$  10 minutes);(30)
- d) Analyze Early vs. Analyze Later cohorts.

#### **Expected Adverse Events**



The following will be considered major adverse events if they occur during the resuscitative effort or the hospital stay:

**Pulmonary Edema-** *The presence of pulmonary edema in patients who survive long enough to receive a hospital-based chest x-ray (first emergency department or ICU chest x-ray).* This will be defined as formal radiographic interpretation as consistent with the presence on x-ray of alveolar pulmonary edema, interstitial pulmonary edema, bilateral pleural effusions, cardiomegaly (cardiothoracic ratio > 0.5 on posteroanterior projection), or pulmonary venous congestion (upper-zone flow redistribution on posteroanterior projection).(35, 36) This will be monitored because failure to remove the ITD immediately following successful resuscitation will require the patient to generate more than 16 cm of H<sub>2</sub>O negative intrathoracic pressure before initiating inhalation. This may result in increased work of respiratory effort during the initial stages of successful resuscitation. This may result in secondary respiratory failure or pulmonary edema and the need for continuing to support the patient's respiration. Similarly, in the out-of-hospital setting, if the valve fills with fluid twice (indicating possibly significant pulmonary edema), its use will be discontinued.

All incidences where the valve fills with fluid will be reported to the DSMB. Additionally, all cases of pulmonary edema who did not survive, will have the field report individually reviewed for evidence of failure to remove the ITD valve and these cases will be presented to the DSMB.

Pulmonary edema is commonly observed after resuscitation from cardiac arrest.((37) and Unpublished Data, ASPIRE Investigators) However device-related pulmonary edema has not been observed in previous published studies of ITD. We anticipate that pulmonary edema associated with use of the ITD would be unlikely except if the device were left on a patient who is breathing spontaneously. Since the rate of pulmonary edema in the control group is unknown, we shall monitor the incidence of pulmonary edema in sham and active ITD groups and assess whether there is a significant difference between treatment groups.

**Device Failure-** *Mechanical failure (i.e., the device breaks).* Malfunctions are unlikely due to the simple construction and durable materials of the device. There have been no instances of the ITD breaking in the Milwaukee feasibility study, ongoing European studies or during clinical use in Europe.

**Other-** The following are commonly observed in patients who experience cardiac arrest or resuscitative efforts after its onset, and may or may not be attributable to specific resuscitation therapies. These will be monitored and reported but not classified as major adverse events. *Vomiting During CPR.* Vomiting during CPR is a common and anticipated complication of any method of CPR. Immediate clearing of the airway is necessary to prevent complications from aspiration. Rescuers are experienced in handling this type of complication and have portable and stationary suction available to them. The occurrence of vomiting during the application of the ITD will be recorded from the prehospital clinical record. *Clinical diagnoses of cerebral bleeding, stroke, seizures, bleeding requiring transfusion or surgical intervention, rearrest, pulmonary edema, serious rib fractures, sternal fractures, internal thoracic or abdominal injuries as well as any other major medical or surgical outcomes* will be recorded as noted in the hospital discharge summary. Since the treating physicians will be blinded as to whether the patient received active or sham ITD, there is unlikely to be a treatment-related bias in identifying these events.

#### **Unexpected Adverse Device Events (UADE)**

These will be defined as any serious unexpected adverse effect on health or safety or any unexpected life-threatening problem caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan or application (including a supplementary plan or application), or any other unexpected serious problem associated with a device that relates to the rights, safety or welfare of subjects. The death or neurological impairment of an individual patient is not considered an adverse event in this study.

## Analyses

### Primary Efficacy Analysis

The primary analysis of treatment efficacy will be based on a comparison across treatment arms active and sham ITD of the observed proportion of patients in the efficacy population (see page 12 for definition of efficacy population) with neurologically intact (MRS  $\leq 3$ ) survival to hospital discharge. We assume that ITD would not be implemented if it were associated with worse neurologically-intact survival to discharge. A one-sided level 0.025 hypothesis test will be used to test the null hypothesis of equal rates of such favorable events ( $H_0: \pi_{ITD} = \pi_{SHAM}$ ) versus the alternative hypothesis that patients on the active ITD arm have a higher probability of neurologically intact survival to hospital discharge than do patients on the sham device arm ( $H_1: \pi_{ITD} > \pi_{SHAM}$ ). The test statistic comparing those proportions will be a one-sided version of Pearson's chi squared statistic: the Z statistic defined as the difference of the proportions (ITD arm minus sham device arm) divided by its estimated standard error computed assuming the null hypothesis of equality of proportions.

$$Z = \frac{(\hat{\pi}_{ITD} - \hat{\pi}_{SHAM})}{\sqrt{\hat{\pi}_{Null}(1 - \hat{\pi}_{Null})\left(\frac{1}{n_{ITD}} + \frac{1}{n_{SHAM}}\right)}} \quad \text{with } \hat{\pi}_{Null} = \frac{n_{ITD}\hat{\pi}_{ITD} + n_{SHAM}\hat{\pi}_{SHAM}}{n_{ITD} + n_{SHAM}}$$

The fixed sample P value corresponding to that Z statistic will be compared to the boundaries of the protocol defined group sequential stopping rule when expressed on the fixed sample P value scale. At the end of the study, analysis results will be summarized using point estimates of the difference in probability of favorable events, 95% confidence intervals, and P values adjusted for the true sampling distribution imposed by the group sequential stopping rule. (See the discussion of the group sequential monitoring plan below.)

This analytic approach assumes unbiased random allocation of patients to treatment group and relies on the sample size being large enough for asymptotic theory to provide good distributional approximations. With the exception of the inclusion criterion regarding actual application of the device, determination of whether patients meet study criteria or not will be made on the basis of data available prior to randomization (i.e., available prior to opening of the bag containing the device) (see p. 12 for more detail).

### Secondary Efficacy Analyses

All secondary analyses of efficacy endpoints are directed toward finding supporting evidence for the findings of the primary efficacy analysis. As such, they will not be used as the primary basis for establishing benefit of the ITD relative to the sham device, nor will they be used as the primary basis for obtaining regulatory approval of the ITD. Hence, there is no plan to make any statistical adjustment for the multiple comparisons inherent in the secondary efficacy analyses, which include:

*Modified Rankin Score (MRS) at hospital discharge.* The mean MRS at hospital discharge will be compared across treatment groups using the t test which allows for unequal variances across groups. For the purposes of this analysis, patients dying before admission to the hospital will be treated the same as admitted patients dying before hospital discharge and will be assigned an MRS of 6.

*Survival to hospital discharge.* This secondary analysis of treatment efficacy will be based on a comparison across treatment arms of the observed proportion of patients in the efficacy population with survival to hospital discharge. This analysis shall proceed in a manner entirely analogous to that for the primary efficacy endpoint. The test statistic comparing those proportions will be a one-sided version of Pearson's chi squared statistic: the Z statistic as defined for the primary analysis.

*Neurologically intact survival to hospital discharge adjusted for prognostic variables.* A secondary analysis of the primary endpoint will adjust for those pre-randomization variables which might reasonably be expected to be predictive of favorable outcomes. Generalized linear models will be used to model the proportion of subjects with neurologically intact ( $MRS \leq 3$ ) survival to hospital discharge by ITD/sham device group adjusted for site (dummy variables modeling the 11 ROC sites), patient sex, patient age (continuous variable), witness status (dummy variables modeling the three categories of unwitnessed arrest, non-EMS witnessed arrest, and EMS witnessed arrest), location of arrest (public versus non-public), time or response (continuous variable modeling minutes between call to 911 and arrival of EMS providers on scene), presenting rhythm (dummy variables modeling asystole, PEA, VT/VF, or unknown), and treatment assignment in the Analyze Late vs. Analyze Early intervention. The test statistic used to assess any benefit of the ITD relative to the sham device will be computed as the generalized linear model regression coefficient divided by the estimated "robust" standard error based on the Huber-White sandwich estimator(38, 39) in order to account for within group variability which might depart from the classical assumptions. Statistical inference will be based on one-sided P values and 95% confidence intervals which adjust for the stopping rule used for the primary analysis.

*Post-discharge neurological function, quality of life, and depression.* Surviving patients will be contacted post-discharge to obtain consent for additional follow-up via telephone with consenting patients or their proxies regarding cognition, quality of life, and depression. Analyses of each of these outcomes at each time point will be compared across treatment groups by using the t test which allows for unequal variances. Analyses will first be conducted conditional on survival to the relevant time point by using only data from those patients offering consent, as well as using data imputed from discharge data for those surviving patients refusing consent. The data missing due to lack of consent for follow-up will be multiply imputed using measurements of patient age, sex, length of hospital stay, incidence of major adverse outcomes during hospitalization, MRS at hospital discharge, and whether the patient was discharged to home or a nursing facility. Additional analyses of neurological function and quality of life will then incorporate measurements for patients dying prior to hospital admission, during hospitalization, or within 3 or 6 months post discharge. Dead patients will be assigned the worse category of neurological function and quality of life for each measurement.

*Morbidity.* As a measure of morbidity during hospitalization, the number of days hospitalized conditional upon survival to discharge will be compared across treatment groups using the t test which allows unequal variances. A similar analysis will also be conducted comparing the days of hospitalization for patients admitted to the hospital, but dying prior to hospital discharge. Finally,

treatment groups will also be compared with respect to the number of days alive post hospital discharge during the first 6 months post OOHCA in order to incorporate information about both dead and surviving patients. In this analysis, data missing due to lack of consent for follow-up will be multiply imputed using data available at hospital discharge, and patients dying before hospital admittance or prior to hospital discharge will be scored as 0.

### ***Safety Analyses***

The incidence of adverse events will be recorded for all patients in the safety population and presented by treatment arm (ITD vs. sham device) to the DSMB for their review during the conduct of the study, as well as summarized and compared across treatment arms in the final report of study results. Assessment of the statistical significance of differences in the incidence of safety endpoints plays a lesser role, due to the need to be cautious in the introduction of new treatments in a human population. Hence, emphasis is placed on the presentation of results, with statistical tests provided for guidance on the precision of estimates as indicated. Specific measures that may reflect the safety of the ITD include:

*Delay of treatment.* The process of opening and applying the device could delay treatment and/or potentially cause harm in patients other than those for whom the device is conjectured to provide benefit, as well as in the evaluable patient population. The distribution of time from EMS arrival to initiation of CPR will be described using mean, standard deviation, minimum, 25th, 50th, and 75th percentiles, and maximum. When indicated, statistical tests comparing the distribution of times to initiation of CPR will be effected using the t test which allows for unequal variances. Similar analyses will be conducted for the time between EMS arrival and first assessment for defibrillation, stratified within Analyze Late vs. Analyze Early clusters.

*Complications of treatment.* The incidence of vomiting during CPR, device filling with fluid, mechanical failure of the device, and any UADE will be reported by treatment arm and compared as indicated using Pearson's chi squared statistic.

*Serious adverse events.* The incidence of each serious adverse event, along with other major adverse medical or surgical outcomes identified during review of hospital records, will be tabulated by treatment arm and compared when indicated using Pearson's chi squared test. In order to facilitate the identification of differences in rates of such events that might be due to greater survival to hospital admission and/or hospital discharge on one of the treatment arms, the incidence of any of the above specific events and/or death (either prehospital or during hospitalization) will be reported in a combined fashion and compared as indicated by using Pearson's chi squared statistic.

### ***Subgroup Analyses***

Analyses will be performed in each subgroup, along with tests for statistically significant interactions. However, it is recognized that the study is not powered adequately to detect interactions, and thus all subgroup analyses are judged exploratory.

### ***Exploratory Analyses***

Data from the clinical trial will also be used to explore two hypotheses unrelated to the treatment effect of ITD on neurologically intact survival post OOHCA.

*Correlation between MRS and other measures of cognition and quality of life.* Analyses will evaluate the correlation between simultaneous measures using the MRS, ALFI-MMSE, HUI or GDS at 3 and 6 months using linear regression analyses and standard errors computed using the Huber-White sandwich estimator. Additional analyses will evaluate the value of MRS at hospital discharge as a surrogate variable for the ALFI-MMSE and HUI at 6 months post hospital discharge. In this latter analysis, the effect of treatment with ITD vs. sham device on the 6 month cognitive function and quality of life measures will be analyzed both without and with adjustment for MRS at hospital discharge. A descriptive measure of the usefulness of the MRS at hospital discharge as a surrogate for the later validated measures will be based on the difference in the estimates of treatment effect between the unadjusted and adjusted analyses.

*Cerebral Performance Category* To assess the validity of the Cerebral Performance Category for use in future studies, CPC scores at discharge as well as three and six months after discharge will be analysed in a manner similar to the analyses of post-discharge neurologic function described above in the secondary efficacy analyses. However the results of any analysis of CPC scores will not be used to make labeling claims for ITD.

*Association between use of hypothermia and neurologically intact survival.* Some patients may be treated with hypothermia according to local standards of best medical care. Data will be collected on both the pre-hospital and in-hospital use of hypothermia. In order to explore any association between the use of hypothermia and the probability of survival to hospital discharge proportional hazards regression models will be fit using use of hypothermia as a binary time-varying covariate, adjusted for treatment with ITD vs. sham device. Test statistics will be based on the estimated hazard ratio for the hypothermia covariate and the Wald statistic computed from the regression parameter divided by the “robust” standard error computed using the Huber-White sandwich estimator. Comparisons of neurologic function will use measures derived from the MRS, ALFI-MMSE, HUI and GDS over time in a generalized estimating equation (GEE) analysis restricted to patients surviving to hospital discharge and incorporating the multiple measurements made on each patient. Test statistics will be based on the Wald test using the regression parameter estimate for the hypothermia covariate and its “robust” standard error computed using the Huber-White sandwich estimator.

## **Sample Size and Study Duration**

The sample size for the factorial trial is driven by the power analysis for the ITD intervention. These calculations are based on the estimated probability of survival to hospital discharge averaged over the participating ROC sites, which is then adjusted to reflect the estimated probability of survival to hospital discharge with acceptable neurological status ( $MRS \leq 3$ ).

Patients with OOHCA who are treated by participating agencies and subagencies and who meet the inclusion/exclusion criteria will be randomized to the ITD or sham device, unless resuscitated prior to the placement of such a device. This latter possibility may tend to occur with patients who present in VT/VF and who initially achieve ROSC following a first, early defibrillation as might be applied under the AE strategy. Thus, in computing sample sizes for the ITD intervention, we must consider the distribution of patients by presenting rhythm and their assignment to the AE or AL treatment strategies. We also must consider the number of patients who have EMS witnessed CA, because all such patients will be treated using an AE strategy, regardless of the cluster randomization of the responding unit to the AL vs. AE intervention.

It is estimated that approximately 50% of patients accrued to the factorial study will present in asystole, 25% of patients will present with pulseless electrical activity (PEA), and the remaining 25% will present in VT/VF. It is also estimated that approximately 10% of all EMS

treated OOHCA will involve EMS witnessed arrest. In the ASPIRE trial, the presenting rhythm of EMS witnessed arrest occurred in the ratio of 2.20 asystole: 2.57 PEA : 4.74 VT/VF. The anticipated distribution of patients by presenting rhythm and whether CA was EMS witnessed or not was estimated based on these assumptions (Table 1).

**Table 1: Proportion of all EMS treated OOHCA patients according to presenting rhythm and EMS Witness status**

Presenting Rhythm	EMS Witnessed	EMS Unwitnessed	Total
Asystole	0.0231	0.4769	0.500
Pulseless Electrical Activity (PEA)	0.0270	0.2230	0.250
VT/VF	0.0499	0.2001	0.250
<b>TOTAL</b>	<b>0.1000</b>	<b>0.9000</b>	<b>1.000</b>

Eligibility criteria for the ITD intervention excludes subjects for whom no device (ITD or sham) was used, and it is anticipated that approximately 30% of the patients presenting in VT/VF will not have a device placed when treated under the AE strategy, On the other hand, it is anticipated that all such patients would have a device placed when treated under the Analyze Later (AL) strategy. Taking into account that patients with OOHCA that is not witnessed by EMS will be randomized (by cluster) in a 1:1 ratio to the AE or AL strategies, the expected distribution of patients to the various treatment strategies by presenting rhythm was estimated (Table 2).

**Table 2: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total ITD/Sham Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	Sham	ITD
Asystole	0.000	0.012	0.012	0.000	0.119	0.119	0.119	0.119	0.250	0.250
PEA	0.000	0.014	0.014	0.000	0.056	0.056	0.056	0.056	0.125	0.125
VT/VF	0.015	0.017	0.017	0.030	0.035	0.035	0.050	0.050	0.103	0.103
<b>TOTAL</b>	<b>0.015</b>	<b>0.043</b>	<b>0.043</b>	<b>0.030</b>	<b>0.210</b>	<b>0.210</b>	<b>0.225</b>	<b>0.225</b>	<b>0.478</b>	<b>0.478</b>

Based on ranges of estimates in published data and results of the ASPIRE trial, and allowing for 1-5% improvement due to better CPR process in the clinical trial setting, It is estimated that in the absence of an ITD and when managed according to the Analyze Early (AE) strategy, the probability of survival to hospital discharge would be 1.05% for patients presenting with asystole, 4.02% for patients presenting with PEA, and 20.2% for VT/VF. These assumptions lead to an estimated probability of survival to hospital discharge of 0.0599 when treated under the AE strategy with a sham valve. We assume that 88.9% of such survivors would have acceptable neurological status ( $MRS \leq 3$ ) based on a combination of observed rates from the ASPIRE and PAD trials where 35 of 45 and 42 of 45 survivors had CPC scores  $\leq 2$ . Therefore we estimate a rate of 0.0532 for neurologically intact survival to hospital discharge under treatment with the AE strategy and a sham valve.

Under the alternative hypothesis used for sample size calculations, the effect of the ITD on neurologically intact survival is presumed to vary by presenting rhythm. Because a more substantial relative benefit is presumed for those patients receiving CPR for a longer period of time, neurologically intact survival is presumed to be 1.4 fold higher for patients treated with the ITD if their presenting rhythm was asystole or PEA. For patients presenting in VT/VF a relative benefit of 1.20 is hypothesized to account for a lesser benefit for those patients who would

respond well to early defibrillation. Applying these hypothesized effects to the numbers given above results in an estimated probability of survival to hospital discharge of 0.0751 for patients treated with an ITD under the AE strategy, with a corresponding hypothesized rate of 0.0668 for neurologically intact survival to discharge. Details of these calculations are provided below (Table 3).

**Table 3: Estimated proportions of all EMS treated OOHCA patients surviving to discharge and surviving to discharge with MRS  $\leq$  3 by ITD/sham treatment arm and presenting rhythm.**

Presenting Rhythm	Stratum Weight	Sham Device Probability of Survival to Discharge	ITD / Sham Relative Benefit	ITD Probability of Survival to Discharge
Asystole	0.5235	0.0105	1.40	0.0147
PEA	0.2618	0.0420	1.40	0.0588
VT/VF	0.2147	0.2020	1.20	0.2424
<b>Probability of Survival to Discharge (weighted average)</b>		0.0599		0.0751
<b>Probability of Neurologically Intact Survival to Discharge (88.9% of patients surviving to hospital discharge)</b>		0.0532		0.0668

The number of patients to be accrued to the ITD vs. sham device comparison is based on the ability of a one-sided level 0.025 test to reject a null hypothesis that the probability of neurologically intact survival to hospital discharge is 0.0532 on both treatment arms. Sample size computations are based on a two-sample test of binomial proportions using Pearson's chi squared statistic. The test should have approximately 90% statistical power to reject the null hypothesis when the ITD treatment arm would have a 0.0668 probability of neurologically intact survival.

The clinical trial will be conducted using a group sequential stopping rule based on up to three evenly spaced analyses (two interim analyses and the final analysis). The stopping rule corresponds to a Pampallona and Tsiatis design(40) as described in more detail under the monitoring plan. Using that stopping rule, a sample size of 14,154 evaluable patients will provide 90% power to reject the null hypothesis under the conjectured treatment effect. However, it is anticipated that approximately 4% of accrued patients will be judged nonevaluable due to non-cardiac origin of cardiac arrest or response time in excess of 15 minutes. Hence, a maximum of 14,742 patients will be potentially treated with the ITD or sham device in order to obtain 14,154 evaluable patients for testing the effect of ITD on the primary endpoint of neurologically intact survival to hospital discharge.

The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 15,742 patients (1,000 during the run-in phase, 14,742 during the actual trial) will require 18 months.

In the event that the Analyze Late vs. Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the number of subjects accrued to the study will be increased to achieve the planned maximal sample size in the superior rhythm analysis strategy arm. The primary analyses of the effectiveness of the ITD will then be evaluated in just those patients who were treated with the

rhythm analysis strategy deemed to be superior. The stopping rule will be applied to the data in the efficacy population restricted to that superior ALvE treatment arm.

## **Human Subjects**

### **Risks to Subjects**

#### **Population**

This study will enroll approximately 15,742 adult patients who have sustained a nontraumatic out-of-hospital cardiac arrest and are known or presumed to be at the local age of consent.

#### **Potential Risks**

ITD administration during standard manual CPR has been tested in three animal studies(5, 22, 41) and three human studies(23-25) with no serious device-related adverse effects reported. ITD increases negative intrathoracic pressure and coronary perfusion pressure, which has raised a concern for potential increased pulmonary edema. However previous studies have not observed device-related adverse events.

Other potential concerns are mechanical failure of the device. We will report any evidence of pulmonary edema, or device failure as a serious adverse event. If failure of the device or pulmonary edema occurs (the device fills with fluid twice) in the out-of-hospital setting, application of the device will be immediately stopped and appropriate clinical management undertaken. As part of the training of the prehospital providers for the study, potential signs and symptoms of serious adverse events will be clearly described.

#### **Potential Benefits to Subjects and Society**

There are several potential benefits to subjects who receive an active ITD. These include increased venous return, coronary perfusion pressure, cardiac output and admittance to intensive care with the use of the ITD during standard CPR in humans. We contend that use of the ITD may significantly increase survival to hospital discharge. The efficacy of this device can only be assessed by performing clinical studies such as the one proposed in this application.

#### **Inclusion of Women or Minorities**

There will be no exclusion on the basis of gender, race or ethnicity. Known pregnant women and prisoners will be excluded. Since this is the first large human trial using the ITD with standard CPR, there is no available evidence to determine whether or not there is a clinically important sex/gender and/or race/ethnicity difference with its use. Investigators will compare primary and secondary study outcomes between the treatment and control groups broken down by sex/gender and race/ethnicity categories.

#### **Inclusion of Children**

The ITD has not been applied during standard CPR in humans < 21 years of age. For this reason, clinical equipoise has not been established in the pediatric population. Therefore the ROC Investigators believe that it is inappropriate to first use the ITD during standard CPR in children in a randomized trial such as that proposed in this protocol. Accordingly, victims of cardiac arrest less than the local age of consent (which varies from 17 to 21 years in ROC sites) will not be entered in the study.



### 3. Analyze Later versus Analyze Early

#### Analyze Later Trial - Comparison of a Strategy of Analyze Later Combined with CPR Early Versus a Strategy of Analyze Early Combined with CPR Later in Patients With Out-Of-Hospital Cardiac Arrest

##### Study Summary

**Background:** While patients with the shockable rhythms of VF and pulseless VT (PVT) have the best chance of survival of amongst out-of-hospital cardiac arrest victims, the vast majority of such patients do not survive to hospital discharge. The traditional approach to these patients has been to analyze the cardiac rhythm and deliver defibrillatory shocks as quickly as possible with the onset of CPR delayed. Recent thinking suggests three phases for VF cardiac arrest: a) an early “electrical” phase where rapid defibrillation is effective, b) an intermediate phase where “priming” the heart with CPR enhances the effectiveness of defibrillation, and c) a late phase where defibrillation is rarely effective. Some now advocate delaying electrical shocks and providing early CPR in cases of VF where defibrillation cannot be carried out immediately. Three clinical studies have each attempted to evaluate this hypothesis of early CPR and delayed analysis. While two studies supported early CPR and one did not, none were definitive and all had important limitations. We believe there is an urgent need for a large and definitive clinical trial to determine the optimal strategy for rhythm analysis and CPR in patients with out-of-hospital cardiac arrest.

**Aims:** The primary aim of the trial is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  between a strategy of Analyze Later consisting of CPR first followed by rhythm analysis versus a strategy of Analyze Early consisting of early rhythm analysis in patients with out-of-hospital cardiac arrest. The secondary aims of the trial are to compare survival to discharge, functional status at discharge and at 1, 3 months and 6 months as well as depression at 3 and 6 months.

**Hypotheses:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed between Analyze Later versus Analyze Early in patients with cardiac arrest. The secondary null hypotheses are that survival to discharge, functional status at discharge and at 1, 3 months and 6 months as well as depression at 3 and 6 months will be identically distributed between Analyze Later versus Analyze Early in patients with cardiac arrest.

**Design:** Cluster randomized trial with cluster units defined by geographic region, or monitor/defibrillator machine.

**Population:** Patients with non-traumatic out-of-hospital cardiac arrest, known or presumed to be local age of consent or greater and treated by EMS providers.

**Setting:** EMS systems participating in the Resuscitation Outcomes Consortium.

**Sample Size:** Based on a two-sided significance level of 0.05,  $p=0.99$ , a survival to discharge with modified Rankin score  $\leq 3$  rate of 5.41% after Analyze Early, and two interim analyses, a maximum of 13,560 evaluable patients are needed to detect a 7.45% absolute survival to discharge with modified Rankin score  $\leq 3$  after Analyze Later.

**Anticipated Clinical Impact:** If this trial demonstrates a significant improvement in survival with a strategy of Analyze Later, we estimate that the premature death of 4,000 victims of cardiac arrest per year would be averted annually in North America alone.

## Specific Aims

**Primary Aim:** The primary aim of this study is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  in a variety of communities in patients with out-of-hospital cardiac arrest between a protocol of compressions equivalent to approximately 3 minutes prior to cardiac rhythm analysis (Analyze Later) compared with cardiac rhythm analysis as soon as possible after 50 compressions (Analyze Early).

**Hypothesis:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed with use of Analyze Later versus Analyze Early in patients with cardiac arrest.

**Secondary Aims:** The secondary aims of this trial are to compare survival to discharge, functional status scores at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months between Analyze Later versus Analyze Early in patients with out-of-hospital cardiac arrest.

**Hypotheses:** The null hypotheses are that survival to discharge, functional status at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months are identically distributed with use of Analyze Later versus Analyze Early in patients with cardiac arrest.

**Prespecified Subgroup Analyses:** These include assessment of treatment effect by:

- a) Rhythm immediately post electrode placement: VF/VT, PEA, asystole, and not obtained.
- b) Response time from 911 call to arrival at the patient's side  $< 4$  minutes and  $\geq 4$  minutes.
- c) CPR being performed by bystanders.

## Background and Significance

### Conceptual Framework for Analyze Later

Our current paradigm of cardiac arrest defines VF as “shockable,” with the optimal therapeutic approach being immediate direct countershock.(42) Integral to this approach is the concept that defibrillation attempts should occur without delay upon recognition of VF, either by prehospital personnel or the analysis software contained within AEDs, which can then be applied by first responders with limited training or even laypersons.(43) This approach has defined current Advanced Cardiac Life Support (ACLS) algorithms and shaped the development of EMS systems, with prehospital providers that can rapidly respond to victims of cardiac arrest, and the placement of AEDs in public areas for use by non-medical personnel. (44-48) The ability to provide early defibrillation has resulted in improved survival for cardiac arrest victims with an initial rhythm of VF in some EMS systems and has defined the current standard of care. (4, 49)

One of the major limitations to this cardiac arrest paradigm is its consideration of VF as homogenous, without regard for variability in VF morphology or elapsed time since the arrest. In contrast, experimental models of VF arrest support three distinct phases, each with a different optimal therapeutic approach.(50) The early moments following arrest define an “electrical phase” during which little ischemic injury has occurred and rapid defibrillation attempts appear to be most efficacious. After some time period, probably around 3-4 min, the optimal therapeutic approach no longer appears to be immediate countershock but instead includes a

period of chest compressions prior to defibrillation attempts. It is unclear whether this is related to a “priming” effect with the delivery of substrate necessary for successful return of spontaneous circulation (ROSC) or the removal of toxic metabolites that have accumulated during the ischemic period. Effective chest compressions, traditionally held to provide approximately 30% of normal cardiac output during the first several minutes of CPR, may provide sufficient myocardial perfusion and improve the metabolic state of those myocytes in patients with ventricular fibrillation. Immediate defibrillation attempts during the circulatory phase may be unsuccessful due to persistent or recurrent VF or may result in terminal PEA or asystole. Interestingly, outcomes in patients “shocked” into PEA or asystole are significantly worse than when these are the presenting rhythms. (51)

After some additional elapsed time period, even chest compressions prior to defibrillation attempts do not appear to change outcome. This may be due to the initiation of irreversible ischemic changes that ultimately lead to substantial myocyte and neuronal cell death. This “metabolic phase” is thought to start after about 10 min of total arrest duration, with no currently available therapies demonstrating efficacy once this phase is reached.

### **Preliminary Studies**

The effect of early rhythm analysis versus later rhythm analysis has been evaluated in animal and human studies. Animal models demonstrate improved ROSC and neurological outcomes with delayed countershock following a period of chest compressions in VF of moderate duration.(52-55) Several investigators have utilized this period of chest compressions as a therapeutic window in which to deliver various pharmacological agents designed to increase the likelihood of successful ROSC and improve neurological outcomes. Yakaitis et al compared immediate countershock to delayed defibrillation following administration of epinephrine and 5 min of chest compressions in a dog model of VF.(52) Immediate defibrillation was superior with VF of 1- or 3-min duration, while the delayed approach was optimal with VF of 5- or 9-min duration. Niemann et al observed improved outcomes with delayed countershock following administration of epinephrine and 5 min of chest compressions alone with a VF duration of 7.5 min but not 5 min in a swine model.(53) Menegazzi et al observed substantially higher ROSC and better neurological outcomes with administration of a pharmacologic “cocktail” followed by chest compressions alone prior to defibrillation attempts versus immediate countershock in a swine model of VF of 8-min duration.(54, 55)

Other parameters besides duration of ischemia may better indicate the likelihood of successful defibrillation in VF arrest victims. Various VF morphologic features have been identified as potentially useful in predicting successful defibrillation in animal models of VF.(56-58) Limited human data exist to support morphological analysis of VF/PVT as a predictor of successful ROSC.(58-60) In addition, animal and human data suggest that chest compressions alone can modulate these morphological features to a more favorable configuration for successful ROSC. (57-59) Berg et al used a swine model of VF to demonstrate that CPR alone can modulate VF median frequency to a value predictive of successful defibrillation; improvements in ROSC and cardiac function at 1 hour were also observed with CPR prior to defibrillation attempts.(57) Eftestol et al demonstrated improvements in spectral flatness measure, centroid frequency, and amplitude spectrum relationship. Improvement in ROSC was also observed in patients with at least 3 min of chest compressions prior to countershock. None of these morphological features have demonstrated adequate predictive value to justify their clinical use; however, these data further support the therapeutic value of chest compressions prior to defibrillation in VF of moderate duration. Finally, the duration between cessation of chest compressions and direct countershock appears to influence success of ROSC and ultimate survival.(61, 62) This suggests that prehospital providers should attempt to minimize delays after chest compressions due to rhythm analysis or ventilation prior to defibrillation attempts.

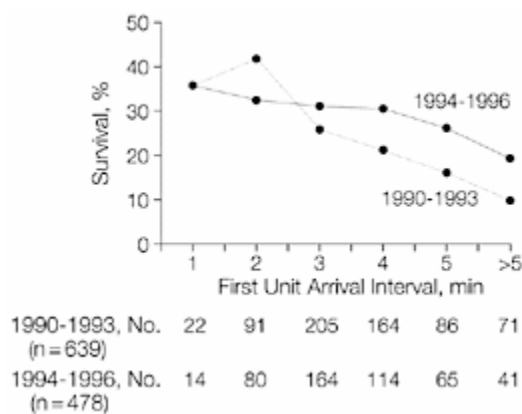
## Clinical Studies

Three clinical studies have compared outcomes from out-of-hospital cardiac arrest due to VF when a period of CPR has or has not been prescribed prior to the first attempts at defibrillation.(63-65)

**Cobb et al.** conducted an observational, population-based study(63) of 639 patients treated for out-of-hospital VF at a time when AED application and use was given the highest priority compared with 478 patients for whom 90 seconds of chest compressions and ventilation (CPR) were mandated before AED application and use. An a priori hypothesis was that the survival benefit would be most evident in those cases with the greater delay from collapse to delivery of the first shock. Survival to hospital discharge and favorable neurological status at discharge (defined as full or nearly full neurological recovery, or requiring some but not complete dependence upon others for assistance in activities of daily living) were the primary outcomes of the study.

Survival to hospital discharge was greater during the intervention period (mandated CPR prior to shock) than in the preintervention period (high priority for AED use): 30% vs. 24% ( $p=0.04$ ). There was a non-significant trend toward a more favorable neurological outcome observed during the intervention period (79% of patients with mandated CPR versus 71% of patients in whom AED use was prioritized,  $p=0.11$ ). A significant interaction also described a relatively greater survival benefit for CPR before defibrillation as the response interval of the first arriving unit increased, particularly in cases in which the response interval of the first arriving unit was 4 minutes or longer ( $p=0.04$ ) (Figure 4).

**Figure 4: Survival versus Response Time Interval With and Without Initial CPR**



Although its hypotheses were prospectively defined, this study was observational, and hence subject to the influence of factors, including the potential biases inherent in non-randomized studies that tend to overestimate treatment effects. For example, a change in the *sequence* of CPR could have been accompanied by an unconscious change in *emphasis* of CPR over shock or even over other interventions during resuscitation. As the authors themselves stated, their “observations represent an encouraging pilot study and that the development of randomized clinical trials be considered to evaluate further the influence of CPR before the delivery of a shock for patients who have a significant delay prior to treatment”.

**Wik et al.** (64) conducted a randomized trial of 200 patients with out-of-hospital cardiac arrest due to VF to compare standard care with immediate defibrillation ( $n=96$ ) or 3 minutes of basic CPR prior to defibrillation ( $n=104$ ). In both treatment groups, if three sequential defibrillations were unsuccessful, 1 minute of CPR was given for VF/VT or three minutes for other rhythms before a new rhythm analysis. Based on the report by Cobb et al that was

published subsequent to the start of the study but before analysis of outcomes, the authors hypothesized that survival benefit would be most evident in cases with longer response intervals, and analyzed subgroups with response times either up to or longer than 5 minutes.

The primary outcome of survival rate to hospital discharge did not differ significantly between the two treatment arms of the study (22% in those randomized to CPR-first versus 15% in the standard group,  $p=0.17$ ). Nor were there significant differences in ROSC, 1 year survival, “good neurological recovery” at hospital discharge or 1 year after cardiac arrest between treatment groups. For those with a response time interval (time from dispatch to arrival of first EMS provider) of 5 minutes or less, there were no significant differences in ROSC, survival to hospital discharge, 1 year survival, or neurological outcome of survivors. Among 119 patients with response times longer than 5 minutes, more patients in the CPR first than in the standard group achieved ROSC (58% vs. 38%,  $p=0.04$ ), survived to hospital discharge (22% vs. 4%,  $p=0.006$ ) and survived to 1 year (20% vs. 4%  $p=0.01$ ).

However the criterion for statistical significance in this trial ( $p<0.05$ ) was not adjusted for sequential monitoring performed at six, 18 and 30 months, nor for subgroup analysis. The reported confidence intervals surrounding the estimated benefit were also wide. Hence the findings of this study have to be interpreted with caution, and the observed results not interpreted as definitive of benefit from a CPR first strategy. Moreover, this study had a long interval from collapse to EMS arrival (approximately 12 minutes), limiting the generalizability of the conclusions.

**Jacobs et al.** conducted a prospective prehospital randomized trial performed in Western Australia which randomized 256 patients to a strategy of 90 seconds of CPR before defibrillation versus immediate defibrillation.<sup>(65)</sup> Survival to hospital discharge was not significantly different in the CPR first group, 4.2%, compared with 5.1% in the immediate defibrillation group. There was no significant difference in survival to hospital discharge among patients with a response interval of  $\leq 5$  versus  $>5$  minutes (12% in the CPR first group, compared with 0% in the immediate defibrillation group among patients with a response interval  $\leq 5$  minutes ( $p= 0.24$ ); and 3.5% vs. 4.9%, respectively, among patients with a response interval of  $>5$  minutes ( $p=0.7$ ). Unfortunately this trial was underpowered due to failure to recruit a total sample size of 390 patients, lower than expected baseline survival rates, and exclusion of 41 eligible cases. Notably, the overall low survival rate and longer response intervals observed in this trial should have favored a greater benefit from CPR before defibrillation if the interactions observed by Wik and Cobb et al. between survival and benefit from CPR hold true.

## Summary of Rationale

Survival after cardiac arrest is poor. The most treatable arrhythmias immediately following cardiac arrest are VF and PVT. Current ACLS algorithms emphasize the importance of immediate defibrillation attempts in these patients. While it has been recognized for many years that chest compressions on OOH-CA patients who received “bystander CPR” result in positive outcomes,<sup>(66)</sup> this impact has been relegated to a secondary or even tertiary role in resuscitation sequencing. Small randomized or observational studies suggest that CPR before defibrillation may increase survival but the results to date are inconclusive. Although there is some evidence that favors immediate defibrillation in cases where the response time is  $\leq 2$  minutes, such response times are rare and the frequent delay in recognition of the OOH-CA and calling 911, as well as the complexity of the resuscitation protocol, convince us that response time should not be used as an intervention modifier. We believe that there is clinical equipoise with regard to the competing strategies of Analyze Early vs. Analyze Later. A large, randomized clinical trial is needed to examine the impact of delayed defibrillation on survival to hospital discharge in patients who are presumed to be without circulation for several minutes. Since the only cost of the intervention is training or retraining providers, the proposed study has the

potential to have substantial impact upon prevention of premature cardiac death at comparatively little cost.

## **Research Design and Methods**

### **Study Design Overview**

This protocol will be a single-blinded (i.e. blinded to data management team) cluster randomized crossover controlled trial with two intervention groups: a) an Analyze Early group, and b) Analyze Later group. Subjects in the Analyze Early group will be assigned to receive 50 (or more) compressions of CPR prior to early ECG analysis and defibrillation shocks if indicated and those in the Analyze Later group will receive compressions equivalent to approximately 3 minutes of CPR prior to ECG analysis and rescue defibrillation. The intervention will be implemented by the first qualified provider to arrive at the scene of cardiac arrest and continued by subsequent providers in all ROC sites. Qualified providers are defibrillation-capable first-responders, emergency medical technicians (EMTs), and paramedics.

We will include all out-of-hospital locations within the participating study communities within the Resuscitation Outcomes Consortium. Outcomes will be assessed in the field and at the receiving hospitals.

### **Study Population**

#### **Inclusion Criteria**

All persons of local age of consent or older who suffer non-traumatic cardiopulmonary arrest outside of the hospital in the study communities with defibrillation and/or delivery of chest compressions provided by defibrillation equipped EMS providers dispatched to the scene and do not meet any of the exclusion criteria below.

#### **Exclusion Criteria**

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy;
- EMS-witnessed arrests;
- Non-EMS rhythm analysis (AED placed by police or lay responder is an exclusion but CPR by lay or other non-EMS responders is not);
- Non-ROC EMS agency/provider.

EMS responders will generally provide CPR according to the cluster randomization even for patients with exclusions. Those with a clear exclusion will not be included in the primary analysis. However, all eligible patients are considered enrolled into the Analyze Later protocol regardless of how they are treated and will be included in the primary analysis.

### **Primary Comparison Populations**

The Analyze Late treatment strategy is conjectured to provide an improvement in the rate of neurologically intact ( $MRS \leq 3$ ) survival to hospital discharge in those patients experiencing OOHCA of cardiac origin unwitnessed by EMS and not previously defibrillated. EMS witnessed OOHCA should be treated by an Analyze Early strategy. There is, however, no contraindication to the use of either Analyze Late or Analyze Early in the relatively few patients

experiencing OOHCA due to such noncardiac events as strangulation, drowning, or electrocution. In the emergency setting, unnecessarily introducing a need for EMS providers to evaluate eligibility criteria and randomize individual patients could potentially delay the institution of appropriate life saving treatments. Furthermore, if either the Analyze Late or Analyze Early strategy is proven superior to the other and therefore adopted widely, the eventual use of the superior treatment strategy would likely be applied to all OOHCA unwitnessed by EMS. Hence, this study protocol uses cluster randomization and allows for the evaluation of the safety of the treatment strategies in some patients for whom there is no conjecture of clear benefit. On the other hand, efficacy of the treatment strategies will be analyzed in only those patients who are determined to meet the criteria defining the pre-hospital conditions for which the Analyze Late strategy is conjectured to be of benefit.

**Efficacy Population:** Analysis of primary and secondary efficacy outcomes will be conducted on a modified intent-to-treat basis. In order to be included in the efficacy analyses, patients must meet the inclusion/exclusion criteria for the Analyze Late vs. Analyze Early intervention. In particular, they must not have DNAR orders, have blunt or penetrating traumatic injury or burns, be visibly pregnant, a prisoner, a minor, or have had OOHCA witnessed by EMS. Furthermore, in order to be evaluable, they must also have not have experienced cardiac arrest secondary to drowning, electrocution, or strangulation.

**Safety Population:** Evaluation of the safety of the Analyze Late versus Analyze Early strategies will be made using all data from patients who were treated, regardless of whether they are a member of the efficacy population or not.

## **Random Allocation**

The intervention will be randomly allocated according to the cluster assignment (i.e., Analyze Later or Analyze Early). Each ROC site has been subdivided into multiple clusters (see Sample Size section below) by various means. We believe that randomization by event or by individual patient is not feasible because the intervention is a psychomotor skill and there would be a significant risk of carryover effect from event to event. In addition, randomization by event would add unacceptable complexity for EMS providers who already must deal with randomization of the ITD protocol. Each RCC will be subdivided into a goal of at least 20 clusters by the following means: a) according to EMS agency or geographical boundaries, or b) according to individual defibrillator devices, rig, or station.

The randomization of clusters will be stratified by site. Within each site, clusters will be organized in blocks of varying size (hidden from investigators) according to the number of patients expected to be treated over the course of the study in that cluster. Within each block, clusters will be assigned in equal numbers to order of treatment. All clusters will crossover between intervention assignments at least once (i.e. have at least two distinct treatment periods). Some clusters will crossover more than once (e.g. have four or more distinct treatment periods). There will always be an even number of treatment periods. Among clusters having a single crossover, equal numbers will be assigned to Analyze Late first and Analyze Early second as are assigned to Analyze Early first and Analyze Late second. Among clusters having four treatment periods, equal numbers within each block will be assigned to each of the following four orders of treatment: Late-Early-Late-Early, Late-Early-Early-Late, Early-Late-Late-Early, and Early-Late-Early-Late. Randomization assignment will be performed at the Data Coordinating Center prior to the start of the study. Clusters will not be informed as to which group they are assigned until it is time to crossover to another intervention. Responders will, however, know that each intervention will be tested in the first two periods, and each intervention will be tested in the last two periods in each cluster.

## Intervention

Detailed descriptions and algorithms demonstrating the sequence of action for Analyze Early versus Analyze Later with use of an ITD are presented in Section 4. For those clusters allocated to Analyze Later, defibrillator analysis will not be initiated until after delivery of compressions equivalent to approximately 3 minutes of CPR, after which a rescue shock will be administered, if indicated. For those clusters allocated to Analyze Early, defibrillator analysis will not be initiated until the chest compression count reaches 50 (e.g., 30-60 seconds), or as soon thereafter as possible, after which a rescue shock will be administered if indicated.

### Both Early and Later Arms

**Chest Compressions:** Initiation of chest compressions will not be delayed. Recognition that a patient is in cardiac arrest will immediately prompt one rescuer to initiate and count chest compressions. If the scene is first attended by two EMS rescuers, chest compressions will be performed by one while the second will set up the monitor/defibrillator and place the defibrillator pads. Then ventilation with the ITD will proceed. If three rescuers are present, ventilation and defibrillation readiness can proceed simultaneously (see Appendix 3 for Resuscitation Standards).

**Minimum Interruptions:** Training will emphasize that chest compressions should not be interrupted, except for required ventilations. If endotracheal intubation or other advanced airway procedures are deemed medically necessary, the providers should proceed, but continue chest compressions with minimum interruption. However, training will emphasize that interruption of chest compressions while securing the airway may dilute the theoretical benefit of the initial intervention. Interruption of chest compressions for airway manipulations will be documented when feasible.

**ITD Use:** Training will emphasize that rescuers will use the ITD during initial airway management (either facemask or advanced airway).

### Analyze Later Arm

AED analysis will not be initiated until the chest compression count reaches 300, after which a rescue shock will be administered if indicated.

### Analyze Early Arm

Analysis will be initiated as soon as defibrillation pads are in place and 50 compressions have occurred and a rescue shock will be administered if indicated. The rescuers will note the compression count or time that has been reached by the rescuer assigned to CPR. After the initial analysis, the standard resuscitation protocol will be followed.

### Arrival of Additional EMS Personnel

In tiered response systems, or when backup EMS crews arrive on scene, first-responders delivering the chest compressions consistent with cluster assignment prior to initial ECG analysis should complete this intervention even if paramedics arrive on scene, and, if the subject has defibrillation pads in place, continue using the first crew's equipment until the first ECG analysis (and shock, if indicated).

Additional personnel are encouraged to assist with ongoing activities that do not interrupt chest compressions or initial rhythm analysis. For example, airway management, rotation of chest compressions, and placement of AED/monitor electrodes may benefit from additional personnel. If sufficient personnel arrive, they may also begin attempts at IV access.

### Adherence to Protocol



Personnel will be discouraged from terminating the protocol prematurely. As intention-to-treat principles apply, any breach of protocol will not alter the study group to which a patient has been assigned.

### **Intervention – Compliance**

The time interval from power-on to first ECG analysis (power-to-analysis interval) and to first rescue shock (power-to-shock) will be calculated from the time stamps on the electronic record. Explicit criteria will be used to define successful delivery of the intended therapy and this information will later be fed back to the EMS providers (Table 4).

**Table 4: Intervention Compliance Time Intervals**

	<b>Power-to-analysis interval</b>	<b>Power-to-shock interval</b>
<b>Analyze Early</b>	30-60 seconds	<90 seconds
<b>Analyze Later</b>	180-200 seconds	180-220 seconds

### **Outcome Measures**

#### **Primary**

The primary outcome is survival to hospital discharge with modified Rankin score  $\leq 3$ . Patients who are transferred to another acute care facility (e.g., to undergo ICD placement) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

#### **Secondary Outcomes**

The secondary outcomes are survival to discharge; MRS at 3 and 6 months following hospital discharge; Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) at 1, 3 and 6 months;(31, 32) Health Utilities Index III (HUI3) score(33) at 3 and 6 months following hospital discharge; and Geriatric Depression Scale (T-GDS)(34) score at 3 and 6 months (details in Section 4 and Appendix 4).

#### **Exploratory**

Cerebral Performance Category (CPC) will be assessed at discharge, 3 and 6 months following hospital discharge.

#### **In-Hospital Morbidity**

Number of hospital days and time interval from 911 call to patient death will be described for all hospitalized patients as measures of morbidity after resuscitation.

### **Analyses Methods**

#### ***Primary Efficacy Analysis***

The primary analysis of treatment efficacy will be based on a comparison across treatment arms of the observed proportion of patients in the efficacy population with neurologically intact (MRS  $\leq 3$ ) survival to hospital discharge. A two-sided level 0.05 hypothesis test will be used to test the null hypothesis of equal rates of such favorable events ( $H_0: \pi_{AE} = \pi_{AL}$ ) versus the alternative hypothesis that patients on the Analyze Late arm have a different probability of neurologically intact survival to hospital discharge than do patients on the Analyze Early arm ( $H_1: \pi_{AE} \neq \pi_{AL}$ ). The data will be analyzed in the context of a generalized linear mixed effects model which includes a fixed effect for treatment arm and random effects for each

randomization cluster. The test statistic comparing treatment arms will be the Wald statistic computed as the regression parameter estimate for the treatment indicator divided by its estimated standard error. The fixed sample upper one-sided P value corresponding to that Z statistic will be compared to the boundaries of the protocol defined group sequential stopping rule when expressed on the fixed sample P value scale. At the end of the study, analysis results will be summarized using point estimates of the difference in probability of favorable events, 95% confidence intervals, and P values adjusted for the true sampling distribution imposed by the group sequential stopping rule. (See the discussion of the group sequential monitoring plan below.)

### **Secondary Efficacy Analyses**

All secondary analyses of efficacy endpoints are directed toward finding supporting evidence for the findings of the primary efficacy analysis. As such, they will not be used as the primary basis for establishing superiority of one treatment strategy over the other. Hence, there is no plan to make any statistical adjustment for the multiple comparisons inherent in the secondary efficacy analyses, which include:

*Modified Rankin Score (MRS) at hospital discharge.* The mean MRS at hospital discharge will be compared across treatment groups using a general linear mixed model including the binary variable indicating AL vs. AE assignment and random effects for the randomization clusters. For the purposes of this analysis, patients dying before admission to the hospital will be treated the same as admitted patients dying before hospital discharge and will be assigned an MRS of 6.

*Survival to hospital discharge.* This secondary analysis of treatment efficacy will be based on a comparison across treatment arms of the observed proportion of patients in the efficacy population with survival to hospital discharge. This analysis shall proceed in a manner entirely analogous to that for the primary efficacy endpoint.

*Neurologically intact survival to hospital discharge adjusted for prognostic variables.* A secondary analysis of the primary endpoint will adjust for those pre-randomization variables which might reasonably be expected to be predictive of favorable outcomes. Generalized linear mixed models will be used to model the proportion of subjects with neurologically intact (MRS  $\leq$  3) survival to hospital discharge by AL vs. AE group adjusted for randomization cluster (random effect), site (dummy variables modeling the 11 ROC sites), patient sex, patient age (continuous variable), witnessed arrest (binary variable), location of arrest (public versus non-public), time of response (continuous variable modeling minutes between call to 911 and arrival of EMS), presenting rhythm (dummy variables modeling asystole, PEA, VT/VF, or unknown), and treatment assignment in the ITD/sham device intervention. The test statistic used to assess any benefit of one strategy over the other will be computed as the generalized linear mixed model regression coefficient for the AL vs. AE treatment assignment divided by the estimated standard error. Statistical inference will be based on one-sided P values and 95% confidence intervals which adjust for the stopping rule used for the primary analysis.

*Post-discharge neurological function, quality of life, and depression.* Surviving patients will be contacted post-discharge to obtain consent for additional follow-up via telephone with consenting patients or their proxies regarding cognition, quality of life, and depression. Primary emphasis will be placed on analysis of outcomes at 6 months post hospital discharge, though additional analyses will also compare these secondary endpoints 3 months after hospital discharge. Analyses of each of these outcomes at each time point will be compared across treatment groups using a general linear mixed model including the binary variable indicating AL

vs. AE assignment and random effects for the randomization clusters. Analyses will first be conducted conditional on survival to the relevant time point by using only data from those patients offering consent, as well as using data imputed from discharge data for those surviving patients refusing consent. The data missing due to lack of consent for follow-up will be multiply imputed using measurements of patient age, sex, length of hospital stay, incidence of major adverse outcomes during hospitalization, MRS at hospital discharge, and whether the patient was discharged to home or a nursing facility. Additional analyses of neurological function and quality of life will then incorporate measurements for patients dying prior to hospital admission, during hospitalization, or within 3 or 6 months post discharge. Dead patients will be assigned the worse category of neurological function and quality of life for each measurement.

*Morbidity* As a measure of morbidity during hospitalization, the number of days hospitalized conditional upon survival to discharge will be compared across treatment groups using the t test which allows unequal variances. A similar analysis will also be conducted comparing the days of hospitalization for patients admitted to the hospital, but dying prior to hospital discharge. Finally, treatment groups will also be compared with respect to the number of days alive post hospital discharge during the first 6 months post OOHCA in order to incorporate information about both dead and surviving patients. In this analysis, data missing due to lack of consent for follow-up will be multiply imputed using data available at hospital discharge, and patients dying before hospital admittance or prior to hospital discharge will be scored as 0.

### **Safety Analyses**

The incidence of adverse events will be recorded for all patients in the safety population and presented by treatment arm (AL vs. AE) to the DSMB for their review during the conduct of the study, as well as summarized and compared across treatment arms in the final report of study results. Statistical significance of differences in the incidence of safety endpoints plays a lesser role, due to the need to be cautious in the introduction of new treatments in a human population. Hence, emphasis is placed on the presentation of results, with statistical tests provided for guidance on the precision of estimates as indicated.

Since both interventions, Analyze Early and Analyze Late, are in current use, there is no anticipation that the study itself will present any safety issue, for example, because of new or difficult procedures. Indeed, one would expect a study benefit in any treatment arm because of the increased training and monitoring of CPR performance. Nevertheless specific measures that will be monitored include:

*Delay of treatment.* Witnessed episodes of cardiac arrest with response times (911 call to arrival) of less than 4 minutes might be expected to respond to early defibrillation. This subgroup of patients will be carefully monitored for potential harm from an Analyze Later strategy. The Data and Safety Monitoring Board will be asked to make recommendation concerning protocol modification, should any safety issue appear.

*Compliance with protocol.* Patients with EMS witnessed arrest are to be treated with early analysis for defibrillation regardless of cluster randomization to AL or AE. The adherence of EMS providers to this aspect of the protocol will be closely monitored. In addition, sites will be monitored with respect to adherence to the guidelines for either the Analyze Late or Analyze Early strategies according to the cluster randomization scheme. In particular, adherence to protocol will be monitored and reported separately for times immediately preceding and following sites' crossover from one strategy to the other. The Data and Safety Monitoring Board will be asked to make recommendation concerning protocol modification, should any safety issue related to protocol adherence appear.

*Serious adverse events.* The incidence of each serious adverse event, along with other major adverse medical or surgical outcomes identified during review of hospital records, will be tabulated by treatment arm and compared when indicated using Pearson's chi squared test. In order to facilitate the identification of differences in rates of such events that might be due to greater survival to hospital admission and/or hospital discharge on one of the treatment arms, the incidence of any of the above specific events and/or death (either prehospital or during hospitalization) will be reported in a combined fashion and compared as indicated using Pearson's chi squared statistic.

### **Subgroup Analyses**

Analyses will be performed in each subgroup, along with tests for statistically significant interactions. However, it is recognized that the study is not powered adequately to detect interactions, and thus all subgroup analyses are judged exploratory.

### **Sample Size, and Study Duration**

The sample size for the factorial trial is driven by the power analysis for the ITD intervention. A full description of the assumptions that were used to estimate the sample size required for that intervention is given in section 2. The anticipated distribution of patients by presenting rhythm and whether arrest was EMS witnessed or not was estimated based on these assumptions (Table 5.)

**Table 5: Proportion of all EMS treated OOHCA patients according to presenting rhythm and EMS Witness status**

Presenting Rhythm	EMS Witnessed	EMS Unwitnessed	Total
Asystole	0.0231	0.4769	0.500
Pulseless Electrical Activity (PEA)	0.0270	0.2230	0.250
VT/VF	0.0499	0.2001	0.250
<b>TOTAL</b>	<b>0.1000</b>	<b>0.9000</b>	<b>1.000</b>

Eligibility criteria for the AL vs. AE intervention excludes subjects for whom the arrest was witnessed by EMS. The distribution of patients to the various treatment strategies by presenting rhythm was estimated by taking into account that patients with EMS Unwitnessed OOHCA will be randomized (by cluster) in a 1:1 ratio to the AE or AL strategies (Table 6).

**Table 6: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total AE vs AL Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	AE	AL
Asystole	0.000	0.012	0.012	0.000	0.119	0.119	0.119	0.119	0.250	0.250
PEA	0.000	0.014	0.014	0.000	0.056	0.056	0.056	0.056	0.125	0.125
VT/VF	0.015	0.017	0.017	0.030	0.035	0.035	0.050	0.050	0.103	0.103
<b>TOTAL</b>	<b>0.015</b>	<b>0.043</b>	<b>0.043</b>	<b>0.030</b>	<b>0.210</b>	<b>0.210</b>	<b>0.225</b>	<b>0.225</b>	<b>0.478</b>	<b>0.478</b>

Based on ranges of estimates in published data and results of the ASPIRE trial, and allowing for 1-5% improvement due to greater quality control on CPR process in the clinical trial setting, It is estimated that in the absence of an ITD and when managed according to the Analyze Early (AE) strategy, the probability of survival to hospital discharge would be 1.05% for patients presenting with asystole, 4.02% for patients presenting with PEA, and 20.20% for VT/VF. These assumptions lead to an estimated probability of survival to hospital discharge of 0.0609 when treated under the AE strategy with a sham valve. Assuming that 88.9% of such survivors would have acceptable neurological status ( $MRS \leq 3$ ), we thus estimate a rate of 0.0541 for neurologically intact survival to hospital discharge under treatment with the AE strategy and a sham valve.

Under the alternative hypothesis used for power calculations, the effect of the Analyze Late strategy on neurologically intact survival is presumed to vary by presenting rhythm. While patients with initial rhythms of asystole and PEA cannot expect to benefit from an Analyze Early versus Analyze Later protocol in the sense of potentially obtaining early defibrillation, they could benefit from the Analyze Later strategy by having fewer delays in blood circulation due to taking time for early analysis. We therefore hypothesize a 3% relative increase in survival for patients in the AL arm over the AE arm for these two rhythms. A relative benefit of 1.50 is hypothesized for those patients in the VT/VF, with the benefit occurring primarily in patients who would not respond rapidly to early defibrillation, though that group cannot be identified *a priori*. Applying these hypothesized effects to the numbers given above results in an estimated probability of survival to hospital discharge of 0.0838 for patients treated with an AL strategy in the absence of an ITD, with a corresponding hypothesized rate of 0.0745 for neurologically intact survival to discharge. Details of these calculations are provided below (Table 7).

**Table 7: Estimated proportions of all EMS treated OOHCA patients surviving to discharge and surviving to discharge with  $MRS \leq 3$  by AL vs. AE treatment arm and presenting rhythm**

Presenting Rhythm	Stratum Weight	Analyze Early Probability of Survival to Discharge	AL / AE Relative Benefit	AL Probability of Survival to Discharge
<b>Asystole</b>	0.5299	0.0105	1.03	0.0108
<b>PEA</b>	0.2478	0.0420	1.03	0.0433
<b>VT/VF</b>	0.2224	0.2020	1.50	0.3030
<b>Probability of Survival to Discharge (weighted average)</b>		0.0609		0.0838
<b>Probability of Neurologically Intact Survival to Discharge (88.9% of patients surviving to hospital discharge)</b>		0.0541		0.0745

In the process of accruing 14,154 evaluable patients to the ITD/sham device intervention, it is estimated that approximately 15,436 patients with OOHCA will be treated by EMS at one of the participating ROC sites, with approximately 13,893 of these patients (90%) not having EMS witnessed arrest and therefore receiving Analyze Late or Analyze Early. Estimating that 98% of these patients will be judged evaluable, 13,560 patients will be used for the comparison of Analyze Late versus Analyze Early strategies. We therefore consider the ability of a two-sided level 0.05 test with 13,560 subjects to reject a null hypothesis that the probability of neurologically intact survival to hospital discharge is 0.0541 on both treatment arms, with statistical power computed under the alternative hypothesis that the AL arm would instead have a 0.0745 probability of neurologically intact survival. The data will be analyzed in

the context of a generalized linear mixed effects model which includes a fixed effect for treatment arm and random effects for each randomization cluster. The test statistic comparing treatment arms will be the Wald statistic computed as the regression parameter estimate for the treatment indicator divided by its estimated standard error. Power computations are based on formulas appropriate for a two-sample test of binomial proportions using Pearson's chi squared statistic. We incorporate into those computations an assumed 5% loss of efficiency due to the cluster randomization with crossover.

The clinical trial will be conducted using a two-sided level 0.05 group sequential stopping rule based on up to three analyses (two interim analyses and the final analysis) after accruing approximately one-third, two-thirds, and all of the maximal sample size. The stopping rule corresponds to an O'Brien-Fleming design as described in more detail under the monitoring plan. Using that stopping rule, a sample size of 13,560 evaluable patients will provide approximately 99% power to reject the null hypothesis under the conjectured treatment effect.

The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 13,560 evaluable patients for the Analyze Late versus Analyze Early comparison will require 16 -18 months.

### **Effect of Clustering and Crossover Upon Required Sample Size**

It is anticipated that the number of cardiac arrest episodes in each cluster will vary, as the underlying size of the geographic area and population served are variable. Some sites will cross a large geographic area over from one intervention to the other during the trial to reduce the expected number of episodes; others will cross monitor/defibrillators from one intervention to the other. Most cluster designs assume equal-sized clusters, but the presence of unequal cluster size has implications for sample size (Appendix 5).

The clusters and annual expected number of cardiac arrests episodes in each site are shown below (Table 8). Since most clusters employ crossover, and those that do not have small expected numbers, the effective sample size of each cluster should be at least 95% efficient compared to individual randomization. This is a conservative assumption since utilizing the crossover design is actually more efficient than even individual randomization.

Having close to 20 or more clusters at each site with no overly large cluster, as well as using crossover and randomizing so that each intervention is being used by half of the clusters at any time will provide reasonable balance between temporal factors, as well as system and patient factors.

We can think of no likely crossover effect except that compliance might be compromised by habit or forgetfulness at the time of crossover. We will be monitoring compliance, and if non-compliance is  $\geq 2$ -fold higher in the 2 weeks following crossover than in the several months before at a site level, then all episodes from that 2-week period at that site will be dropped from the primary analysis. Of course, measures would be taken by the local site to address the "crossover compliance" issue.

Other designs were taken into consideration, particularly individual episode randomization. Devices (AEDs) are not currently capable of being programmed to randomize individual episodes and then provide correct prompts. Other forms of individual randomization (e.g. envelope) would therefore result in expecting EMS providers to ignore existing prompts. The consensus of the ROC investigators was that this would create serious compliance issues and individual randomization was not seen as a viable option. The simplest design is to invoke

cluster design without crossover. This method is less efficient than crossover, or individual, randomization. Therefore clustering design with crossover is seen as the most efficient design from the choice of feasible and practical designs.

**Table 8: Summary of ROC Site Cluster Plans**

	<b>Pop Served (#)</b>	<b>Annual CA Treated (#)</b>	<b>Cluster Type</b>	<b># of Clusters</b>
<b>Toronto</b>	<b>2,456,800</b>	<b>1,777</b>	geographic, agency, station	<b>214</b>
<b>Alabama</b>	<b>1,278,936</b>	<b>485</b>	rig	<b>75</b>
<b>Portland</b>	<b>1,444,219</b>	<b>604</b>	agency, station defib	<b>166</b>
<b>Pittsburgh</b>	<b>670,911</b>	<b>690</b>	rig	<b>124</b>
<b>Seattle/King Co</b>	<b>1,763,000</b>	<b>888</b>	agency, geographic	<b>23</b>
<b>Dallas</b>	<b>2,023,705</b>	<b>1,331</b>	rig	<b>151</b>
<b>Ottawa</b>	<b>3,000,000</b>	<b>1,468</b>	geographic, agency, defib	<b>246</b>
<b>Milwaukee</b>	<b>928,018</b>	<b>794</b>	station	<b>61</b>
<b>BC</b>	<b>3,115,331</b>	<b>1,364</b>	geographic	<b>32</b>
<b>San Diego</b>	<b>2,900,000</b>	<b>2,161</b>	rig	<b>334</b>
<b>Iowa</b>	<b>956,188</b>	<b>875</b>	geographic	<b>15</b>
<b>Totals</b>	<b>20,537,108</b>	<b>12,437</b>		<b>1441</b>

## 4. Factorial Implementation of Both Protocols

### Summary

The background, significance, aims, and hypotheses of the ITD and Analyze Later versus Analyze Early trials have been previously described. Investigators intend to implement these studies simultaneously (though staggered start and stop times may occur because of resource/regulatory logistics), capitalizing on the common infrastructure necessary to accomplish the studies, thereby improving efficiency and speed of their completion. The following describes study issues common to both the ITD and Analyze Later versus Analyze Early studies including Study Setting, Study Population, Resuscitation Guidelines, Monitoring of CPR Process, Outcome Measures, Data Collection, Training, Data Safety Monitoring Strategy (DSMB), and Human Subjects.

### Setting

The Resuscitation Outcomes Consortium (ROC) includes ten Regional Clinical Centers. These ROC sites are served by approximately 200 EMS agencies. The baseline characteristics of these ROC sites are summarized in Table 9. Of greater than 12,000 cardiac arrest episodes among the sites, annually, approximately 10,000 are treatable by EMS.

**Table 9: Distribution of Initial Cardiac Rhythm and Outcome for Cardiac Arrest Episodes Among ROC Sites**

	Dallas	Iowa	Milwaukee	Ottawa	Ottawa	Pittsburgh	Portland	Seattle	Seattle	Alabama	Toronto	San Diego	Total
<b>EMS System</b>	Biotel			OPALS	BC			King County	Seattle EMS				
<b>Year Reported</b>	2003	2003	2004	2002	2003	Average of 1998-2002	2003	2003	2003	2004	2002	2004	
<b>Population Served</b>	2M	956k	928k	3M	3.1M	671k	1.4M	1.2M	600k	1.3M	2.5M	2.9M	20.6M
<b>VF or PVT</b>	297	294	162	470	431	235	151	158	95	106	462	648	3509
<b>Survived to discharge</b>	50	44	32	62	74	33	37	44	29	24	39	97	565
<b>Received &lt;=1 shock</b>	178	217	158	281	258	141	112	116	70	73	120	427	2151
<b>Asystole</b>	676	349	437	601	577	289	211	235	147	285	817	1102	5726
<b>Survived to discharge</b>	14	5	10	5	12	12	3	6	0	5	7	33	112
<b>PEA</b>	358	232	195	397	356	166	242	162	91	94	498	411	3202
<b>Survived to discharge</b>	25	12	18	9	7	10	15	16	12	6	12	21	163
<b>Cardiac arrests</b>	1331	875	794	1468	1364	690	604	555	333	485	1777	2161	<b>Totals</b> 12437
<b>Survived to discharge</b>	89	61	60	76	93	55	55	66	41	35	58	151	840

**Note: Shaded numbers are estimated**



## **Study Population**

Except for some specific situations, the inclusion and exclusion criteria for both ITD and Analyze Later protocols will be the same.

### **Inclusion Criteria**

All persons of local age of consent or older who suffer non-traumatic cardiopulmonary arrest outside of the hospital in the study communities with defibrillation and/or delivery of chest compressions provided by EMS providers dispatched to the scene and do not meet any of the exclusion criteria below.

### **Common Exclusion Criteria**

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy.
- Non-ROC EMS agency/provider.

### **ITD Exclusion Criteria**

- Tracheostomy present;
- CPR performed with the mechanical compression “Autopulse” device;

### **Analyze Later Exclusion Criteria**

- EMS witnessed arrests;
- Non-EMS rhythm analysis (AED placed by police or lay responder);

## **Resuscitation Guidelines**

The ROC Investigators have developed and will disseminate consensus guidelines on how the patient with cardiac arrest should be treated in the prehospital, emergency department and hospital setting (see Appendix 3).

## **Monitoring of CPR Process**

A long-term goal of the Resuscitation Outcome Consortium (ROC) is for all participating first EMS responders and ALS providers to have technology on, or adjunctive to, their automated (AED) and/or manual monitor/defibrillators that can monitor individual components of resuscitation. These data will serve as the basis for regular, systematic monitoring and review of the CPR process for purposes of quality improvement at each ROC site before and during clinical trials. Such processes will assure the safety of CPR performance in the field. Also feedback of this knowledge is essential to care delivery since improved quality assurance has been associated with improved outcomes after resuscitation.(67) Finally, it is essential to efficient trial conduct since low baseline rates of survival are associated with larger sample sizes to detect a clinically important difference.

### **Rationale**

Recent studies have demonstrated that CPR is frequently not performed according to evidence-based guidelines in the out-of-hospital and in-hospital setting.(28, 29) Although these studies lacked power to detect a significant relationship between CPR process and patient outcome, a related study demonstrated that a greater rate of chest compressions was

associated with a greater likelihood of achieving restoration of spontaneous circulation.(68) The importance of monitoring and improving CPR process was confirmed by the observation of potentially deleterious hyperventilation in the Milwaukee pilot study of ITD.(26)

A variety of evolving technologies offer the ability to monitor CPR process either directly or indirectly through AEDs. These include chest impedance (69) (used to monitor chest compression rate and ventilation rate(70)), chest acceleration(71) (used to monitor chest compression rate, depth, release, and duty cycle), and audio recording (used to monitor audible events during resuscitation). Each of these measures has advantages and limitations. For example, a recent prehospital study reported that even when obtaining data related to CPR process was emphasized, technical and signal quality limitations prevented its analysis in more than 25% of episodes(29). In addition, there is also considerable site heterogeneity across the Consortium that precludes the use of a single manufacturer or a single CPR monitoring technology. Accordingly, the Consortium has defined and will monitor a minimal data set pertinent to the CPR process but allow each participating site to individually specify and implement the means by which such data will be obtained. Please see Appendix 2 for a list of how each EMS Agency will monitor CPR process.

### ***Method of Monitoring CPR Process***

**Overview-** In preparation for the start of formal CPR process monitoring and the proposed ROC cardiac arrest trial, an educational program will be developed and implemented at each site to refresh provider skills on chest compression and ventilation, with emphasis on uninterrupted chest compressions, minimizing of "hands-off" intervals, and avoidance of hyperventilation.

All ROC clinical trial sites will implement a high-quality system for monitoring individual components of CPR, to include, at a minimum, the rate of chest compressions, the rate of ventilation, and the proportion of pulseless resuscitation time during which chest compressions are provided (i.e. CPR fraction). Recent studies show no significant differences in these parameters during the first five minutes of resuscitation as compared with the entire resuscitation episode.(28, 29) It is anticipated that during the initial period interruption of CPR due to rhythm analysis or other procedures is more likely than throughout the resuscitation episode. After insertion of an advanced airway and initiation of ventilation that is asynchronous with chest compressions, hyperventilation is more likely than during the early resuscitation period. Therefore CPR process will be quantified during the first analyzable five minutes for 100% resuscitations as well as ventilations throughout the resuscitation episode in those who receive an advanced airway, until a sustained return of spontaneous circulation or resuscitation efforts are terminated. Sites will be encouraged to monitor the entire episode.

Sites will be required to demonstrate an ability to adequately acquire and analyze these CPR process data, identify and attempt to correct any observed deficiencies, and meet minimum performance standards (Appendix 2 CPR Process Monitoring: CPR Performance Standards) before being eligible to enroll patients in the present trial. In addition, ongoing monitoring and review of CPR process, will be used throughout the conduct of the trial.

**Monitoring Devices-** A range of monitoring/defibrillator devices will be deployed across the ROC sites that have capabilities to monitor CPR process. These devices and their capabilities are summarized in Appendix 2 CPR Process Monitoring: CPR Process Monitoring Devices.

**Specific Methods-** BLS and ALS providers will be trained to turn on the power of their AED or monitor immediately upon recognition of a subject in cardiac arrest. Monitoring hardware will be applied to the patient as soon as possible. This power-on event will initiate the recording by the device, and serve as a surrogate marker for "time zero" of initiating CPR. Each site will make efforts to maintain synchronization of monitor clocks with a common time standard (e.g. atomic clock time).

At the completion of every resuscitation attempt, the electronic record from the BLS and ALS devices used during the call will be obtained by the investigators. All electronic records will be reviewed manually by using the commercial software specific to the device, assisted where available, by proprietary automated analysis software. The record will be annotated from the time of power-on (“zero time”), and the parameters of resuscitation quantified during these periods (Appendix 2). Determination of whether a resuscitation effort meets minimally acceptable CPR performance standards for the Consortium will be based on whether it meets acceptable chest compression rate, ventilation rate and CPR fraction criteria as defined in Appendix 2.

Use of immediate (real-time) feedback software will be at the discretion of individual ROC sites and EMS agencies. Depending on system configuration, providers may be prompted by such software to modify the rate or depth of chest compressions, and to minimize interruptions in the provision of CPR. When such feedback is deployed, prompts will conform to the same target ranges specified in ROC CPR performance standards. Regardless of whether or not real-time feedback is provided, all resuscitations will be reviewed for adherence to the same performance standards, and a mechanism in place for remediation, if necessary. CPR process data derived from resuscitations during which real-time feedback was provided will be designated by an appropriate identifier. These sites may separately examine the impact of using real-time feedback in their systems.

## **Outcome Measures**

### **Primary**

The primary outcome for both studies is survival to hospital discharge with modified Rankin score  $\leq 3$ . Patients who are transferred to another acute care facility (e.g., to undergo ICD placement) will be considered still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

### **Secondary**

Note that additional background information, rationale for selection, and details about specific functional status measures are given in Appendix 4. An interesting methodological issue is how to measure post-discharge outcomes. Physician and neuropsychological evaluations are considered the gold standard for the diagnosis of cognitive impairment. However such methods are unlikely to be feasible and likely to be associated with a high proportion of missing data in a population that resides in such a diverse geographic area as that participating in the Resuscitation Outcomes Consortium. For example, data from the ROC EMS structures serve demonstrates that participating EMS agencies (72% reporting) serve a total catchment area of 78,521 square miles. If the pattern of missingness is informative (e.g. patients from rural areas with delayed resuscitation less likely to be interviewed), then the post-discharge outcome data are susceptible to bias. Therefore all post-discharge outcome assessments will be made by using measures validated for phone administration to increase the response rate. All assessments will be made by trained interviewers.

Our criteria for choosing particular instruments to measure neurological status include prior data about reliability and reproducibility, availability of instruments suitable for a multicenter trial, and prior data in cardiac arrest survivors. The **Modified Rankin Scale (MRS)** has face validity and can be determined via review of the clinical record, in person or over the telephone.(72, 73) MRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.(74, 75) MRS has prior use in a cohort of neurosurgical patients

with in-hospital cardiac arrest(76) and in a cohort of survivors of out-of-hospital cardiac arrest.(77)

We are aware that CPC is less validated compared to some other measures that will be utilized in this study. CPC will be assessed by using a structured questionnaire via telephone administration (Appendix 4 of protocol). These latter questions were developed based on experience assessing outcomes after discharge in the OPALS study, PAD trial and ASPIRE trial. However it should be recognized that these questions have not been validated in their current format.

The **Health Utilities Index (HUI)** is a generic measure of health-related quality of life. (33) It has reliable interview, telephone, and proxy instruments with extensive validation in a multiple populations, including two cohort studies of survivors of cardiac arrest.(84, 85) HUI was positively correlated with bystander CPR, suggesting construct validity for measuring neurological injury incurred during cardiac arrest.(85)

The Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) is a measure of cognitive status.(31, 32) ALFI-MMSE correlates with severity of cognitive impairment as measured by the Clinical Dementia Rating Scale class.(31) Compared to the brief neuropsychiatric screening test, which is a weighted score of the Trailmaking A,(86) Word Fluency,(87) Weschler Memory Scale-Mental Control and Logical Memory,(88) ALFI-MMSE had a sensitivity of 68% and specificity of 100% for mild cognitive impairment. The corresponding MMSE values were 67% and 100%.(31)

The telephone version of the Geriatric Depression Scale (T-GDS)(34) detects the presence or absence of depression. Using a cutoff of 10/11T-GDS has a sensitivity of 86% and specificity of 70% for detecting depression compared to a comprehensive assessment by a geriatric psychiatrist.

**Table 10: Timing and Content of Secondary and Exploratory Outcome Measures**

	Discharge	1 Month	3 Months	6 Months
MRS	X		X	X
CPC	X		X	X
ALFI- MMSE		X	X	X
HUI			X	X
GDS			X	X

**Exploratory Outcome**

Consensus statements recommend use of the **Cerebral Performance Category (CPC)** to assess functional outcomes after resuscitation from cardiac arrest.(78, 79) CPC is a five-point scale that was adapted from the Glasgow Outcome Scale.(80, 81) CPC had limited discrimination between mild and moderate brain injury, and only moderate correlation with a generic measure of health-related quality of life in a small study that was limited by a high rate

of loss to follow-up.(82) However, CPC predicts long-term survival after resuscitation from cardiac arrest.(83)

## Method of Assessing Post Discharge Outcomes

All post-discharge assessments will be performed by using instruments that will be made available in English and Spanish. Study coordinators will be trained to administer these instruments prior to study implementation by using didactic instruction, standardized patients and mock interview of each other according to current standards.(89) Spanish-language translators will be used as required. Interviewers will be instructed to speak clearly and articulate distinctly; ascertain the interviewee's ability to hear a spoken language at a conversational volume; try to ensure no one other than a proxy and the interviewee are present; if a precise answer is not given, probe for the correct response; exercise judgment about allowing sufficient time to answer a question before proceeding on to the next question; record the interviewee's last response as their answer to each question. Only research staff that completed this training successfully will be allowed to perform post-discharge assessments.

We are aware that some patients may be too impaired to complete an interview. Therefore, the ALFI-MMSE will be the instrument administered first during the three month interview. Patients who score  $\geq 17$  will be asked to complete the interview by self-report. Patients who score  $< 17$  will be assessed further by interview of a proxy. We and others used a similar approach to assessment of post-discharge outcomes in the Public Access Defibrillation (PAD) trial. Contact details for the patient and their proxy will be identified at the time of notification of participation in hospital. Consent will be sought from the patient and their proxy for interview after discharge.

## In-Hospital Morbidity

Number of hospital days and time interval from 911 call to patient death will be described for all hospitalized patients as measures of morbidity after resuscitation.

## Other Outcomes

Other surrogate outcomes will be collected for descriptive purposes:

**i) Return of Spontaneous Circulation:** (ROSC) defined as the documented presence of a measurable pulse and blood pressure at any time after initiation of resuscitative efforts. There is no minimum duration for this return of spontaneous circulation.

**ii) Admission to Hospital.**

**iii) Survival to 24 Hours.**

**iv) Process Outcomes:** a) Number of Shocks Required: The total number of defibrillatory shocks; b) Duration of Pulselessness: The duration of pulselessness (from 911 to ROSC).

## Data Collection

### Data Forms

Appendix 6 contains draft data forms for both protocols.

### Source of Data Collection

Data will be collected prospectively as patient care progresses. This will include a review of all the EMS patient care report(s), EMS dispatch times, EMS/fire/first responder electronic ECGs, emergency and hospital records. No additional studies or patient contact (except for notification of study participation) will be required for collection of this data up to hospital discharge.

## **Data Common to Both Protocols**

### ***Out-of-Hospital***

Demographics, EMS response times (call receipt to arrival, arrival at patient side, etc.), witnessed arrest, bystander CPR, location of arrest, CPR process monitoring measures (ventilation rate, compression rate, CPR fraction), cause of arrest (cardiac vs. non cardiac), EMS therapies (drugs, shocks, advanced airway, hypothermia), first ECG rhythm, disposition, return of spontaneous circulation, potential adverse events.

### ***Emergency and Hospital***

Major procedures, possible complications of intervention, admittance to the hospital, cause of arrest, ICU days, date of awakening, disposition at discharge, withdrawal of care (DNR status) as well as MRS and CPC at hospital discharge.

### ***Follow-up***

Patients will be contacted by study personnel at 1 month after discharge and will have the ALFI-MMSE applied by telephone interview. They will be contacted by study personnel at 3 months and 6 months to have the MRS, CPC, ALFI-MMSE, HUI and GDS applied by telephone interview.

### ***Initial ECG Rhythm***

The initial ECG tracing will be analyzed off-line. The individuals performing this analysis will be blind to the interpretation that was performed in real-time by the AED and/or rescuers. The entire tracing that is available for analysis will be provided, and three possible ECG rhythms will be defined.

Asystole will be defined as background electrical activity less than 0.2 mV in amplitude with  $\leq 10$  beats per minute average rate (e.g., a 6-second strip without ventricular complexes).

VF will be defined as irregular, disorganized ventricular electrical activity of variable amplitude exceeding 0.2 mV.

Pulseless electrical activity (PEA) will be defined as electrical activity with R-waves of any width at an average rate of  $>10$  beats per minute (e.g., organized ventricular electrical activity with R waves of any width that occur more than once over a 6-second period). The rate of PEA will be recorded as well.

## **Items Specific to ITD Protocol**

Items specific to the ITD protocol will generally deal with events surrounding the use of the device; approximate time ITD attached, vomit with ITD, attachment of ITD to bag-mask or advanced airway, adverse/unusual events (device fills with fluid twice, device failure, patient complications) and protocol adherence.

## **Items Specific to Analyze Later Protocol**

Items specific to the Analyze Later protocol will generally deal with events surrounding the compliance with the assigned cluster. Each event will be reviewed to determine whether the assigned protocol was followed.

## **Data Entry**

The DCC will provide web-based HTML forms to collect necessary information from the RCCs. 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 DCC 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.

## **Database Management**

The DCC will use a two-tiered database structure. A front-end database serves the web entry needs, using a database management system well-suited to handling updates from multiple interactive users. The data from this database will be transferred periodically (e.g. bi-weekly) to a “warehouse” database, on which data queries for analyses and monitoring will be run. Various versions of this database are kept as needed, e.g. for quarterly or DSMB reports. The “warehouse” database management system was selected for its ability to manage large quantities of data, to merge data from multiple databases as required, to handle complex and possibly changing relationships, and to produce analysis datasets that can be imported into a variety of statistical analysis packages.

## **Training**

### ***Overview***

The training objectives include the following (each detailed below): review of optimal CPR performance, scientific basis for and review of study protocols, practicum/“hands-on” session, and post-test. It is anticipated that approximately 2 hours of didactic instruction and 1 hour of practicum will be required.

### ***Optimal CPR Performance***

The purpose of this component is to provide training in optimal chest compression and ventilation skills for all participating EMS personnel and to standardize the performance of CPR across all ROC sites as much as possible. This training component will be implemented either as part of the protocol training or as a separate training module prior to specific study training. Key concepts include: optimal chest compression rate (100/min) and depth (38-51 mm), correct hand position on the distal sternum, complete chest wall recoil with each compression, minimizing “hands-off” intervals, avoiding hyperventilation (target rate 10-12/min), and proper breath duration (<2 seconds for an unprotected airway and 1 second for a protected airway). Training will also emphasize maintaining a continuously tight facemask seal with the “E-C” hand technique (one airway rescuer) or two-handed technique (two airway rescuers) when using the ITD and the use of ventilation timing assist lights with advanced airways (e.g., Combitube, laryngeal mask airway [LMA], or endotracheal tube).

### ***Scientific Basis for ITD and Analyze Later Protocols***

Level-appropriate presentation of the scientific principles underlying the ITD and Analyze Early versus Analyze Later studies will increase provider investment and improve protocol adherence. This should include presentation of prior work in both animals and humans and justification for a randomized clinical trial, including discussion as to why these approaches require further investigation prior to widespread implementation.

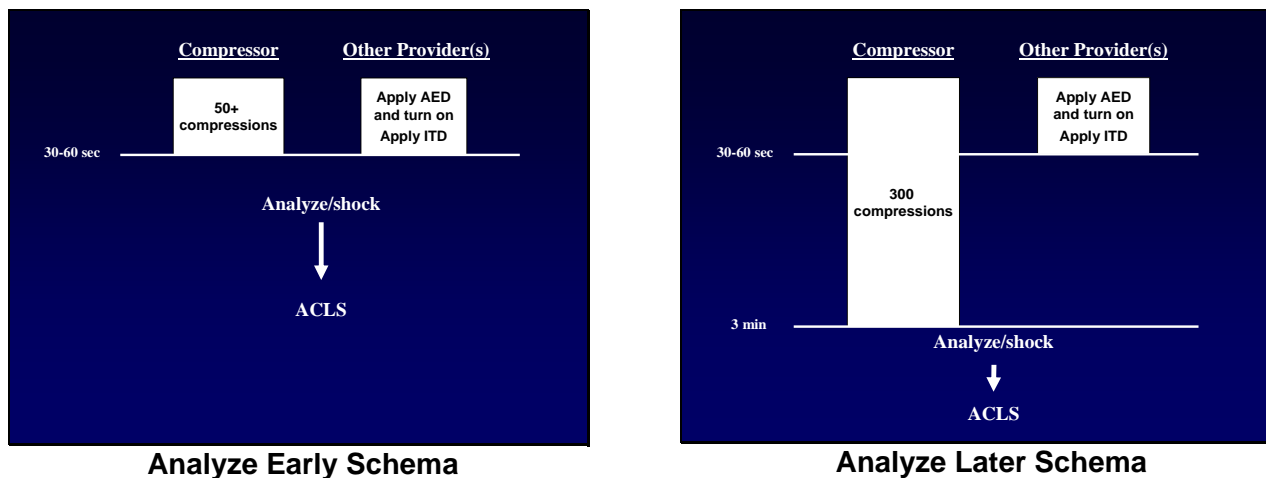
### ***Study Protocols***

This section will include the following: overall study design, inclusion and exclusion criteria, the process of exception to informed consent under emergency circumstances, and the study protocol. While the overall factorial design makes the analytic methodology somewhat complex, the operational protocol has been simplified for the purposes of training and actual trial implementation. From the provider perspective, there are only two arms to the study, as an ITD will be applied to all eligible patients but the group assignment (active or sham device) will be unknown to the providers. This creates an Analyze Early arm and an Analyze Later arm, both with ITD application existing as part of the study protocol. The training will mandate that one of the providers be designated the “compressor”; this designation should occur prior to the patient

encounter to avoid confusion about role assignments once an arrest is recognized. The two study arms are then defined by the number of compressions delivered by the “compressor” before a pause for rhythm analysis and defibrillation attempts when indicated. In the Analyze Later arm, a number of compressions equivalent to approximately 3 minutes (e.g. 300 if the local CPR protocol is 100 compressions per minute with ventilations interposed, 180 if the local protocol is a compression:ventilation ratio of 15:2) will be delivered, while in the Analyze Early arm a minimum of 50 compressions will be delivered (see schematics below). The “compressor” should count the number of compressions out loud to alert the other providers as to the ongoing duration of chest compressions and to maintain an accurate count. Visual reminders (such as a colored tag on the AED/defibrillator) designating “300” or “50” compressions will be used to enhance protocol compliance, especially with a crossover design. In addition, crews will be encouraged to review their designated number of compressions as part of the daily checklist. The use of the term “compressor” should be encouraged, not only to enhance protocol compliance but also to underscore the importance of chest compressions during resuscitation.

Training will define two tasks for the remaining provider(s): a) placement of the monitor/defibrillator pads and preparation for analysis/defibrillation, and b) proper application of the ITD/facemask, including maintenance of a continuously adequate seal during chest compressions and ventilations. The first priority following initiation of chest compressions by the “compressor” is the rapid placement of defibrillator pads; the monitor/defibrillator should be “powered-up” immediately upon recognition of pulselessness or sooner. The ITD and facemask should then be attached to the resuscitation bag and oxygen canister and a continuously tight seal maintained. When additional personnel are available, the two tasks should be performed simultaneously. Training will emphasize immediate use of the ITD with initial airway management and continued use throughout the resuscitation while chest compressions are being performed as well as dedication of a single individual to maintaining adequate mask seal using a two-handed facemask technique whenever possible. Upon completion of rhythm analysis and defibrillation when indicated, standard ACLS procedure will ensue. Providers will receive specific training to transfer the ITD to the advanced airway and activate the ventilation assist timing lights on the ITD (both sham and active) once tube confirmation has occurred. Asynchronous ventilations should be performed using the assist timing lights as a guide. The proper ITD “clearing” procedure, indications for discontinuation of the ITD, and completion of study protocol will also be covered, including turnover report to ED personnel and retrieval of the ITD.

**Figure 5: Training Scheme**





### ***Protocol Practicum***

Providers will be given the opportunity to practice to proficiency each component of the protocol. The number of providers used during these rehearsals should simulate actual clinical practice whenever possible. The use of an AED or ALS defibrillator should also be dictated by clinical practice, using the identical brand and technology that will be available during the trial. Various permutations of the study protocol should be presented, including each of the study arms as discussed above. Specific assessment goals should emphasize inclusion/exclusion criteria, role assignment, correct number of compressions, maintenance of continuous tight facemask seal during CPR using “E-C” hand technique or two-handed technique, transfer of ITD to advanced airway and performance of optimal CPR (minimal “hands-off” time). All EMS personnel need to demonstrate proficiency in adequately managing a factorial study cardiac arrest patient. See Appendix 7 for a list of training proficiency goals.

### ***Cognitive post-test***

A cognitive post test will cover key enrollment procedures and may be completed online or as a written or verbal component of the training sessions. A record of training completion will be maintained by each site or EMS agency

### ***Run-in Phase***

After personnel have been formally trained, they will receive additional training through feedback during a run-in phase. Compliance with the protocol and completion and submission of the data will be required before the DCC will notify the site that that agency is now in the active phase of the trial. Compliance monitoring includes: correct inclusion/exclusion criteria, adherence to study protocol, CPR process measures reported, and correct completion of data elements including reporting of adverse events.

## **DSMB and Monitoring Strategy**

### ***Data Safety and Monitoring Committee***

An independent data safety and monitoring committee will help ensure the safety of the trial by monitoring adverse outcomes throughout the trial and by reviewing outcome data for possible harm. In addition, the committee will review the results of the interim analyses. The committee 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 intervals to be determined by the DSMB, expected to be approximately semi-annually and anticipated to correspond roughly to patient enrollment of one-third and two-thirds of total enrollment. The DSMB will also monitor primary and secondary study outcomes between the treatment and control groups. The DCC will forward DSMB reports to study investigators, the Institutions Research Board, the Food and Drug Administration, and the NIH in accordance with federal regulations 45 CFR Part 46 Subpart A and 21 CFR 312 and the IDE regulations, as well as appropriate Canadian oversight bodies.

### ***Safety and Data Monitoring***

The plans for monitoring protocol implementation/compliance, and data collection/quality are detailed elsewhere. Clinical centers will report all potential adverse events to the DCC as soon as possible. These will be collected in both a structured (standard form) and open (describing any difficulties encountered) form. All potentially

serious adverse events will be reviewed by an events committee of ROC Investigators blinded as to treatment arm and further classified by: a) Severity (life-threatening, serious, non-serious); and b) Expected vs. unexpected; and c) Relation to study device. For serious adverse events, the DCC will notify the DSMB as well as appropriate regulatory agencies, sites, and NIH promptly.

The DCC will tabulate and report compliance, data quality, and non-serious adverse events on a regular basis.

### ***Proposed Interim Monitoring Plan***

Each factor will be monitored independently by the DSMB and either study could be terminated, without terminating the other. However, interactions will be evaluated. Interim analyses will be conducted after accrual of 1/3 and 2/3 of the sample size target (Appendix 8).

### ***Proposed Interaction and Extension Monitoring Plan***

We are aware that some may believe that the ITD will be ineffective for patients who receive Analyze Early care. Others may believe that this is not a realistic scenario. If it were true, it would require twice the duration to have the same power for observing the hypothesized effect in the Analyze Later cohort. The outcome will be observed during the course of the study by the independent DSMB as described in Appendix 9.

In the event that the Analyze Late vs Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the efficacy population for the ITD/sham device comparison will be restricted to those subjects treated under the rhythm analysis strategy found to be superior. The number of subjects accrued to the study will be increased to achieve the planned maximal sample size in the superior rhythm analysis strategy arm.

In the event that the ITD/sham device intervention is terminated early, future patients will receive no device, and the efficacy population for the ALvE treatment comparison will be otherwise unchanged.

## **Human Subjects**

### **Protection Against Risks**

In accordance with the FDA, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. In accordance with the regulations 21 CFR 312.32, we have outlined the expected serious and non-serious adverse events, our plans to identify these and the time line for reporting them to the FDA, IRB and DMSB and other overseeing agencies.

An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. 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.

### **Recruitment and Informed Consent**

This study qualifies for exception from informed consent required for emergency research as outlined in FDA regulation 21CFR50.24. The study intervention needs to be

administered quickly following the onset of cardiac arrest. In this uncontrolled setting the patient is unconscious. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the scene, nor is it practical for the prehospital provider to explain the study and receive consent while caring for a patient in cardiac arrest. Taken together, these issues provide sufficient support for an exception from consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. We have outlined below each criterion stipulated in the regulations for this exception and how our study design applies to these criteria.

#### **Sec. 50.24 Exception from informed consent requirements for emergency research**

**(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 is a factorial trial of use of either an active or sham ITD supplemented by either of two resuscitation strategies (Analyze Later and Analyze Early) in patients with nontraumatic out-of-hospital cardiac arrest. These patients are in an immediate life-threatening situation with a mortality approaching 95%. The standard of care for prehospital management of these patients includes the timely provision of CPR and advanced life support including airway management.

As reviewed in this proposal, previous studies of ITD have suggested a short-term survival advantage with this device but have not been definitive. These studies attest to the safety of ITD in the cardiac arrest population and to the practicality of using them in the prehospital environment. The major limitations of previous studies are their lack of focus on the specific intervention and their lack of sufficient size to detect significant clinical differences in outcome. Also, in contrast to the previous human studies, the present trial will evaluate the device in patients with unprotected airways in which case potentially harmful hyperventilation is less common. Thus, critical evaluation of this intervention in humans has not been undertaken.

Animal and human data demonstrate the safety of Analyze Later. Studies in animal models of cardiac arrest indicate that a period of artificial circulation prior to the initial rescue shock can increase the likelihood of successful defibrillation when VF and circulatory arrest lasts more than 3-4 minutes. Small randomized trials in humans with cardiac arrest show that an initial period of CPR may or may not improve survival. However, the prior studies lacked concurrent control groups or were too small to detect meaningful differences in survival. Therefore, no study has adequately answered the question of whether an EMS provider, upon reaching a subject who has already developed cardiac arrest, should a) deploy a defibrillator and administer an immediate rescue shock or b) perform CPR for an interval prior to deploying the defibrillator and rescue shock.

We propose a large randomized trial focused on evaluation of these two interventions in the out-of-hospital cardiac arrest population, with sufficient statistical power to detect changes in outcome. Furthermore, an emphasis on the neurological outcome of resuscitated cardiac arrest patients will define the clinical utility of this resuscitation approach for these patients.

**(2) Obtaining informed consent is not feasible because:**

**(i) The subjects will not be able to give their informed consent as a result of their medical condition;**

- (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and**
- (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.**

The study interventions need to be administered as an early intervention after the onset of cardiac arrest (see discussion of therapeutic window below). In this uncontrolled setting the patient is unconscious and unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the scene, nor is it practical for the prehospital provider to explain the study and receive consent while caring for the cardiac arrest patient. 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.

**(3) Participation in the research holds out the prospect of direct benefit to the subjects because:**

- (i) Subjects are facing a life-threatening situation that necessitates intervention;**
- (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and**
- (iii) 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.**

- (i) As defined, these patients with cardiac arrest are facing a life-threatening situation that requires immediate intervention.
- (ii) Previous animal and human studies have been conducted, and suggest the potential for a direct benefit to individual subjects in cardiac arrest via improved hemodynamics and short-term survival advantage.
- (iii) ITD administration has been tested in three previous clinical trials no serious adverse effects reported. Both Analyze Early and Analyze Late are currently used strategies. Three studies give inconsistent results, but no adverse effects have been noted. As discussed above, there are potential risks to subjects that may have not been observed in previous trials. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal and the current poor outcome for patients with out-of-hospital cardiac arrest.

**(4) The clinical investigation could not practicably be carried out without the waiver.**

This study could not be conducted without the waiver of consent due to the need to administer the interventions as early as possible after the onset of cardiac arrest.

**(5) 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.**

There have been three clinical studies of ITD use during standard manual CPR for the treatment of patients with out-of-hospital cardiac arrest. These demonstrated a potential survival benefit for patients treated with ITD vs. standard CPR. Animal models of cardiac arrest suggest that the ITD may increase venous return during the decompression phase of CPR. Based on these data, coupled with the previous clinical trials, the therapeutic window for this agent is for the time of initial resuscitation, which occurs when CPR is administered by prehospital care providers, up to hospital discharge.

It is well established that the probability of rescue shock success declines quickly during cardiac arrest.(49, 90) The decay in the probability of rescue shock success occurs over minutes, and approaches zero by 10-12 minutes. Therefore, the Analyze Early vs. Analyze Late intervention must be performed within the first few minutes of treatment in order to be meaningful.

Since this is an immediately life-threatening situation, it will not be possible to contact legal representatives at the time of study entry. We will make every effort to contact legal representatives after admission to the hospital to notify them that the patient was enrolled in a randomized trial. Requiring consent to review a hospital chart to determine the presence or absence of serious adverse events is likely to be associated with a biased estimate of the safety and efficacy of the intervention. Therefore we propose to use exception from informed consent for emergency consent, public notification, community consultation, patient notification of enrollment, and waiver of documented informed consent to review clinical records.

If legal representatives are not immediately available, research personnel will attempt to contact the subject's legal representative 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.

**(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.**

All procedures and consent forms will be approved by the Institutional Review Board (IRB) of the regional study site (or Research Ethics Boards (REBs) in Canada) prior to the onset of the trial.

**(7) 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;**
- (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;**  
**(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and**  
**(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**

(i) In U.S, centers, community consultation as outlined by the local IRB will be undertaken prior to IRB approval. Similarly, the Canadian centers will follow the requirements of their local REBs. Since the population eligible for enrollment includes all citizens in the study regions it will not be possible to target any particular small group. The community consultation plan for each study site will have to be individualized to fit the IRB requirements. Attached is an example of a proposed plan for community consultation, which has been used in a prior ITD trial (Appendix 10). Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. If requested, bracelets will be made available that could be worn by members of the community who do not want to participate.

(ii) & (iii) Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the Resuscitation Outcomes Consortium. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study.

(iv) An independent data monitoring committee will exercise oversight of the study as described below.

(v) We expect that all patients who meet the enrollment criteria will be unconscious. Any delay in medical care that would be required for the paramedic to attempt to obtain consent from the patient's legal guardian would be life threatening. Thus it will not be feasible to attempt to obtain informed consent during the initial therapeutic window.

Once enrolled in an emergency research trial, patients die in the field, die in the hospital or survive the event. Review of the clinical record is important to ascertain adverse events and important outcomes such as hospital discharge status. This does not require further participation of the patient.

The local ROC investigator will provide information about the emergency research study to the patient or their representative at the earliest feasible opportunity after administration of the intervention. Since in many cases this will be while the patient is still hospitalized, this will not include a request for consent for further participation/intervention, but will provide the patient/representative contact names/numbers for purposes of obtaining further information if desired. Since only patients who survive several months after discharge will be asked for further participation (in the form of telephone administered functional status measures at 3

months and 6 months), the timing of the request for consent for this participation will be determined by the local IRBs. However, we suggest that it should be during the first month after discharge so that patients who die before that time are not inconvenienced with a decision and so that those who have not died have had time to recover sufficiently to make a reasoned decision.

In summary, we shall notify patients enrolled under waiver of consent for emergency research as quickly as feasible, and seek consent from those who survive to discharge for ongoing participation.

Please see Appendix 10 for a sample Exception to Consent plan.

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PROTOCOL AMENDMENT  
IDE G980125/S52

**Resuscitation Outcomes Consortium**  
**Prehospital Resuscitation using an**  
**IMpedance valve and Early vs Delayed**  
**analysis (ROC PRIMED) Trial**

This protocol amendment

- clarifies the conditions under which patients who are initially treated by emergency medical services (EMS) providers from an agency that is not participating in the Resuscitation Outcomes Consortium would be considered eligible for enrollment in the trial,
- clarifies when the impedance threshold device (ITD) can be used with other resuscitation devices in light of a recent study of the ITD in an animal model of cardiac arrest, and
- clarifies the partial factorial nature of the clinical trial and explicitly describes the participation of the Seattle Medic One EMS agency in the ITD/sham device intervention, but not the Analyze Later/Analyze Early intervention..

This amendment has been approved by all study investigators and will take effect immediately upon initiation of patient enrollment. This amendment will be submitted to Health Canada as well as all IRBs (U.S.) and REBs (Canada) that provide local oversight for this trial.

**1. Section 1 – Factorial Study Summary-Background (pg. 3):**

**Change:**

“... propose a large clinical trial, using a factorial design, to test two strategies ...”

to

“... propose a large clinical trial, using a **partial** factorial design, to test two strategies ...”

Rationale: To emphasize the partial factorial (as opposed to full factorial) nature of the clinical trial design.

**2. Section 1 – Factorial Study Summary-Rationale (pg. 3):**

**Change:**

“... rationale for the factorial design is based on ...”

to

“...rationale for the **partial** factorial design is based on ...”

Rationale: To emphasize the partial factorial (as opposed to full factorial) nature of the clinical trial design.

### **3. Section 1 – Factorial Study Summary-Rationale (pg. 3):**

**Add:**

- “A partial factorial design, as opposed to a full factorial design, is necessary because eligibility criteria for the two interventions are not identical. Current medical standards would dictate that the Analyze Later strategy is inappropriate for patients whose cardiac arrest was witnessed by EMS, but some such patients might have an ITD or sham device applied during their resuscitation. Similarly, some patients on either the Analyze Later or Analyze Early arm might achieve resumption of spontaneous circulation (ROSC) prior to the application of the ITD or sham device. Further, because a greater sample size is required to achieve the desired statistical power to detect the anticipated effect of the ITD than that required to detect the effect of the Analyze Later strategy, the ROC investigators have allowed for the inclusion of one agency (Seattle Medic One) that would participate only in the ITD/sham comparison and not the Analyze Later vs Analyze Early comparison. We anticipate that of all cardiac arrests treated by participating ROC agencies during the course of the study, approximately 85% will be judged evaluable for both the ITD/sham and Analyze Later/Analyze Early comparisons.”

Rationale: To emphasize the reasons for a partial factorial (as opposed to full factorial) nature of the clinical trial design and to explicitly note the participation of the Seattle Medic One EMS in the ITD/sham device intervention, but not the Analyze Later/Analyze Early intervention.

### **4. Section 1 – Factorial Study Summary-Challenges (pg. 4):**

**Change:**

“The factorial design poses three challenges: ...”

**to**

“The **partial** factorial design poses three challenges:”

Rationale: To emphasize the partial factorial (as opposed to full factorial) nature of the clinical trial design.

### **5. Section 1 – Factorial Study Summary-Design (pg. 5):**

**Change:**

“The trial will be factorial with: ...”

**to**

“The trial will be **partial** factorial with:”

Rationale: To emphasize the partial factorial (as opposed to full factorial) nature of the clinical trial design.

### **6. Section 1 – Factorial Study Summary-Remainder of This Protocol (pg. 6):**

**Change:**

“and/or specific to the factorial design of the study: ...”

**to**

“and/or specific to the **partial** factorial design of the study:”

Rationale: To emphasize the partial factorial (as opposed to full factorial) nature of the clinical trial design.

**7. Section 2 – Impedance Threshold Device Trial-Study Summary-Sample Size (pg. 7):**

**Change:**

“...to discharge rate of 5.32% with standard CPR and sham ITD, and two interim analyses, a maximum of 14,742 evaluable patients are needed to detect a 6.68% absolute survival: ...”

**to**

“...to discharge rate of 5.33% with standard CPR and sham ITD, and two interim analyses, a maximum of 14,742 evaluable patients are needed to detect a 6.69% absolute survival...”

Rationale: To reflect aspects of the sample size calculations that change due to the Seattle agency participating only in the ITD/sham device intervention and not in the Analyze Later/Analyze Early intervention. A slight change in weighting of the strata resulted in a change in the third significant digit for the hypothesized response probabilities.

**8. Section 2 – Impedance Threshold Device Trial-Research Design and Methods-Exclusion Criteria (pg. 13):**

**Change:**

– “CPR performed with the mechanical compression “Autopulse” device”

**to**

– “CPR performed with any mechanical compression device (e.g. Autopulse, LUCAS, Thumper)

– Ventilated with a mechanical device (e.g. automated transport ventilator) Note: a bag-mask is not considered a mechanical ventilation device.”

Rationale: Dr. Jim Menegazzi of the University of Pittsburgh and colleagues recently completed a controlled study of the use of the Impedance Threshold Device in an animal model of cardiac arrest. He observed a significantly greater mortality in the animals that were treated with cardiac arrest compared to those that were not. A subcommittee of ROC investigators supplemented by two independent experts in animal models of cardiac arrest reviewed these unpublished data as well as published controlled studies of ITD in animals models of cardiac arrest or humans in cardiac arrest. A summary of the methods and results of this review process is attached to this amendment. In brief, we concluded that that there were a variety of plausible explanations for Dr. Menegazzi’s results. After weighing the totality of animal and human evidence, the subcommittee recommended that the ROC PRIMED trial proceed as planned. In doing so, we recognized that the Menegazzi experiment used a mechanical compression device as well as a mechanical ventilator whereas the Milwaukee pilot study of ITD use in out of hospital cardiac arrest did not. We shall continue to monitor ongoing animal and human research that evaluates the ITD, and will advise the ROC DSMB and FDA if we believe the ROC PRIMED design should be altered.



**9. Section 2 – Impedance Threshold Device Trial-Research Design and Methods-Exclusion Criteria (pg. 13):**

**Change:**

– “Non-ROC EMS agency/provider began CPR or placed pads”

**to**

– “A non-ROC EMS agency/provider, **for whom time call received at dispatch cannot be obtained,** began CPR or placed pads.”

Rationale: We need to be able to determine the time interval from 911 call to arrival of EMS providers in order to determine whether the patient should be included in efficacy analysis of ITD. The geographic coverage area of some ROC EMS agencies overlaps with that of some other agencies that are not participating in ROC. It is not feasible to train, equip and monitor all EMS providers within a fixed geographic area. Nor is it possible to obtain response time interval data from all non-ROC EMS agencies. Hence we are focusing on training, equipping and monitoring ROC EMS providers, as well as enrolling patients treated by these individuals. We shall exclude patients who are initially treated by non-ROC EMS providers in the event that we are unable to determine whether the patients are eligible for enrollment in the trial.

**10. Section 2-Impedance Threshold Device Trial-Research Design and Methods-Efficacy Population (pg. 13):**

**Change:**

“arrival of EMS providers at scene”

**to**

“arrival of **ROC** EMS providers at scene”.

Rationale: The efficacy analysis will focus on patients who are promptly treated by ROC EMS providers, as delay in care could attenuate any possible treatment effect.

**11. Section 2. Impedance Threshold Device Trial- Prespecified Subgroup Analyses (pg. 15):**

**Change:**

“initiation of CPR by EMS”

**to**

“initiation of CPR by **ROC** EMS”

Rationale: The subgroup analysis will focus on patients who are promptly treated by ROC EMS providers, as delay in care could attenuate any possible treatment effect.

**12. Section 2 – Impedance Threshold Device Trial-Outcome Measures-Prespecified Subgroup Analyses (pg. 15):**

**Change:**

“Analyze Early vs. Analyze Later cohorts”

**to**

“Analyze Early vs. Analyze Later **vs. not participating in ALvE** cohorts”

Rationale: To clarify partial factorial nature of design and its impact on the subgroup analyses.

**13. Section 2 – Impedance Threshold Device Trial-Analyses-Sample Size and Study Duration (pg. 21):**

**Change:**

“...will be randomized (by cluster) in a 1:1 ratio to the AE or AL strategies, the expected distribution of patients to the various treatment strategies...”

to

“...will be randomized (by cluster) in a 1:1 ratio to the AE or AL strategies at all participating agencies except Seattle Medic One (which is projected to accrue approximately 2.7% of all patients—see Table 9), the expected distribution of patients to the various treatment strategies...”

Rationale: To explicitly note the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention.

**14. Section 2 – Impedance Threshold Device Trial-Analyses-Sample Size and Study Duration (pg. 21):**

**Change:**

**Table 2: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total ITD/Sham Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	Sham	ITD
Asystole	0.000	0.012	0.012	0.000	0.119	0.119	0.119	0.119	0.250	0.250
PEA	0.000	0.014	0.014	0.000	0.056	0.056	0.056	0.056	0.125	0.125
VT/VF	0.015	0.017	0.017	0.030	0.035	0.035	0.050	0.050	0.103	0.103
<b>TOTAL</b>	0.015	0.043	0.043	0.030	0.210	0.210	0.225	0.225	0.478	0.478

to

**Table 2: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA or Seattle Medic One (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total ITD/Sham Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	Sham	ITD
Asystole	0.000	0.018	0.018	0.000	0.116	0.116	0.116	0.116	0.250	0.250
PEA	0.000	0.017	0.017	0.000	0.054	0.054	0.054	0.054	0.125	0.125
VT/VF	0.015	0.020	0.020	0.029	0.034	0.034	0.049	0.049	0.103	0.103
<b>TOTAL</b>	0.015	0.055	0.055	0.029	0.204	0.204	0.219	0.219	0.478	0.478

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. This did not affect the proportion of subjects randomized to the ITD/sham device intervention, but did affect the relative size of the strata defined by Analyze Early, Analyze Late, or ALvE ineligible.

**15. Section 2 – Impedance Threshold Device Trial-Analyses-Sample Size and Study Duration (pg. 21):**

**Change:**

“survival to hospital discharge of 0.0599 when treated under the AE strategy with a sham valve. We assume that 88.9% of such survivors would have acceptable neurological status ( $MRS \leq 3$ ) based on a combination of observed rates from the ASPIRE and PAD trials where 35 of 45 and 42 of 45 survivors had CPC scores  $\leq 2$ . Therefore we estimate a rate of 0.0532 for neurologically intact”

**to**

“survival to hospital discharge of 0.0600 when treated under the AE strategy with a sham valve. We assume that 88.9% of such survivors would have acceptable neurological status ( $MRS \leq 3$ ) based on a combination of observed rates from the ASPIRE and PAD trials where 35 of 45 and 42 of 45 survivors had CPC scores  $\leq 2$ . Therefore we estimate a rate of 0.0533 for neurologically intact”

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. The consequent slight change in weighting of the strata resulted in a change in the third significant digit for the hypothesized response probabilities.

**16. Section 2 – Impedance Threshold Device Trial-Analyses-Sample Size and Study Duration (pg. 22):**

**Change:**

“... estimated probability of survival to hospital discharge of 0.0751 for patients treated with an ITD under the AE strategy, with a corresponding hypothesized rate of 0.0668 for”

**to**

“... estimated probability of survival to hospital discharge of 0.0753 for patients treated with an ITD under the AE strategy, with a corresponding hypothesized rate of 0.0669 for”

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. A slight change in weighting of the strata resulted in a change in the third significant digit for the hypothesized response probabilities.

**17. Section 2 – Impedance Threshold Device Trial-Analyses-Sample Size and Study Duration (pg. 22):**

**Change:**

“Table 3: Estimated proportions of all EMS treated OOHCA patients surviving to discharge and surviving to discharge with MRS ≤ 3 by ITD/sham treatment arm and presenting rhythm.

Presenting Rhythm	Stratum Weight	Sham Device Probability of Survival to Discharge	ITD / Sham Relative Benefit	ITD Probability of Survival to Discharge
Asystole	0.5235	0.0105	1.40	0.0147
PEA	0.2618	0.0420	1.40	0.0588
VT/VF	0.2147	0.2020	1.20	0.2424
Probability of Survival to Discharge (weighted average)		0.0599		0.0751
Probability of Neurologically Intact Survival to Discharge (88.9% of patients surviving to hospital discharge)		0.0532		0.0668

The number of patients to be accrued to the ITD vs. sham device comparison is based on the ability of a one-sided level 0.025 test to reject a null hypothesis that the probability of neurologically intact survival to hospital discharge is 0.0532 on both treatment arms. Sample size computations are based on a two-sample test of binomial proportions using Pearson’s chi squared statistic. The test should have approximately 90% statistical power to reject the null hypothesis when the ITD treatment arm would have a 0.0668 probability of neurologically intact survival.”

to

“Table 3: Estimated proportions of all EMS treated OOHCA patients surviving to discharge and surviving to discharge with MRS ≤ 3 by ITD/sham treatment arm and presenting rhythm.

Presenting Rhythm	Stratum Weight	Sham Device Probability of Survival to Discharge	ITD / Sham Relative Benefit	ITD Probability of Survival to Discharge
Asystole	0.523 <sup>1</sup>	0.0105	1.40	0.0147
PEA	0.261 <sup>6</sup>	0.0420	1.40	0.0588
VT/VF	0.21 <sup>5</sup> <sup>3</sup>	0.2020	1.20	0.2424
Probability of Survival to Discharge (weighted average)		0.0 <sup>6</sup> <sup>00</sup>		0.075 <sup>3</sup>
Probability of Neurologically Intact Survival to Discharge (88.9% of patients surviving to hospital discharge)		0.053 <sup>3</sup>		0.066 <sup>9</sup>

The number of patients to be accrued to the ITD vs. sham device comparison is based on the ability of a one-sided level 0.025 test to reject a null hypothesis that the probability of neurologically intact survival to hospital discharge is 0.053<sup>3</sup> on both treatment arms. Sample size computations are based on a two-sample test of binomial proportions using Pearson’s chi squared statistic. The test should have approximately 90% statistical power to reject the null hypothesis when the ITD treatment arm would have a 0.066<sup>9</sup> probability of neurologically intact survival.”

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. A slight change in weighting of the strata resulted in a change in the third significant digit for the hypothesized response probabilities.

**18. Section 2 – Impedance Threshold Device Trial-Analyses-Sample Size and Study Duration (pg. 22):**

**Change:**

“The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 15,742 patients (up to 1,000 during the run-in phase, 14,742 during the actual trial) will require 18 months.”

**to**

“The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 16,542 patients (up to 1,800 during the run-in phase, 14,742 during the actual trial) will require 20 months.”

Rationale: To correct the protocol to reflect the 1,800 run-in patients approved by the FDA.

**19. Section 2 – Impedance Threshold Device Trial-Human Subjects-Risk to Subjects-Population (pg. 23):**

**Change:**

“study will enroll approximately 15,742 adult patients”

**to**

“study will enroll approximately 16,542 adult patients”

Rationale: To correct the protocol to reflect the 1,800 run-in patients approved by the FDA.

**20. Section 3 – Analyze Later versus Analyze Early-Study Summary-Setting (pg. 25):**

**Change:**

“EMS systems participating in the Resuscitation Outcomes Consortium.”

**to**

“EMS systems participating in the Resuscitation Outcomes Consortium and agreeing to cluster randomization to the Analyze Later/Analyze Early intervention in a crossover fashion.”

Rationale: To explicitly note the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention.

**21. Section 3 – Analyze Later versus Analyze Early-Study Summary-Sample Size (pg. 25):**

**Change:**

“Based on a two-sided significance level of 0.05,  $p=0.99$ , a survival to discharge with modified Rankin score  $\leq 3$  rate of 5.41% after Analyze Early, and two interim analyses, a maximum of 13,560 evaluable patients are needed to detect a 7.45% absolute survival to discharge with modified Rankin score  $\leq 3$  after Analyze Later.”

**to**

“Based on a two-sided significance level of 0.05, a maximum of 13,239 evaluable patients will allow statistical power of 0.996 to detect an improvement in the probability of survival to discharge with modified Rankin score  $\leq 3$  rate from 5.41% after Analyze Early to 7.45% after Analyze Later.”

Rationale: To explicitly note the impact on the ALvE sample size of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. The projected net loss of 321 evaluable subjects in the ALvE comparison had negligible impact on the statistical power (now reported to 3 significant digits).

**22. Section 3 – Analyze Later versus Analyze Early-Specific Aims-Prespecified Subgroup Analyses (pg. 25):**

**Change:**

“Response time from 911 call to arrival at patient’s side  $<4$  minutes and  $\geq 4$  minutes.”

**to**

“Response time from 911 call to initiation of EMS CPR  $<4$  minutes and  $\geq 4$  minutes.”

Rationale: EMS agencies routinely obtain the time of initiation of EMS CPR whereas few agencies collect the time of arrival at patient’s side.

**23. Section 3 – Analyze Later versus Analyze Early-Research Design and Methods-Study Design Overview (pg. 29):**

**Change:**

“...within the Resuscitation Outcomes Consortium. Outcomes will be assessed in the field and at the receiving hospitals.”

**to**

“... within the Resuscitation Outcomes Consortium and served by an EMS agency participating in the Analyze Later/Analyze Early intervention (the Seattle Medic One EMS agency is participating only in the ITD/sham device intervention of the partial factorial ROC PRIMED study). Outcomes will be assessed in the field and at the receiving hospitals.”

Rationale: To explicitly note the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention.

**24. Section 3 – Analyze Later versus Analyze Early-Research Design and Methods-Study Population-Exclusion Criteria (pg. 29):**

**Change:**

“Non-ROC EMS agency/provider

to

“Non-ROC EMS agency/provider on scene and CPR begun or pads placed.”

Rationale: We need to exclude patients who have already received CPR or rhythm analysis by EMS prior to arrival of participating ROC EMS providers from our assessment of whether early rhythm analysis or late analysis (i.e. CPR before rhythm analysis) by EMS is effective. Failure to exclude patients with such concurrent intervention would attenuate any possible treatment effect.

**25. Section 3-Analyze Later versus Analyze Early- Primary Comparison Populations-Safety Population (pg. 30):**

**Add:**

“This will include patients who were defibrillated by ROC EMS providers but did not receive CPR from ROC EMS providers.”

Rationale: We need to include all patients who received the study intervention in our assessment of its safety.

**26. Section 3 – Impedance Threshold Device Trial-Analyses Methods-Sample Size and Study Duration (pg. 36):**

**Change:**

**Table 6: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total AE vs AL Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	AE	AL
Asystole	0.000	0.012	0.012	0.000	0.119	0.119	0.119	0.119	0.250	0.250
PEA	0.000	0.014	0.014	0.000	0.056	0.056	0.056	0.056	0.125	0.125
VT/VF	0.015	0.017	0.017	0.030	0.035	0.035	0.050	0.050	0.103	0.103
<b>TOTAL</b>	0.015	0.043	0.043	0.030	0.210	0.210	0.225	0.225	0.478	0.478

to

**Table 6: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA or Seattle Medic One (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total AE vs AL Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	AE	AL
Asystole	0.000	0.018	0.018	0.000	0.116	0.116	0.116	0.116	0.232	0.232
PEA	0.000	0.017	0.017	0.000	0.054	0.054	0.054	0.054	0.109	0.109
VT/VF	0.015	0.020	0.020	0.029	0.034	0.034	0.049	0.049	0.097	0.097
<b>TOTAL</b>	0.015	0.055	0.055	0.029	0.204	0.204	0.219	0.219	0.438	0.438

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. Note: In the previous protocol there had been an error in the proportions given in Table 6 for the total randomized. This error has also been corrected in this amendment.

**27. Section 3 – Analyze Later versus Analyze Early-Analyses Methods-Sample Size and Study Duration (pg. 37):**

**Change:**

“In the process of accruing 14,154 evaluable patients to the ITD/sham device intervention, it is estimated that approximately 15,436 patients with OOHCA will be treated by EMS at one of the participating ROC sites, with approximately 13,893 of these patients (90%) not having EMS witnessed arrest and therefore receiving Analyze Late or Analyze Early. Estimating that 98% of these patients will be judged evaluable, 13,560 patients will be used for the comparison of Analyze Late versus Analyze Early strategies. We therefore consider the ability of a two-sided level 0.05 test with 13,560 subjects...”

**to**

“In the process of accruing 14,154 evaluable patients to the ITD/sham device intervention, it is estimated that approximately 15,423 patients with OOHCA will be treated by EMS at one of the participating ROC sites, with approximately 13,509 of these patients eligible to participate in the Analyze Late or Analyze Early interventions. Estimating that 98% of these patients will be judged evaluable, 13,239 patients will be used for the comparison of Analyze Late versus Analyze Early strategies. We therefore consider the ability of a two-sided level 0.05 test with 13,239 subjects...”

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention. This decreases the number of evaluable patients by 321.

**28. Section 3 – Analyze Later versus Analyze Early-Analyses Methods-Sample Size and Study Duration (pg. 37):**

**Change:**

“Using that stopping rule, a sample size of 13,560 evaluable patients will provide approximately 99% power to reject the null hypothesis under the conjectured treatment effect.

The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 13,560 evaluable patients for the Analyze Late versus Analyze Early comparison will require 16-18 months.”

**to**

“Using that stopping rule, a sample size of 13,239 evaluable patients will provide approximately 99.6% power to reject the null hypothesis under the conjectured treatment effect.

The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 13,239 evaluable patients for the Analyze Late versus Analyze Early comparison will require 20 months.”

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention.



**29. Section 3 – Analyze Later versus Analyze Early-Analyses Methods-Effect of Clustering and Crossover on Required Sample Size (pg. 38, Table 8):**

**Change:**

Seattle/King Co	1,763,000	888	agency, geographic	23
...				
Totals	20,537,108	12,437		1441

**to**

Seattle/King Co	1,191,204	555	agency, geographic	31
...				
Totals	19,965,312	12,104		1449

Rationale: To explicitly note the impact on the sample size calculations of the decision by the Seattle Medic One agency to participate only in the ITD/sham device intervention and not the Analyze Later/Analyze Early intervention, as well as to update the clustering plan for King County. Seattle Medic One is projected to provide 333 or the 888 OOHCA treated annually in Seattle/King County.

**30. Section 4 – Factorial Implementation of Both Protocols-Study Population (pg. 40):**

**Change:**

**Common Exclusion Criteria**

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy.
- Non-ROC EMS agency/provider

**ITD Exclusion Criteria**

- Tracheostomy present;
- CPR performed with the mechanical compression “Autopulse” device;

**Analyze Later Exclusion Criteria**

- EMS witnessed arrests;
- Non-EMS rhythm analysis (AED placed by police or lay responder);

**to**

**Common Exclusion Criteria**

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy.

**ITD Exclusion Criteria**

- Tracheostomy present;
- CPR performed with any mechanical compression device (e.g. AutoPulse, Thumper, ACD-CPR).

- Ventilated with a mechanical device (e.g. automated transport ventilator).  
Note: a bag-mask is not considered a mechanical ventilator device.
- A non-ROC EMS agency/provider, for whom time call received at dispatch cannot be obtained, began CPR or placed pads.

**Analyze Later Exclusion Criteria**

- EMS witnessed arrests;
- Non-EMS rhythm analysis (AED placed by police or lay responder);
- Non-ROC EMS agency/provider on scene and began CPR or placed pads.

Rationale: Criteria for exclusion of patients treated by non-ROC EMS agency/provider differ slightly between factors. Also to reflect changes to exclusion criteria related to mechanical compression devices and mechanical ventilation devices.

**31. Appendix 8 – Interim Monitoring Plan – Impedance Threshold Device Factor: Change:**

```
itdDesign <- seqDesign(  
  prob.model = "proportions",  
  arms = 2,  
  test.type = "greater",  
  nbr.analyses = 3,  
  alpha = c(0.1, 0.025), beta = c(0.975, 0.9),  
  P = c(1.2, 0.8), R= c(0,0), A= c(0,0),  
  null.hypothesis = 0.0532, alt.hypothesis = 0.0668,  
  variance = "alternative",  
  sample.size=14154,  
  power= "calculate")
```

to

```
itdDesign <- seqDesign(  
  prob.model = "proportions",  
  arms = 2,  
  test.type = "greater",  
  nbr.analyses = 3,  
  alpha = c(0.1, 0.025), beta = c(0.975, 0.9),  
  P = c(1.2, 0.8), R= c(0,0), A= c(0,0),  
  null.hypothesis = 0.0533, alt.hypothesis = 0.0669,  
  variance = "alternative",  
  sample.size=14154,  
  power= "calculate")
```

Rationale: To update code for stopping rule to reflect changes due to Seattle Medic One's participation in only the ITD/sham device comparison. The consequent slight change in weighting of the strata resulted in a change in the third significant digit for the hypothesized response probabilities.

### 32. Appendix 8 – Interim Monitoring Plan – Impedance Threshold Device Factor:

#### Change:

“...rate of 5.32% on the sham device arm, a sample size of 14,154 evaluable patients (7,077 patients on each of the sham device and ITD treatment arms) will provide approximately 90% power to detect an improvement to a 6.68% rate of neurologically intact survival on the active ITD treatment arm (corresponding to a relative improvement of 25.0% in neurologically intact survival...”

to

“...rate of 5.33% on the sham device arm, a sample size of 14,154 evaluable patients (7,077 patients on each of the sham device and ITD treatment arms) will provide approximately 90% power to detect an improvement to a 6.69% rate of neurologically intact survival on the active ITD treatment arm (corresponding to a relative improvement of 25.5% in neurologically intact survival...”

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. A slight change in weighting of the strata resulted in a change in the third significant digit for the hypothesized response probabilities. Similar changes from 5.32% to 5.33% and from 6.68% to 6.69% were made throughout this section of the Appendix 8. These changes had no impact on the tables of statistical power or statistical inference.

### 33. Appendix 8 – Interim Monitoring Plan – Analyze Early versus Analyze Late

#### Factor:

#### Change:

```
alveDesign <- seqDesign(  
  prob.model = "proportions",  
  arms = 2,  
  test.type = "two.sided", early.stopping="alternative",  
  nbr.analyses = 3,  
  size = 0.05,  
  P = 1, R= 0, A= 0,  
  null.hypothesis = 0.0541, alt.hypothesis = 0.0745,  
  variance = "alternative",  
  sample.size= c(1,3,6)/6*13560*0.95,  
  power= "calculate")
```

to

```
alveDesign <- seqDesign(  
  prob.model = "proportions",  
  arms = 2,  
  test.type = "two.sided", early.stopping="alternative",  
  nbr.analyses = 3,  
  size = 0.05,  
  P = 1, R= 0, A= 0,  
  null.hypothesis = 0.0541, alt.hypothesis = 0.0745,  
  variance = "alternative",  
  sample.size= c(1,3,6)/6*13239*0.95,  
  power= "calculate")
```

Rationale: To update code for stopping rule to reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 321 evaluable patients in the ALvE comparison.

**34. Appendix 8 – Interim Monitoring Plan – Analyze Early versus Analyze Late Factor:**

**Change:**

“...rate of 5.41% on the Analyze Early arm, a sample size of 13,560 evaluable patients (6,780 patients on each of the Analyze Late and Analyze Early treatment arms) will provide approximately 99.7% power to detect an improvement to a 7.45% rate of neurologically intact survival on the Analyze Late treatment arm (corresponding to a relative improvement of 25.0% in neurologically intact survival to discharge). A more ...”  
**to**

“...rate of 5.41% on the Analyze Early arm, a sample size of 13,239 evaluable patients (6,620 patients on each of the Analyze Late and Analyze Early treatment arms) will provide approximately 99.6% power to detect an improvement to a 7.45% rate of neurologically intact survival on the Analyze Late treatment arm (corresponding to a relative improvement of 37.7% in neurologically intact survival to discharge). A more ...”

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison, as well as to correct one typographical error in the original protocol. This change resulted in a projected net decrease of 321 evaluable patients in the ALvE comparison, but had only negligible effects on the statistical power or precision of inference.

**35. Appendix 8 – Interim Monitoring Plan – Analyze Early versus Analyze Late Factor:  
 Change:**

**Table 4: Alternatives for which a sample size of 13,560 subjects provides the specified power as a function of Analyze Early arm rates of neurologically intact (MRS ≤ 3) survival to hospital discharge**

Power	0.0475 AE Neuro Intact Surv to Hosp Discharge			0.0541 AE Neuro Intact Surv to Hosp Discharge			0.0606 AE Neuro Intact Surv to Hosp Discharge		
	AL Neur Intact Surv to Hosp D/C	Abs Diff	Rel Diff	AL Neuro Intact Surv to Hosp D/C	AL Neur Intact Surv to Hosp D/C	Abs Diff	Rel Diff	Abs Diff	AL Neur Intact Surv to Hosp D/C
80%	.0584	.0109	22.9%	80%	.0584	.0109	22.9%	80%	.0584
90%	.0602	.0127	26.7%	90%	.0602	.0127	26.7%	90%	.0602
95%	.0617	.0142	29.9%	95%	.0617	.0142	29.9%	95%	.0617
97.5%	.0631	.0156	32.7%	97.5%	.0631	.0156	32.7%	97.5%	.0631
99%	.0646	.0171	36.1%	99%	.0646	.0171	36.1%	99%	.0646

to

**Table 4: Alternatives for which a sample size of 13,239 subjects provides the specified power as a function of Analyze Early arm rates of neurologically intact (MRS ≤ 3) survival to hospital discharge**

Power	0.0475 AE Neuro Intact Surv to Hosp Discharge			0.0541 AE Neuro Intact Surv to Hosp Discharge			0.0606 AE Neuro Intact Surv to Hosp Discharge		
	AL Neur Intact Surv to Hosp D/C	Abs Diff	Rel Diff	AL Neuro Intact Surv to Hosp D/C	Abs Diff	Rel Diff	AL Neuro Intact Surv to Hosp D/C	Abs Diff	Rel Diff
80%	.0584	.0109	22.9%	.0656	.0115	21.3%	.0727	.0121	20.0%
90%	.0602	.0127	26.7%	.0675	.0134	24.9%	.0747	.0141	23.3%
95%	.0617	.0142	29.9%	.0691	.0150	27.8%	.0764	.0158	26.1%
97.5%	.0631	.0156	32.7%	.0706	.0165	30.4%	.0779	.0173	28.5%
99%	.0646	.0171	36.1%	.0722	.0181	33.5%	.0796	.0190	31.4%

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. Note that this table had multiple formatting errors in the original protocol. These have been corrected as well. This change resulted in a projected net decrease of 321 evaluable patients in the ALvE comparison, but had only negligible effects on the statistical power or precision of inference.

**36. Appendix 8 – Interim Monitoring Plan – Analyze Early versus Analyze Late  
 Factor:  
 Change:**

“Table 5: Stopping boundaries for a level  $\alpha=0.05$  two-sided group sequential design in the unified family (Kittelson and Emerson 1999) to detect a two-sided alternative, early stopping only to declare superiority or inferiority of the AL strategy, boundary shape parameters corresponding to O’Brien-Fleming boundaries, three analyses after accrual of 33%, 67%, and 100% of the maximal sample size of 13,560 evaluable subjects, and a rate of neurologically intact survival to hospital discharge of approximately 0.0643 on both treatment arms combined (e.g., 0.0541 on the Analyze Early arm and 0.0745 on the Analyze Late arm)

Analysis	Sample Size	Prop of Max Stat Info	Inferiority (lower) stopping boundary			Superiority (upper) stopping boundary		
			Abs Diff	Z statistic	Fixed P (lower)	Abs Diff	Z statistic	Fixed P (lower)
1	4520	0.17	-.0512	-4.844	1.0000	.0512	4.844	.0000
2	9040	0.50	-.0171	-2.797	.9974	.0171	2.797	.0026
3	13560	1.00	-.0085	-1.977	.9760	.0085	1.977	.0240

Thus, according to the above table, if the rate of neurologically intact survival to hospital discharge on the combined treatment arms is 6.43%, an absolute difference of 5.12% or more (e.g., 3.87% on the AE arm and 8.99% on the AL arm) when 4,520 evaluable subjects have been accrued to the study (2,260 subjects on each arm), the stopping rule would suggest that the study be terminated early with a decision that treatment with the Analyze Late strategy results in a statistically significant improvement in neurologically intact survival to hospital discharge. On the other hand, if at that first analysis the results were reversed (e.g., 8.99% on the AE arm and 3.87% on the AL arm), the stopping...

to

“Table 5: Stopping boundaries for a level  $\alpha=0.05$  two-sided group sequential design in the unified family (Kittelson and Emerson 1999) to detect a two-sided alternative, early stopping only to declare superiority or inferiority of the AL strategy, boundary shape parameters corresponding to O’Brien-Fleming boundaries, three analyses after accrual of 33%, 67%, and 100% of the maximal sample size of 13,239 evaluable subjects, and a rate of neurologically intact survival to hospital discharge of approximately 0.0643 on both treatment arms combined (e.g., 0.0541 on the Analyze Early arm and 0.0745 on the Analyze Late arm)

Analysis	Sample Size	Prop of Max Stat Info	Inferiority (lower) stopping boundary			Superiority (upper) stopping boundary		
			Abs Diff	Z statistic	Fixed P (lower)	Abs Diff	Z statistic	Fixed P (lower)
1	4413	0.17	-.0519	-4.844	1.0000	.0519	4.844	.0000
2	8826	0.50	-.0173	-2.797	.9974	.0173	2.797	.0026
3	13236	1.00	-.0086	-1.977	.9760	.0086	1.977	.0240

Thus, according to the above table, if the rate of neurologically intact survival to hospital discharge on the combined treatment arms is 6.43%, an absolute difference of 5.19% or more (e.g., 3.84% on the AE arm and 9.03% on the AL arm) when 4,413 evaluable subjects have been accrued to the study (2,206 subjects on each arm), the stopping rule would suggest that the study be terminated early with a decision that treatment with the

Analyze Late strategy results in a statistically significant improvement in neurologically intact survival to hospital discharge. On the other hand, if at that first analysis the results were reversed (e.g., 9.03% on the AE arm and 3.84% on the AL arm), the stopping...

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 321 evaluable patients in the ALvE comparison, but had only negligible effects on the statistical power or precision of inference.

**37. Appendix 8 – Interim Monitoring Plan – Analyze Early versus Analyze Late**

**Factor:**

**Change:**

**Table 6: Statistical inference regarding the effect of the Analyze Late strategy on rates of neurologically intact survival to hospital discharge (measured as the absolute difference in favorable outcome rates between the AL and AE arms) which would be reported if observed results corresponded exactly to the stopping boundaries for a level 0.05 two-sided group sequential design as presented in Table 5**

Analysis	Proportion of Maximal Statistical Information	AL Inferiority (lower) stopping boundary			AL Superiority (upper) stopping boundary		
		Adjusted estimate	Exact 95% conf intvl	Adjusted Two-sided P value	Adjusted estimate	Exact 95% conf intvl	Adjusted Two-sided P value
1	0.17	-4.85%	(-6.19%, -3.05%)	0.000	4.85%	(3.05%, 6.19%)	0.000
2	0.50	-1.59%	(-2.47%, -0.50%)	0.003	1.59%	(0.50%, 2.47%)	0.003
3	1.00	-0.81%	(-1.70%, 0.00%)	0.025	0.81%	(0.00%, 1.70%)	0.025

to

**Table 6: Statistical inference regarding the effect of the Analyze Late strategy on rates of neurologically intact survival to hospital discharge (measured as the absolute difference in favorable outcome rates between the AL and AE arms) which would be reported if observed results corresponded exactly to the stopping boundaries for a level 0.05 two-sided group sequential design as presented in Table 5**

Analysis	Proportion of Maximal Statistical Information	AL Inferiority (lower) stopping boundary			AL Superiority (upper) stopping boundary		
		Adjusted estimate	Exact 95% conf intvl	Adjusted Two-sided P value	Adjusted estimate	Exact 95% conf intvl	Adjusted Two-sided P value
1	0.17	-4.91%	(-6.26%, -3.08%)	0.000	4.91%	(3.08%, 6.26%)	0.000
2	0.50	-1.61%	(-2.50%, -0.51%)	0.003	1.61%	(0.51%, 2.50%)	0.003
3	1.00	-0.82%	(-1.72%, 0.00%)	0.025	0.82%	(0.00%, 1.72%)	0.025

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 321 evaluable patients in the ALvE comparison, but had only negligible effects on the statistical power or precision of inference.

**38. Appendix 9 – Interaction and Extension Monitoring Plan:**

**Change:**

“14,154 evaluable patients for the comparison of the ITD to the sham device and 13,560 evaluable patients for the comparison of the Analyze Late to the Analyze Early strategy. The following table details regarding the distribution of those 15,436 patients according to presenting rhythm and randomized treatment group.

**Table 1: Estimated distribution of 15,436 potentially eligible EMS treated OOHCA patients by presenting rhythm and randomization group.**

Initial Rhythm	EMS Witnessed CA (AL vs AE Ineligible)			Analyze Early			Analyze Late	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD
<b>Asystole</b>	0	179	179	0	1840	1840	1840	1840
<b>PEA</b>	0	209	209	0	860	860	860	860
<b>VT/VF</b>	231	269	269	463	541	541	772	772
<b>TOTAL</b>	231	656	656	463	3241	3241	3473	3473

to

“14,154 evaluable patients for the comparison of the ITD to the sham device and 13,239 evaluable patients for the comparison of the Analyze Late to the Analyze Early strategy. The following table details regarding the distribution of those 15,436 patients according to presenting rhythm and randomized treatment group.

**Table 1: Estimated distribution of 15,436 potentially eligible EMS treated OOHCA patients by presenting rhythm and randomization group.**

Initial Rhythm	EMS Witnessed CA (AL vs AE Ineligible)			Analyze Early			Analyze Late	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD
<b>Asystole</b>	0	277	277	0	1789	1789	1789	1789
<b>PEA</b>	0	254	254	0	837	837	837	837
<b>VT/VF</b>	231	310	310	451	526	526	751	751
<b>TOTAL</b>	231	842	842	451	3152	3152	3377	3377

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 321 evaluable patients in the ALvE comparison.



**39. Appendix 9 – Interaction and Extension Monitoring Plan:  
 Change:**

**Table 3: Estimated maximal sample size of 13,286 evaluable patients available for safety analyses related to treatment combinations.**

Initial Rhythm	Analyze Early			Analyze Late	
	No Device	Sham	ITD	Sham	ITD
Asystole	0	1767	1767	1767	1767
PEA	0	826	826	826	826
VT/VF	445	519	519	742	742
<b>TOTAL</b>	445	3112	3112	3335	3335

to

**Table 3: Estimated maximal sample size of 12,970 evaluable patients available for safety analyses related to treatment combinations.**

Initial Rhythm	Analyze Early			Analyze Late	
	No Device	Sham	ITD	Sham	ITD
Asystole	0	1718	1718	1718	1718
PEA	0	803	803	803	803
VT/VF	433	505	505	721	721
<b>TOTAL</b>	433	3026	3026	3243	3243

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 316 evaluable patients in analyses related to interactions.

**40. Appendix 9 – Interaction and Extension Monitoring Plan:  
 Change:**

“...intervals for the difference in the proportion with favorable response between any two treatment combinations will be approximately  $\pm 0.047$ ,  $\pm 0.023$ , and  $\pm 0.012$ . Issues ...”  
 to

“...intervals for the difference in the proportion with favorable response between any two treatment combinations will be approximately  $\pm 0.047$ ,  $\pm 0.024$ , and  $\pm 0.012$ . Issues ...”

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 316 evaluable patients in analyses related to interactions, but had only negligible effects on the statistical power or precision of inference.

**41. Appendix 9 – Interaction and Extension Monitoring Plan:  
Change:**

“...the estimated precision of the repeated confidence intervals for the difference in the ITD treatment effect in the Analyze Late stratum and the ITD treatment effect in the Analyze Early stratum will be approximately  $\pm 0.066$ ,  $\pm 0.033$ , and  $\pm 0.016$  ...”

**to**

“...the estimated precision of the repeated confidence intervals for the difference in the ITD treatment effect in the Analyze Late stratum and the ITD treatment effect in the Analyze Early stratum will be approximately  $\pm 0.067$ ,  $\pm 0.034$ , and  $\pm 0.017$  ...”

Rationale: To reflect changes due to Seattle Medic One’s participation in only the ITD/sham device comparison. This change resulted in a projected net decrease of 316 evaluable patients in analyses related to interactions, but had only negligible effects on the statistical power or precision of inference.



**Resuscitation Outcomes Consortium  
Prehospital Resuscitation using an  
Impedance valve and Early vs Delayed  
analysis (ROC PRIMED) Trial**

FDA APPROVED PROTOCOL dated 5/11/2006  
PROTOCOL AMENDMENT 1 dated 12/28/2006

**Title: A Factorial Design of An Active  
Impedance Threshold Valve versus Sham  
Valve and  
Analyze Later versus Analyze Early**

Abbreviations commonly used in this protocol:

ACLS	advanced cardiac life support
AED	automated external defibrillator
CPR	cardiopulmonary resuscitation
DCC	data coordinating center
ED	emergency department
EMS	emergency medical services
EMT	emergency medical technicians
ICU	intensive care unit
PEA	pulseless electrical activity
RCC	regional coordinating center
ROC	Resuscitation Outcomes Consortium
ROSC	resumption of spontaneous circulation
VF	ventricular fibrillation

**IDE G980125/S52**

## Table of Contents

1. Factorial Study Summary.....	3
2. Impedance Threshold Device Trial .....	7
Study Summary.....	7
Specific Aims.....	8
Background and Significance.....	8
Conceptual Framework for ITD .....	8
Preliminary Studies .....	9
Choice of Intervention .....	12
Summary of Rationale.....	12
Research Design and Methods.....	12
Experimental Design .....	12
Study Episodes .....	12
Study Population .....	12
Inclusion Criteria.....	12
Exclusion Criteria .....	13
Primary Comparison Population.....	13
Intervention .....	14
Random Allocation .....	14
Intervention–Compliance .....	15
Outcome Measures.....	15
Primary .....	15
Secondary .....	15
In-Hospital Morbidity.....	15
Prespecified Subgroup Analyses .....	15
Expected Adverse Events .....	16
Analyses.....	17
Sample Size and Study Duration .....	20
Human Subjects.....	23
Risks to Subjects.....	23
Inclusion of Women or Minorities .....	23
Inclusion of Children.....	23
3. Analyze Later versus Analyze Early.....	24
Study Summary.....	24
Specific Aims.....	25
Background and Significance.....	25
Conceptual Framework for Analyze Later.....	25
Summary of Rationale.....	28
Research Design and Methods.....	29
Study Design Overview .....	29
Study Population .....	29
Inclusion Criteria.....	29
Exclusion Criteria .....	29
Primary Comparison Populations.....	30
Random Allocation .....	30
Intervention .....	31
Adherence to Protocol.....	32
Outcome Measures .....	32
Primary .....	32
Secondary Outcomes.....	32

In-Hospital Morbidity.....	32
Sample Size, and Study Duration .....	35
Effect of Clustering and Crossover Upon Required Sample Size .....	37
4. Factorial Implementation of Both Protocols .....	39
Summary.....	39
Study Population.....	40
Except for some specific situations, the inclusion and exclusion criteria for both ITD and Analyze Later protocols will be the same.....	40
Inclusion Criteria.....	40
Common Exclusion Criteria.....	40
Resuscitation Guidelines.....	40
Monitoring of CPR Process.....	40
Outcome Measures.....	42
Primary.....	42
Secondary .....	42
In-Hospital Morbidity.....	44
Other Outcomes.....	44
Data Collection.....	45
Data Forms .....	45
Source of Data Collection .....	45
Data Entry .....	46
Database Management.....	46
Training .....	46
Overview .....	46
<i>Optimal CPR Performance</i> .....	46
<i>Scientific Basis for ITD and Analyze Later Protocols</i> .....	47
<i>Study Protocols</i> .....	47
<i>Protocol Practicum</i> .....	48
<i>Cognitive post-test</i> .....	48
<i>Run-in Phase</i> .....	48
DSMB and Monitoring Strategy.....	49
Human Subjects.....	50
Protection Against Risks .....	50
Recruitment and Informed Consent .....	50
References.....	55

## 1. Factorial Study Summary

### Background

Little is known about how to optimize resuscitation for patients with out-of-hospital cardiac arrest. This is evident from the very low survival rates that are currently reported. The advent of automatic external defibrillators (AEDs) and their potential for wide-spread use by less highly trained emergency medical service (EMS) providers and lay persons has not resulted in the substantial increased survival rates anticipated. This has led to speculation that more and sooner circulation of oxygenated blood to the brain and heart may be important. Resuscitation Outcomes Consortium (ROC) Investigators propose a large clinical trial, using a partial factorial design, to test two strategies to increase blood flow. One strategy involves the impedance threshold device (ITD), which enhances venous return and cardiac output by increasing the degree of negative intrathoracic pressure during decompression. The second involves initiating resuscitation with a period of manual compressions and ventilations (Analyze Later), rather than attempting defibrillation immediately (Analyze Early).

### Rationale

The rationale for the partial factorial design is based on several arguments.

- Most importantly, both interventions are worthy of study in their own right. Both interventions were proposed by several of the participating ROC sites in their initial applications.
- A number of ROC EMS agencies currently use cardiopulmonary resuscitation (CPR) first (i.e., Analyze Later) as their standard protocol, whereas others analyze the rhythm and shock as required before initiating CPR (i.e. Analyze Early.) Thus, if the ITD intervention were to be studied alone, we would be faced with an uncontrolled heterogeneity of practice, possibly changing during the course of the trial. This would necessitate, at a minimum, stratifying by the EMS protocol.
- We anticipate no substantial interactive effect between these two interventions. One relates to when assisted circulation takes place, compared with when the defibrillatory attempt takes place. The other has to do with the quantity of flow during assisted circulation. Both include some blood flow prior to any defibrillation attempt.
- The infrastructures to conduct the two trials are virtually identical, thus assuring substantial efficiencies in costs, and virtually cutting in half the number of patients and the time needed to study the two interventions sequentially, providing there are no interactions between the interventions.
- A partial factorial design, as opposed to a full factorial design, is necessary because eligibility criteria for the two interventions are not identical. Current medical standards would dictate that the Analyze Later strategy is inappropriate for patients whose cardiac arrest was witnessed by EMS, but some such patients might have an ITD or sham device applied during their resuscitation. Similarly, some patients on either the Analyze Later or Analyze Early arm might achieve resumption of spontaneous circulation (ROSC) prior to the application of the ITD or sham device. Further, because a greater sample size is required to achieve the desired statistical power to detect the anticipated effect of the ITD than that required to detect the effect of the Analyze Later strategy, the ROC investigators have allowed for the inclusion of one agency (Seattle Medic One) that would participate only in the ITD/sham comparison and not the Analyze Later vs

Analyze Early comparison. We anticipate that of all cardiac arrests treated by participating ROC agencies during the course of the study, approximately 85% will be judged evaluable for both the ITD/sham and Analyze Later/Analyze Early comparisons.

### **Challenges**

The partial factorial design poses three challenges:

- Implementation of two interventions may be difficult for the persons who must conduct these interventions; the emergency medical technicians and paramedics, who must perform their efforts under the duress of life-threatening emergent conditions. This potential challenge has been mitigated by adopting cluster randomization for the Analyze Later protocol, whereby each cluster will be randomized to either always doing CPR first (Analyze Later) or always doing rhythm analysis first (Analyze Early). These clusters will consist of geographic areas or monitor/defibrillators within the EMS agencies. EMS personnel will place an active or sham ITD on all patients meeting criteria. Hence, EMS providers will always follow the same procedures: a) place an active or sham ITD on all patients, and b) analyze the rhythm either early or later consistently according to cluster randomization. No on-the-spot decisions regarding randomization will be required for use of either intervention.
- The cluster randomization will require that all out-of-hospital cardiac arrest events be accounted for. This requirement is actually beneficial, in that it provides additional motivation for the implementation of a comprehensive epidemiologic database of all life-threatening out-of-hospital events (what we have termed the ROC Registry). Whether the trial benefits from the Registry or the Registry benefits from the trial is unclear at this point and will depend in part upon the timing of various funding mechanisms.
- When a factorial design is used, there is an almost irresistible temptation to test for an interactive effect (i.e., risk difference for one factor depends on the level of the other factor). While a factorial design is the only reasonably efficient way of testing for an interaction between several interventions, to power the trial for the specific interaction effect generally requires a substantially increased sample size. As noted previously, we do not anticipate any substantial interaction between these two therapies. Nonetheless, potential interactions will be assessed by the DSMB at interim analyses and the sample size adjusted accordingly.

### **Potential Advantage**

It should be noted that the intervention of Analyze Later probably cannot be appropriately compared by randomizing individual episodes. The issues with compliance caused by the confusion of having an EMS provider alternate between the basic concept of aggressively doing CPR initially versus assiduously assessing rhythm and defibrillating initially can be easily appreciated. The choice of the cluster will vary depending upon the realities of training and the fluidity of personnel within an agency. All clusters will be encouraged, and large clusters will be required, to switch from Analyze Later to Analyze Early or vice versa at midpoint, or more often through the trial, thus serving as their own control.

### **Outcomes**

The trials share a common primary outcome, namely survival to hospital discharge with modified Rankin score  $\leq 3$ , and common secondary outcomes, namely

survival to discharge as well as functional status at discharge and at 1, 3 and 6 months after discharge as well as depression at 3 and 6 months.

### **Design**

The trial will be partial factorial with one intervention based on a double-blind randomization of individuals through the use of an active versus a sham ITD (identical to the user), and the other intervention based on non-blinded randomized clusters.

### **Setting**

The trial will be conducted in all EMS agencies participating in the Resuscitation Outcomes Consortium.

### **Sample Size and Analysis**

Since we are not testing for an interaction, sample size for each intervention will be based on the traditional significance levels of .05 for two-sided and .025 for one-sided and a power of 0.9. Each will require approximately 16-18 months of enrollment. The specific inclusion criteria, sample size, and analytic techniques are defined with each of the specific interventions.

### **CPR Performance**

Critical to understanding both interventions is the monitoring of CPR performance. All sites will implement procedures to attempt to collect 100% of data sources needed to assess CPR performance. Three performance measures will be abstracted: the ventilation rate, the compression rate, and the CPR fraction as defined in Appendix 2. It is known, based on the longstanding effort in Seattle, as well as more recent efforts in Chicago and Norway, that the data sources will be missing or incomplete in approximately 25% of episodes. Details for the CPR performance monitoring are dealt with in Section 4, since the process is applicable to both interventions.

### **Run-in Phase**

After personnel have been trained in use of the ITD and the methods for Analyze Later vs. Analyze Early according to their cluster randomization, they will initiate a run-in phase. Evidence of compliance with the protocol and completion and submission of the data will be required before the site can enroll in the active phase of the trial.

### **Anticipated Clinical Impact**

If the ITD demonstrates the hypothesized improvement in survival, we estimate that the premature death of approximately 2,700 victims of cardiac arrest<sup>1</sup> per year would be averted in North America compared to standard CPR. If the Analyze Later approach demonstrates the hypothesized improvement in survival, we estimate approximately 4,000 lives will be saved per year in North America. By implementing a factorial study design, these benefits to clinical practice can be achieved more efficiently and faster than otherwise would be the case.

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<sup>1</sup> Number of treatable cardiac arrests X Proportion of cases with non VF initial rhythm or VF that does not respond to initial shock X Absolute difference in survival i.e. (US population 295,483,056 X 0.53 per 1000 population (52) + Canadian population 31,127,234 X 0.57 per 1000 population (53)) X Absolute difference



**Remainder of This Protocol**

The remainder of this protocol is split into three parts. The second section contains the materials specific to the ITD intervention. The third section contains the materials specific to the Analyze Later intervention. The fourth section contains materials common to both interventions and/or specific to the partial factorial design of the study.

## 2. Impedance Threshold Device Trial

### Comparison of Standard CPR Plus Active Impedance Threshold Device Versus Standard CPR Plus Sham Impedance Threshold Device In Patients With Out-Of-Hospital Cardiac Arrest

#### Study Summary

**Background:** Most patients with out-of-hospital cardiac arrest do not survive to hospital discharge. Survival after cardiac arrest is correlated with the time from its onset to the circulation of oxygenated blood to the brain and heart. Compression of the chest during cardiopulmonary resuscitation (CPR) increases intrathoracic pressure and compresses the heart. Decompression of the chest results in negative intrathoracic pressure, which enhances venous return and cardiac output. Collectively these actions circulate blood to the brain and heart. The impedance threshold device (ITD) is a novel respiratory device intended to increase the degree of negative intrathoracic pressure during decompression. Studies in animal models of cardiac arrest or small randomized trials in humans demonstrate that the ITD improves hemodynamics and short-term outcomes but it remains unclear whether ITD improves survival to discharge or neurological outcome. Therefore we propose a large clinical trial to test whether standard CPR supplemented by active ITD is effective compared to standard CPR supplemented by sham ITD.

**Aims:** The primary aim of the trial is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  between standard CPR plus active ITD versus standard CPR plus sham ITD in patients with out-of-hospital cardiac arrest. The secondary aims of the trial are to compare survival to discharge, functional status at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months.

**Hypotheses:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest. The secondary null hypotheses are that survival to discharge, functional status at discharge and at 1, 3 and 6 months after discharge as well as depression at 3 and 6 months will be identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest.

**Design:** Double-blind randomized controlled trial.

**Population:** Patients with non-traumatic out-of-hospital cardiac arrest, presumed to be local age of consent or greater and treated by EMS providers.

**Setting:** EMS systems participating in the Resuscitation Outcomes Consortium.

**Sample Size:** Based on a one-sided significance level of 0.025, power = 0.90, a survival with modified Rankin score  $\leq 3$  to discharge rate of 5.33% with standard CPR and sham ITD, and two interim analyses, a maximum of 14,742 evaluable patients are needed to detect a 6.69% absolute survival with modified Rankin score  $\leq 3$  to discharge with standard CPR and active ITD.

**Anticipated Clinical Impact:** If this trial demonstrates a significant improvement in survival with use of the ITD, we estimate that the premature deaths of approximately 2,700 victims of cardiac arrest per year would be averted annually in North America alone.

## Specific Aims

**Primary Aim:** The primary aim of the trial is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  between standard CPR plus active ITD versus standard CPR plus sham ITD in patients with out-of-hospital cardiac arrest.

**Hypothesis:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest.

**Secondary Aims:** The secondary aims of this trial are to compare survival to discharge, functional status scores at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months between standard CPR plus active ITD versus standard CPR plus sham ITD in patients with out-of-hospital cardiac arrest.

**Hypotheses:** The null hypotheses are that survival to discharge, functional status scores at discharge and at 1, 3 and 6 months as well as depression score at 3 and 6 months are identically distributed with use of standard CPR plus active ITD versus standard CPR plus sham ITD in patients with cardiac arrest.

**Prespecified Subgroup Analyses:** These include assessment of treatment effect by:

- a) First recorded cardiac arrest rhythm before application of the ITD.
- b) Observational status of an arrest (e.g., witnessed versus unwitnessed).
- c) EMS response time interval of  $<10$  minutes and  $\geq 10$  minutes from 911 call to initiation of CPR by EMS.

## Background and Significance

### Conceptual Framework for ITD

Despite the widespread availability of basic and advanced life support for patients with out-of-hospital cardiac arrest, few survive to hospital discharge.(1-3) In the most efficient EMS systems, less than 15% of all patients with out-of-hospital cardiac arrest are discharged from the hospital with intact neurological function.(1-3) Furthermore, the median published survival to hospital discharge after out-of-hospital cardiac arrest is only 6.4%.(4)

While there are many variables that impact on the potential for a patient in cardiac arrest to survive, the timely circulation of oxygenated blood to the heart and brain is considered critical.(2) An airway device such as a facemask or an endotracheal tube is commonly used to assist in oxygenating and ventilating the patient. However, the inherent mechanical inefficiencies of standard CPR limit the ability to circulate blood by even the most highly skilled rescuers.(5)

The purpose of CPR is to pump blood from the chest to the vital organs. Blood flow to the vital organs is highly dependent on the amount of blood return to the chest after each compression phase.(6, 7) During standard CPR, chest compression results in an elevation of intrathoracic pressure and direct cardiac compression. Both of these mechanisms result in forward blood flow out of the chest to perfuse the brain and other vital organs. When the chest recoils, intrathoracic pressures decrease relative to extrathoracic pressures, enhancing venous return to the right heart. Blood flow back to the chest is highly dependent on the degree of chest wall recoil.(8)

Blood flows through the coronary arteries predominantly during the chest decompression phase. The pressure gradient generated between the aorta and the right atrium during the

decompression phase of CPR has been termed the coronary perfusion pressure.(9) The pressure gradient between the aorta and left ventricular cavity is also a fundamental determinant of blood flow to the heart during CPR. During standard CPR, the coronary perfusion pressures are only marginally adequate, resulting in inadequate venous return during the chest wall recoil phase.(10, 11)

Since the description of standard CPR by Kouwenhoven and colleagues in 1960,(12) several new CPR techniques have been described. These include circumferential vest CPR,(13, 14) interposed abdominal counterpulsation CPR, (15-19) and phased abdominal counterpulsation CPR.(20) These techniques are not widely applied as they have not been shown to significantly improve survival to discharge or other long-term outcomes compared with standard CPR in patients with out-of-hospital cardiac arrest.

This trial is focused on evaluating the ITD (see Appendix 1 for detailed information regarding the ITD). This novel device is designed to increase the coronary perfusion pressure during the decompression phase of CPR, thereby enhancing delivery of oxygenated blood to the heart. The concept of the ITD was discovered while evaluating the mechanism of another new method of CPR termed active compression decompression (ACD) CPR.(21) ACD CPR is performed with a hand-held suction device. When measuring intrathoracic pressures in patients undergoing ACD CPR, investigators realized that if the endotracheal tube was transiently occluded during the active decompression phase, intrathoracic pressures became markedly more negative. This led to the concept of impeding inspiratory gas exchange during the chest wall decompression phase of CPR to create a greater pressure differential between the thorax and the rest of the body, thereby enhancing venous return to the heart. As such, the impedance valve harnesses the kinetic energy of the chest wall recoil, thereby augmenting the “bellows-like” action of the chest with each compression-decompression cycle.(22)

The ITD is based on the principle that this impedance leads to a greater negative intrathoracic pressure, creating a small vacuum within the thorax relative to the rest of the body, leading to increased venous blood return to the heart and increased cardiac output. This concept has been evaluated in animals undergoing standard CPR (22) or active compression decompression (ACD) CPR,(6) as well as in human patients with prolonged cardiac arrest undergoing standard manual CPR (23-25) and ACD CPR.(7)

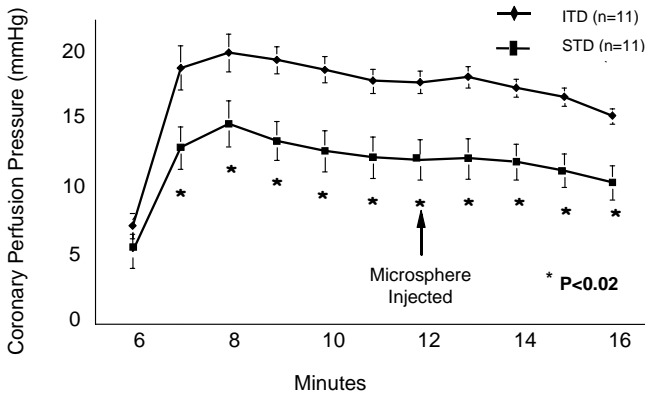
### **Preliminary Studies**

Initial studies to test the impedance valve concept were performed in a pig model of cardiac arrest.(6) Two positive end expiratory valves (PEEP) were coupled together and placed in reverse in the respiratory circuit. These were designed to prevent respiratory gases from entering the lungs during the chest decompression phase of CPR. The pigs were ventilated by overcoming the 40 cm H<sub>2</sub>O resistance of the PEEP valves. After four minutes of cardiac arrest, the combination of this impedance valve combined with ACD CPR significantly improved vital organ blood flow compared with ACD CPR alone ( $p < 0.05$ ). Brain blood flow increased to greater than baseline values (normal = 0.35 ml/min/gm) ( $p < 0.05$ ) and blood flow to the heart increased to greater than 50% of baseline values (normal = 1.2ml/min/gm) ( $p < 0.05$ ).<sup>(6)</sup> This enhanced myocardial perfusion was associated with lower energy requirements to defibrillate the animals at the end of that study. Use of the active ITD resulted in a marked improvement in coronary perfusion pressures compared to sham valve. These studies led to the development of the current ITD.

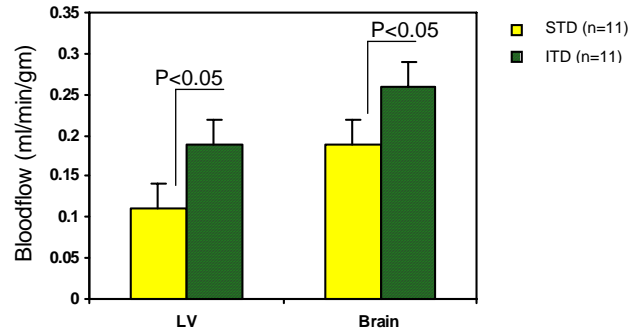
The first controlled animal studies of the ITD with standard CPR utilized a four-minute period of cardiac arrest followed by standard CPR with an automated compression device.(22) Standard CPR was performed with and without the ITD in an alternating fashion. Each time the ITD was removed from the respiratory circuit, the coronary perfusion pressures and vital organ perfusion decreased; and each time the ITD was added back, perfusion pressures stabilized or increased. A similar study evaluated active ITD versus sham ITD for 11 minutes after a six-

minute period of cardiac arrest without CPR.(5) A sham ITD was used in the control group and an active ITD in the other.

After 6 minutes of cardiac arrest and 6 minutes of standard CPR, radiolabeled microspheres were injected to measure vital organ blood flow. The active ITD increased left ventricular flow by 100%, and nearly normalized blood flow to the brain compared to the sham ITD (Figures 1 and 2).



**Figure 1**



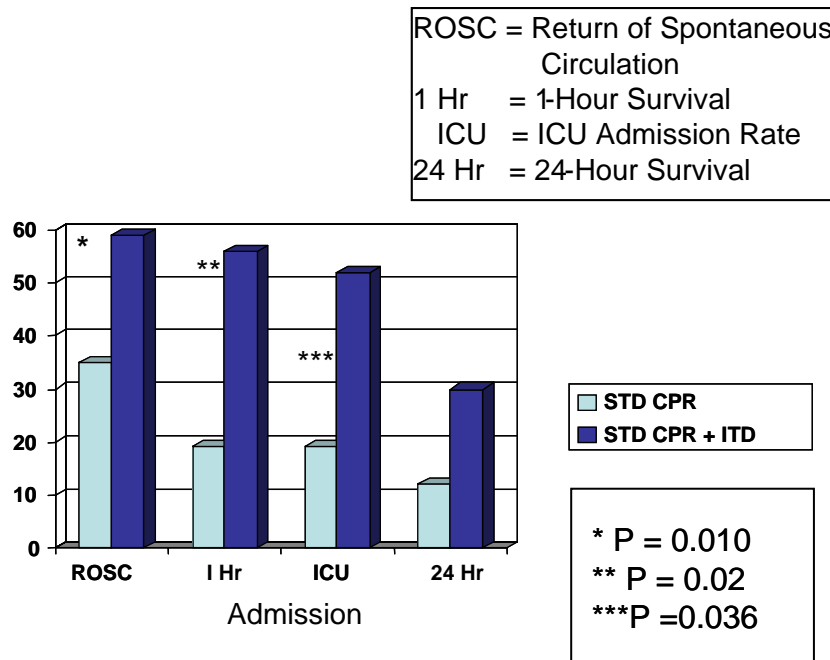
**Figure 2**

After a total of 17 minutes of ventricular fibrillation and 11 minutes of CPR, 3/11 pigs in the sham ITD group and 6/11 pigs in the active ITD group were resuscitated by direct current shock. In many ways, this six-minute arrest time prior to start of CPR more closely resembles clinical field experience where the time from arrest to the start of CPR in the United States ranges between 4-8 minutes in cities with highly efficient emergency medical services systems.

The Milwaukee ROC investigators recently randomized 230 adults who had protected airways after out-of-hospital cardiac arrest to receive standard CPR and sham ITD versus standard CPR and active ITD.(23, 24) The primary outcome of this study was admittance to ICU. Femoral arterial blood pressures were also evaluated by the research team during standard CPR at the scene of cardiac arrest in 22 other patients using the same protocol.

ICU admissions for all patients were not significantly different with use of the active ITD versus sham ITD (25% vs. 17%, respectively, P=NS). However, there was significantly increased ICU admissions in patients presenting in pulseless electrical activity (PEA) with use of active ITD, 19% (5 of 26) vs. 52% (14 of 27) (P = 0.02; not significant when corrected for comparisons in three rhythm groups-.05/3=.017) (Figure 3). In the hemodynamic study, systolic blood pressure was significantly increased with the active ITD versus the sham ITD: 85.1 ± 28.9 mmHg (n = 10) versus 42.9 ± 15.1 mmHg (n = 12), respectively; P < 0.001. Collectively these findings imply that by increasing venous return, and thus cardiac output, the ITD provides a novel means to increase circulation during standard CPR and cardiac arrest.

**Figure 3: Outcomes Presenting in Patients with PEA**



In a secondary analysis of the same study, the Milwaukee ROC investigators found that paramedics and EMTs ventilated patients in cardiac arrest an average of  $30 \pm 3$  breaths per minute, nearly twice that recommended by the American Heart Association.(26) Subsequent studies in pigs demonstrated that excessive ventilation rates (similar to that observed in the clinical setting) significantly decreased coronary perfusion pressures and survival rates.(26) Two other studies demonstrated excessive ventilation rates delivered by healthcare professionals during in-hospital cardiac arrest.(27, 28) However a recent study demonstrated ventilation at the recommended rate during resuscitation by paramedics or nurse anesthetists in a different out-of-hospital setting.(29) Most chest compressions were too shallow and nearly half the time, chest compressions were not delivered at all.

In another analysis of the Milwaukee pilot study, rescuers were observed to maintain some residual and continuous pressure on the chest wall during the decompression phase of CPR, preventing full chest wall recoil.(8) Airway pressures were consistently positive during those periods. When this incomplete chest wall decompression was reproduced in a porcine model of ventricular fibrillation cardiac arrest, it was associated with significantly increased intrathoracic pressure and significantly decreased coronary and cerebral perfusion pressures. When monitoring CPR performance of professional EMS rescuers using a recording manikin, only 16.3% of decompressions were associated with complete recoil. A slight modification in the technique of manual CPR increased the frequency of complete chest recoil to 95.0% (OR: 129.0; CI: 43.4-382.0,  $P < 0.0001$ ). (8)

The ITD in combination with conventional manual CPR was evaluated in a case-control study in large EMS system in Staffordshire, England. Survival to emergency department admittance was significantly greater among patients with any initial rhythm who received the ITD (61/181 [34%]) compared with historical controls (180/808 [22%]) ( $p < 0.01$ ). No device-related adverse effects were observed.(25)

In summary, these studies demonstrate that the ITD improves hemodynamics and short-term outcomes but may be associated with poor performance of other components of CPR. In-field monitoring facilitates identification of such poor performance and provides opportunities for corrective feedback to EMS personnel.

### **Choice of Intervention**

The investigators chose to evaluate the ITD alone rather than in combination with ACD CPR for several reasons. While the results with simultaneous use of ACD CPR and the ITD are promising,(6, 7, 30) use of the ACD CPR device requires more energy than standard CPR to perform it correctly.(6, 7, 30) Also, the sample size required to assess the effect of ACD CPR, ITD, combined therapy or standard CPR upon survival to discharge is impractical. Furthermore, a double-blind trial of ACD-CPR with or without ITD is not feasible, so the treatment effect from such a trial would be susceptible to bias. Therefore we propose a large clinical trial to assess the effect of standard CPR plus active ITD versus standard CPR plus sham ITD.

### **Summary of Rationale**

Survival after out-of-hospital cardiac arrest is poor. Studies in animal models of cardiac arrest demonstrate enhanced myocardial perfusion and vital organ blood flow when using the ITD. Studies in humans with out-of-hospital cardiac arrest demonstrated that the ITD increased systolic blood pressure and tended to improve short-term clinical outcomes without any adverse effects. A large trial is required to demonstrate whether ITD significantly improves survival and functional status. Evaluation of the effect of ITD requires monitoring whether CPR process is consistent with currently recommended methods of resuscitation.

## **Research Design and Methods**

### **Experimental Design**

This randomized trial will evaluate manual CPR with either an active or sham ITD in adult patients with out-of-hospital cardiac arrest. Randomization will occur through use of a study ITD that is constructed such that the sham and active valves are indistinguishable. The intervention will be implemented by the first qualified provider to arrive at the scene of cardiac arrest and continued by subsequent providers in all ROC sites. The first qualified providers will most often be EMT-certified responders but will also include responders able to mechanically ventilate the patient using either a bag-mask or an advanced airway. Ventilation rates will be consistent with AHA guidelines.

### **Study Episodes**

Episodes attended by EMS will be included if a study device was taken from its sealed container. All such episodes will be followed for purposes of safety evaluation.

### **Study Population**

#### **Inclusion Criteria**

Persons aged 18 years or more (or local age of consent) who suffer non-traumatic cardiopulmonary arrest outside of the hospital in the study communities who receive defibrillation and/or chest compressions by EMS providers dispatched to the scene and do not meet any of the exclusion criteria below. Note: The etiology will be presumed to be non-traumatic in origin unless the apparent cause is due to trauma, drowning, strangulation, electrocution, or exsanguination.

## Exclusion Criteria

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy;
- Tracheostomy present;
- CPR performed with any mechanical compression device (e.g. AutoPulse, LUCAS, Thumper).
- **Ventilated with a mechanical device (e.g. automated transport ventilator) Note: a bag-mask is not considered a mechanical ventilation device.**
- A non-ROC EMS agency/provider, for whom time call received at dispatch cannot be obtained, began CPR or placed pads.

## Primary Comparison Population

The ITD is conjectured to provide an improvement in the rate of neurologically intact ( $MRS \leq 3$ ) survival to hospital discharge in those patients experiencing OOHCA of cardiac origin and treated by EMS within 15 minutes of initial call to 911. There is, however, no contraindication to the use of the ITD in the relatively few patients whom experience OOHCA due to such noncardiac events as strangulation, drowning, or electrocution. In the emergency setting, unnecessarily introducing a need for EMS providers to evaluate eligibility criteria could potentially delay the institution of appropriate life saving treatments. Furthermore, if the ITD is proven effective and adopted widely, the eventual use of the device may include patients for whom the cardiac origin of OOHCA could not be accurately determined. Hence, this study protocol allows for the evaluation of the safety of the ITD device in some patients for whom the indication of the ITD could not be firmly established in the emergency setting. On the other hand, efficacy of the device will be analyzed in only those patients who are determined to meet the criteria defining the pre-hospital conditions for which the use of ITD is conjectured to be of benefit.

*Efficacy Population:* Analysis of primary and secondary efficacy outcomes will be conducted on a modified intent-to-treat basis. In order to be included in the efficacy analyses, patients must meet the inclusion/exclusion criteria for the ITD/sham device intervention. Furthermore, they must also meet the following criteria

- Not have experienced cardiac arrest secondary to drowning, electrocution, or strangulation;
- Have a response time (time from 911 call to time of arrival of ROC EMS providers at scene) less than 15 minutes, and
- Have the device actually applied.

With the exception of the criterion regarding actual application of the device, determination of whether patients meet these criteria or not will be made on the basis of data available prior to randomization (i.e., available prior to opening of the bag containing the device). In every case, the determination of whether a patient belongs in the efficacy population will be made in a blinded fashion (without knowledge of whether the device bag opened was an active ITD or a sham device). Within the efficacy population, analyses will be conducted on an intent-to-treat basis. Hence in the rare event that first and second responders in a tiered response system might both open a bag containing a device, the patient will be analyzed according to the treatment arm corresponding to the first arriving vehicle.

In the event that the Analyze Late vs Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the efficacy population for the ITD/sham device comparison will be restricted to those subjects



treated under the rhythm analysis strategy found to be superior. The number of subjects accrued to the study will be increased to achieve the planned maximal sample size in the superior rhythm analysis strategy arm.

Safety Population: Evaluation of the safety of the ITD will be made using all data from patients who were treated with a device, regardless of whether they are a member of the efficacy population or not.

In the event that the Analyze Late vs Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the safety of the ITD will also be evaluated separately in subgroups defined by the rhythm analysis strategy arm (AL or AE).

## **Intervention**

Upon arrival of EMS providers at a patient with cardiac arrest, CPR will be initiated. Defibrillation will be performed consistent with local practice and cluster assignment. For subjects who are being ventilated with bag-mask or advanced airway (e.g., Combitube, laryngeal mask airway [LMA], or endotracheal tube) and receiving chest compressions, EMS providers will insert a study valve between the bag and the mask/airway, whichever is available. Training will target use of the ITD with initial management of the airway to assure the earliest placement of the ITD during CPR. To assure correct ventilation rate, the rescuers will turn on the ventilation timing assist lights on the device once an advanced airway has been established. The providers will be instructed to immediately remove the valve if the patient has return of spontaneous circulation or is breathing spontaneously, to facilitate rapid elimination of inspiratory impedance in a resuscitated patient. (The ITD has a safety check valve that opens if the pressure in the airway is <16 cm H<sub>2</sub>O in the event the rescuer does not recognize that the patient is able to breathe on their own). The providers will be instructed to immediately reapply the mask if such a patient ceases to have spontaneous circulation or to breath spontaneously (i.e., has recurrent cardiac arrest).

The EMS providers will be instructed to remove the ITD from the advanced airway if the valve fills with fluid; removing this fluid by forcing air through the device with the ventilation bag, suctioning the patient, and reapplying the ITD. If the device fills with fluid a second time, EMS personnel will be instructed to remove the ITD completely and continue resuscitative efforts without use of the device.

Use of the ITD will be discontinued on arrival to the hospital.

All other resuscitative measures will follow common guidelines (Appendix 3).

## **Random Allocation**

Study devices will be randomly allocated in a proportion of 1:1 active vs. sham, with distribution determined by the CTC based on permuted blocks of concealed size within strata defined by participating site and within site by participating agency or subagency. Devices will be packaged with a flexible connector to facilitate adjunct equipment such as CO<sub>2</sub> monitoring. A mask will also be provided to facilitate achievement of a good seal between the patient's face and the ventilatory circuit so as to maintain the intrathoracic pressure. These will be placed at each base station where they can be retrieved by the medic. One device will be kept on each EMS vehicle. Study site personnel will keep inventory records for each EMS site and conduct EMS site visits to confirm inventory status. When a base station has less than three ITDs remaining, an additional set will be distributed. Each ITD package will have several stickers denoting its number. These will be placed on the medic report and emergency care record. Each site must establish a notification process with their EMS system and emergency department to notify study personnel of patient enrollment. In this manner, the subjects,

investigators, study coordinators and all persons caring for the patient will be blinded to the treatment assignment. Note that active and sham devices will not be distinguishable visually even when removed from the opaque packaging. Patients will be considered to have been randomized as soon as the ITD package has been opened. In the event that two bags are opened for the same patient during the same arrest episode, the patient will be assigned to the treatment group of the device used by the first-arriving vehicle.

### **Intervention–Compliance**

The location and number of devices supplied to each EMS rig and station for appropriate distribution will vary with the structure of the system. When an ITD is used, ambulance personnel will document the unique number of the device on their run report by using pull-off labels located within the packaging of the device. Following use, EMS providers will be encouraged to place the used device at a predetermined location and replace the used device with a new valve. After each use, the research team will be notified and will replace the used device. The coordinating center will maintain a record of where each device is distributed, and track their use.

### **Outcome Measures**

#### **Primary**

The primary outcome is survival to hospital discharge with MRS  $\leq 3$ . Patients who are transferred to another acute care facility (e.g., to undergo ICD placement) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

#### **Secondary**

The secondary outcomes are survival to discharge; MRS at 3 and 6 months following hospital discharge; Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) at 1, 3 and 6 months;(31, 32) as well as Health Utilities Index III (HUI3) score(33) and Geriatric Depression Scale (T-GDS)(34) score at 3 and 6 months (details in Section 4 and Appendix 4).

#### **Exploratory**

Cerebral Performance Category (CPC) will be assessed at discharge, 3 and 6 months following hospital discharge.

#### **In-Hospital Morbidity**

Number of hospital days and time interval from 911 call to patient death will be described for all hospitalized patients as measures of morbidity after resuscitation.

#### **Prespecified Subgroup Analyses**

- a) First recorded cardiac arrest rhythm prior to valve application (VF/VT vs. PEA vs. asystole vs. not obtained before device implementation);
- b) Observational status of arrest (Witnessed by EMS vs. witnessed by bystanders vs. unwitnessed);
- c) In witnessed cardiac arrests, response time interval from call to initiation of CPR by ROC EMS (<10 vs.  $\geq 10$  minutes);(30)
- d) Analyze Early vs. Analyze Later vs. not participating in ALvE cohorts.

## Expected Adverse Events

The following will be considered major adverse events if they occur during the resuscitative effort or the hospital stay:

**Pulmonary Edema-** *The presence of pulmonary edema in patients who survive long enough to receive a hospital-based chest x-ray (first emergency department or ICU chest x-ray).* This will be defined as formal radiographic interpretation as consistent with the presence on x-ray of alveolar pulmonary edema, interstitial pulmonary edema, bilateral pleural effusions, cardiomegaly (cardiothoracic ratio > 0.5 on posteroanterior projection), or pulmonary venous congestion (upper-zone flow redistribution on posteroanterior projection).(35, 36) This will be monitored because failure to remove the ITD immediately following successful resuscitation will require the patient to generate more than 16 cm of H<sub>2</sub>O negative intrathoracic pressure before initiating inhalation. This may result in increased work of respiratory effort during the initial stages of successful resuscitation. This may result in secondary respiratory failure or pulmonary edema and the need for continuing to support the patient's respiration. Similarly, in the out-of-hospital setting, if the valve fills with fluid twice (indicating possibly significant pulmonary edema), its use will be discontinued.

All incidences where the valve fills with fluid will be reported to the DSMB. Additionally, all cases of pulmonary edema who did not survive, will have the field report individually reviewed for evidence of failure to remove the ITD valve and these cases will be presented to the DSMB.

Pulmonary edema is commonly observed after resuscitation from cardiac arrest.((37) and Unpublished Data, ASPIRE Investigators) However device-related pulmonary edema has not been observed in previous published studies of ITD. We anticipate that pulmonary edema associated with use of the ITD would be unlikely except if the device were left on a patient who is breathing spontaneously. Since the rate of pulmonary edema in the control group is unknown, we shall monitor the incidence of pulmonary edema in sham and active ITD groups and assess whether there is a significant difference between treatment groups.

**Device Failure-** *Mechanical failure (i.e., the device breaks).* Malfunctions are unlikely due to the simple construction and durable materials of the device. There have been no instances of the ITD breaking in the Milwaukee feasibility study, ongoing European studies or during clinical use in Europe.

**Other-** The following are commonly observed in patients who experience cardiac arrest or resuscitative efforts after its onset, and may or may not be attributable to specific resuscitation therapies. These will be monitored and reported but not classified as major adverse events. *Vomiting During CPR.* Vomiting during CPR is a common and anticipated complication of any method of CPR. Immediate clearing of the airway is necessary to prevent complications from aspiration. Rescuers are experienced in handling this type of complication and have portable and stationary suction available to them. The occurrence of vomiting during the application of the ITD will be recorded from the prehospital clinical record. *Clinical diagnoses of cerebral bleeding, stroke, seizures, bleeding requiring transfusion or surgical intervention, rearrest, pulmonary edema, serious rib fractures, sternal fractures, internal thoracic or abdominal injuries as well as any other major medical or surgical outcomes* will be recorded as noted in the hospital discharge summary. Since the treating physicians will be blinded as to whether the

patient received active or sham ITD, there is unlikely to be a treatment-related bias in identifying these events.

### Unexpected Adverse Device Events (UADE)

These will be defined as any serious unexpected adverse effect on health or safety or any unexpected life-threatening problem caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan or application (including a supplementary plan or application), or any other unexpected serious problem associated with a device that relates to the rights, safety or welfare of subjects. The death or neurological impairment of an individual patient is not considered an adverse event in this study.

## Analyses

### Primary Efficacy Analysis

The primary analysis of treatment efficacy will be based on a comparison across treatment arms active and sham ITD of the observed proportion of patients in the efficacy population (see page 12 for definition of efficacy population) with neurologically intact (MRS  $\leq 3$ ) survival to hospital discharge. We assume that ITD would not be implemented if it were associated with worse neurologically-intact survival to discharge. A one-sided level 0.025 hypothesis test will be used to test the null hypothesis of equal rates of such favorable events ( $H_0: \pi_{ITD} = \pi_{SHAM}$ ) versus the alternative hypothesis that patients on the active ITD arm have a higher probability of neurologically intact survival to hospital discharge than do patients on the sham device arm ( $H_1: \pi_{ITD} > \pi_{SHAM}$ ). The test statistic comparing those proportions will be a one-sided version of Pearson's chi squared statistic: the Z statistic defined as the difference of the proportions (ITD arm minus sham device arm) divided by its estimated standard error computed assuming the null hypothesis of equality of proportions.

$$Z = \frac{(\hat{\pi}_{ITD} - \hat{\pi}_{SHAM})}{\sqrt{\hat{\pi}_{Null}(1 - \hat{\pi}_{Null})\left(\frac{1}{n_{ITD}} + \frac{1}{n_{SHAM}}\right)}} \quad \text{with } \hat{\pi}_{Null} = \frac{n_{ITD}\hat{\pi}_{ITD} + n_{SHAM}\hat{\pi}_{SHAM}}{n_{ITD} + n_{SHAM}}$$

The fixed sample P value corresponding to that Z statistic will be compared to the boundaries of the protocol defined group sequential stopping rule when expressed on the fixed sample P value scale. At the end of the study, analysis results will be summarized using point estimates of the difference in probability of favorable events, 95% confidence intervals, and P values adjusted for the true sampling distribution imposed by the group sequential stopping rule. (See the discussion of the group sequential monitoring plan below.)

This analytic approach assumes unbiased random allocation of patients to treatment group and relies on the sample size being large enough for asymptotic theory to provide good distributional approximations. With the exception of the inclusion criterion regarding actual application of the device, determination of whether patients meet study criteria or not will be made on the basis of data available prior to randomization (i.e., available prior to opening of the bag containing the device) (see p. 12 for more detail).

### Secondary Efficacy Analyses

All secondary analyses of efficacy endpoints are directed toward finding supporting evidence for the findings of the primary efficacy analysis. As such, they will not be used as the primary basis

for establishing benefit of the ITD relative to the sham device, nor will they be used as the primary basis for obtaining regulatory approval of the ITD. Hence, there is no plan to make any statistical adjustment for the multiple comparisons inherent in the secondary efficacy analyses, which include:

*Modified Rankin Score (MRS) at hospital discharge.* The mean MRS at hospital discharge will be compared across treatment groups using the t test which allows for unequal variances across groups. For the purposes of this analysis, patients dying before admission to the hospital will be treated the same as admitted patients dying before hospital discharge and will be assigned an MRS of 6.

*Survival to hospital discharge.* This secondary analysis of treatment efficacy will be based on a comparison across treatment arms of the observed proportion of patients in the efficacy population with survival to hospital discharge. This analysis shall proceed in a manner entirely analogous to that for the primary efficacy endpoint. The test statistic comparing those proportions will be a one-sided version of Pearson's chi squared statistic: the Z statistic as defined for the primary analysis.

*Neurologically intact survival to hospital discharge adjusted for prognostic variables.* A secondary analysis of the primary endpoint will adjust for those pre-randomization variables which might reasonably be expected to be predictive of favorable outcomes. Generalized linear models will be used to model the proportion of subjects with neurologically intact ( $MRS \leq 3$ ) survival to hospital discharge by ITD/sham device group adjusted for site (dummy variables modeling the 11 ROC sites), patient sex, patient age (continuous variable), witness status (dummy variables modeling the three categories of unwitnessed arrest, non-EMS witnessed arrest, and EMS witnessed arrest), location of arrest (public versus non-public), time or response (continuous variable modeling minutes between call to 911 and arrival of EMS providers on scene), presenting rhythm (dummy variables modeling asystole, PEA, VT/VF, or unknown), and treatment assignment in the Analyze Late vs. Analyze Early intervention. The test statistic used to assess any benefit of the ITD relative to the sham device will be computed as the generalized linear model regression coefficient divided by the estimated "robust" standard error based on the Huber-White sandwich estimator(38, 39) in order to account for within group variability which might depart from the classical assumptions. Statistical inference will be based on one-sided P values and 95% confidence intervals which adjust for the stopping rule used for the primary analysis.

*Post-discharge neurological function, quality of life, and depression.* Surviving patients will be contacted post-discharge to obtain consent for additional follow-up via telephone with consenting patients or their proxies regarding cognition, quality of life, and depression. Analyses of each of these outcomes at each time point will be compared across treatment groups by using the t test which allows for unequal variances. Analyses will first be conducted conditional on survival to the relevant time point by using only data from those patients offering consent, as well as using data imputed from discharge data for those surviving patients refusing consent. The data missing due to lack of consent for follow-up will be multiply imputed using measurements of patient age, sex, length of hospital stay, incidence of major adverse outcomes during hospitalization, MRS at hospital discharge, and whether the patient was discharged to home or a nursing facility. Additional analyses of neurological function and quality of life will then incorporate measurements for patients dying prior to hospital admission, during hospitalization, or within 3 or 6 months post discharge. Dead patients will be assigned the worse category of neurological function and quality of life for each measurement.

*Morbidity.* As a measure of morbidity during hospitalization, the number of days hospitalized conditional upon survival to discharge will be compared across treatment groups using the t test which allows unequal variances. A similar analysis will also be conducted comparing the days of hospitalization for patients admitted to the hospital, but dying prior to hospital discharge. Finally, treatment groups will also be compared with respect to the number of days alive post hospital discharge during the first 6 months post OOHCA in order to incorporate information about both dead and surviving patients. In this analysis, data missing due to lack of consent for follow-up will be multiply imputed using data available at hospital discharge, and patients dying before hospital admittance or prior to hospital discharge will be scored as 0.

### **Safety Analyses**

The incidence of adverse events will be recorded for all patients in the safety population and presented by treatment arm (ITD vs. sham device) to the DSMB for their review during the conduct of the study, as well as summarized and compared across treatment arms in the final report of study results. Assessment of the statistical significance of differences in the incidence of safety endpoints plays a lesser role, due to the need to be cautious in the introduction of new treatments in a human population. Hence, emphasis is placed on the presentation of results, with statistical tests provided for guidance on the precision of estimates as indicated. Specific measures that may reflect the safety of the ITD include:

*Delay of treatment.* The process of opening and applying the device could delay treatment and/or potentially cause harm in patients other than those for whom the device is conjectured to provide benefit, as well as in the evaluable patient population. The distribution of time from EMS arrival to initiation of CPR will be described using mean, standard deviation, minimum, 25th, 50th, and 75th percentiles, and maximum. When indicated, statistical tests comparing the distribution of times to initiation of CPR will be effected using the t test which allows for unequal variances. Similar analyses will be conducted for the time between EMS arrival and first assessment for defibrillation, stratified within Analyze Late vs. Analyze Early clusters.

*Complications of treatment.* The incidence of vomiting during CPR, device filling with fluid, mechanical failure of the device, and any UADE will be reported by treatment arm and compared as indicated using Pearson's chi squared statistic.

*Serious adverse events.* The incidence of each serious adverse event, along with other major adverse medical or surgical outcomes identified during review of hospital records, will be tabulated by treatment arm and compared when indicated using Pearson's chi squared test. In order to facilitate the identification of differences in rates of such events that might be due to greater survival to hospital admission and/or hospital discharge on one of the treatment arms, the incidence of any of the above specific events and/or death (either prehospital or during hospitalization) will be reported in a combined fashion and compared as indicated by using Pearson's chi squared statistic.

### **Subgroup Analyses**

Analyses will be performed in each subgroup, along with tests for statistically significant interactions. However, it is recognized that the study is not powered adequately to detect interactions, and thus all subgroup analyses are judged exploratory.

### **Exploratory Analyses**

Data from the clinical trial will also be used to explore two hypotheses unrelated to the treatment effect of ITD on neurologically intact survival post OOHCA.

*Correlation between MRS and other measures of cognition and quality of life.* Analyses will evaluate the correlation between simultaneous measures using the MRS, ALFI-MMSE, HUI or GDS at 3 and 6 months using linear regression analyses and standard errors computed using the Huber-White sandwich estimator. Additional analyses will evaluate the value of MRS at hospital discharge as a surrogate variable for the ALFI-MMSE and HUI at 6 months post hospital discharge. In this latter analysis, the effect of treatment with ITD vs. sham device on the 6 month cognitive function and quality of life measures will be analyzed both without and with adjustment for MRS at hospital discharge. A descriptive measure of the usefulness of the MRS at hospital discharge as a surrogate for the later validated measures will be based on the difference in the estimates of treatment effect between the unadjusted and adjusted analyses.

*Cerebral Performance Category* To assess the validity of the Cerebral Performance Category for use in future studies, CPC scores at discharge as well as three and six months after discharge will be analysed in a manner similar to the analyses of post-discharge neurologic function described above in the secondary efficacy analyses. However the results of any analysis of CPC scores will not be used to make labeling claims for ITD.

*Association between use of hypothermia and neurologically intact survival.* Some patients may be treated with hypothermia according to local standards of best medical care. Data will be collected on both the pre-hospital and in-hospital use of hypothermia. In order to explore any association between the use of hypothermia and the probability of survival to hospital discharge proportional hazards regression models will be fit using use of hypothermia as a binary time-varying covariate, adjusted for treatment with ITD vs. sham device. Test statistics will be based on the estimated hazard ratio for the hypothermia covariate and the Wald statistic computed from the regression parameter divided by the “robust” standard error computed using the Huber-White sandwich estimator. Comparisons of neurologic function will use measures derived from the MRS, ALFI-MMSE, HUI and GDS over time in a generalized estimating equation (GEE) analysis restricted to patients surviving to hospital discharge and incorporating the multiple measurements made on each patient. Test statistics will be based on the Wald test using the regression parameter estimate for the hypothermia covariate and its “robust” standard error computed using the Huber-White sandwich estimator.

## **Sample Size and Study Duration**

The sample size for the factorial trial is driven by the power analysis for the ITD intervention. These calculations are based on the estimated probability of survival to hospital discharge averaged over the participating ROC sites, which is then adjusted to reflect the estimated probability of survival to hospital discharge with acceptable neurological status ( $MRS \leq 3$ ).

Patients with OOHCA who are treated by participating agencies and subagencies and who meet the inclusion/exclusion criteria will be randomized to the ITD or sham device, unless resuscitated prior to the placement of such a device. This latter possibility may tend to occur with patients who present in VT/VF and who initially achieve ROSC following a first, early defibrillation as might be applied under the AE strategy. Thus, in computing sample sizes for the ITD intervention, we must consider the distribution of patients by presenting rhythm and their assignment to the AE or AL treatment strategies. We also must consider the number of patients who have EMS witnessed CA, because all such patients will be treated using an AE strategy, regardless of the cluster randomization of the responding unit to the AL vs. AE intervention.

It is estimated that approximately 50% of patients accrued to the factorial study will present in asystole, 25% of patients will present with pulseless electrical activity (PEA), and the remaining 25% will present in VT/VF. It is also estimated that approximately 10% of all EMS treated OOHCA will involve EMS witnessed arrest. In the ASPIRE trial, the presenting rhythm of EMS witnessed arrest occurred in the ratio of 2.20 asystole: 2.57 PEA : 4.74 VT/VF. The anticipated distribution of patients by presenting rhythm and whether CA was EMS witnessed or not was estimated based on these assumptions (Table 1).

**Table 1: Proportion of all EMS treated OOHCA patients according to presenting rhythm and EMS Witness status**

Presenting Rhythm	EMS Witnessed	EMS Unwitnessed	Total
Asystole	0.0231	0.4769	0.500
Pulseless Electrical Activity (PEA)	0.0270	0.2230	0.250
VT/VF	0.0499	0.2001	0.250
<b>TOTAL</b>	0.1000	0.9000	1.000

Eligibility criteria for the ITD intervention excludes subjects for whom no device (ITD or sham) was used, and it is anticipated that approximately 30% of the patients presenting in VT/VF will not have a device placed when treated under the AE strategy, On the other hand, it is anticipated that all such patients would have a device placed when treated under the Analyze Later (AL) strategy. Taking into account that patients with OOHCA that is not witnessed by EMS will be randomized (by cluster) in a 1:1 ratio to the AE or AL strategies at all participating agencies except Seattle Medic One (which is projected to accrue approximately 2.7% of all patients—see Table 9), the expected distribution of patients to the various treatment strategies by presenting rhythm was estimated (Table 2).

**Table 2: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA or Seattle Medic One (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total ITD/Sham Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	Sham	ITD
Asystole	0.000	0.018	0.018	0.000	0.116	0.116	0.116	0.116	0.250	0.250
PEA	0.000	0.017	0.017	0.000	0.054	0.054	0.054	0.054	0.125	0.125
VT/VF	0.015	0.020	0.020	0.029	0.034	0.034	0.049	0.049	0.103	0.103
<b>TOTAL</b>	0.015	0.055	0.055	0.029	0.204	0.204	0.219	0.219	0.478	0.478

Based on ranges of estimates in published data and results of the ASPIRE trial, and allowing for 1-5% improvement due to better CPR process in the clinical trial setting, It is estimated that in the absence of an ITD and when managed according to the Analyze Early (AE) strategy, the probability of survival to hospital discharge would be 1.05% for patients presenting with asystole, 4.02% for patients presenting with PEA, and 20.2% for VT/VF. These assumptions lead to an estimated probability of survival to hospital discharge of 0.0600 when treated under the AE strategy with a sham valve. We assume that 88.9% of such survivors would have acceptable neurological status (MRS  $\leq$  3) based on a combination of observed rates from the ASPIRE and PAD trials where 35 of 45 and 42 of 45 survivors had CPC scores  $\leq$  2. Therefore we estimate a rate of 0.0533 for neurologically intact survival to hospital discharge under treatment with the AE strategy and a sham valve.



Under the alternative hypothesis used for sample size calculations, the effect of the ITD on neurologically intact survival is presumed to vary by presenting rhythm. Because a more substantial relative benefit is presumed for those patients receiving CPR for a longer period of time, neurologically intact survival is presumed to be 1.4 fold higher for patients treated with the ITD if their presenting rhythm was asystole or PEA. For patients presenting in VT/VF a relative benefit of 1.20 is hypothesized to account for a lesser benefit for those patients who would respond well to early defibrillation. Applying these hypothesized effects to the numbers given above results in an estimated probability of survival to hospital discharge of 0.0753 for patients treated with an ITD under the AE strategy, with a corresponding hypothesized rate of 0.0669 for neurologically intact survival to discharge. Details of these calculations are provided below (Table 3).

**Table 3: Estimated proportions of all EMS treated OOHCA patients surviving to discharge and surviving to discharge with MRS  $\leq$  3 by ITD/sham treatment arm and presenting rhythm.**

Presenting Rhythm	Stratum Weight	Sham Device Probability of Survival to Discharge	ITD / Sham Relative Benefit	ITD Probability of Survival to Discharge
Asystole	0.5231	0.0105	1.40	0.0147
PEA	0.2616	0.0420	1.40	0.0588
VT/VF	0.2153	0.2020	1.20	0.2424
<b>Probability of Survival to Discharge (weighted average)</b>		0.0600		0.0753
<b>Probability of Neurologically Intact Survival to Discharge (88.9% of patients surviving to hospital discharge)</b>		0.0533		0.0669

The number of patients to be accrued to the ITD vs. sham device comparison is based on the ability of a one-sided level 0.025 test to reject a null hypothesis that the probability of neurologically intact survival to hospital discharge is 0.0533 on both treatment arms. Sample size computations are based on a two-sample test of binomial proportions using Pearson's chi squared statistic. The test should have approximately 90% statistical power to reject the null hypothesis when the ITD treatment arm would have a 0.0669 probability of neurologically intact survival.

The clinical trial will be conducted using a group sequential stopping rule based on up to three evenly spaced analyses (two interim analyses and the final analysis). The stopping rule corresponds to a Pampallona and Tsiatis design(40) as described in more detail under the monitoring plan. Using that stopping rule, a sample size of 14,154 evaluable patients will provide 90% power to reject the null hypothesis under the conjectured treatment effect. However, it is anticipated that approximately 4% of accrued patients will be judged nonevaluable due to non-cardiac origin of cardiac arrest or response time in excess of 15 minutes. Hence, a maximum of 14,742 patients will be potentially treated with the ITD or sham device in order to obtain 14,154 evaluable patients for testing the effect of ITD on the primary endpoint of neurologically intact survival to hospital discharge.

The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 16,542 patients (up to 1,800 during the run-in phase, 14,742 during the actual trial) will require 20 months.

In the event that the Analyze Late vs. Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the number of subjects accrued to the study will be increased to achieve the planned maximal sample size in the superior rhythm analysis strategy arm. The primary analyses of the effectiveness of the ITD will then be evaluated in just those patients who were treated with the rhythm analysis strategy deemed to be superior. The stopping rule will be applied to the data in the efficacy population restricted to that superior ALvE treatment arm.

## **Human Subjects**

### **Risks to Subjects**

#### **Population**

This study will enroll approximately 16,542 adult patients who have sustained a nontraumatic out-of-hospital cardiac arrest and are known or presumed to be at the local age of consent.

#### **Potential Risks**

ITD administration during standard manual CPR has been tested in three animal studies(5, 22, 41) and three human studies(23-25) with no serious device-related adverse effects reported. ITD increases negative intrathoracic pressure and coronary perfusion pressure, which has raised a concern for potential increased pulmonary edema. However previous studies have not observed device-related adverse events.

Other potential concerns are mechanical failure of the device. We will report any evidence of pulmonary edema, or device failure as a serious adverse event. If failure of the device or pulmonary edema occurs (the device fills with fluid twice) in the out-of-hospital setting, application of the device will be immediately stopped and appropriate clinical management undertaken. As part of the training of the prehospital providers for the study, potential signs and symptoms of serious adverse events will be clearly described.

#### **Potential Benefits to Subjects and Society**

There are several potential benefits to subjects who receive an active ITD. These include increased venous return, coronary perfusion pressure, cardiac output and admittance to intensive care with the use of the ITD during standard CPR in humans. We contend that use of the ITD may significantly increase survival to hospital discharge. The efficacy of this device can only be assessed by performing clinical studies such as the one proposed in this application.

#### **Inclusion of Women or Minorities**

There will be no exclusion on the basis of gender, race or ethnicity. Known pregnant women and prisoners will be excluded. Since this is the first large human trial using the ITD with standard CPR, there is no available evidence to determine whether or not there is a clinically important sex/gender and/or race/ethnicity difference with its use. Investigators will compare primary and secondary study outcomes between the treatment and control groups broken down by sex/gender and race/ethnicity categories.

#### **Inclusion of Children**

The ITD has not been applied during standard CPR in humans < 21 years of age. For this reason, clinical equipoise has not been established in the pediatric population. Therefore the ROC Investigators believe that it is inappropriate to first use the ITD during standard CPR in

children in a randomized trial such as that proposed in this protocol. Accordingly, victims of cardiac arrest less than the local age of consent (which varies from 17 to 21 years in ROC sites) will not be entered in the study.

### 3. Analyze Later versus Analyze Early

#### Analyze Later Trial - Comparison of a Strategy of Analyze Later Combined with CPR Early Versus a Strategy of Analyze Early Combined with CPR Later in Patients With Out-Of-Hospital Cardiac Arrest

##### Study Summary

**Background:** While patients with the shockable rhythms of VF and pulseless VT (PVT) have the best chance of survival of amongst out-of-hospital cardiac arrest victims, the vast majority of such patients do not survive to hospital discharge. The traditional approach to these patients has been to analyze the cardiac rhythm and deliver defibrillatory shocks as quickly as possible with the onset of CPR delayed. Recent thinking suggests three phases for VF cardiac arrest: a) an early “electrical” phase where rapid defibrillation is effective, b) an intermediate phase where “priming” the heart with CPR enhances the effectiveness of defibrillation, and c) a late phase where defibrillation is rarely effective. Some now advocate delaying electrical shocks and providing early CPR in cases of VF where defibrillation cannot be carried out immediately. Three clinical studies have each attempted to evaluate this hypothesis of early CPR and delayed analysis. While two studies supported early CPR and one did not, none were definitive and all had important limitations. We believe there is an urgent need for a large and definitive clinical trial to determine the optimal strategy for rhythm analysis and CPR in patients with out-of-hospital cardiac arrest.

**Aims:** The primary aim of the trial is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  between a strategy of Analyze Later consisting of CPR first followed by rhythm analysis versus a strategy of Analyze Early consisting of early rhythm analysis in patients with out-of-hospital cardiac arrest. The secondary aims of the trial are to compare survival to discharge, functional status at discharge and at 1, 3 months and 6 months as well as depression at 3 and 6 months.

**Hypotheses:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed between Analyze Later versus Analyze Early in patients with cardiac arrest. The secondary null hypotheses are that survival to discharge, functional status at discharge and at 1, 3 months and 6 months as well as depression at 3 and 6 months will be identically distributed between Analyze Later versus Analyze Early in patients with cardiac arrest.

**Design:** Cluster randomized trial with cluster units defined by geographic region, or monitor/defibrillator machine.

**Population:** Patients with non-traumatic out-of-hospital cardiac arrest, known or presumed to be local age of consent or greater and treated by EMS providers.

**Setting:** EMS systems participating in the Resuscitation Outcomes Consortium and agreeing to cluster randomization to the Analyze Later/Analyze Early intervention in a crossover fashion.

**Sample Size:** Based on a two-sided significance level of 0.05, a maximum of 13,239 evaluable patients will allow statistical power of 0.996 to detect an improvement in the probability of survival to discharge with modified Rankin score  $\leq 3$  rate from 5.41% after Analyze Early to 7.45% after Analyze Later.

**Anticipated Clinical Impact:** If this trial demonstrates a significant improvement in survival with a strategy of Analyze Later, we estimate that the premature death of 4,000 victims of cardiac arrest per year would be averted annually in North America alone.

## Specific Aims

**Primary Aim:** The primary aim of this study is to compare survival to hospital discharge with modified Rankin score  $\leq 3$  in a variety of communities in patients with out-of-hospital cardiac arrest between a protocol of compressions equivalent to approximately 3 minutes prior to cardiac rhythm analysis (Analyze Later) compared with cardiac rhythm analysis as soon as possible after 50 compressions (Analyze Early).

**Hypothesis:** The null hypothesis is that survival to hospital discharge with modified Rankin score  $\leq 3$  is identically distributed with use of Analyze Later versus Analyze Early in patients with cardiac arrest.

**Secondary Aims:** The secondary aims of this trial are to compare survival to discharge, functional status scores at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months between Analyze Later versus Analyze Early in patients with out-of-hospital cardiac arrest.

**Hypotheses:** The null hypotheses are that survival to discharge, functional status at discharge and at 1, 3 and 6 months as well as depression at 3 and 6 months are identically distributed with use of Analyze Later versus Analyze Early in patients with cardiac arrest.

**Prespecified Subgroup Analyses:** These include assessment of treatment effect by:

- a) Rhythm immediately post electrode placement: VF/VT, PEA, asystole, and not obtained.
- b) Response time from 911 call to initiation of EMS CPR  $< 4$  minutes and  $\geq 4$  minutes.
- c) CPR being performed by bystanders.

## Background and Significance

### Conceptual Framework for Analyze Later

Our current paradigm of cardiac arrest defines VF as “shockable,” with the optimal therapeutic approach being immediate direct countershock.(42) Integral to this approach is the concept that defibrillation attempts should occur without delay upon recognition of VF, either by prehospital personnel or the analysis software contained within AEDs, which can then be applied by first responders with limited training or even laypersons.(43) This approach has defined current Advanced Cardiac Life Support (ACLS) algorithms and shaped the development of EMS systems, with prehospital providers that can rapidly respond to victims of cardiac arrest, and the placement of AEDs in public areas for use by non-medical personnel. (44-48) The ability to provide early defibrillation has resulted in improved survival for cardiac arrest victims

with an initial rhythm of VF in some EMS systems and has defined the current standard of care. (4, 49)

One of the major limitations to this cardiac arrest paradigm is its consideration of VF as homogenous, without regard for variability in VF morphology or elapsed time since the arrest. In contrast, experimental models of VF arrest support three distinct phases, each with a different optimal therapeutic approach.(50) The early moments following arrest define an “electrical phase” during which little ischemic injury has occurred and rapid defibrillation attempts appear to be most efficacious. After some time period, probably around 3-4 min, the optimal therapeutic approach no longer appears to be immediate countershock but instead includes a period of chest compressions prior to defibrillation attempts. It is unclear whether this is related to a “priming” effect with the delivery of substrate necessary for successful return of spontaneous circulation (ROSC) or the removal of toxic metabolites that have accumulated during the ischemic period. Effective chest compressions, traditionally held to provide approximately 30% of normal cardiac output during the first several minutes of CPR, may provide sufficient myocardial perfusion and improve the metabolic state of those myocytes in patients with ventricular fibrillation. Immediate defibrillation attempts during the circulatory phase may be unsuccessful due to persistent or recurrent VF or may result in terminal PEA or asystole. Interestingly, outcomes in patients “shocked” into PEA or asystole are significantly worse than when these are the presenting rhythms. (51)

After some additional elapsed time period, even chest compressions prior to defibrillation attempts do not appear to change outcome. This may be due to the initiation of irreversible ischemic changes that ultimately lead to substantial myocyte and neuronal cell death. This “metabolic phase” is thought to start after about 10 min of total arrest duration, with no currently available therapies demonstrating efficacy once this phase is reached.

### **Preliminary Studies**

The effect of early rhythm analysis versus later rhythm analysis has been evaluated in animal and human studies. Animal models demonstrate improved ROSC and neurological outcomes with delayed countershock following a period of chest compressions in VF of moderate duration.(52-55) Several investigators have utilized this period of chest compressions as a therapeutic window in which to deliver various pharmacological agents designed to increase the likelihood of successful ROSC and improve neurological outcomes. Yakaitis et al compared immediate countershock to delayed defibrillation following administration of epinephrine and 5 min of chest compressions in a dog model of VF.(52) Immediate defibrillation was superior with VF of 1- or 3-min duration, while the delayed approach was optimal with VF of 5- or 9-min duration. Niemann et al observed improved outcomes with delayed countershock following administration of epinephrine and 5 min of chest compressions alone with a VF duration of 7.5 min but not 5 min in a swine model.(53) Menegazzi et al observed substantially higher ROSC and better neurological outcomes with administration of a pharmacologic “cocktail” followed by chest compressions alone prior to defibrillation attempts versus immediate countershock in a swine model of VF of 8-min duration.(54, 55)

Other parameters besides duration of ischemia may better indicate the likelihood of successful defibrillation in VF arrest victims. Various VF morphologic features have been identified as potentially useful in predicting successful defibrillation in animal models of VF.(56-58) Limited human data exist to support morphological analysis of VF/PVT as a predictor of successful ROSC.(58-60) In addition, animal and human data suggest that chest compressions alone can modulate these morphological features to a more favorable configuration for successful ROSC. (57-59) Berg et al used a swine model of VF to demonstrate that CPR alone can modulate VF median frequency to a value predictive of successful defibrillation; improvements in ROSC and cardiac function at 1 hour were also observed with CPR prior to defibrillation attempts.(57) Eftestol et al demonstrated improvements in spectral flatness

measure, centroid frequency, and amplitude spectrum relationship. Improvement in ROSC was also observed in patients with at least 3 min of chest compressions prior to countershock. None of these morphological features have demonstrated adequate predictive value to justify their clinical use; however, these data further support the therapeutic value of chest compressions prior to defibrillation in VF of moderate duration. Finally, the duration between cessation of chest compressions and direct countershock appears to influence success of ROSC and ultimate survival.(61, 62) This suggests that prehospital providers should attempt to minimize delays after chest compressions due to rhythm analysis or ventilation prior to defibrillation attempts.

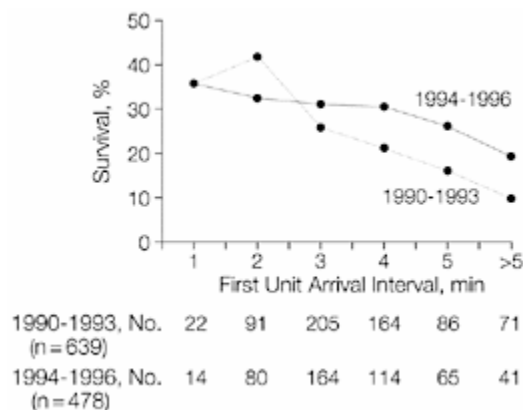
### Clinical Studies

Three clinical studies have compared outcomes from out-of-hospital cardiac arrest due to VF when a period of CPR has or has not been prescribed prior to the first attempts at defibrillation.(63-65)

**Cobb et al.** conducted an observational, population-based study(63) of 639 patients treated for out-of-hospital VF at a time when AED application and use was given the highest priority compared with 478 patients for whom 90 seconds of chest compressions and ventilation (CPR) were mandated before AED application and use. An a priori hypothesis was that the survival benefit would be most evident in those cases with the greater delay from collapse to delivery of the first shock. Survival to hospital discharge and favorable neurological status at discharge (defined as full or nearly full neurological recovery, or requiring some but not complete dependence upon others for assistance in activities of daily living) were the primary outcomes of the study.

Survival to hospital discharge was greater during the intervention period (mandated CPR prior to shock) than in the preintervention period (high priority for AED use): 30% vs. 24% (p=0.04). There was a non-significant trend toward a more favorable neurological outcome observed during the intervention period (79% of patients with mandated CPR versus 71% of patients in whom AED use was prioritized, p=0.11). A significant interaction also described a relatively greater survival benefit for CPR before defibrillation as the response interval of the first arriving unit increased, particularly in cases in which the response interval of the first arriving unit was 4 minutes or longer (p=0.04) (Figure 4).

**Figure 4: Survival versus Response Time Interval With and Without Initial CPR**



Although its hypotheses were prospectively defined, this study was observational, and hence subject to the influence of factors, including the potential biases inherent in non-randomized studies that tend to overestimate treatment effects. For example, a change in the *sequence* of CPR could have been accompanied by an unconscious change in *emphasis* of

CPR over shock or even over other interventions during resuscitation. As the authors themselves stated, their “observations represent an encouraging pilot study and that the development of randomized clinical trials be considered to evaluate further the influence of CPR before the delivery of a shock for patients who have a significant delay prior to treatment”.

**Wik et al.** (64) conducted a randomized trial of 200 patients with out-of-hospital cardiac arrest due to VF to compare standard care with immediate defibrillation (n=96) or 3 minutes of basic CPR prior to defibrillation (n=104). In both treatment groups, if three sequential defibrillations were unsuccessful, 1 minute of CPR was given for VF/VT or three minutes for other rhythms before a new rhythm analysis. Based on the report by Cobb et al that was published subsequent to the start of the study but before analysis of outcomes, the authors hypothesized that survival benefit would be most evident in cases with longer response intervals, and analyzed subgroups with response times either up to or longer than 5 minutes.

The primary outcome of survival rate to hospital discharge did not differ significantly between the two treatment arms of the study (22% in those randomized to CPR-first versus 15% in the standard group,  $p=0.17$ ). Nor were there significant differences in ROSC, 1 year survival, “good neurological recovery” at hospital discharge or 1 year after cardiac arrest between treatment groups. For those with a response time interval (time from dispatch to arrival of first EMS provider) of 5 minutes or less, there were no significant differences in ROSC, survival to hospital discharge, 1 year survival, or neurological outcome of survivors. Among 119 patients with response times longer than 5 minutes, more patients in the CPR first than in the standard group achieved ROSC (58% vs. 38%,  $p=0.04$ ), survived to hospital discharge (22% vs. 4%,  $p=0.006$ ) and survived to 1 year (20% vs. 4%  $p=0.01$ ).

However the criterion for statistical significance in this trial ( $p<0.05$ ) was not adjusted for sequential monitoring performed at six, 18 and 30 months, nor for subgroup analysis. The reported confidence intervals surrounding the estimated benefit were also wide. Hence the findings of this study have to be interpreted with caution, and the observed results not interpreted as definitive of benefit from a CPR first strategy. Moreover, this study had a long interval from collapse to EMS arrival (approximately 12 minutes), limiting the generalizability of the conclusions.

**Jacobs et al.** conducted a prospective prehospital randomized trial performed in Western Australia which randomized 256 patients to a strategy of 90 seconds of CPR before defibrillation versus immediate defibrillation.(65) Survival to hospital discharge was not significantly different in the CPR first group, 4.2%, compared with 5.1% in the immediate defibrillation group. There was no significant difference in survival to hospital discharge among patients with a response interval of  $\leq 5$  versus  $>5$  minutes (12% in the CPR first group, compared with 0% in the immediate defibrillation group among patients with a response interval  $\leq 5$  minutes ( $p= 0.24$ ); and 3.5% vs. 4.9%, respectively, among patients with a response interval of  $>5$  minutes ( $p=0.7$ ). Unfortunately this trial was underpowered due to failure to recruit a total sample size of 390 patients, lower than expected baseline survival rates, and exclusion of 41 eligible cases. Notably, the overall low survival rate and longer response intervals observed in this trial should have favored a greater benefit from CPR before defibrillation if the interactions observed by Wik and Cobb et al. between survival and benefit from CPR hold true.

## Summary of Rationale

Survival after cardiac arrest is poor. The most treatable arrhythmias immediately following cardiac arrest are VF and PVT. Current ACLS algorithms emphasize the importance of immediate defibrillation attempts in these patients. While it has been recognized for many years that chest compressions on OOH-CA patients who received “bystander CPR” result in positive outcomes,(66) this impact has been relegated to a secondary or even tertiary role in resuscitation sequencing. Small randomized or observational studies suggest that CPR before

defibrillation may increase survival but the results to date are inconclusive. Although there is some evidence that favors immediate defibrillation in cases where the response time is  $\leq 2$  minutes, such response times are rare and the frequent delay in recognition of the OOH-CA and calling 911, as well as the complexity of the resuscitation protocol, convince us that response time should not be used as an intervention modifier. We believe that there is clinical equipoise with regard to the competing strategies of Analyze Early vs. Analyze Later. A large, randomized clinical trial is needed to examine the impact of delayed defibrillation on survival to hospital discharge in patients who are presumed to be without circulation for several minutes. Since the only cost of the intervention is training or retraining providers, the proposed study has the potential to have substantial impact upon prevention of premature cardiac death at comparatively little cost.

## **Research Design and Methods**

### **Study Design Overview**

This protocol will be a single-blinded (i.e. blinded to data management team) cluster randomized crossover controlled trial with two intervention groups: a) an Analyze Early group, and b) Analyze Later group. Subjects in the Analyze Early group will be assigned to receive 50 (or more) compressions of CPR prior to early ECG analysis and defibrillation shocks if indicated and those in the Analyze Later group will receive compressions equivalent to approximately 3 minutes of CPR prior to ECG analysis and rescue defibrillation. The intervention will be implemented by the first qualified provider to arrive at the scene of cardiac arrest and continued by subsequent providers in all ROC sites. Qualified providers are defibrillation-capable first-responders, emergency medical technicians (EMTs), and paramedics.

We will include all out-of-hospital locations within the participating study communities within the Resuscitation Outcomes Consortium and served by an EMS agency participating in the Analyze Later/Analyze Early intervention (the Seattle Medic One EMS agency is participating only in the ITD/sham device intervention of the partial factorial ROC PRIMED study). Outcomes will be assessed in the field and at the receiving hospitals.

### **Study Population**

#### **Inclusion Criteria**

All persons of local age of consent or older who suffer non-traumatic cardiopulmonary arrest outside of the hospital in the study communities with defibrillation and/or delivery of chest compressions provided by defibrillation equipped EMS providers dispatched to the scene and do not meet any of the exclusion criteria below.

#### **Exclusion Criteria**

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy;
- EMS-witnessed arrests;
- Non-EMS rhythm analysis (AED placed by police or lay responder is an exclusion but CPR by lay or other non-EMS responders is not);
- Non-ROC EMS agency/provider on scene and CPR begun or pads placed.



EMS responders will generally provide CPR according to the cluster randomization even for patients with exclusions. Those with a clear exclusion will not be included in the primary analysis. However, all eligible patients are considered enrolled into the Analyze Later protocol regardless of how they are treated and will be included in the primary analysis.

## **Primary Comparison Populations**

The Analyze Late treatment strategy is conjectured to provide an improvement in the rate of neurologically intact ( $MRS \leq 3$ ) survival to hospital discharge in those patients experiencing OOHCA of cardiac origin unwitnessed by EMS and not previously defibrillated. EMS witnessed OOHCA should be treated by an Analyze Early strategy. There is, however, no contraindication to the use of either Analyze Late or Analyze Early in the relatively few patients experiencing OOHCA due to such noncardiac events as strangulation, drowning, or electrocution. In the emergency setting, unnecessarily introducing a need for EMS providers to evaluate eligibility criteria and randomize individual patients could potentially delay the institution of appropriate life saving treatments. Furthermore, if either the Analyze Late or Analyze Early strategy is proven superior to the other and therefore adopted widely, the eventual use of the superior treatment strategy would likely be applied to all OOHCA unwitnessed by EMS. Hence, this study protocol uses cluster randomization and allows for the evaluation of the safety of the treatment strategies in some patients for whom there is no conjecture of clear benefit. On the other hand, efficacy of the treatment strategies will be analyzed in only those patients who are determined to meet the criteria defining the pre-hospital conditions for which the Analyze Late strategy is conjectured to be of benefit.

*Efficacy Population:* Analysis of primary and secondary efficacy outcomes will be conducted on a modified intent-to-treat basis. In order to be included in the efficacy analyses, patients must meet the inclusion/exclusion criteria for the Analyze Late vs. Analyze Early intervention. In particular, they must not have DNAR orders, have blunt or penetrating traumatic injury or burns, be visibly pregnant, a prisoner, a minor, or have had OOHCA witnessed by EMS. Furthermore, in order to be evaluable, they must also have not have experienced cardiac arrest secondary to drowning, electrocution, or strangulation.

*Safety Population:* Evaluation of the safety of the Analyze Late versus Analyze Early strategies will be made using all data from patients who were treated, regardless of whether they are a member of the efficacy population or not. This will include patients who were defibrillated by ROC EMS providers but did not receive CPR from ROC EMS providers.

## **Random Allocation**

The intervention will be randomly allocated according to the cluster assignment (i.e., Analyze Later or Analyze Early). Each ROC site has been subdivided into multiple clusters (see Sample Size section below) by various means. We believe that randomization by event or by individual patient is not feasible because the intervention is a psychomotor skill and there would be a significant risk of carryover effect from event to event. In addition, randomization by event would add unacceptable complexity for EMS providers who already must deal with randomization of the ITD protocol. Each RCC will be subdivided into a goal of at least 20 clusters by the following means: a) according to EMS agency or geographical boundaries, or b) according to individual defibrillator devices, rig, or station.

The randomization of clusters will be stratified by site. Within each site, clusters will be organized in blocks of varying size (hidden from investigators) according to the number of patients expected to be treated over the course of the study in that cluster. Within each block, clusters will be assigned in equal numbers to order of treatment. All clusters will crossover between intervention assignments at least once (i.e. have at least two distinct treatment

periods). Some clusters will crossover more than once (e.g. have four or more distinct treatment periods). There will always be an even number of treatment periods. Among clusters having a single crossover, equal numbers will be assigned to Analyze Late first and Analyze Early second as are assigned to Analyze Early first and Analyze Late second. Among clusters having four treatment periods, equal numbers within each block will be assigned to each of the following four orders of treatment: Late-Early-Late-Early, Late-Early-Early-Late, Early-Late-Late-Early, and Early-Late-Early-Late. Randomization assignment will be performed at the Data Coordinating Center prior to the start of the study. Clusters will not be informed as to which group they are assigned until it is time to crossover to another intervention. Responders will, however, know that each intervention will be tested in the first two periods, and each intervention will be tested in the last two periods in each cluster.

## **Intervention**

Detailed descriptions and algorithms demonstrating the sequence of action for Analyze Early versus Analyze Later with use of an ITD are presented in Section 4. For those clusters allocated to Analyze Later, defibrillator analysis will not be initiated until after delivery of compressions equivalent to approximately 3 minutes of CPR, after which a rescue shock will be administered, if indicated. For those clusters allocated to Analyze Early, defibrillator analysis will not be initiated until the chest compression count reaches 50 (e.g., 30-60 seconds), or as soon thereafter as possible, after which a rescue shock will be administered if indicated.

### **Both Early and Later Arms**

**Chest Compressions:** Initiation of chest compressions will not be delayed. Recognition that a patient is in cardiac arrest will immediately prompt one rescuer to initiate and count chest compressions. If the scene is first attended by two EMS rescuers, chest compressions will be performed by one while the second will set up the monitor/defibrillator and place the defibrillator pads. Then ventilation with the ITD will proceed. If three rescuers are present, ventilation and defibrillation readiness can proceed simultaneously (see Appendix 3 for Resuscitation Standards).

**Minimum Interruptions:** Training will emphasize that chest compressions should not be interrupted, except for required ventilations. If endotracheal intubation or other advanced airway procedures are deemed medically necessary, the providers should proceed, but continue chest compressions with minimum interruption. However, training will emphasize that interruption of chest compressions while securing the airway may dilute the theoretical benefit of the initial intervention. Interruption of chest compressions for airway manipulations will be documented when feasible.

**ITD Use:** Training will emphasize that rescuers will use the ITD during initial airway management (either facemask or advanced airway).

### **Analyze Later Arm**

AED analysis will not be initiated until the chest compression count reaches 300, after which a rescue shock will be administered if indicated.

### **Analyze Early Arm**

Analysis will be initiated as soon as defibrillation pads are in place and 50 compressions have occurred and a rescue shock will be administered if indicated. The rescuers will note the compression count or time that has been reached by the rescuer assigned to CPR. After the initial analysis, the standard resuscitation protocol will be followed.

### **Arrival of Additional EMS Personnel**

In tiered response systems, or when backup EMS crews arrive on scene, first-responders delivering the chest compressions consistent with cluster assignment prior to initial ECG analysis should complete this intervention even if paramedics arrive on scene, and, if the subject has defibrillation pads in place, continue using the first crew's equipment until the first ECG analysis (and shock, if indicated).

Additional personnel are encouraged to assist with ongoing activities that do not interrupt chest compressions or initial rhythm analysis. For example, airway management, rotation of chest compressions, and placement of AED/monitor electrodes may benefit from additional personnel. If sufficient personnel arrive, they may also begin attempts at IV access.

### **Adherence to Protocol**

Personnel will be discouraged from terminating the protocol prematurely. As intention-to-treat principles apply, any breach of protocol will not alter the study group to which a patient has been assigned.

### **Intervention – Compliance**

The time interval from power-on to first ECG analysis (power-to-analysis interval) and to first rescue shock (power-to-shock) will be calculated from the time stamps on the electronic record. Explicit criteria will be used to define successful delivery of the intended therapy and this information will later be fed back to the EMS providers (Table 4).

**Table 4: Intervention Compliance Time Intervals**

	<b>Power-to-analysis interval</b>	<b>Power-to-shock interval</b>
<b>Analyze Early</b>	30-60 seconds	<90 seconds
<b>Analyze Later</b>	180-200 seconds	180-220 seconds

### **Outcome Measures**

#### **Primary**

The primary outcome is survival to hospital discharge with modified Rankin score  $\leq 3$ . Patients who are transferred to another acute care facility (e.g., to undergo ICD placement) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

#### **Secondary Outcomes**

The secondary outcomes are survival to discharge; MRS at 3 and 6 months following hospital discharge; Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) at 1, 3 and 6 months;(31, 32) Health Utilities Index III (HUI3) score(33) at 3 and 6 months following hospital discharge; and Geriatric Depression Scale (T-GDS)(34) score at 3 and 6 months (details in Section 4 and Appendix 4).

#### **Exploratory**

Cerebral Performance Category (CPC) will be assessed at discharge, 3 and 6 months following hospital discharge.

#### **In-Hospital Morbidity**

Number of hospital days and time interval from 911 call to patient death will be described for all hospitalized patients as measures of morbidity after resuscitation.

## Analyses Methods

### ***Primary Efficacy Analysis***

The primary analysis of treatment efficacy will be based on a comparison across treatment arms of the observed proportion of patients in the efficacy population with neurologically intact (MRS  $\leq 3$ ) survival to hospital discharge. A two-sided level 0.05 hypothesis test will be used to test the null hypothesis of equal rates of such favorable events ( $H_0: \pi_{AE} = \pi_{AL}$ ) versus the alternative hypothesis that patients on the Analyze Late arm have a different probability of neurologically intact survival to hospital discharge than do patients on the Analyze Early arm ( $H_1: \pi_{AE} \neq \pi_{AL}$ ). The data will be analyzed in the context of a generalized linear mixed effects model which includes a fixed effect for treatment arm and random effects for each randomization cluster. The test statistic comparing treatment arms will be the Wald statistic computed as the regression parameter estimate for the treatment indicator divided by its estimated standard error. The fixed sample upper one-sided P value corresponding to that Z statistic will be compared to the boundaries of the protocol defined group sequential stopping rule when expressed on the fixed sample P value scale. At the end of the study, analysis results will be summarized using point estimates of the difference in probability of favorable events, 95% confidence intervals, and P values adjusted for the true sampling distribution imposed by the group sequential stopping rule. (See the discussion of the group sequential monitoring plan below.)

### ***Secondary Efficacy Analyses***

All secondary analyses of efficacy endpoints are directed toward finding supporting evidence for the findings of the primary efficacy analysis. As such, they will not be used as the primary basis for establishing superiority of one treatment strategy over the other. Hence, there is no plan to make any statistical adjustment for the multiple comparisons inherent in the secondary efficacy analyses, which include:

*Modified Rankin Score (MRS) at hospital discharge.* The mean MRS at hospital discharge will be compared across treatment groups using a general linear mixed model including the binary variable indicating AL vs. AE assignment and random effects for the randomization clusters. For the purposes of this analysis, patients dying before admission to the hospital will be treated the same as admitted patients dying before hospital discharge and will be assigned an MRS of 6.

*Survival to hospital discharge.* This secondary analysis of treatment efficacy will be based on a comparison across treatment arms of the observed proportion of patients in the efficacy population with survival to hospital discharge. This analysis shall proceed in a manner entirely analogous to that for the primary efficacy endpoint.

*Neurologically intact survival to hospital discharge adjusted for prognostic variables.* A secondary analysis of the primary endpoint will adjust for those pre-randomization variables which might reasonably be expected to be predictive of favorable outcomes. Generalized linear mixed models will be used to model the proportion of subjects with neurologically intact (MRS  $\leq 3$ ) survival to hospital discharge by AL vs. AE group adjusted for randomization cluster (random effect), site (dummy variables modeling the 11 ROC sites), patient sex, patient age (continuous variable), witnessed arrest (binary variable), location of arrest (public versus non-public), time of response (continuous variable modeling minutes between call to 911 and arrival of EMS), presenting rhythm (dummy variables modeling asystole, PEA, VT/VF, or unknown), and treatment assignment in the ITD/sham device intervention. The test statistic used to assess any

benefit of one strategy over the other will be computed as the generalized linear mixed model regression coefficient for the AL vs. AE treatment assignment divided by the estimated standard error. Statistical inference will be based on one-sided P values and 95% confidence intervals which adjust for the stopping rule used for the primary analysis.

*Post-discharge neurological function, quality of life, and depression.* Surviving patients will be contacted post-discharge to obtain consent for additional follow-up via telephone with consenting patients or their proxies regarding cognition, quality of life, and depression. Primary emphasis will be placed on analysis of outcomes at 6 months post hospital discharge, though additional analyses will also compare these secondary endpoints 3 months after hospital discharge. Analyses of each of these outcomes at each time point will be compared across treatment groups using a general linear mixed model including the binary variable indicating AL vs. AE assignment and random effects for the randomization clusters. Analyses will first be conducted conditional on survival to the relevant time point by using only data from those patients offering consent, as well as using data imputed from discharge data for those surviving patients refusing consent. The data missing due to lack of consent for follow-up will be multiply imputed using measurements of patient age, sex, length of hospital stay, incidence of major adverse outcomes during hospitalization, MRS at hospital discharge, and whether the patient was discharged to home or a nursing facility. Additional analyses of neurological function and quality of life will then incorporate measurements for patients dying prior to hospital admission, during hospitalization, or within 3 or 6 months post discharge. Dead patients will be assigned the worse category of neurological function and quality of life for each measurement.

*Morbidity* As a measure of morbidity during hospitalization, the number of days hospitalized conditional upon survival to discharge will be compared across treatment groups using the t test which allows unequal variances. A similar analysis will also be conducted comparing the days of hospitalization for patients admitted to the hospital, but dying prior to hospital discharge. Finally, treatment groups will also be compared with respect to the number of days alive post hospital discharge during the first 6 months post OOHCA in order to incorporate information about both dead and surviving patients. In this analysis, data missing due to lack of consent for follow-up will be multiply imputed using data available at hospital discharge, and patients dying before hospital admittance or prior to hospital discharge will be scored as 0.

### **Safety Analyses**

The incidence of adverse events will be recorded for all patients in the safety population and presented by treatment arm (AL vs. AE) to the DSMB for their review during the conduct of the study, as well as summarized and compared across treatment arms in the final report of study results. Statistical significance of differences in the incidence of safety endpoints plays a lesser role, due to the need to be cautious in the introduction of new treatments in a human population. Hence, emphasis is placed on the presentation of results, with statistical tests provided for guidance on the precision of estimates as indicated.

Since both interventions, Analyze Early and Analyze Late, are in current use, there is no anticipation that the study itself will present any safety issue, for example, because of new or difficult procedures. Indeed, one would expect a study benefit in any treatment arm because of the increased training and monitoring of CPR performance. Nevertheless specific measures that will be monitored include:

*Delay of treatment.* Witnessed episodes of cardiac arrest with response times (911 call to arrival) of less than 4 minutes might be expected to respond to early defibrillation. This subgroup of patients will be carefully monitored for potential harm from an Analyze Later

strategy. The Data and Safety Monitoring Board will be asked to make recommendation concerning protocol modification, should any safety issue appear.

*Compliance with protocol.* Patients with EMS witnessed arrest are to be treated with early analysis for defibrillation regardless of cluster randomization to AL or AE. The adherence of EMS providers to this aspect of the protocol will be closely monitored. In addition, sites will be monitored with respect to adherence to the guidelines for either the Analyze Late or Analyze Early strategies according to the cluster randomization scheme. In particular, adherence to protocol will be monitored and reported separately for times immediately preceding and following sites' crossover from one strategy to the other. The Data and Safety Monitoring Board will be asked to make recommendation concerning protocol modification, should any safety issue related to protocol adherence appear.

*Serious adverse events.* The incidence of each serious adverse event, along with other major adverse medical or surgical outcomes identified during review of hospital records, will be tabulated by treatment arm and compared when indicated using Pearson's chi squared test. In order to facilitate the identification of differences in rates of such events that might be due to greater survival to hospital admission and/or hospital discharge on one of the treatment arms, the incidence of any of the above specific events and/or death (either prehospital or during hospitalization) will be reported in a combined fashion and compared as indicated using Pearson's chi squared statistic.

### **Subgroup Analyses**

Analyses will be performed in each subgroup, along with tests for statistically significant interactions. However, it is recognized that the study is not powered adequately to detect interactions, and thus all subgroup analyses are judged exploratory.

### **Sample Size, and Study Duration**

The sample size for the factorial trial is driven by the power analysis for the ITD intervention. A full description of the assumptions that were used to estimate the sample size required for that intervention is given in section 2. The anticipated distribution of patients by presenting rhythm and whether arrest was EMS witnessed or not was estimated based on these assumptions (Table 5.)

**Table 5: Proportion of all EMS treated OOHCA patients according to presenting rhythm and EMS Witness status**

<b>Presenting Rhythm</b>	<b>EMS Witnessed</b>	<b>EMS Unwitnessed</b>	<b>Total</b>
<b>Asystole</b>	0.0231	0.4769	0.500
<b>Pulseless Electrical Activity (PEA)</b>	0.0270	0.2230	0.250
<b>VT/VF</b>	0.0499	0.2001	0.250
<b>TOTAL</b>	0.1000	0.9000	1.000

Eligibility criteria for the AL vs. AE intervention excludes subjects for whom the arrest was witnessed by EMS. The distribution of patients to the various treatment strategies by presenting rhythm was estimated by taking into account that patients with EMS Unwitnessed OOHCA will be randomized (by cluster) in a 1:1 ratio to the AE or AL strategies (Table 6).

**Table 6: Proportion of all EMS treated OOHCA patients randomized to treatment combinations according to presenting rhythm and EMS Witness status**

Initial Rhythm	EMS Witnessed CA or Seattle Medic One (AL vs. AE Ineligible)			Analyze Early			Analyze Late		Total AE vs AL Randomized	
	No Device	Sham	ITD	No Device	Sham	ITD	Sham	ITD	AE	AL
<b>Asystole</b>	0.000	0.018	0.018	0.000	0.116	0.116	0.116	0.116	0.232	0.232
<b>PEA</b>	0.000	0.017	0.017	0.000	0.054	0.054	0.054	0.054	0.109	0.109
<b>VT/VF</b>	0.015	0.020	0.020	0.029	0.034	0.034	0.049	0.049	0.097	0.097
<b>TOTAL</b>	0.015	0.055	0.055	0.029	0.204	0.204	0.219	0.219	0.438	0.438

Based on ranges of estimates in published data and results of the ASPIRE trial, and allowing for 1-5% improvement due to greater quality control on CPR process in the clinical trial setting, it is estimated that in the absence of an ITD and when managed according to the Analyze Early (AE) strategy, the probability of survival to hospital discharge would be 1.05% for patients presenting with asystole, 4.02% for patients presenting with PEA, and 20.20% for VT/VF. These assumptions lead to an estimated probability of survival to hospital discharge of 0.0609 when treated under the AE strategy with a sham valve. Assuming that 88.9% of such survivors would have acceptable neurological status ( $MRS \leq 3$ ), we thus estimate a rate of 0.0541 for neurologically intact survival to hospital discharge under treatment with the AE strategy and a sham valve.

Under the alternative hypothesis used for power calculations, the effect of the Analyze Late strategy on neurologically intact survival is presumed to vary by presenting rhythm. While patients with initial rhythms of asystole and PEA cannot expect to benefit from an Analyze Early versus Analyze Later protocol in the sense of potentially obtaining early defibrillation, they could benefit from the Analyze Later strategy by having fewer delays in blood circulation due to taking time for early analysis. We therefore hypothesize a 3% relative increase in survival for patients in the AL arm over the AE arm for these two rhythms. A relative benefit of 1.50 is hypothesized for those patients in the VT/VF, with the benefit occurring primarily in patients who would not respond rapidly to early defibrillation, though that group cannot be identified *a priori*. Applying these hypothesized effects to the numbers given above results in an estimated probability of survival to hospital discharge of 0.0838 for patients treated with an AL strategy in the absence of an ITD, with a corresponding hypothesized rate of 0.0745 for neurologically intact survival to discharge. Details of these calculations are provided below (Table 7).

**Table 7: Estimated proportions of all EMS treated OOHCA patients surviving to discharge and surviving to discharge with  $MRS \leq 3$  by AL vs. AE treatment arm and presenting rhythm**

Presenting Rhythm	Stratum Weight	Analyze Early Probability of Survival to Discharge	AL / AE Relative Benefit	AL Probability of Survival to Discharge
<b>Asystole</b>	0.5299	0.0105	1.03	0.0108
<b>PEA</b>	0.2478	0.0420	1.03	0.0433
<b>VT/VF</b>	0.2224	0.2020	1.50	0.3030
<b>Probability of Survival to Discharge (weighted average)</b>		0.0609		0.0838
<b>Probability of Neurologically Intact Survival to Discharge (88.9% of patients surviving to hospital discharge)</b>		0.0541		0.0745

In the process of accruing 14,154 evaluable patients to the ITD/sham device intervention, it is estimated that approximately 15,423 patients with OOHCA will be treated by EMS at one of the participating ROC sites, with approximately 13,509 of these patients eligible to participate in the Analyze Late or Analyze Early interventions. Estimating that 98% of these patients will be judged evaluable, 13,239 patients will be used for the comparison of Analyze Late versus Analyze Early strategies. We therefore consider the ability of a two-sided level 0.05 test with 13,239 subjects to reject a null hypothesis that the probability of neurologically intact survival to hospital discharge is 0.0541 on both treatment arms, with statistical power computed under the alternative hypothesis that the AL arm would instead have a 0.0745 probability of neurologically intact survival. The data will be analyzed in the context of a generalized linear mixed effects model which includes a fixed effect for treatment arm and random effects for each randomization cluster. The test statistic comparing treatment arms will be the Wald statistic computed as the regression parameter estimate for the treatment indicator divided by its estimated standard error. Power computations are based on formulas appropriate for a two-sample test of binomial proportions using Pearson's chi squared statistic. We incorporate into those computations an assumed 5% loss of efficiency due to the cluster randomization with crossover.

The clinical trial will be conducted using a two-sided level 0.05 group sequential stopping rule based on up to three analyses (two interim analyses and the final analysis) after accruing approximately one-third, two-thirds, and all of the maximal sample size. The stopping rule corresponds to an O'Brien-Fleming design as described in more detail under the monitoring plan. Using that stopping rule, a sample size of 13,239 evaluable patients will provide approximately 99.6% power to reject the null hypothesis under the conjectured treatment effect.

The 11 participating ROC sites are estimated to have approximately 10,000 OOHCA treatable by EMS each year, so it is estimated that accrual of 13,239 evaluable patients for the Analyze Late versus Analyze Early comparison will require 20 months.

### **Effect of Clustering and Crossover Upon Required Sample Size**

It is anticipated that the number of cardiac arrest episodes in each cluster will vary, as the underlying size of the geographic area and population served are variable. Some sites will cross a large geographic area over from one intervention to the other during the trial to reduce the expected number of episodes; others will cross monitor/defibrillators from one intervention to the other. Most cluster designs assume equal-sized clusters, but the presence of unequal cluster size has implications for sample size (Appendix 5).

The clusters and annual expected number of cardiac arrests episodes in each site are shown below (Table 8). Since most clusters employ crossover, and those that do not have small expected numbers, the effective sample size of each cluster should be at least 95% efficient compared to individual randomization. This is a conservative assumption since utilizing the crossover design is actually more efficient than even individual randomization.

Having close to 20 or more clusters at each site with no overly large cluster, as well as using crossover and randomizing so that each intervention is being used by half of the clusters at any time will provide reasonable balance between temporal factors, as well as system and patient factors.

We can think of no likely crossover effect except that compliance might be compromised by habit or forgetfulness at the time of crossover. We will be monitoring compliance, and if non-



compliance is  $\geq 2$ -fold higher in the 2 weeks following crossover than in the several months before at a site level, then all episodes from that 2-week period at that site will be dropped from the primary analysis. Of course, measures would be taken by the local site to address the “crossover compliance” issue.

Other designs were taken into consideration, particularly individual episode randomization. Devices (AEDs) are not currently capable of being programmed to randomize individual episodes and then provide correct prompts. Other forms of individual randomization (e.g. envelope) would therefore result in expecting EMS providers to ignore existing prompts. The consensus of the ROC investigators was that this would create serious compliance issues and individual randomization was not seen as a viable option. The simplest design is to invoke cluster design without crossover. This method is less efficient than crossover, or individual, randomization. Therefore clustering design with crossover is seen as the most efficient design from the choice of feasible and practical designs.

**Table 8: Summary of ROC Site Cluster Plans**

	<b>Pop Served (#)</b>	<b>Annual CA Treated (#)</b>	<b>Cluster Type</b>	<b># of Clusters</b>
<b>Toronto</b>	<b>2,456,800</b>	<b>1,777</b>	geographic, agency, station	<b>214</b>
<b>Alabama</b>	<b>1,278,936</b>	<b>485</b>	rig	<b>75</b>
<b>Portland</b>	<b>1,444,219</b>	<b>604</b>	agency, station defib	<b>166</b>
<b>Pittsburgh</b>	<b>670,911</b>	<b>690</b>	rig	<b>124</b>
<b>Seattle/King Co</b>	<b>1,191,204</b>	<b>555</b>	agency, geographic	<b>31</b>
<b>Dallas</b>	<b>2,023,705</b>	<b>1,331</b>	rig	<b>151</b>
<b>Ottawa</b>	<b>3,000,000</b>	<b>1,468</b>	geographic, agency, defib	<b>246</b>
<b>Milwaukee</b>	<b>928,018</b>	<b>794</b>	station	<b>61</b>
<b>BC</b>	<b>3,115,331</b>	<b>1,364</b>	geographic	<b>32</b>
<b>San Diego</b>	<b>2,900,000</b>	<b>2,161</b>	rig	<b>334</b>
<b>Iowa</b>	<b>956,188</b>	<b>875</b>	geographic	<b>15</b>
<b>Totals</b>	<b>19,965,312</b>	<b>12,104</b>		<b>1449</b>

## 4. Factorial Implementation of Both Protocols

### Summary

The background, significance, aims, and hypotheses of the ITD and Analyze Later versus Analyze Early trials have been previously described. Investigators intend to implement these studies simultaneously (though staggered start and stop times may occur because of resource/regulatory logistics), capitalizing on the common infrastructure necessary to accomplish the studies, thereby improving efficiency and speed of their completion. The following describes study issues common to both the ITD and Analyze Later versus Analyze Early studies including Study Setting, Study Population, Resuscitation Guidelines, Monitoring of CPR Process, Outcome Measures, Data Collection, Training, Data Safety Monitoring Strategy (DSMB), and Human Subjects.

### Setting

The Resuscitation Outcomes Consortium (ROC) includes ten Regional Clinical Centers. These ROC sites are served by approximately 200 EMS agencies. The baseline characteristics of these ROC sites are summarized in Table 9. Of greater than 12,000 cardiac arrest episodes among the sites, annually, approximately 10,000 are treatable by EMS.

**Table 9: Distribution of Initial Cardiac Rhythm and Outcome for Cardiac Arrest Episodes Among ROC Sites**

	Dallas	Iowa	Milwaukee	Ottawa	Ottawa	Pittsburgh	Portland	Seattle	Seattle	Alabama	Toronto	San Diego	Total
<b>EMS System</b>	Biotel			OPALS	BC			King County	Seattle EMS				
<b>Year Reported</b>	2003	2003	2004	2002	2003	Average of 1998-2002	2003	2003	2003	2004	2002	2004	
<b>Population Served</b>	2M	956k	928k	3M	3.1M	671k	1.4M	1.2M	600k	1.3M	2.5M	2.9M	20.6M
<b>VF or PVT</b>	297	294	162	470	431	235	151	158	95	106	462	648	3509
<b>Survived to discharge</b>	50	44	32	62	74	33	37	44	29	24	39	97	565
<b>Received &lt;=1 shock</b>	178	217	158	281	258	141	112	116	70	73	120	427	2151
<b>Asystole</b>	676	349	437	601	577	289	211	235	147	285	817	1102	5726
<b>Survived to discharge</b>	14	5	10	5	12	12	3	6	0	5	7	33	112
<b>PEA</b>	358	232	195	397	356	166	242	162	91	94	498	411	3202
<b>Survived to discharge</b>	25	12	18	9	7	10	15	16	12	6	12	21	163
													<b>Totals</b>

<b>Cardiac arrests</b>	1331	875	794	1468	1364	690	604	555	333	485	1777	2161	12437
<b>Survived to discharge</b>	89	61	60	76	93	55	55	66	41	35	58	151	840

**Note: Shaded numbers are estimated**

## Study Population

Except for some specific situations, the inclusion and exclusion criteria for both ITD and Analyze Later protocols will be the same.

### Inclusion Criteria

All persons of local age of consent or older who suffer non-traumatic cardiopulmonary arrest outside of the hospital in the study communities with defibrillation and/or delivery of chest compressions provided by EMS providers dispatched to the scene and do not meet any of the exclusion criteria below.

### Common Exclusion Criteria

- Do not attempt resuscitation (DNAR) orders;
- Blunt, penetrating, or burn-related injury;
- Patients with exsanguinations;
- Known prisoners;
- Known pregnancy.

### ITD Exclusion Criteria

- Tracheostomy present;
- CPR performed with any mechanical compression device (e.g. AutoPulse, Thumper, ACD-CPR).
- Ventilated with a mechanical device (e.g. automated transport ventilator). Note: a bag-mask is not considered a mechanical ventilator device.
- A non-ROC EMS agency/provider, for whom time call received at dispatch cannot be obtained, began CPR or placed pads.

### Analyze Later Exclusion Criteria

- EMS witnessed arrests;
- Non-EMS rhythm analysis (AED placed by police or lay responder);
- [Non-ROC EMS agency/provider on scene and began CPR or placed pads.](#)

## Resuscitation Guidelines

The ROC Investigators have developed and will disseminate consensus guidelines on how the patient with cardiac arrest should be treated in the prehospital, emergency department and hospital setting (see Appendix 3).

## Monitoring of CPR Process

A long-term goal of the Resuscitation Outcome Consortium (ROC) is for all participating first EMS responders and ALS providers to have technology on, or adjunctive to, their automated (AED) and/or manual monitor/defibrillators that can monitor individual components of resuscitation. These data will serve as the basis for regular, systematic monitoring and review of the CPR process for purposes of quality improvement at each ROC site before and during clinical trials. Such processes will assure the safety of CPR performance in the field. Also

feedback of this knowledge is essential to care delivery since improved quality assurance has been associated with improved outcomes after resuscitation.(67) Finally, it is essential to efficient trial conduct since low baseline rates of survival are associated with larger sample sizes to detect a clinically important difference.

### ***Rationale***

Recent studies have demonstrated that CPR is frequently not performed according to evidence-based guidelines in the out-of-hospital and in-hospital setting.(28, 29) Although these studies lacked power to detect a significant relationship between CPR process and patient outcome, a related study demonstrated that a greater rate of chest compressions was associated with a greater likelihood of achieving restoration of spontaneous circulation.(68) The importance of monitoring and improving CPR process was confirmed by the observation of potentially deleterious hyperventilation in the Milwaukee pilot study of ITD.(26)

A variety of evolving technologies offer the ability to monitor CPR process either directly or indirectly through AEDs. These include chest impedance (69) (used to monitor chest compression rate and ventilation rate(70)), chest acceleration(71) (used to monitor chest compression rate, depth, release, and duty cycle), and audio recording (used to monitor audible events during resuscitation). Each of these measures has advantages and limitations. For example, a recent prehospital study reported that even when obtaining data related to CPR process was emphasized, technical and signal quality limitations prevented its analysis in more than 25% of episodes(29). In addition, there is also considerable site heterogeneity across the Consortium that precludes the use of a single manufacturer or a single CPR monitoring technology. Accordingly, the Consortium has defined and will monitor a minimal data set pertinent to the CPR process but allow each participating site to individually specify and implement the means by which such data will be obtained. Please see Appendix 2 for a list of how each EMS Agency will monitor CPR process.

### ***Method of Monitoring CPR Process***

**Overview-** In preparation for the start of formal CPR process monitoring and the proposed ROC cardiac arrest trial, an educational program will be developed and implemented at each site to refresh provider skills on chest compression and ventilation, with emphasis on uninterrupted chest compressions, minimizing of "hands-off" intervals, and avoidance of hyperventilation.

All ROC clinical trial sites will implement a high-quality system for monitoring individual components of CPR, to include, at a minimum, the rate of chest compressions, the rate of ventilation, and the proportion of pulseless resuscitation time during which chest compressions are provided (i.e. CPR fraction). Recent studies show no significant differences in these parameters during the first five minutes of resuscitation as compared with the entire resuscitation episode.(28, 29) It is anticipated that during the initial period interruption of CPR due to rhythm analysis or other procedures is more likely than throughout the resuscitation episode. After insertion of an advanced airway and initiation of ventilation that is asynchronous with chest compressions, hyperventilation is more likely than during the early resuscitation period. Therefore CPR process will be quantified during the first analyzable five minutes for 100% resuscitations as well as ventilations throughout the resuscitation episode in those who receive an advanced airway, until a sustained return of spontaneous circulation or resuscitation efforts are terminated. Sites will be encouraged to monitor the entire episode.

Sites will be required to demonstrate an ability to adequately acquire and analyze these CPR process data, identify and attempt to correct any observed deficiencies, and meet minimum performance standards (Appendix 2 CPR Process Monitoring: CPR Performance Standards) before being eligible to enroll patients in the present trial. In addition, ongoing monitoring and review of CPR process, will be used throughout the conduct of the trial.

**Monitoring Devices-** A range of monitoring/defibrillator devices will be deployed across the ROC sites that have capabilities to monitor CPR process. These devices and their capabilities are summarized in Appendix 2 CPR Process Monitoring: CPR Process Monitoring Devices.

**Specific Methods-** BLS and ALS providers will be trained to turn on the power of their AED or monitor immediately upon recognition of a subject in cardiac arrest. Monitoring hardware will be applied to the patient as soon as possible. This power-on event will initiate the recording by the device, and serve as a surrogate marker for “time zero” of initiating CPR. Each site will make efforts to maintain synchronization of monitor clocks with a common time standard (e.g. atomic clock time).

At the completion of every resuscitation attempt, the electronic record from the BLS and ALS devices used during the call will be obtained by the investigators. All electronic records will be reviewed manually by using the commercial software specific to the device, assisted where available, by proprietary automated analysis software. The record will be annotated from the time of power-on (“zero time”), and the parameters of resuscitation quantified during these periods (Appendix 2). Determination of whether a resuscitation effort meets minimally acceptable CPR performance standards for the Consortium will be based on whether it meets acceptable chest compression rate, ventilation rate and CPR fraction criteria as defined in Appendix 2.

Use of immediate (real-time) feedback software will be at the discretion of individual ROC sites and EMS agencies. Depending on system configuration, providers may be prompted by such software to modify the rate or depth of chest compressions, and to minimize interruptions in the provision of CPR. When such feedback is deployed, prompts will conform to the same target ranges specified in ROC CPR performance standards. Regardless of whether or not real-time feedback is provided, all resuscitations will be reviewed for adherence to the same performance standards, and a mechanism in place for remediation, if necessary. CPR process data derived from resuscitations during which real-time feedback was provided will be designated by an appropriate identifier. These sites may separately examine the impact of using real-time feedback in their systems.

## **Outcome Measures**

### **Primary**

The primary outcome for both studies is survival to hospital discharge with modified Rankin score  $\leq 3$ . Patients who are transferred to another acute care facility (e.g., to undergo ICD placement) will be considered still hospitalized. Patients transferred to a non-acute ward or facility will be considered discharged.

### **Secondary**

Note that additional background information, rationale for selection, and details about specific functional status measures are given in Appendix 4. An interesting methodological issue is how to measure post-discharge outcomes. Physician and neuropsychological evaluations are considered the gold standard for the diagnosis of cognitive impairment. However such methods are unlikely to be feasible and likely to be associated with a high proportion of missing data in a population that resides in such a diverse geographic area as that participating in the Resuscitation Outcomes Consortium. For example, data from the ROC EMS structures serve demonstrates that participating EMS agencies (72% reporting) serve a total catchment area of 78,521 square miles. If the pattern of missingness is informative (e.g. patients from rural areas with delayed resuscitation less likely to be interviewed), then the post-discharge outcome data

are susceptible to bias. Therefore all post-discharge outcome assessments will be made by using measures validated for phone administration to increase the response rate. All assessments will be made by trained interviewers.

Our criteria for choosing particular instruments to measure neurological status include prior data about reliability and reproducibility, availability of instruments suitable for a multicenter trial, and prior data in cardiac arrest survivors. The **Modified Rankin Scale (MRS)** has face validity and can be determined via review of the clinical record, in person or over the telephone.(72, 73) MRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.(74, 75) MRS has prior use in a cohort of neurosurgical patients with in-hospital cardiac arrest(76) and in a cohort of survivors of out-of-hospital cardiac arrest.(77)

We are aware that CPC is less validated compared to some other measures that will be utilized in this study. CPC will be assessed by using a structured questionnaire via telephone administration (Appendix 4 of protocol). These latter questions were developed based on experience assessing outcomes after discharge in the OPALS study, PAD trial and ASPIRE trial. However it should be recognized that these questions have not been validated in their current format.

The **Health Utilities Index (HUI)** is a generic measure of health-related quality of life.(33) It has reliable interview, telephone, and proxy instruments with extensive validation in a multiple populations, including two cohort studies of survivors of cardiac arrest.(84, 85) HUI was positively correlated with bystander CPR, suggesting construct validity for measuring neurological injury incurred during cardiac arrest.(85)

The Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) is a measure of cognitive status.(31, 32) ALFI-MMSE correlates with severity of cognitive impairment as measured by the Clinical Dementia Rating Scale class.(31) Compared to the brief neuropsychiatric screening test, which is a weighted score of the Trailmaking A,(86) Word Fluency,(87) Weschler Memory Scale-Mental Control and Logical Memory,(88) ALFI-MMSE had a sensitivity of 68% and specificity of 100% for mild cognitive impairment. The corresponding MMSE values were 67% and 100%.(31)

The telephone version of the Geriatric Depression Scale (T-GDS)(34) detects the presence or absence of depression. Using a cutoff of 10/11T-GDS has a sensitivity of 86% and specificity of 70% for detecting depression compared to a comprehensive assessment by a geriatric psychiatrist.

**Table 10: Timing and Content of Secondary and Exploratory Outcome Measures**

	Discharge	1 Month	3 Months	6 Months
MRS	X		X	X
CPC	X		X	X
ALFI- MMSE		X	X	X
HUI			X	X
GDS			X	X

### Exploratory Outcome

Consensus statements recommend use of the **Cerebral Performance Category (CPC)** to assess functional outcomes after resuscitation from cardiac arrest.(78, 79) CPC is a five-point scale that was adapted from the Glasgow Outcome Scale.(80, 81) CPC had limited discrimination between mild and moderate brain injury, and only moderate correlation with a generic measure of health-related quality of life in a small study that was limited by a high rate of loss to follow-up.(82) However, CPC predicts long-term survival after resuscitation from cardiac arrest.(83)

### Method of Assessing Post Discharge Outcomes

All post-discharge assessments will be performed by using instruments that will be made available in English and Spanish. Study coordinators will be trained to administer these instruments prior to study implementation by using didactic instruction, standardized patients and mock interview of each other according to current standards.(89) Spanish-language translators will be used as required. Interviewers will be instructed to speak clearly and articulate distinctly; ascertain the interviewee's ability to hear a spoken language at a conversational volume; try to ensure no one other than a proxy and the interviewee are present; if a precise answer is not given, probe for the correct response; exercise judgment about allowing sufficient time to answer a question before proceeding on to the next question; record the interviewee's last response as their answer to each question. Only research staff that completed this training successfully will be allowed to perform post-discharge assessments.

We are aware that some patients may be too impaired to complete an interview. Therefore, the ALFI-MMSE will be the instrument administered first during the three month interview. Patients who score  $\geq 17$  will be asked to complete the interview by self-report. Patients who score  $< 17$  will be assessed further by interview of a proxy. We and others used a similar approach to assessment of post-discharge outcomes in the Public Access Defibrillation (PAD) trial. Contact details for the patient and their proxy will be identified at the time of notification of participation in hospital. Consent will be sought from the patient and their proxy for interview after discharge.

### In-Hospital Morbidity

Number of hospital days and time interval from 911 call to patient death will be described for all hospitalized patients as measures of morbidity after resuscitation.

### Other Outcomes

Other surrogate outcomes will be collected for descriptive purposes:

**i) Return of Spontaneous Circulation:** (ROSC) defined as the documented presence of a measurable pulse and blood pressure at any time after initiation of resuscitative efforts. There is no minimum duration for this return of spontaneous circulation.

**ii) Admission to Hospital.**

**iii) Survival to 24 Hours.**

**iv) Process Outcomes:** a) Number of Shocks Required: The total number of defibrillatory shocks; b) Duration of Pulselessness: The duration of pulselessness (from 911 to ROSC).

## Data Collection

### Data Forms

Appendix 6 contains draft data forms for both protocols.

### Source of Data Collection

Data will be collected prospectively as patient care progresses. This will include a review of all the EMS patient care report(s), EMS dispatch times, EMS/fire/first responder electronic ECGs, emergency and hospital records. No additional studies or patient contact (except for notification of study participation) will be required for collection of this data up to hospital discharge.

### Data Common to Both Protocols

#### **Out-of-Hospital**

Demographics, EMS response times (call receipt to arrival, arrival at patient side, etc.), witnessed arrest, bystander CPR, location of arrest, CPR process monitoring measures (ventilation rate, compression rate, CPR fraction), cause of arrest (cardiac vs. non cardiac), EMS therapies (drugs, shocks, advanced airway, hypothermia), first ECG rhythm, disposition, return of spontaneous circulation, potential adverse events.

#### **Emergency and Hospital**

Major procedures, possible complications of intervention, admittance to the hospital, cause of arrest, ICU days, date of awakening, disposition at discharge, withdrawal of care (DNR status) as well as MRS and CPC at hospital discharge.

#### **Follow-up**

Patients will be contacted by study personnel at 1 month after discharge and will have the ALFI-MMSE applied by telephone interview. They will be contacted by study personnel at 3 months and 6 months to have the MRS, CPC, ALFI-MMSE, HUI and GDS applied by telephone interview.

#### **Initial ECG Rhythm**

The initial ECG tracing will be analyzed off-line. The individuals performing this analysis will be blind to the interpretation that was performed in real-time by the AED and/or rescuers. The entire tracing that is available for analysis will be provided, and three possible ECG rhythms will be defined.

Asystole will be defined as background electrical activity less than 0.2 mV in amplitude with  $\leq 10$  beats per minute average rate (e.g., a 6-second strip without ventricular complexes).

VF will be defined as irregular, disorganized ventricular electrical activity of variable amplitude exceeding 0.2 mV.

Pulseless electrical activity (PEA) will be defined as electrical activity with R-waves of any width at an average rate of  $>10$  beats per minute (e.g., organized ventricular electrical activity with R waves of any width that occur more than once over a 6-second period). The rate of PEA will be recorded as well.



### **Items Specific to ITD Protocol**

Items specific to the ITD protocol will generally deal with events surrounding the use of the device; approximate time ITD attached, vomit with ITD, attachment of ITD to bag-mask or advanced airway, adverse/unusual events (device fills with fluid twice, device failure, patient complications) and protocol adherence.

### **Items Specific to Analyze Later Protocol**

Items specific to the Analyze Later protocol will generally deal with events surrounding the compliance with the assigned cluster. Each event will be reviewed to determine whether the assigned protocol was followed.

### **Data Entry**

The DCC will provide web-based HTML forms to collect necessary information from the RCCs. 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 DCC 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.

### **Database Management**

The DCC will use a two-tiered database structure. A front-end database serves the web entry needs, using a database management system well-suited to handling updates from multiple interactive users. The data from this database will be transferred periodically (e.g. bi-weekly) to a “warehouse” database, on which data queries for analyses and monitoring will be run. Various versions of this database are kept as needed, e.g. for quarterly or DSMB reports. The “warehouse” database management system was selected for its ability to manage large quantities of data, to merge data from multiple databases as required, to handle complex and possibly changing relationships, and to produce analysis datasets that can be imported into a variety of statistical analysis packages.

### **Training**

#### ***Overview***

The training objectives include the following (each detailed below): review of optimal CPR performance, scientific basis for and review of study protocols, practicum/“hands-on” session, and post-test. It is anticipated that approximately 2 hours of didactic instruction and 1 hour of practicum will be required.

#### ***Optimal CPR Performance***

The purpose of this component is to provide training in optimal chest compression and ventilation skills for all participating EMS personnel and to standardize the performance of CPR across all ROC sites as much as possible. This training component will be implemented either as part of the protocol training or as a separate training module prior to specific study training. Key concepts include: optimal chest compression rate (100/min) and depth (38-51 mm), correct hand position on the distal sternum, complete chest wall recoil with each compression, minimizing “hands-off” intervals, avoiding hyperventilation (target rate 10-12/min), and proper breath duration (<2 seconds for an unprotected airway and 1 second for a protected airway). Training will also emphasize maintaining a continuously tight facemask seal with the “E-C” hand technique (one airway rescuer) or two-handed technique (two airway rescuers) when using the

ITD and the use of ventilation timing assist lights with advanced airways (e.g., Combitube, laryngeal mask airway [LMA], or endotracheal tube).

### ***Scientific Basis for ITD and Analyze Later Protocols***

Level-appropriate presentation of the scientific principles underlying the ITD and Analyze Early versus Analyze Later studies will increase provider investment and improve protocol adherence. This should include presentation of prior work in both animals and humans and justification for a randomized clinical trial, including discussion as to why these approaches require further investigation prior to widespread implementation.

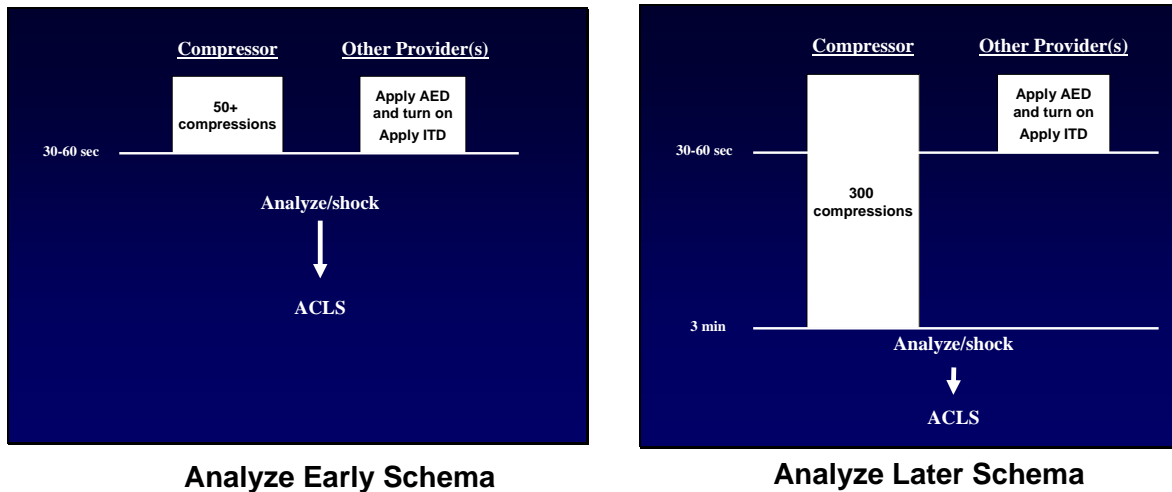
### ***Study Protocols***

This section will include the following: overall study design, inclusion and exclusion criteria, the process of exception to informed consent under emergency circumstances, and the study protocol. While the overall factorial design makes the analytic methodology somewhat complex, the operational protocol has been simplified for the purposes of training and actual trial implementation. From the provider perspective, there are only two arms to the study, as an ITD will be applied to all eligible patients but the group assignment (active or sham device) will be unknown to the providers. This creates an Analyze Early arm and an Analyze Later arm, both with ITD application existing as part of the study protocol. The training will mandate that one of the providers be designated the “compressor”; this designation should occur prior to the patient encounter to avoid confusion about role assignments once an arrest is recognized. The two study arms are then defined by the number of compressions delivered by the “compressor” before a pause for rhythm analysis and defibrillation attempts when indicated. In the Analyze Later arm, a number of compressions equivalent to approximately 3 minutes (e.g. 300 if the local CPR protocol is 100 compressions per minute with ventilations interposed, 180 if the local protocol is a compression:ventilation ratio of 15:2) will be delivered, while in the Analyze Early arm a minimum of 50 compressions will be delivered (see schematics below). The “compressor” should count the number of compressions out loud to alert the other providers as to the ongoing duration of chest compressions and to maintain an accurate count. Visual reminders (such as a colored tag on the AED/defibrillator) designating “300” or “50” compressions will be used to enhance protocol compliance, especially with a crossover design. In addition, crews will be encouraged to review their designated number of compressions as part of the daily checklist. The use of the term “compressor” should be encouraged, not only to enhance protocol compliance but also to underscore the importance of chest compressions during resuscitation.

Training will define two tasks for the remaining provider(s): a) placement of the monitor/defibrillator pads and preparation for analysis/defibrillation, and b) proper application of the ITD/facemask, including maintenance of a continuously adequate seal during chest compressions and ventilations. The first priority following initiation of chest compressions by the “compressor” is the rapid placement of defibrillator pads; the monitor/defibrillator should be “powered-up” immediately upon recognition of pulselessness or sooner. The ITD and facemask should then be attached to the resuscitation bag and oxygen canister and a continuously tight seal maintained. When additional personnel are available, the two tasks should be performed simultaneously. Training will emphasize immediate use of the ITD with initial airway management and continued use throughout the resuscitation while chest compressions are being performed as well as dedication of a single individual to maintaining adequate mask seal using a two-handed facemask technique whenever possible. Upon completion of rhythm analysis and defibrillation when indicated, standard ACLS procedure will ensue. Providers will receive specific training to transfer the ITD to the advanced airway and activate the ventilation assist timing lights on the ITD (both sham and active) once tube confirmation has occurred. Asynchronous ventilations should be performed using the assist timing lights as a guide. The

proper ITD “clearing” procedure, indications for discontinuation of the ITD, and completion of study protocol will also be covered, including turnover report to ED personnel and retrieval of the ITD.

**Figure 5: Training Scheme**



### ***Protocol Practicum***

Providers will be given the opportunity to practice to proficiency each component of the protocol. The number of providers used during these rehearsals should simulate actual clinical practice whenever possible. The use of an AED or ALS defibrillator should also be dictated by clinical practice, using the identical brand and technology that will be available during the trial. Various permutations of the study protocol should be presented, including each of the study arms as discussed above. Specific assessment goals should emphasize inclusion/exclusion criteria, role assignment, correct number of compressions, maintenance of continuous tight facemask seal during CPR using “E-C” hand technique or two-handed technique, transfer of ITD to advanced airway and performance of optimal CPR (minimal “hands-off” time). All EMS personnel need to demonstrate proficiency in adequately managing a factorial study cardiac arrest patient. See Appendix 7 for a list of training proficiency goals.

### ***Cognitive post-test***

A cognitive post test will cover key enrollment procedures and may be completed online or as a written or verbal component of the training sessions. A record of training completion will be maintained by each site or EMS agency

### ***Run-in Phase***

After personnel have been formally trained, they will receive additional training through feedback during a run-in phase. Compliance with the protocol and completion and submission of the data will be required before the DCC will notify the site that that

agency is now in the active phase of the trial. Compliance monitoring includes: correct inclusion/exclusion criteria, adherence to study protocol, CPR process measures reported, and correct completion of data elements including reporting of adverse events.

## **DSMB and Monitoring Strategy**

### ***Data Safety and Monitoring Committee***

An independent data safety and monitoring committee will help ensure the safety of the trial by monitoring adverse outcomes throughout the trial and by reviewing outcome data for possible harm. In addition, the committee will review the results of the interim analyses. The committee 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 intervals to be determined by the DSMB, expected to be approximately semi-annually and anticipated to correspond roughly to patient enrollment of one-third and two-thirds of total enrollment. The DSMB will also monitor primary and secondary study outcomes between the treatment and control groups. The DCC will forward DSMB reports to study investigators, the Institutions Research Board, the Food and Drug Administration, and the NIH in accordance with federal regulations 45 CFR Part 46 Subpart A and 21 CFR 312 and the IDE regulations, as well as appropriate Canadian oversight bodies.

### ***Safety and Data Monitoring***

The plans for monitoring protocol implementation/compliance, and data collection/quality are detailed elsewhere. Clinical centers will report all potential adverse events to the DCC as soon as possible. These will be collected in both a structured (standard form) and open (describing any difficulties encountered) form. All potentially serious adverse events will be reviewed by an events committee of ROC Investigators blinded as to treatment arm and further classified by: a) Severity (life-threatening, serious, non-serious); and b) Expected vs. unexpected; and c) Relation to study device. For serious adverse events, the DCC will notify the DSMB as well as appropriate regulatory agencies, sites, and NIH promptly.

The DCC will tabulate and report compliance, data quality, and non-serious adverse events on a regular basis.

### ***Proposed Interim Monitoring Plan***

Each factor will be monitored independently by the DSMB and either study could be terminated, without terminating the other. However, interactions will be evaluated. Interim analyses will be conducted after accrual of 1/3 and 2/3 of the sample size target (Appendix 8).

### ***Proposed Interaction and Extension Monitoring Plan***

We are aware that some may believe that the ITD will be ineffective for patients who receive Analyze Early care. Others may believe that this is not a realistic scenario. If it were true, it would require twice the duration to have the same power for observing the hypothesized effect in the Analyze Later cohort. The outcome will be observed during the course of the study by the independent DSMB as described in Appendix 9.

In the event that the Analyze Late vs Analyze Early (ALvE) intervention is terminated early due to demonstrated superiority of one rhythm analysis strategy over the other, the efficacy population for the ITD/sham device comparison will be restricted to those subjects treated under the rhythm analysis strategy found to be superior. The

number of subjects accrued to the study will be increased to achieve the planned maximal sample size in the superior rhythm analysis strategy arm.

In the event that the ITD/sham device intervention is terminated early, future patients will receive no device, and the efficacy population for the ALvE treatment comparison will be otherwise unchanged.

## **Human Subjects**

### **Protection Against Risks**

In accordance with the FDA, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. In accordance with the regulations 21 CFR 312.32, we have outlined the expected serious and non-serious adverse events, our plans to identify these and the time line for reporting them to the FDA, IRB and DMSB and other overseeing agencies.

An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. 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.

### **Recruitment and Informed Consent**

This study qualifies for exception from informed consent required for emergency research as outlined in FDA regulation 21CFR50.24. The study intervention needs to be administered quickly following the onset of cardiac arrest. In this uncontrolled setting the patient is unconscious. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the scene, nor is it practical for the prehospital provider to explain the study and receive consent while caring for a patient in cardiac arrest. Taken together, these issues provide sufficient support for an exception from consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. We have outlined below each criterion stipulated in the regulations for this exception and how our study design applies to these criteria.

#### **Sec. 50.24 Exception from informed consent requirements for emergency research**

**(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 is a factorial trial of use of either an active or sham ITD supplemented by either of two resuscitation strategies (Analyze Later and Analyze Early) in patients with nontraumatic out-of-hospital cardiac arrest. These patients are in an immediate life-threatening situation with a mortality approaching 95%. The standard of care for prehospital management of these patients includes the timely provision of CPR and advanced life support including airway management.

As reviewed in this proposal, previous studies of ITD have suggested a short-term survival advantage with this device but have not been definitive. These studies

attest to the safety of ITD in the cardiac arrest population and to the practicality of using them in the prehospital environment. The major limitations of previous studies are their lack of focus on the specific intervention and their lack of sufficient size to detect significant clinical differences in outcome. Also, in contrast to the previous human studies, the present trial will evaluate the device in patients with unprotected airways in which case potentially harmful hyperventilation is less common. Thus, critical evaluation of this intervention in humans has not been undertaken.

Animal and human data demonstrate the safety of Analyze Later. Studies in animal models of cardiac arrest indicate that a period of artificial circulation prior to the initial rescue shock can increase the likelihood of successful defibrillation when VF and circulatory arrest lasts more than 3-4 minutes. Small randomized trials in humans with cardiac arrest show that an initial period of CPR may or may not improve survival. However, the prior studies lacked concurrent control groups or were too small to detect meaningful differences in survival. Therefore, no study has adequately answered the question of whether an EMS provider, upon reaching a subject who has already developed cardiac arrest, should a) deploy a defibrillator and administer an immediate rescue shock or b) perform CPR for an interval prior to deploying the defibrillator and rescue shock.

We propose a large randomized trial focused on evaluation of these two interventions in the out-of-hospital cardiac arrest population, with sufficient statistical power to detect changes in outcome. Furthermore, an emphasis on the neurological outcome of resuscitated cardiac arrest patients will define the clinical utility of this resuscitation approach for these patients.

**(2) Obtaining informed consent is not feasible because:**

- (i) The subjects will not be able to give their informed consent as a result of their medical condition;**
- (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and**
- (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.**

The study interventions need to be administered as an early intervention after the onset of cardiac arrest (see discussion of therapeutic window below). In this uncontrolled setting the patient is unconscious and unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the scene, nor is it practical for the prehospital provider to explain the study and receive consent while caring for the cardiac arrest patient. 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.

**(3) Participation in the research holds out the prospect of direct benefit to the subjects because:**

- (i) Subjects are facing a life-threatening situation that necessitates intervention;**
- (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and**
- (iii) 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.**

- (i) As defined, these patients with cardiac arrest are facing a life-threatening situation that requires immediate intervention.
- (ii) Previous animal and human studies have been conducted, and suggest the potential for a direct benefit to individual subjects in cardiac arrest via improved hemodynamics and short-term survival advantage.
- (iii) ITD administration has been tested in three previous clinical trials no serious adverse effects reported. Both Analyze Early and Analyze Late are currently used strategies. Three studies give inconsistent results, but no adverse effects have been noted. As discussed above, there are potential risks to subjects that may have not been observed in previous trials. We contend that these risks are reasonable in light of the potential benefits outlined in this proposal and the current poor outcome for patients with out-of-hospital cardiac arrest.

**(4) The clinical investigation could not practicably be carried out without the waiver.**

This study could not be conducted without the waiver of consent due to the need to administer the interventions as early as possible after the onset of cardiac arrest.

**(5) 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.**

There have been three clinical studies of ITD use during standard manual CPR for the treatment of patients with out-of-hospital cardiac arrest. These demonstrated a potential survival benefit for patients treated with ITD vs. standard CPR. Animal models of cardiac arrest suggest that the ITD may increase venous return during the decompression phase of CPR. Based on these data, coupled with the previous clinical trials, the therapeutic window for this agent is for the time of initial resuscitation, which occurs when CPR is administered by prehospital care providers, up to hospital discharge.

It is well established that the probability of rescue shock success declines quickly during cardiac arrest.(49, 90) The decay in the probability of rescue shock success occurs over minutes, and approaches zero by 10-12 minutes. Therefore, the Analyze Early vs. Analyze Late intervention must be performed within the first few minutes of treatment in order to be meaningful.

Since this is an immediately life-threatening situation, it will not be possible to contact legal representatives at the time of study entry. We will make every effort to contact legal representatives after admission to the hospital to notify them that the patient was enrolled in a randomized trial. Requiring consent to review a hospital chart to determine the presence or absence of serious adverse events is likely to be associated with a biased estimate of the safety and efficacy of the intervention. Therefore we propose to use exception from informed consent for emergency consent, public

notification, community consultation, patient notification of enrollment, and waiver of documented informed consent to review clinical records.

If legal representatives are not immediately available, research personnel will attempt to contact the subject's legal representative 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.

**(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.**

All procedures and consent forms will be approved by the Institutional Review Board (IRB) of the regional study site (or Research Ethics Boards (REBs) in Canada) prior to the onset of the trial.

**(7) 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;**
- (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;**
- (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and**
- (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**

(i) In U.S, centers, community consultation as outlined by the local IRB will be undertaken prior to IRB approval. Similarly, the Canadian centers will follow the requirements of their local REBs. Since the population eligible for enrollment includes all citizens in the study regions it will not be possible to target any particular small group. The community consultation plan for each study site will have to be individualized to fit the IRB requirements. Attached is an example of a proposed plan for community consultation, which has been used in a prior ITD trial (Appendix 10). Feedback from the community will be obtained by research personnel regarding any concerns they may



have about potential enrollment. If requested, bracelets will be made available that could be worn by members of the community who do not want to participate.

(ii) & (iii) Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the Resuscitation Outcomes Consortium. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study.

(iv) An independent data monitoring committee will exercise oversight of the study as described below.

(v) We expect that all patients who meet the enrollment criteria will be unconscious. Any delay in medical care that would be required for the paramedic to attempt to obtain consent from the patient's legal guardian would be life threatening. Thus it will not be feasible to attempt to obtain informed consent during the initial therapeutic window.

Once enrolled in an emergency research trial, patients die in the field, die in the hospital or survive the event. Review of the clinical record is important to ascertain adverse events and important outcomes such as hospital discharge status. This does not require further participation of the patient.

The local ROC investigator will provide information about the emergency research study to the patient or their representative at the earliest feasible opportunity after administration of the intervention. Since in many cases this will be while the patient is still hospitalized, this will not include a request for consent for further participation/intervention, but will provide the patient/representative contact names/numbers for purposes of obtaining further information if desired. Since only patients who survive several months after discharge will be asked for further participation (in the form of telephone administered functional status measures at 3 months and 6 months), the timing of the request for consent for this participation will be determined by the local IRBs. However, we suggest that it should be during the first month after discharge so that patients who die before that time are not inconvenienced with a decision and so that those who have not died have had time to recover sufficiently to make a reasoned decision.

In summary, we shall notify patients enrolled under waiver of consent for emergency research as quickly as feasible, and seek consent from those who survive to discharge for ongoing participation.

Please see Appendix 10 for a sample Exception to Consent plan.

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