Trial of Continuous Compressions versus Standard CPR in Patients with Out-Of-Hospital Cardiac Arrest

(CCC Protocol)

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SUMMARY

Trial of Continuous Compressions Versus Standard CPR in Patients with Out-Of-Hospital Cardiac Arrest

Aims: The primary aim of the trial is to compare survival to hospital discharge after continuous chest compressions (CCC) versus standard American Heart Association (AHA) recommended cardiopulmonary resuscitation (CPR) with interrupted chest compressions (ICC) in patients with out-of-hospital cardiac arrest (OOHCA). For this study, CCC consists of a series of three cycles of continuous chest compressions without pauses for ventilation followed by rhythm analysis or until restoration of spontaneous circulation (ROSC), whichever occurs first. ICC consists of series of three cycles of standard CPR each cycle comprised of chest compressions with interposed ventilations at a compression:ventilation ratio of 30:2 (per AHA guidelines) followed by rhythm analysis or until ROSC, whichever occurs first. In either patient group, the duration of manual CPR before the first rhythm analysis will be 30 seconds or 120 seconds. This treatment period will be followed by two cycles of compressions then rhythm analysis (i.e. each of approximately 2 minutes duration) in either group. Other aims of the trial are to compare survival to discharge among patients grouped by first-recorded rhythm or other a priori subgroups, as well as to compare neurological status at discharge, mechanistic outcomes or adverse events between control and intervention groups.

Rationale: Out-of-hospital cardiac arrest is common, life-threatening and debilitating. Greater coronary perfusion pressure (CPP) is associated with greater ROSC in animals and humans. Interruptions in chest compression reduce CPP with a consequent reduced chance for a successful outcome. Studies in animal models of cardiac arrest show that a strategy of CCC is at least as efficacious as standard CPR. Observational studies in humans suggest that a strategy of CCC is efficacious compared to standard CPR. But each of these studies implemented multiple changes simultaneously, so it is difficult to assess the relative contribution of CCC versus other changes in CPR strategies to improve survival. Therefore a randomized trial of CCC versus standard CPR is needed to understand the role of pausing for ventilation during the circulatory phase of OOHCA. Since the ROC PRIMED trial did not demonstrate a significant or important difference between a duration of manual CPR before the first rhythm analysis of 30 seconds or 120 seconds, the duration of this period will be determined a priori by local medical directive. All participating EMS agencies will require their providers to give active ventilation (i.e. bag mask or advanced airway rather than non-rebreather). Also, since insertion of an advanced airway is often associated with interruption of CPR, participating EMS agencies will defer insertion of an advanced airway until after ROSC or three cycles of manual CPR followed by rhythm analysis. The Resuscitation Outcomes Consortium (ROC) is an ongoing cardiac arrest trials network funded by the National Institutes of Health and other agencies, which has the necessary expertise to conduct an assessment of these interventions.

Hypotheses: The primary null hypothesis will be that the rate of survival to hospital discharge is not affected by use of continuous compressions with passive or positive pressure ventilation (intervention group) versus CPR with compressions interrupted for ventilation at a ratio of 30:2 (control group). Secondary hypotheses include that the rate of survival to hospital discharge is identical between control and intervention groups among patients grouped by first-recorded rhythm or other a priori subgroups, and that other outcomes are identically distributed between control and intervention groups.

Study Design: Clusters consisting of EMS agencies or stations will be randomized to control versus intervention and will be scheduled to crossover to the opposite treatment at least once during the trial.

Study Population: Included will be: a) Adults; b) Non-traumatic arrest outside of the hospital; and c) Chest compressions by ROC EMS providers dispatched to the scene. Excluded will be those with: a) Written do not attempt resuscitation orders; b) Blunt, penetrating, or burn-related injury; c) obvious primary asphyxia or respiratory cause of arrest or advanced airway placed prior to ROC EMS arrival; d) Uncontrolled bleeding or exsanguination; e) Known prisoner; f) Known pregnancy; g) Non-participating agency/provider started CPR; h) EMS witnessed arrest.

Study Therapies: After EMS arrival patients randomized to the control group shall receive three cycles of standard CPR, each cycle comprised of chest compressions with interposed ventilations at a compression:ventilation ratio of 30:2 (i.e. current AHA guideline) followed by rhythm analysis, until ROSC or three cycles of CPR, whichever occurs first. Ventilation will consist of two positive pressure ventilations using ½ the volume of an adult bag (i.e. volume ~400-500 mL) over 1-1.5 seconds after 30 compressions. Patients randomized to the intervention group shall receive three cycles continuous compressions without pauses for ventilations followed by rhythm analysis. Ventilation will be performed at a rate of 10/minute using ½ the volume of an adult bag (i.e. volume ~400-500 mL) over 1-1.5 seconds without interruption in chest compressions. In either patient group, the duration of manual CPR before the first rhythm analysis will be 30 seconds or 120 seconds. This treatment period will be followed by two cycles of manual CPR then rhythm analysis (i.e. each of approximately 2 minutes duration) in either group. In both patient groups, IV or IO access will be obtained, and epinephrine 1 mg or vasopressin 40 IU given within five minutes of arrival of an ALS-capable EMS provider. Insertion of an advanced airway will be deferred until completion of three cycles of CPR (about six minutes). After an advanced airway is inserted, both groups will continue with compressions 100/min. and ventilations 10/min. without pause until ROSC is achieved or the resuscitation effort is terminated. All other care in both arms will be per local practice.

Outcomes: The primary outcome will be survival to hospital discharge. Secondary outcomes include modified Rankin score (MRS) at discharge, mechanistic outcomes and adverse events.

Analysis: Analyses of primary and secondary outcomes will be conducted on an intent-to-treat basis. To be included in these analyses, patients must meet the eligibility criteria listed. Secondary analyses will assess treatment effect in patients by initial rhythm. The primary analysis will use generalized estimating equations to compare the rate of survival to discharge in the two treatment groups with robust standard errors used to accommodate clustering.

Sample Size: We require a maximum of 23,600 patients (11,800 per group) to have at least 90% power to detect a difference of 1.3% between treatment groups in the rate of survival to hospital discharge using an overall significance level (adjusted for interim analyses) equal to 0.05.

1. Aims

The primary aim of the trial is to compare the rate of survival to hospital discharge after continuous chest compressions (CCC) versus interrupted chest compressions (ICC) in patients with non-traumatic out-of-hospital cardiac arrest (OOHCA). For this study, CCC consists of a series of three cycles of continuous chest compressions without pauses for ventilation followed by rhythm analysis until restoration of spontaneous circulation (ROSC) or completion of the three cycles of CPR, whichever occurs first. ICC consists of a series of three cycles of standard CPR, each cycle comprised of sets of 30 chest compressions with a pause for ventilations at a compression: ventilation ratio of 30:2. In either patient group, the duration of manual CPR before the first rhythm analysis will be 30 seconds or 120 seconds. This treatment period will be followed by two cycles of manual CPR then rhythm analysis (i.e. each of approximately 2 minutes duration) in either group. Each cycle will be followed by rhythm analysis until ROSC or three cycles of CPR, whichever occurs first.

The study will be implemented simultaneously in all patients treated for cardiac arrest. The primary analysis will be conducted using all enrolled patients. Secondary analyses will assess treatment effects by first-recorded rhythm, or by other a priori subgroups. Other aims of the trial are to assess the impact of interventions on neurological status at discharge, mechanistic outcomes and adverse events with CCC versus ICC in patients with OOHCA.

2. Background

2.1 Conceptual Framework

Only 7.4% of those who experience OOHCA survive to discharge.(1) Reperfusion injury occurs during restoration of circulation after cardiac arrest. It is associated with marked release of pro-inflammatory then anti-inflammatory cytokines. This leads to poor capillary perfusion, tissue ischemia, and microcirculatory dysfunction within 24 hours. Cardiac function improves but vascular and intestinal permeability increase over the next three days, predisposing the patient to sepsis-like hemodynamic states,(2) neurologic injury, multiple organ dysfunction and death. The extent of reperfusion injury is correlated with the duration of ischemia and adequacy of resuscitation.

The importance of adequate coronary perfusion pressure (CPP) as a marker for the successful return of spontaneous circulation has been established in animals and humans.(2, 3) Once chest compressions are initiated, it takes time to develop an adequate CPP and in the absence of effective and continuous external chest compressions, the CPP decreases rapidly.(4) Interruptions in chest compression have been shown to have a detrimental effect on CPP with a consequent reduced chance for a successful outcome.(5) The CPP achieved during resuscitation has also been correlated with the quantity and quality of external chest compressions.(6) Current CPR guidelines call for 100 compressions per minute with complete recoil following each compression.(7) The optimal compression rate may actually be higher.(6) Studies of CPR performance suggest that CPR quality is poor and that improvements in CPR quality may be associated with improved outcomes.(8, 9) The ability to achieve a high compression fraction during resuscitation is affected by the need to provide ventilations, device considerations (analysis by automated external defibrillator (AED) along with time required to charge) and human factors (rhythm assessment, pulse checks, advanced airway placement, rescuer fatigue). Recognition that the prior standard of a compression:ventilation ratio of 15:2 with stacked shocks was associated with a low CPR fraction and fewer compressions per minute led experts to recommend in 2005 a ratio of 30:2 combined with single shocks be used in non-intubated patients in cardiac arrest.(7) Compression at a rate of 100 per minute with

ventilations at a rate of 10 per minute without pauses was recommended for patients who have had an advanced airway (e.g. endotracheal tube) placed.

An observational analysis of data from the Resuscitation Outcomes Consortium demonstrated that greater survival is associated with a higher CPR fraction compared to a lower fraction in patients with cardiac arrest with a first recorded rhythm of ventricular fibrillation.(10) Although ventilations could be delivered more rapidly through an advanced airway such as an endotracheal tube, intubation during cardiac arrest has been associated with significant and prolonged interruptions in CPR.(11) EMS personnel can also take up to 10-12 seconds to deliver two quick breaths.(6) A single center study showed that hyperventilation by EMS personnel is common and can persist despite retraining.(12) Ventilation of large areas of dead space during the low flow state of cardiac arrest may be deleterious.(6) The magnitude of metabolic derangement is correlated with the duration of resuscitation.(13) Most EMS providers encounter patients who are in the circulatory phase of cardiac arrest when interruptions in chest compressions to allow for two breaths are associated with a deleterious decrease in CPP. Positive pressure hyperventilation in these instances could be detrimental because it further reduces CPP by decreasing venous return. Collectively, these studies suggest that it is reasonable to believe that positive pressure ventilation, pauses for ventilation and interruptions in CPR for endotracheal intubation during the early resuscitation period could be deleterious. This has led some experts to advocate for CCC without positive pressure ventilation and with delayed advanced airway placement during the circulatory phase of cardiac arrest.(6) Conversely, an observational study in a EMS system that achieves good overall survival after OOHCA suggested that shorter time to insertion of an advanced airway is associated with greater survival.(14) Therefore a randomized comparison of CCC with or without positive pressure ventilation versus ICC using a 30:2 compression-ventilation ratio is needed to understand the effect of interruptions in compressions upon outcomes after cardiac arrest.

2.2 Preliminary Studies

2.2.1 Animal

Interruptions in chest compressions rapidly lead to a loss of CPP and decreased rates of survival in animal models of cardiac arrest.(5) Resuscitation studies in a swine model of non-asphyxial cardiac arrest demonstrate that a strategy of CCC is as effective as chest compressions with rescue breathing when ventilations only interrupt compressions for four seconds (i.e. compression: ventilation ratio 15:2).(4) When ventilations interrupted compressions for longer periods in a similar swine model, CCC resulted in significantly better neurological survival.(5) Recently, Ewy et al compared the CCC strategy against the 30:2 CPR strategy in a swine model of non-asphyxial OHCA.(15) The primary outcome was 24-hour neurologically intact survival between the two groups. Ventricular fibrillation (VF) was electrically induced and was untreated for three, four, five or six minutes before resuscitation was initiated with either CCC or ICC with a compression:ventilation ratio of 30:2. Defibrillation was attempted 12 minutes after induction of VF followed by additional resuscitation according to the 2005 guidelines. Neurologically-intact survival at 24 hours was observed in 23 of 33 (70%) of the CCC group compared to 13 of 31 (42%) in the ICC group ($p = 0.03$). Collectively, these studies suggest that CCC is efficacious in non-asphyxial cardiac arrest in swine.

2.2.2 Human

The use of CCC has been studied in observational studies of humans with OOHCA. Providers were taught and expected to perform CCC which included 200 uninterrupted chest compressions before any rhythm analysis in two rural Wisconsin communities.(16) They also were instructed to use single rather than stacked shocks and to eliminate post-shock rhythm as

well as pulse checks. Initial airway management was limited to an oral airway with passive delivery of supplemental oxygen through a non-rebreather mask. Assisted ventilations and endotracheal intubation were delayed until at least three cycles of compression, rhythm analysis and shock had been completed or there was return of spontaneous circulation. During the historical control period, which was assessed retrospectively, EMS providers were taught and expected to perform CPR according to the 2000 AHA guidelines (i.e. compression:ventilation ratio of 15:2). Among patients with bystander-witnessed arrest with an initial shockable rhythm, neurologically intact survival rate was 48% (16/33) during the intervention period versus 15% (14/92) during the control period (p value = 0.001). Among patients with cardiac arrest of presumed cardiac etiology with any initial rhythm, neurologically intact survival rate was 18% (42/230) during the intervention period versus 8% (21/268) during the control period (p value not stated). The original publication from this group covered data from the first year following implementation of the CCC protocol.

A recent analysis by the same group evaluated the impact of CCC from 2004 to 2007 compared to a control period from 2001 to 2003 that was assessed retrospectively.(17) Among patients with bystander-witnessed arrest with an initial shockable rhythm, neurologically intact survival rate was 39% (35/89) during the intervention period versus 15% (14/92) during the control period (p value not stated).

The effect of CCC in combination with early administration of epinephrine and delayed endotracheal intubation was assessed in two metropolitan cities in Arizona.(18) Among those with witnessed arrest with an initial shockable rhythm, survival was 4.7% (2/43) during the control period versus 17.6% (23/131) during the intervention period (OR = 3.0; 95% CI = 1.1, 8.9). Among those with cardiac arrest with any initial rhythm, survival was 1.8% (4/218) during the control period versus 5.4% (36/668) during the intervention period (OR = 8.6; 95% CI = 1.8, 42.0).

The effect of passive versus positive pressure ventilation in combination with CCC in patients with OOHCA was assessed in an observational study in regions served by 60 fire departments in Arizona.(19) Included were patients who received 200 preshock chest compressions, 200 postshock compressions before rhythm or pulse check, delayed intubation for three cycles of compression and rhythm analysis, and attempted intravenous or intraosseous epinephrine before or during the second cycle of chest compressions. Passive ventilation included placement of an oropharyngeal airway and a non-rebreather face mask with high-flow oxygen. The oxygen flow rate was not specified. Positive pressure ventilation included ventilation rate of eight per minute and tidal volume of 500 mL per breath. Among patients with witnessed arrest with an initial shockable rhythm, survival rate was 38% (39/102) in patients who received passive oxygen insufflation versus 26% (31/120) in patients who received bag-mask assisted ventilation (adjusted OR 2.5, 95% CI 1.3-4.6)). Among patients with an initial non-shockable rhythm, survival rate was 1% (4/316) in patients who received passive oxygen insufflation versus 4% (14/381) in patients who received bag-mask assisted ventilation (adjusted OR 0.5, 95% CI 0.2-1.6). Overall survival rate was 10% (46/459) in patients who received passive oxygen insufflation versus 9.5% (53/560) in patients who received bag-mask assisted ventilation (adjusted OR 1.2, 95% CI 0.8-1.9). Furthermore, ROSC tended to be achieved less often in patients who received passive oxygen insufflation 26.8% (123/459) compared to patients who received bag-mask assisted ventilation (30.2% [169/560], adjusted OR 0.8, 95% CI 0.7-1.0).

More recently, a third observational study from Kansas City, Missouri also showed improved survival from OOHCA following the implementation of a modified CPR strategy.(20) In this study, EMS providers were instructed to provide chest compressions to ventilations at a 50:2 ratio with each ventilation delivered over a maximum time of two seconds. The strategy also included passive ventilation with continuous oxygen delivery through a non-rebreather mask

with an oral airway between ventilations, early use of epinephrine and a delay in endotracheal intubation until at least three cycles of 200 chest compressions (minimum 600 total compressions) or ROSC. This study compared survival to discharge 36 months before and 12 months after the protocol change. Survival from OHCA of presumed cardiac origin improved from 7.5% in the historical cohort to 13.9% (OR 1.80, 95% CI 1.19 to 2.70) with the modified CPR protocol. Among patients with witnessed ventricular fibrillation, survival to hospital discharge improved from an unadjusted survival rate of 22.4% to 43.9% (odds ratio 2.71, 95% CI 1.34 to 1.59) with the protocol.

Each of these studies used observational designs with historical controls that potentially over-estimated the impact of treatment due to the Hawthorne effect.(21) None of them used contemporary methods of CPR process monitoring to assess protocol compliance during either study period. These studies implemented multiple changes simultaneously including CPR before analysis, continuous chest compressions, no ventilations for at least three compression cycles, single rather than stacked shocks, early administration of vasopressor therapy, and elimination of post-shock pulse and rhythm checks. The oxygen flow rates associated with use of non-rebreather mask were not measured in these studies. This lack of measurement is important since others demonstrated that low or high oxygen flow rates are achievable with non-rebreather masks.(22, 23) High dose oxygen is associated with adverse outcomes in animal models of cardiac arrest.(24) A quasi-randomized trial demonstrated better outcomes with room air compared to oxygen supplementation in humans with acute stroke,(25) which has elements of ischemia-reperfusion injury similar to that observed after cardiac arrest. Therefore it is difficult to assess the relative contribution of CCC versus other changes in the CPR strategy to improved survival in these observational studies.

2.2.3 Equipoise Among ROC EMS Agencies

As of September 27, 2009, EMS agencies participating in ROC that use continuous chest compressions without pauses for ventilation include British Columbia Ambulance Service (Vancouver site); Seattle Fire Department (Seattle/King County site); and City of San Diego EMS (San Diego site). Other EMS agencies use compressions interposed with ventilations before insertion of an advanced airway. Agencies that by medical director authorization defer insertion of an advanced airway until at least five minutes after the onset of resuscitation include San Diego Fire Department as well as EMS agencies in the Dallas site. All ROC sites planning to participate in this trial have expressed a willingness to defer by medical director authorization insertion of an advanced airway for three cycles of CPR followed by rhythm analysis (i.e. about 6 minutes). Note that in the recently-completed ROC PRIMED Trial, the time from initiation of CPR to insertion of an advanced airway across all sites was median 7.9 (interquartile range 4.5, 12.0) minutes. No site had a median time to insertion of less than 5 minutes. Therefore we expect that this medical director authorization will have minimal impact on clinical care.

2.2.4 Summary of Rationale

Cardiac arrest is common, lethal and debilitating. Animal models of cardiac arrest and observational studies in humans show that CCC during the early resuscitation period is a promising resuscitation intervention. There exists a state of equipoise regarding the effectiveness of CCC for patients with OOHCA, which is reflected in the variation in practice within ROC. Therefore, we propose a large trial to test CCC versus ICC in patients with OOHCA.

3. Design and Methods

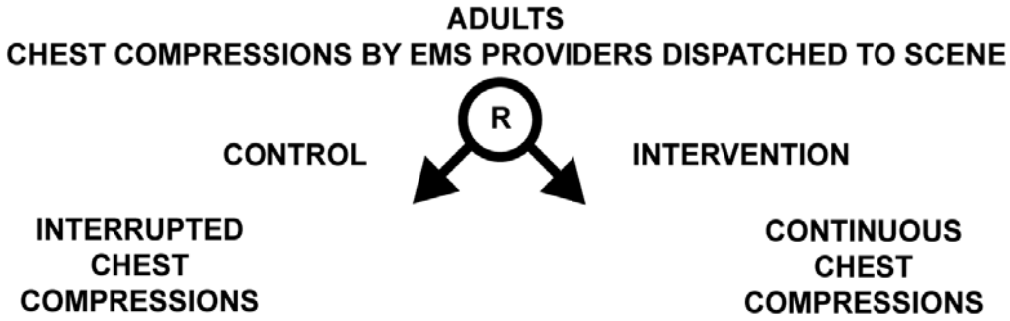
3.1 Hypotheses

The null hypothesis is that the rate of survival to discharge is identical with use of CCC versus ICC in patients with OOHCA. The secondary null hypotheses are that neurologic status at discharge and adverse events will be identically distributed with intervention versus control, and that treatment does not affect outcome, regardless of first recorded rhythm.

3.2 Design

The study design is a cluster randomized trial with crossover. The cluster units will be defined by EMS agency or station in a similar fashion as in our recent ROC PRIMED Trial.(26) Each cluster will crossover at least once during the trial.

Figure 1: Design



3.3 Inclusion Criteria

Included will be non-traumatic OOHCA patients with:

a) Age 18 years or more (or local age of consent);
b) Chest compressions by ROC EMS providers dispatched to the scene;
c) Lack of the exclusion criteria below.

3.4 Exclusion Criteria

Excluded will be those with:

a) EMS witnessed arrest;
b) Written do not attempt resuscitation (DNAR) orders;
c) Obvious primary asphyxia or respiratory cause of arrest (drowning, strangulation, pre-existing tracheostomy); or advanced airway placed prior to ROC EMS arrival;
d) Traumatic cause (blunt, penetrating, burn) of arrest;
e) Known prisoners;
f) Known pregnancy;
g) Non-participating agency/provider started CPR;
h) Use of mechanical chest compression device during initial EMS CPR period;
i) Uncontrolled bleeding or exsanguinations.

The rationale for the exclusion of EMS-witnessed arrests is that the CCC protocol would not be appropriate for EMS-witnessed arrests because the standard of care for such cases is to perform an immediate rhythm assessment followed by attempted defibrillation of shockable

rhythms right away. For simplicity, all EMS-witnessed arrests will be excluded from the protocol, whether shockable or not.

Candidate EMS agencies will need to meet prequalification criteria to participate in the run-in phase of this trial (Appendix 4).

Candidate agencies will need to meet criteria to be promoted from the run-in phase to the evaluable phase of this trial (Appendix 5).

3.5 Setting

EMS agencies participating in the Resuscitation Outcomes Consortium.

3.6 Random Allocation

The intervention (i.e., ICC or CCC) will be randomized using a cluster-crossover design. Each ROC site will be subdivided into multiple clusters by EMS agency, station, or other unit as appropriate to the site's EMS structure, similar to the method used in our recent ROC PRIMED Trial.(27) Each cluster will be scheduled to crossover to the opposite treatment at least once during the trial.

The randomization of clusters will be stratified by site and by blocks within sites. Within each site, clusters will be organized into two or more blocks that are relatively homogeneous with respect 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 approximately equal numbers to order of treatment (i.e., ICC then CCC versus CCC then ICC). All clusters will crossover between intervention assignments at least once (i.e. have at least two distinct treatment periods). If necessary, some clusters with high episode rates will crossover more than once (e.g. have four or more distinct treatment periods). Attempts will be made to ensure that treatment groups are balanced even if the trial is terminated prior to reaching its maximum sample size. For example, among clusters having four treatment periods, equal numbers within each block will be assigned to each of the following four orders of treatment: ICC-CCC-ICC-CCC, ICC-CCC-CCC-ICC, CCC-ICC-ICC-CCC, and CCC-ICC-CCC-ICC. Random assignment of treatment sequence will be performed at the coordinating center prior to the start of the study. Clusters will not be informed of their group assignments until necessary to make preparations to start the trial or crossover to another intervention. Responders will, however, know that each intervention will be tested in the first two periods, and (for clusters with four treatment periods) each intervention will be tested in the last two periods in each cluster.

Other designs were taken into consideration, particularly individual episode randomization. We believe that randomization by event or by individual patient is not feasible because the intervention involves psychomotor skills 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 the need for immediate therapy. Devices (AEDs) are not currently capable of being programmed to provide correct prompts for continuous chest compressions. Other forms of individual randomization (e.g. envelope or telephone) would therefore result in expecting EMS providers to ignore the existing prompts of monitor/defibrillators. 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.

3.7 Intervention

Patients allocated to the intervention group shall receive CCC as outlined (Figure 2). Upon arrival of participating EMS providers (or first responding firefighters) at the side of an eligible patient, chest compressions will be initiated upon confirmation of the arrest. The AED or defibrillator will be applied and powered on at the onset of CPR and continuous chest compressions will be given initially followed by rhythm analysis. The duration of manual CPR before the first rhythm analysis will be 30 seconds or 120 seconds, based on a priori local medical directive. This treatment period will be followed by two cycles of compressions (i.e. 200 compressions over approximately 2 minutes) then rhythm analysis. The duration of this initial cycle of CPR in this study is based on the findings of the recent ROC PRIMED study which did not detect a significant or important difference in neurologically-intact survival to discharge between Analyze Early and Analyze Late strategies.

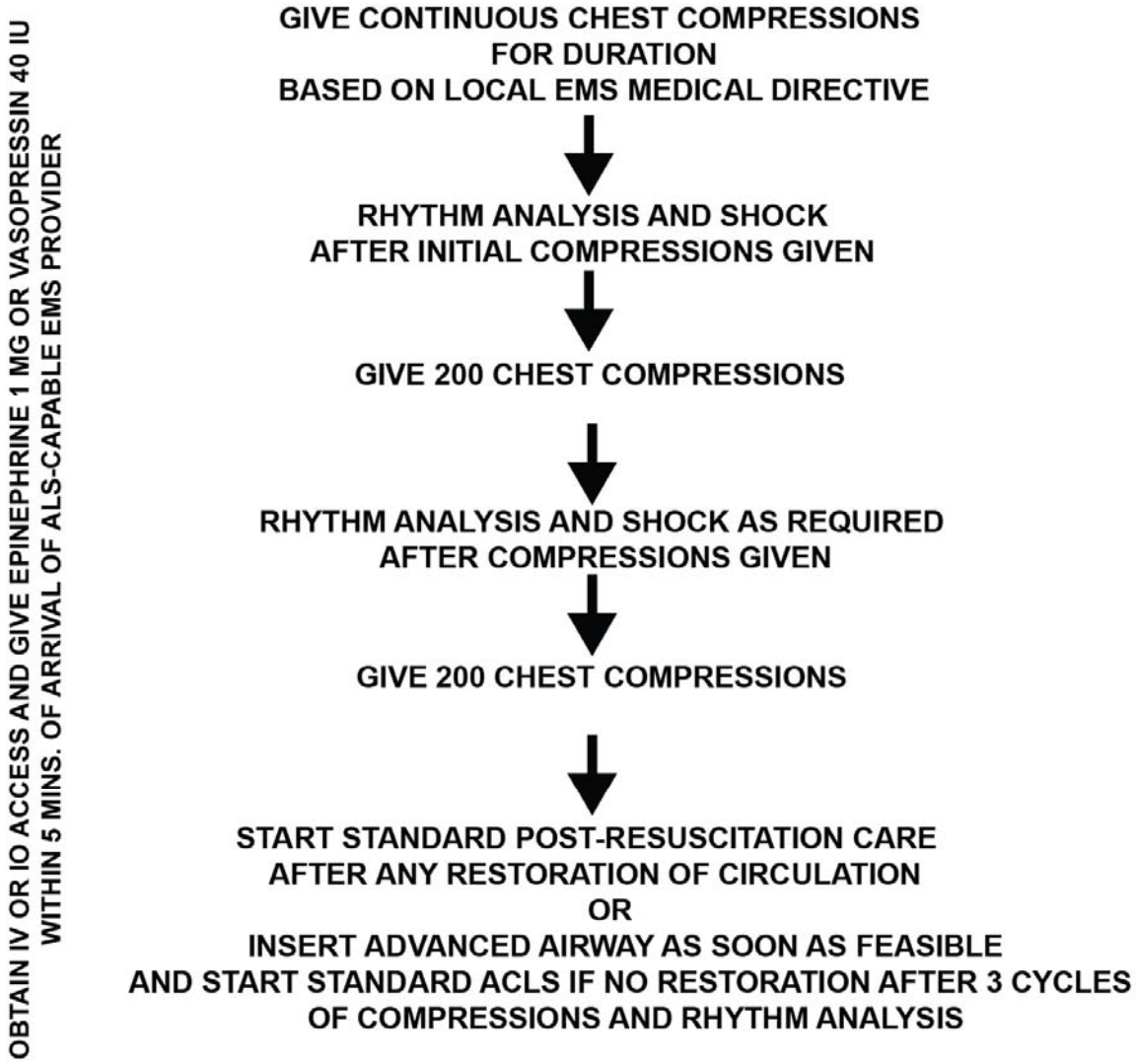
The airway will be opened and maintained with an oral airway. Since prior CCC studies that used passive ventilation achieved mixed results, all participating EMS agencies will require their providers to use active ventilation in either study arm. Also, since insertion of an advanced airway (e.g. endotracheal tube or supraglottic airway) is often associated with interruption of CPR, participating EMS agencies will defer insertion of an advanced airway until after ROSC or three cycles of compressions followed by rhythm analysis (i.e. about 6 minutes). Positive pressure ventilation will consist of insertion of an oral airway followed by positive pressure ventilation at a rate of 10/minute using ½ the volume of an adult bag (i.e. volume ~400-500 mL) over 1-1.5 seconds without interruption in chest compressions. Passive ventilation will consist of insertion of an oral airway with oxygen delivered through a non-rebreather mask at 15 L/min.

Rhythm analysis will be performed as quickly as possible after completion of the first compression cycle (i.e. goal < 10 secs). Patients in VF will be defibrillated once, followed by immediate initiation of a second cycle of 200 compressions with ongoing ventilation (with passive or positive pressure ventilations as determined by the EMS agency) without pauses in compressions, then a second rhythm analysis. IV or IO access along with delivery of a vasopressor (epinephrine 1 mg or vasopressin 40 IU) is recommended before or during the second compression cycle. We expect that this will occur within 5 minutes of arrival of an EMS provider capable of providing advanced life support. For persistent VF after the second cycle of compressions, patients will be defibrillated again and then receive a third cycle of 200 compressions with ongoing ventilation (with active or passive ventilations as determined by the EMS agency) without pauses in compression.

After the third cycle of compressions (i.e. up to 6 minutes after the onset of resuscitation efforts), patients will receive a third analysis with shock as required, undergo insertion of an advanced airway then receive standard Advance Cardiac Life Support (ACLS) care. When an advanced airway is has been inserted CPR will continue with compressions 100/min. and ventilations 10/min. without pause until ROSC is achieved or resuscitation efforts are terminated. This approach to compression and ventilations in a patient with an advanced airway is consistent with prior implementations of cardiocerebral resuscitation (See Figure 2 of Kellum(17), and page 658 of Bobrow(27)) as well as what is recommended by the 2010 AHA guidelines for emergency cardiovascular care.(28)

In the event that an advanced airway is not successfully inserted, then manual CPR will be continued in a manner consistent with the local medical directive. The study intervention will be considered completed when an advanced airway has been inserted or four cycles of manual CPR and rhythm analysis have been completed. The EMS providers will also be taught to NOT pause for any reason during the first three CPR cycles and to perform compressions up to the moment of the rhythm analysis and immediately after the shock is delivered as feasible. EMS

providers will be encouraged to minimize CPR interruptions during all advanced airway placement. All defibrillations will be performed consistent with local practice. All other resuscitation and post-resuscitation care will be per local practice.Figure 2: Treatment Algorithm for Intervention Group



3.8 Control

Patients allocated to the control group shall receive ICC as outlined (Figure 3). Upon arrival of participating EMS providers (or first responding firefighters) at the side of an eligible patient, chest compressions will be initiated upon confirmation of the arrest. The AED or defibrillator will be applied and powered on at the onset of CPR and manual CPR at a compression: ventilation ratio of 30:2 will be given initially followed by rhythm analysis. The duration of manual CPR before the first rhythm analysis will be 30 seconds or 120 seconds, based on a priori local medical directive. This treatment period will be followed by two cycles of manual CPR (i.e. five

sets of 30 compressions followed by two ventilations over approximately 2 minutes) then rhythm analysis.

Ventilations will be given during a pause in compressions of less than 5 seconds duration. Tidal volume will be approximately 400-500 mL per breath. After the first cycle of compressions, patients in VF will be defibrillated followed immediately by initiation of a second cycle of five sets of compressions followed by a pause for ventilations using a compression: ventilation 30:2 ratio.

Rhythm analysis will be performed as quickly as possible after completion of the first compression cycle (i.e. goal < 10 secs.). Patients in VF will be defibrillated once, followed by immediate initiation of second cycle of compressions with ventilation, then a second rhythm analysis. IV or IO access along with delivery of a vasopressor (epinephrine 1 mg or vasopressin 40 IU) is recommended before or during the second compression cycle. We expect that this will occur within 5 minutes of arrival of an EMS provider capable of providing advanced life support. For persistent VF after the second cycle of compressions, patients will be defibrillated again and then receive a third cycle of compressions with ventilation.

After the third cycle of compressions (i.e. up to 6 minutes after the onset of resuscitation efforts), patients will receive a third rhythm analysis with shock as required, undergo insertion of an advanced airway then receive standard ACLS care. When an advanced airway has been inserted, CPR will continue with compressions 100/min. and ventilations 10/min. without pause until ROSC is achieved, resuscitation efforts are terminated or care is transferred to the ED staff. This approach to compression and ventilations in a patient with an advanced airway is consistent with what is recommended by current AHA guidelines for emergency cardiovascular care.(7)

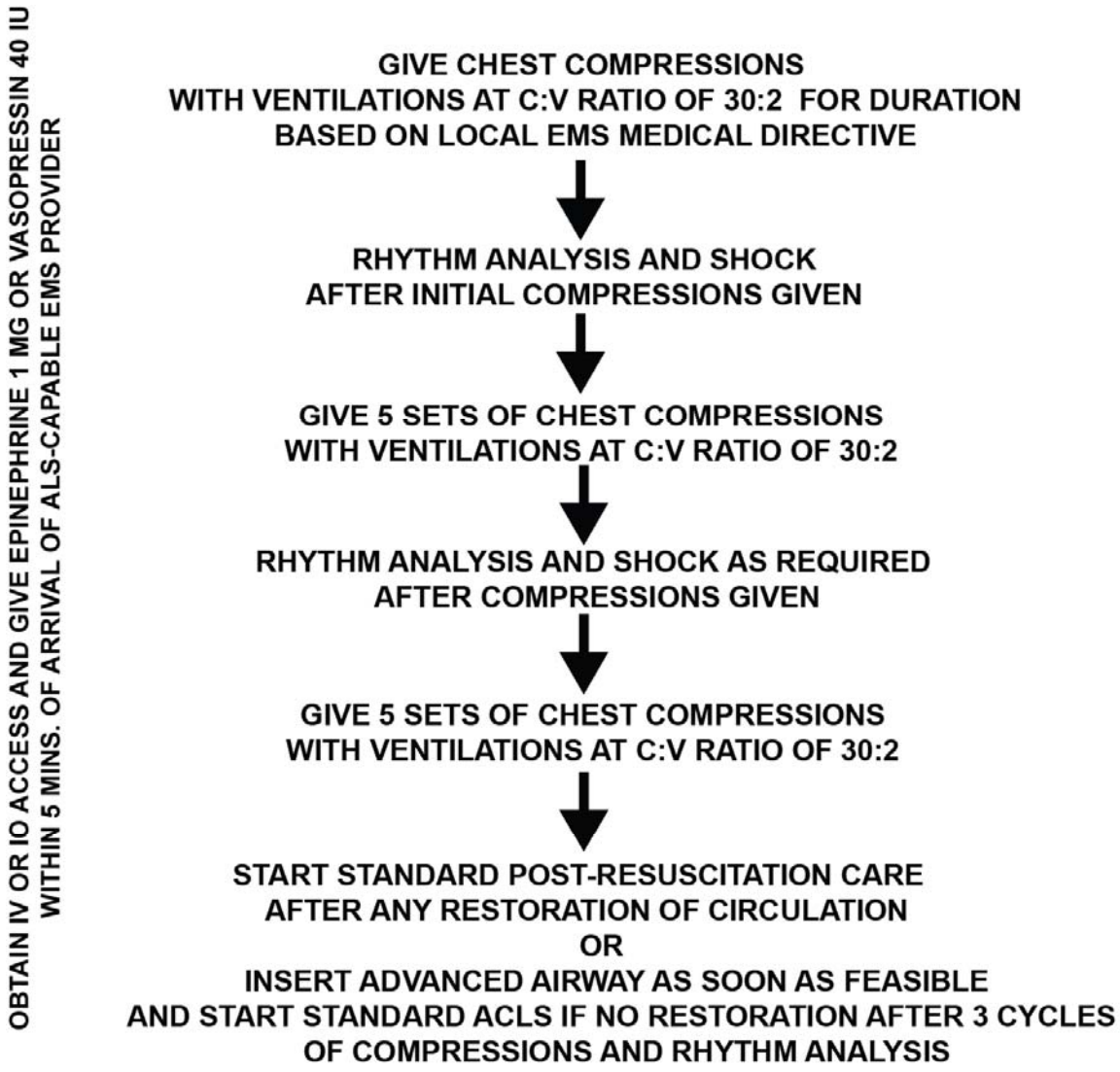
The EMS providers will be taught NOT to pause for any reason other than for ventilation during the first 3 CPR cycles and to perform CPR up to the moment of rhythm analysis and immediately after the shock is delivered. EMS providers will be encouraged to minimize CPR interruptions during all advanced airway placement. In the event that an advanced airway is not successfully inserted, then manual CPR will be continued in a manner consistent with the local medical directive. The study intervention will be considered completed when an advanced airway has been inserted or four cycles of manual CPR and rhythm analysis have been completed. All defibrillations will be performed consistent with local practice. All other resuscitation and post-resuscitation care will be per local practice.

3.9 Monitoring of CPR Process

3.9.1 Rationale

All participating first EMS responders and ALS providers in ROC 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 adequacy and 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.(29) 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.

Figure 3: Treatment Algorithm for Control Group



Recent studies have demonstrated that CPR is frequently not performed according to evidence-based guidelines in the out-of-hospital and in-hospital setting.(8, 9) 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. The importance of monitoring and improving CPR process was confirmed by the observation of potentially deleterious hyperventilation in the Milwaukee pilot study of the ITD.(12)

A variety of evolving technologies offer the ability to monitor CPR process either directly or indirectly through AEDs. These include chest impedance (30) (used to monitor chest compression rate and ventilation rate(31)), chest acceleration(32) (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 pre-hospital 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.(9) In addition, there is also considerable site-to-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.

3.9.2 Method of Monitoring CPR Process

All ROC clinical trial sites have implemented a high-quality system for monitoring individual components of CPR, to include, at a minimum, the rate of chest compressions and the proportion of pulseless resuscitation time during which chest compressions are provided (i.e. CPR fraction). Prior studies have shown no significant differences in these parameters during the first five minutes of resuscitation as compared with the entire resuscitation episode.(8, 9) It is anticipated that during the initial part of the resuscitation interruption of CPR due to rhythm analysis or other procedures will be greater than throughout the resuscitation episode. An observational analysis of CPR process during the first five minutes of resuscitation efforts within ROC sites has demonstrated that a greater CPR fraction is associated with significant and important improvement in survival in patients with a first recorded rhythm of VF.(10)

After insertion of an advanced airway and initiation of chest compressions and ventilations, hyperventilation is more likely than during the early resuscitation period. Therefore CPR process will be quantified during the first analyzable ten minutes of attempted resuscitation as well as ventilations throughout the resuscitation episode in those who receive an advanced airway, until a return of spontaneous circulation in the field or resuscitation efforts are terminated. If technically feasible, the ventilation rate will be monitored before and after insertion of an advanced airway. Sites will be encouraged to monitor CPR process measures and ventilation rates throughout the entire episode if feasible. The duration of CPR process monitoring is increased in this study compared to ROC PRIMED because the intervention is designed to last for up to 3 compression cycles which could be as long as 7-8 minutes. Furthermore, CCC has been associated with increased rescuer fatigue which can be better assessed by a longer period of CPR process monitoring.(33)

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 1) before being eligible to enroll patients in the present trial. In the ROC PRIMED Trial, CPR process data were available on 65% of eligible, enrolled patients.

Ongoing monitoring and review of CPR process will be used throughout the conduct of the trial as follows. Summaries of these CPR process data are monitored monthly by our study monitoring committee (SMC) as well as made available to emergency medical services (EMS) agencies. If SMC determines that an agency's CPR process is much different from others, the responsible site is asked to investigate for cause, and the responsible agency is asked to remediate as required. As well, the SMC will monitor:

a) completion of three cycles of CPR or insertion of an advanced airway < 5 minutes after arrival of EMS providers;
b) lack of administration of epinephrine or pressor < 10 minutes after arrival of ALS capable providers in patients who require ongoing resuscitation attempts;

ROC BLS and ALS providers will be trained to turn on the power of their AED or monitor and apply the pads to the chest immediately upon recognition of a subject in cardiac arrest. Hardware capable of monitoring CPR process 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. Determination of whether a resuscitation effort meets minimally acceptable CPR performance standards for the Consortium will be based on whether it meets acceptable compression rate and CPR fraction criteria as defined in Appendix 1. 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.

3.10 Outcomes

3.10.1 Primary Outcome

The primary outcome is survival to hospital discharge. 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.

3.10.2 Secondary Outcomes

The secondary outcomes are neurologic status at discharge and adverse events. Adverse events are described in detail in the section of this protocol that describes safety monitoring.

Neurologic status at discharge will be assessed using the modified Rankin Score (MRS). The MRS can be determined via review of the clinical record.(34, 35) The MRS uses a seven-point ordinal scale. It is scaled from zero (equal to no symptoms at all) to six (equal to death).(36) Patients who die before discharge will be assigned an MRS of six. MRS at discharge transformed to a binary variable (MRS $\leq$ 3) was the primary outcome measure in the ROC PRIMED Trial.(26, 37) However use of an ordinal primary outcome offers some efficiency in sample size compared to a binary outcome.

MRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.(38, 39) Use of a structured interview in a recent study of stroke patients improved the weighted kappa from 0.71 to 0.91.(40) It has prior use in a cohort of neurosurgical patients with in-hospital cardiac arrest,(41) a cohort of survivors of OOHCA,(42) and a cohort of survivors of arrest in either setting.(43)

The Cerebral Performance Category (CPC) is commonly used in assessments of the outcome of resuscitation. Although conceptually similar to the MRS, there have been limited assessments of its reliability and validity.(43-45) FDA staff have expressed concern about the validity of the CPC as a measure of outcome after resuscitation. (Circulatory System Devices Advisory Panel Meeting Minutes accessed on March 11, 2009). Therefore, we shall use MRS as the primary measure of neurologic status rather than CPC.

3.10.3 Mechanistic Outcomes

Other surrogate outcomes will be collected for descriptive purposes:

a) Number of Shocks Required: The total number of defibrillatory shocks.
b) Sustained Return of Spontaneous Circulation (ROSC): defined as the documented presence of a measurable pulse and blood pressure upon emergency department arrival.
c) Survival to 24 hours from time of arrest (defined as time of 911 call receipt).
d) Survival to Awakening: This will be defined as time from arrest to the day a patient is able to obey verbal commands after emergency department arrival.
e) Survival to Withdrawal of Care: This will be defined as time from arrest to the day care is withdrawn after emergency department arrival.
f) Hemodynamic Instability: This will be defined as use of pressors or mechanical circulatory support within 72 hours of emergency department arrival. Mechanical circulatory support will be defined as use of an internal support device (e.g. intra-aortic balloon pump, TandemHeart, Impella, Lifebridge or similar). Use of an external chest compression device (e.g. LUCAS) will be considered indicative of rearrest, but will not be considered mechanical circulatory support.
g) In-Hospital Morbidity: The number of hospital days and time interval from 911call to patient death will be described for all hospitalized patients as measures of in-hospital morbidity after resuscitation.

3.11 Adverse Events

3.11.1 Unexpected Adverse Events (UAE)

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 the interventions 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 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.

3.11.2 Expected Adverse Events

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. This will be monitored and reported but not considered as adverse events of the study intervention.

a. 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 poster anterior projection), or pulmonary venous congestion (upper-zone flow redistribution on poster anterior projection).(47, 48) Pulmonary edema is commonly observed after resuscitation from cardiac arrest. (49) and Unpublished Data, ASPIRE Investigators).

b. Airway Bleeding

This will be defined as frank blood or bloody fluid observed in the field. This will be recorded as noted in the pre-hospital care record only. Pink sputum or airway secretions observed during CPR will not be included. Airway bleed is commonly observed during attempted resuscitation.

c. Other

Clinical diagnoses of pneumonia, sepsis, cerebral bleeding, stroke, seizures, bleeding requiring transfusion or surgical intervention, rearrest, serious rib fractures, sternal fractures, internal thoracic or abdominal injuries as well as any other major medical or surgical outcomes are commonly observed in patients resuscitated from cardiac arrest. They will be recorded as noted in the hospital discharge summary but not considered adverse effects of the study intervention. We will use an algorithm for defining potential complications specific to insertion of any advanced airway (e.g. main stem intubation, recognized dislodgement, unrecognized dislodgement and esophageal intubation in all cases of possible successful intubation) based on information obtained from the prehospital and emergency department clinical record.(46)

3.12 Analyses

3.12.1 Primary Analysis

CCC is conjectured to provide an improvement in survival to hospital discharge in those patients who have OOHCA with a first recorded rhythm of VT/VF or shockable by AED. Since patients with other initial rhythms have a relatively poor prognosis, we anticipate that the intervention will not confer significant benefit in this population. We expect, however, that if CCC is efficacious in patients with VF/VT, it will also be applied to those with other initial rhythms or non-cardiac events. 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. Hence, this study protocol proposes the randomization of patients with all rhythms, and the primary treatment comparison will include all randomized subjects.

The primary test of the null hypothesis will be performed on the Intent-to-Treat sample using a test statistic calculated as difference in event rates divided by the estimated “robust” standard error based on the Huber-White sandwich estimator(50, 51) in order to account for within cluster correlation and variability which might depart from the classical assumptions. In addition to a test of the null hypothesis, it is important to provide an estimate of a clinically meaningful parameter that quantifies the treatment effect. For this purpose, a 95% CI for the difference in event rates will be calculated with an adjustment for the interim analysis plan.

3.12.2 Secondary Analyses

a. Analyses by First Presenting Rhythm

Following the analysis plan used for the primary analysis, secondary analyses will be performed in subgroups defined by first-presenting rhythm. The groups will be defined as a) patients with a first recorded rhythm of VT/VF, b) patients with a first recorded rhythm of PEA, c) patients with a first recorded rhythm of asystole, and d) patients with other or unknown rhythm.

b. Compliance and As-Treated Analyses

Two additional analyses will be conducted to compare treatment groups accounting for compliance with treatment protocol: i) restricted to only those cases treated as specified by the random assignment, and ii) with assigned treatment replaced with actual treatment administered (provided accurate data on actual treatment modality can be obtained). The results of these analyses will be compared with the intent-to-treat analyses.

c. Secondary Outcomes

Analyses will be performed using the efficacy sample to compare the treatment groups on the distribution of the secondary outcome measures. For these analyses, the Mann-Whitney test

and proportional odds regression will be used for ordinal outcomes, the chi-squared test and logistic regression will be used for binary outcomes, and the log-rank test and Cox regression will be used for comparing survival distributions.

d. Mechanistic Outcomes

Mechanistic outcomes will be assessed to give insight into possible mechanisms underlying any observed treatment effect. These will be summarized descriptively. Results will be reported using point estimates and 95% confidence intervals rather than p-values. These analyses will be considered exploratory and will not be used as a basis for treatment recommendations.

3.12.3 Subgroup Analyses

Modification of the effect of treatment upon primary and secondary outcomes by the presence or absence of prognostic factors will be performed separately in subgroups as defined below. Tests for key interactions (different treatment effects between sub-groups) will also be performed. However, it is recognized that the study is not powered adequately to detect interactions; all subgroup analyses will be considered exploratory and will not be used as a basis for treatment recommendations. Note that an additional sub-group analysis, not listed below, will be done as part of the safety analyses noted above, namely the separate analyses for sub-groups of patient defined by first recorded rhythm: a) VT/VF, b) PEA, c) asystole, and d) other or unknown rhythm. We acknowledge that the power to detect treatment effects in rhythms other than VF/VT is low because of high death rates in these patients and our conjecture that benefits of CCC exist primarily for VF/VT patients. The sub-groups listed below will be examined in the VF/VT group initially; if an overall treatment effect is found in other rhythms (this is not expected) then sub-groups will also be examined in that rhythm group.

a) Response time interval from call to arrival at scene; (i) < 10 minutes, versus (ii) ≥ 10 minutes;(52)
b) Observational status of arrest: (i) arrests witnessed by bystanders, versus (ii) unwitnessed arrests;
c) Location of arrest: (i) arrests in a public place, versus (ii) arrests not occurring in a public place;
d) Method of ventilation (passive vs. positive pressure ventilation);
e) Time of advanced airway placement (early versus late, defined as (i) < 5 minutes of arrival of EMS provider capable of advanced life support versus (ii) > 5 minutes);
f) Hypothermia status: (i) field cooling vs. (ii) hospital cooling vs. (iii) both vs. (iv) neither;
g) Percutaneous coronary intervention status: (i) < 4 h after hospital arrival versus (ii) ≥ 4 h after hospital arrival vs. (iii) not performed during index hospital admission;
h) Incidence rate of neurologic status at discharge in control group by study site;
i) Bystander CPR: (i) was administered vs. (ii) not administered.
j) Etiology of arrest: Cardiac vs. non-cardiac etiology. An arrest is presumed to be of cardiac etiology unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination, or any other non-cardiac cause as best determined by information recorded by EMS providers.

Due to the large number of secondary analyses proposed, results of secondary outcomes will be reported as exploratory and will not be used to derive treatment recommendations.

3.12.4 Comparison of Effect of Duration of First CPR Period

As described elsewhere in the protocol, each participating EMS agency's medical director will authorize whether the duration of the first manual CPR period is to be 30 seconds or 120 seconds prior to initiation of study enrollment. We will monitor adherence to the pre-selected modality for quality control purposes. In addition, we will perform comparisons of outcomes for the two durations of initial manual CPR and present the results to the DSMB at each meeting. If convincing evidence for a difference is found, we would consider modification of the protocol to require use of the manual CPR method with the better outcomes at the discretion of the DSMB. If required by the DSMB, a formal interim analysis plan will be developed for guiding their decision on this issue. Note also that we will perform secondary analyses based on the total duration of exposure to study treatment from initiation of manual CPR to insertion of an advanced airway or completion of four cycles of compressions and rhythm analysis.

3.13 Sample Size

3.13.1 Overview

We estimate that we will require a maximum of 23,600 patients (11,800 per group). This will provide at least 90% power in the primary analysis to detect a change in the rate of survival to discharge from 8.1% to 9.4% with overall significance level (adjusted for interim analyses) equal to 0.05. The baseline survival rate was based on results from the on-going analyses of the ROC PRIMED Trial and accommodates up to a 5% loss of precision due to randomizing by cluster (with crossover) rather than by patient (preliminary results from ROC PRIMED suggest that the penalty for clustering may in fact be even smaller).

3.13.2 Timeline

Based on prior enrollment in the ROC PRIMED Trial, we expect that participating sites will treat at least 8,000 out-of-hospital cardiac arrests annually, including 800 EMS witnessed arrests. With 7,200 arrests eligible for this trial annually, we expect that approximately 3 years of enrollment will be required to achieve our intended maximum sample size of 21,406 patients for the primary analysis (if the trial continues until maximum enrollment is reached). The maximum number of subjects with a first recorded rhythm of VT/VF, a key subgroup, will be approximately 5,352.

3.14 Data

3.14.1 Sources

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.

3.14.2 Elements

a) 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, timing of advanced airway insertion, method of ventilation, hypothermia), first ECG rhythm, disposition, return of spontaneous circulation, potential adverse events.

b) Emergency and Hospital

Spontaneous circulation upon emergency department arrival, major procedures, possible complications of intervention, admittance to the hospital, cause of arrest, ICU days, date of awakening, disposition at discharge, date of designation of DNAR status, date of withdrawal of care as well as MRS at hospital discharge.

c) Initial ECG Rhythm

The initial ECG tracing will be analyzed off-line. 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 <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.

3.14.3 Data Entry

The DCC will provide web-based HTML forms to collect necessary information from the participating sites. Web entry forms will have dynamic features such as immediate checks on data and relationships within a form and between forms. Details and clarification about data items will be provided using pop-up windows and links to appropriate sections of the on-line version of the Manual of Operations. Data encryption and authentication methods will be used. The 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.

3.14.4 Database Management

The DCC will use a two-tiered database structure. A front-end database will serve 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. weekly) to a data repository that can be used by statistical software packages. These data sets will be the basis for data queries, analyses and monitoring reports. Various versions of this database will be kept as needed, e.g. for quarterly performance reports. Backup of data and programs will be performed at frequent intervals. Access to data will be limited to those who need access to perform their tasks. The database management system is able 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.

3.15 Training

Overview of Training

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

3.15.1 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) and less than 10 seconds to administer 2 breaths between compression cycles in the ICC arm, and less than 20 seconds for pre-shock pause in either arm. 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). During CCC with PPV, rescuers will provide ventilation at a fixed rate per minute with a tidal volume of 400-500 mL over 1-1.5 second without any interruption in chest compressions.

3.15.2 Scientific Basis for Continuous Chest Compressions Protocol

Level-appropriate presentation of the scientific principles underlying the ROC continuous chest compressions study 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.

3.15.3 Review of Study Protocol

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. The training will emphasize the need for rapid screening and enrollment, defibrillator/AED on time as start of CPR, timely initiation of chest compressions, and rapid restart of compressions in the event of recurrent arrest, use of epinephrine or vasopressin early in the resuscitation and ECG download after the resuscitation.

3.15.4 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. 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 nature and sequence of compressions and ventilations in the control and intervention groups. All of an agency's EMS personnel will need to demonstrate proficiency in adequately managing a study cardiac arrest patient before the agency can begin enrollment in the run-in phase of the study.

3.15.5 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.

3.15.6 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 Study Monitoring Committee 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 advanced airway placement time and adverse events.

3.15.7 Retraining

EMS personnel will be retrained in study-related procedures in intensity similar to local standards for training in EMS procedures with an emphasis on retraining at each crossover period, and as required by the ROC Study Monitoring Committee to correct errors in the care process described above as the trial progresses.

3.16 Safety Monitoring

Clinical staff will report all potential adverse events to the coordinating center as soon as possible. These will be collected in both a structured (standard form) and open (describing any difficulties encountered) form. Previously published clinical studies and reviews involving patients undergoing chest compressions have suggested that the following are commonly observed in patients who experience cardiac arrest or resuscitative efforts, and may or may not be attributable to specific resuscitation therapies: pulmonary edema, airway bleeding, pneumonia, sepsis, cerebral bleeding, stroke, seizures, bleeding requiring transfusion or surgical intervention, rearrest, serious rib fractures, sternal fractures, internal thoracic or abdominal injuries as well as any other major medical or surgical outcomes. Such expected adverse events will be recorded as noted in the hospital discharge summary by each enrolling site, reported to overseeing agencies as required by federal regulations and local requirements, and reviewed periodically by our independent data safety monitoring board. All other potential adverse events will be reviewed as to treatment arm and further classified by: a) Severity (life-threatening, serious, non-serious); and b) Expected vs. Unexpected. For serious adverse events, the coordinating center will notify the DSMB as well as appropriate regulatory agencies, site, and sponsor promptly. The coordinating center will tabulate and report compliance, data quality, and non-serious adverse events on a regular basis.

An independent data safety and monitoring committee will help ensure the safety of the trial subjects by monitoring adverse outcomes throughout the trial and by reviewing outcome data for possible harm. The committee will review and approve the protocol before the study can commence. In addition, the committee will approve an interim monitoring plan before study initiation and review the results of the interim analyses. Although the DSMB will make the final decision about the interim monitoring plan, we anticipate that the DSMB will evaluate treatment compliance and 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. The DSMB will also monitor primary, secondary and mechanistic study outcomes between the treatment and control groups including main effects and a priori subgroups as specified elsewhere in the protocol. The DSMB will advise the investigators if a change in the protocol is warranted based on this interim monitoring. A preliminary monitoring plan is described in Appendix 2.

We are aware that a high rate of opting out from ongoing participation may limit our ability to ensure the safety of the trial subjects. The SMC will monitor the rate of subjects or their LAR opting out from ongoing participation in this trial, and require remediation as needed if the rate of opt out is excessive. As well, the DSMB will monitor rates of subjects or their LAR opting out from ongoing participation in ROC trials, and require remediation as needed or recommend modification to the study design or conduct as appropriate.

The coordinating center will forward DSMB reports to study investigators, the Institutional Review Board, and the sponsor in accordance with the 1996 guidance from OHRP regulations 46.101 (i), as is our current practice.

4. Human Subjects

We anticipate that this study would be conducted with an exception from consent for emergency research, including community consultation, public notification, as well as notification of patients or their legally-authorized representative as soon as feasible after enrollment. The latter shall include provision of an opportunity to withdraw from ongoing participation that will be given through oral and written communication. See Appendix 3 for more information.

5. Impact of Recent ROC PRIMED Study on Proposed Plan

As mentioned previously, the ROC Primed study did not demonstrate a significant difference in neurologically-intact survival between Analyze Early or Analyze Late, or between active or sham impedance threshold devices (ITD). Therefore we have simplified the compressions sequence in both control and intervention groups in this trial. As well, we will not require use of the ITD in this trial.

6. Impact of Post-Resuscitation Hospital-Based Care

An interesting issue is whether and how to control for potential effect confounders that could be initiated when a patient is hospitalized after resuscitation from cardiac arrest. Case-control studies have evaluated the effectiveness of combinations of hospital-based treatments in patients resuscitated from cardiac arrest in a variety of settings.(53-58) All have reported improved outcomes when compared with historical controls. An analysis of observational data from the ROC cardiac arrest registry demonstrated that patients who were transported to a receiving hospital that had a coronary catheterization laboratory had better outcomes compared to those who were not.(52) Collectively, these studies demonstrate that hospital-based care of those resuscitated from OOHCA impacts patient outcomes and potentially modifies the effect of prehospital interventions for cardiac arrest. Thus experts have recommended a standardized approach to try to achieve optimal outcomes after resuscitation from cardiac arrest.(59)

The effectiveness of each component of post-resuscitation care remains unclear because observational studies may over-estimate the magnitude of the effects of treatment compared to randomized designs.(60, 61) But we will disseminate guidelines on post-resuscitation care to staff of the hospitals that receive patients enrolled in ROC trials. As well, we will monitor components of hospital-based post-resuscitation care including: the method, duration and magnitude of therapeutic hypothermia; withdrawal of care; early PCI; hemodynamic monitoring; hemodynamic support; seizure monitoring, prevention and control; insulin therapy; and implantable defibrillator therapy, if any, for control and intervention patients. A summary of this information will be provided to hospitals periodically. Included in this report will be a descriptive summary of the individual hospital's processes of care in the above domains compared to an anonymized aggregate summary of processes of care among all other participating receiving hospitals. The relevant ROC site PI will determine the appropriate recipient of such reports at each hospital e.g. hospital intensive care committee or equivalent. Also, the ROC Study Monitoring Committee will monitor processes of care in these domains. If performance deviates from expectations, the site PI will be required by SMC to work with the local hospital to address these concerns. In this manner, post-resuscitation care will be monitored but will not be standardized in this ROC trial.

6.1 Efficacy vs. Effectiveness Studies

Randomized trials are used to establish if therapeutic interventions work, and determine the benefits and risks of each alternative in predefined patient populations. Ideally a trial should fulfill its objectives with the fewest patients possible (i.e. statistical efficiency).(62) There is frequently a tradeoff between minimizing chance as well as bias due to confounding, and maximizing efficiency. A consequence of these conflicting objectives is that choices about trial design focus on whether an intervention results in more good than harm for patients or whether it works.(63) ‘‘Efficacy’’ trials attempt to determine whether the interventions work under ideal conditions. ‘‘Effectiveness’’ trials attempt to determine whether interventions work under usual practice conditions. It is noteworthy that randomized trials conducted by the ARDS Network were suspended by the Office of Human Research Protection out of concern that for comparison groups received two extremes of practice rather than more common practice, which may have been safer.(64) Therefore we believe that standardizing post-resuscitation care in hospital is neither necessary nor sufficient in our effectiveness studies.

6.2 Therapeutic Hypothermia

Therapeutic hypothermia reduces intracranial pressure as well as production of glutamate and oxygen-free radicals that are associated with reperfusion injury after restoration of spontaneous circulation.(65) Two randomized trials demonstrated that mild hypothermia (32° to 34°C) via external cooling methods is safe and improves neurologic outcomes significantly in comatose survivors of OOHCA in whom the initial rhythm was ventricular fibrillation.(66, 67) Another trial demonstrated that mild hypothermia (32° to 34°C) is safe and tends to improve neurologic outcomes in comatose survivors of OOHCA in whom the initial rhythm was not VF.(68) Animal data suggest that hypothermia should be initiated as soon as possible during resuscitation.(69, 70) A case-control study of patients without restoration of circulation after OOHCA demonstrated that use of cold intravenous fluids prior to percutaneous cardiopulmonary bypass significantly improved survival to discharge compared to use of cold fluids after restoration of circulation or bypass.(71) Therapeutic hypothermia is used infrequently in the United States.(72) Some regions have attempted to mandate use of hospital-based hypothermia by transporting patients resuscitated in the field from OOHCA only to hospitals capable of inducing hypothermia,(73) other regions have been unable to do so.(74) Use of therapeutic hypothermia in the hospital setting will be monitored.

6.3 Withdrawal of Care

Reliable prognostic factors are established after post-arrest day three,(75, 76) but an analysis of observational data from an in-hospital cardiac arrest registry demonstrated that the majority of declarations of do not attempt resuscitation (DNAR) status or withdrawal of life-supporting therapies occur prematurely.(77) Development of multiple organ failure, intractable cardiopulmonary collapse and neurological injury all contribute to mortality.(78) Different interventions might selectively affect recovery of one or more organ systems, but fail to affect overall survival that requires multiple organ systems. Therefore the timing of assignment of ‘do not resuscitate’ status, withdrawal of care and death will be monitored.

6.4 Early Percutaneous Coronary Intervention

Up to 71% of patients with cardiac arrest have coronary artery disease, and nearly half have an acute coronary occlusion.(79-81) There is a high incidence (97%) of coronary artery disease in patients resuscitated from OOHCA who undergo immediate angiography and a 50% incidence of acute coronary occlusion.(79) However, the absence of ST elevation on a surface 12-lead electrocardiogram (ECG) after resuscitation of circulation from cardiac arrest is not strongly predictive of the absence of coronary occlusion on acute angiography.(79) A case series of

patients with unsuccessful field resuscitation suggested that in such patients, VF is more likely to be due to coronary disease than is asystole or pulseless electrical activity.(82) An autopsy study compared cases who died within six hours of symptom onset due to ischemic heart disease and were not seen by a physician within three weeks with controls who died within six hours of symptom onset due to natural or unnatural noncardiac causes.(83) The controls were matched to cases by age, gender, and socioeconomic status. Sudden ischemic death was defined as sudden death with >75% stenosis of the lumen (>50% of diameter) of a coronary artery with no other cause on autopsy, including toxicological studies. Intraluminal thrombosis was observed in 93% of cases versus 4% of controls. Collectively these studies suggest that patients who are resuscitated from out-of-hospital VF have a high likelihood of acute coronary occlusion. The feasibility and efficacy of primary PCI in patients who survive cardiac arrest with STEMI have been well established.(55, 79, 84-89) Combining mild therapeutic hypothermia with primary PCI is feasible, may not delay time to start of primary PCI in well-organized hospitals, and is associated with good 6-month survival rate as well as neurological outcome. (55, 56, 85) Early use of PCI will be monitored in this ROC trial.

6.5 Hemodynamic Monitoring

Patient resuscitated from cardiac arrest sometimes undergo invasive procedures (e.g. pulmonary artery catheter insertion) to facilitate hemodynamic monitoring that can be used to guide therapy. However, a large randomized trial in patients with severe acute heart failure,(90) and a systematic review of trials in patients with heterogeneous severe acute illnesses demonstrated that pulmonary artery catheters neither increased or decreased mortality.(91) There is ongoing controversy about the role of hemodynamic monitoring in patients resuscitated from cardiac arrest. Therefore use of hemodynamic monitoring in the hospital setting will be monitored in this ROC trial.

6.6 Hemodynamic Support

Myocardial dysfunction is commonly observed after resuscitation from cardiac arrest and is associated with poor prognosis compared to normal cardiac function.(92) This hemodynamic instability responds to fluid administration and vasoactive support. Both cardiac arrest and sepsis are thought to involve multi-organ ischemic injury and microcirculatory dysfunction.(93) Goal-directed therapy with volume and vasoactive drug administration has been effective in improving survival from sepsis.(94) The greatest survival benefit is due to a decreased incidence of acute hemodynamic collapse, which is a problem that is also seen in the post-resuscitation setting. Use of hemodynamic support in the hospital setting will be monitored in this ROC trial.

6.7 Seizure Monitoring, Prevention and Control

Seizures are associated with worse prognosis in patients resuscitated from cardiac arrest, and may cause and exacerbate post–cardiac arrest brain injury.(95) Clinical seizures occur in 7% to 8% of patients resuscitated from cardiac arrest;(66) The incidence of electrographic seizures is unknown. Thiopental and diazepam did not significantly improve clinical outcomes in patients resuscitated from cardiac arrest.(96, 97) Contemporary antiepileptic drugs have not been evaluated in patients resuscitated from cardiac arrest. Prospective studies are needed to determine the benefit of EEG monitoring for seizures and prevention or control of seizures using anticonvulsant therapy during the course of recovery from cardiac arrest. Therefore use of EEG monitoring and anticonvulsant therapy will be monitored during this trial.

6.8 Insulin Therapy

Hyperglycemia after resuscitation from cardiac arrest is associated with a poor prognosis compared to normoglycemia.(98, 99) Randomized trials demonstrated that insulin therapy to maintain normoglycemia improved outcomes in surgical or medical patients who required prolonged care in an intensive care setting,(100, 101) but did not improve outcomes in patients undergoing cardiac surgery.(102) Given the inconsistent evidence of the effectiveness of insulin therapy in patients with acute illness, use of insulin therapy will be monitored.

6.9 Implantable Defibrillators

Patients who have been resuscitated from cardiac arrest are at risk of a recurrent event. Randomized trials demonstrate that implantable cardioverter defibrillator decrease mortality in such patients.(103-105) Since implantable defibrillators lack benefit in selected populations,(106) and patient preferences influence use of such devices, not all patients are candidates for implantable defibrillator during the initial hospitalization. Thus assessment of need for implantable defibrillators will be monitored.

7. Anticipated Clinical Impact

There has been great interest in and development of better methods of blood flow during CPR. Protocols to improve blood flow in the EMS setting have proliferated, including alternative methods of manual or mechanical chest compressions, as well as efforts to increase manual CPR fraction with real-time or downstream feedback. An advantage of CCC is its relative lack of expense because its implementation requires education and practice but no proprietary drug or device. The potential effect of chest compressions on survival is large. CPR has a larger influence on neurological outcomes in laboratory and clinical settings than any drug or device to date.

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9. Appendix 1: CPR Process Monitoring

A. CPR Process Monitoring Devices

ALS Devices (see Table below)

LP-12 and LP-15 (Physio Control, Inc.): These devices measure chest compression, ventilation and calculate CPR fraction based on changes in impedance; audio recording is available as an option. Measuring ventilation rate using impedance, when superimposed on chest compressions, can be problematic and requires adjunctive approaches such as use of audio recording to overhear ventilations, particularly if the provider verbalizes when a breath is delivered or the sound of the ventilation event can be augmented. Capnometry is optional. Data download is performed via a cable computer link, landline modem, or GSM cellular transmission. At the present time, immediate (real-time) feedback to providers is not available.

MRx (Philips Inc. and Laerdal, Inc.): This device combines information obtained from an accelerometer and chest impedance to measure chest compression, ventilation and calculates CPR fraction. Capnometry is optional. An audio recording feature is available. Data download is performed via a removable memory card. Software for immediate (real-time) feedback to CPR providers is included with the device.

M Series and E Series (Zoll, Inc): This device combines information obtained from an accelerometer to measure chest compression and calculate CPR fraction. A separate impedance channel and audio recording are in development and will reportedly soon be available. Capnometry is optional. Data download is performed via a removable memory card. Software for immediate (real-time) feedback to providers is incorporated in the device.

BLS Devices (see Table below)

LifePak 500 and LifePak 1000 AEDs (Physio Control Inc): This device offers audio recording and limited impedance measurement (suitable for chest compressions only), allowing for measurement of chest compression rate and CPR fraction. Measuring ventilation rate via changes in impedance is difficult with this device because of its limited frequency response and requires adjunctive approaches such as use of audio recording to overhear ventilations, particularly if the sound of the ventilation event can be augmented, or the provider verbalizes when a breath is delivered. Data download is performed via a cable computer link, landline modem, or GSM cellular transmission. At the present time, immediate (real-time) feedback to providers is not available.

Heartstart Home and Onsite AEDs (Philips, Inc and Laerdal, Inc): These devices offer audio recording and a high resolution impedance channel suitable for recording chest compression rate, ventilation (with the limitations specified above), and allow for calculation of CPR fraction. A version of the MRx defibrillator is also presently in development, that incorporates the same CPR process monitoring technology as the ALS MRx defibrillator (including real-time feedback), but does not include other ALS features (such as capnometry). Data download is performed via a removable memory card.

AED Pro BLS (Zoll, Inc): This device incorporates the same CPR monitoring features available in the M Series ALS device, but does not include other ALS features (such as capnometry). Real-time feedback for chest compression is incorporated into the device. Data download is performed via a removable memory card.

Table 1: Available CPR Process Monitoring Devices

Device	Chest Compression Measurement Technology	Ventilation Measurement Technology	Other Features	CPR Process Measures Available via Device	Data Download	Data Analysis	Immediate Feedback
ALS Devices							
LP-12 or LP-15*	Impedance	Impedance	Audio optional, capnometry optional	Chest compression rate, ventilation rate, CPR fraction	Computer cable link, landline modem or GSM cellular transmission	Manual review	Not available
MRx^	Accelerometer	Impedance	Audio in development; capnometry optional	Chest compression rate, ventilation rate, CPR fraction	Removable memory card	Manual review and semi-automated software	Software included
M Series or E Series ALS§	Accelerometer	Impedance	Audio in development; capnometry optional	Chest compression rate, CPR fraction; ventilation (in development)¶	Blue tooth, serial cable or removable memory card	Manual review and semi-automated software	In development
BLS Devices							
LifePak 500 or 1000 AED *	Low resolution impedance	Audio recording		Chest compression rate, CPR fraction; ventilation¶	Computer cable link, landline modem or GSM cellular transmission	Manual review	Not available
Heartstart Home and Onsite AED^	Impedance	Impedance	Audio recording	Chest compression rate, ventilation rate, CPR fraction	Removable memory card	Manual review	Not available
MRx for BLS^	Accelerometer	Impedance	Audio in development	Chest compression rate, ventilation rate, CPR fraction	Removable memory card	Manual review and semi-automated software	Software included
AED Pro BLS§	Accelerometer	Impedance in development	Audio in development	Chest compression rate, CPR fraction; ventilation (in development)¶	Infrared port or removable memory card	Manual review and semi-automated software	In development

*Physio Control, Inc.
^ Philips, Inc and Laerdal, Inc
§ Zoll, Inc.
¶ Ventilation rate may also be estimated from pauses in compression or from overheard sounds (breath sounds or vocalized ventilation efforts) during audio recording.

B. CPR Performance Standards

The following table defines the CPR performance standards for the trial:

Table 2: CPR Performance Standards

Parameter	Target	Minimum Acceptable	Maximum Acceptable	Criterion for Remediation/Retraining
Chest compression	100/minute*	80	130	Above maximum or below minimum parameters in > 20% of resuscitations
CPR fraction$^{\infty}$	0.85	0.6	-	Below minimum parameter in >20% of resuscitations

* refers to speed of compressions rather than actual number of compressions per minute

$^{\infty}$ CPR fraction will be the defined as = (Total seconds with chest compressions)÷(Total seconds with interpretable signal and no evidence of spontaneous circulation).

These performance standards are in addition to those that will be monitored by the SMC for the purpose of assessing whether an agency can transition from the run-in phase of the trial to its evaluable phase, as well as in to assess compliance/adherence with study intervention (Appendices 4 and 5. These performance standards may be modified periodically upon the recommendation of the SMC.

Definitions

Compressions will be defined as an accelerometer deflection, an impedance deflection or an ECG artifact accompanied by audio evidence of a compression, and refers to the speed of compressions per minute rather than the actual number of compressions. During the provision of BLS care (i.e. during synchronous chest compression-ventilation in patients with an unprotected airway), a presumed ventilation pause will be defined as a pause in compressions of 4-10 seconds without any other confirmation of ventilation. Recognition of a presumed ventilation pause will be enhanced when CPR employs a set synchronous compression: ventilation ratio in patients without a protected airway. A confirmed ventilation event will be defined as having ancillary evidence of ventilation with or without a pause (e.g., ETCO2 waveform changes, characteristic chest impedance change, and/or audio confirmation of ventilation). To define CPR fraction, it will also be necessary to count the number of seconds that have an interpretable signal (leads connected and obscuring artifact absent) when there is no evidence of spontaneous circulation. Total seconds with compressions will be defined as the number of seconds during which there are countable compression events. CPR fraction will be defined as = (Total seconds with compressions) ÷ (Total seconds with interpretable signal and no evidence of spontaneous circulation).

Determination of whether a resuscitation effort meets minimally acceptable CPR performance standards for the Consortium will be based on the number of one minute epochs having an acceptable chest compression rate, ventilation rate and CPR fraction (as defined in the table above), compared to the total number of interpretable epochs available from that resuscitation. A one-minute epoch will be defined as not meeting performance standards if any CPR process parameter within it falls outside the specified acceptable range. The first-minute epoch will be defined as not meeting performance standards if the time interval from device on to attachment

of leads to the patient exceeds 1 minute. Resuscitation will be defined as overall not meeting CPR performance standards if the majority of its analyzed one-minute epochs (e.g. 3 or more out of 5) fall outside the specified acceptable range. Retraining or other suitable remediation will be initiated if more than 20% of resuscitations at any ROC site do not meet CPR performance standards.

10. Appendix 2: Interim Monitoring Plan

In concert with the DSMB, prior to initiation of the trial, the final monitoring plan will be developed to serve as the guide to the DSMB's decision-making process concerning early stopping of the trial. In making the decision to recommend termination of the study, the DSMB shall be guided by several types of information: (i) a formal stopping rule based on the primary analysis (comparison of treatment groups on rate of survival to hospital discharge using the intent-to-treat sample), (ii) information on safety outcomes by treatment group, (iii) consistency between results for primary and secondary outcomes, and (iv)consistency of treatment effects across subgroups.

The formal stopping boundaries are symmetric, two-sided designs (107) which are included in the unified family of group sequential stopping rules.(108) The tests for superiority of either intervention will be based on boundaries with a shape parameter of P=0.7(109)(108) with a two-sided significance level of 0.05. It is envisioned that formal interim analyses will be performed at semiannual intervals throughout the duration of the trial as for the recently completed ROC PRIMED trial. The stopping rules described above can be implemented using S+SeqTrial (S+SEQTRIAL User's Manual, Insightful, Inc., Seattle WA, 2000).

The DSMB will use the results of implementing the stopping rule as a guideline in evaluating the evidence for treatment effects. In making a recommendation to terminate the study, the DSMB will also consider information on safety outcomes, as well as consistency of outcomes for secondary outcomes and consistency of outcomes within important subgroups as described previously.

At the conclusion of the clinical trial, reported point estimates, 95% confidence intervals, and P values for the primary outcome will be adjusted for the true sampling distribution accounting for the stopping rule. Point estimates will be based on the bias adjusted point estimate (110) and confidence intervals and P values calculated from the ordering of the outcome space based on the maximum likelihood estimate.(111)

Interim stopping boundaries:

Analysis	Sample Size	Prop. Max Stat Info	Lower stopping boundary (30:2 better)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	4720	0.2	-0.026	-0.024	(-0.037, -0.009)	0.003
2	9440	0.4	-0.016	-0.014	(-0.025, -0.003)	0.011
3	14160	0.6	-0.012	-0.010	(-0.020, -0.001)	0.024
4	18880	0.8	-0.010	-0.008	(-0.017, 0.000)	0.039
5	23600	1.0	-0.008	-0.007	(-0.016, 0.000)	0.05

Analysis	Sample Size	Prop. Max Stat Info	Upper stopping boundary (CCC better)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	4720	0.2	0.026	0.024	(0.009, 0.037)	0.003
2	9440	0.4	0.016	0.014	(0.003, 0.025)	0.011
3	14160	0.6	0.012	0.010	(0.001, 0.020)	0.024
4	18880	0.8	0.010	0.008	(0.000, 0.017)	0.039
5	23600	1.0	0.008	0.007	(0.000, 0.016)	0.05

Average sample size and power for different changes in survival:

Change in survival	Average n	Power (upper)
0.0000	23259	0.0250
0.0065	21307	0.3575
0.0130	15164	0.9000
0.0260	7274	1.0000

Probability of stopping at different analysis times for different changes in survival:

Change in survival	Time 1	Time 2	Time 3	Time 4	Time 5
0.0000	0.0028	0.0082	0.0116	0.0133	0.9641
0.0065	0.0126	0.0537	0.0863	0.1015	0.7459
0.0130	0.0686	0.2573	0.2752	0.1908	0.2081
0.0260	0.5085	0.4441	0.0452	0.0021	0.0001

11. Appendix 3: Exception from Informed Consent for Emergency Research

Department of Health and Human Services (HHS)-Office for Human Research Protections

We have outlined below each criterion stipulated in the regulations for this exception and how our study design applies to these criteria.

(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 randomized trial of use of continuous chest compressions versus standard care in patients with OOHCA. These patients are in an immediate life-threatening situation with a mortality rate before discharge of more than 90%. The standard of care for management of these patients includes the timely provision of chest compressions, airway control, vasopressors, inotropes and antiarrhythmic agents.

As reviewed in this proposal, previous studies of continuous chest compressions have suggested a survival advantage with this intervention but have not been definitive. This attests to the safety of continuous compressions in the cardiac arrest population and to the practicality of applying continuous compressions in the out-of-hospital setting. The major limitations of the previous studies are their lack of focus on the specific intervention and their lack of sufficient size to detect significant clinical differences in outcome. Thus, critical evaluation of this intervention in humans has not been undertaken.

We propose a randomized trial focused on evaluation of this intervention in the cardiac arrest population during resuscitation efforts, with sufficient statistical power to detect changes in outcome. Furthermore, an emphasis on the quality of life 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 during ongoing resuscitation from 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 hospital provider to explain the study and receive consent while caring for the patient. Since we are studying patients with 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 patients with cardiac arrest via short-term survival advantage.

(iii) Continuous chest compressions have been tested in previous clinical studies with no serious adverse effects reported. 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 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 during resuscitation from 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.

Observational studies of continuous chest compression in patients with OOHCA demonstrated a survival benefit for patients treated with continuous chest compressions vs. standard care. Continuous chest compressions applied during resuscitation from cardiac arrest improves coronary blood flow and increases the likelihood of restoration of spontaneous circulation. Animal models of cardiac arrest and human studies show that prolonged ischemia is associated with greater release of inflammatory factors and consequent hemodynamic stability that is often associated with intractable shock, multi-organ injury, dysfunction and death. Based on these data, coupled with the previous clinical trial, the therapeutic window for this agent is the initial resuscitation period, which occurs from arrival of EMS provider on scene up to hospital arrival.

Since this is an immediately life-threatening situation, it will not always 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. Research personnel will attempt to contact the subject's LAR as soon as feasible and a summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period then he/she will be approached by research personnel for notification of enrollment.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Department of Health and Human Services (HHS)-Office for Human Research Protections (OHRP) Sec. 46.116 and 46.117 of 45 CFR Part 46.

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 study site 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) Community consultation as outlined by the local IRB will be undertaken prior to IRB approval. Since the population eligible for enrollment includes all citizens in the study region it will not be possible to target any particular small group. 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. Public notification and community consultation will be performed as directed by the local IRB and may include such methods as using random digit dialing telephone surveys of the proposed study community,(112) targeted small group meetings or consultation with community leaders. ROC has experience with community consultation and notification practices.

(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 investigators. 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)The Data Safety Monitoring Board will function as an independent data monitoring committee who will exercise oversight of the study.

(v) We expect that all patients who meet the enrollment criteria will be unconscious. Any delay in medical care that would be required to attempt to obtain informed consent from the patient's legally authorized representative would be life threatening. Thus it will not be feasible to attempt to obtain informed consent during the initial therapeutic window. Therefore we will conduct this trial under an exception from the requirement to obtain informed consent for emergency research which includes public notification, community consultation, patient notification of enrollment, and provision of an opportunity to opt out from ongoing participation in this trial. In the event that a patient or their LAR opts out from ongoing participation in this trial we will either obtain consent from surviving patients or their LAR to obtain vital status at discharge (i.e., a single data point and no other information past the time of their opting out) from their medical records or we shall seek vital status information from publicly-available sources (i.e. sources available to the general public).

12. Appendix 4: Criteria to Enter Run-In Phase of the CCC Trial

In order to be considered for participation in the CCC protocol, an agency must show proficiency with the majority of the following Epistry benchmarks as determined by the SMC. ROC Agencies have 9 months from the date of the first agency entry into the run-in phase to do so themselves. These performance standards may be modified periodically upon the recommendation of the SMC.

- Outcome Measures
    - Missing Vital Status < 1.0% of cases at the site at 90 days past episode date
- CPR Process
    - ECG Download and CPR Process data (at least one minute of CPR Fraction, Compression Rate, or Compression Depth) available for 75% of treated cases within 60 days of episode date
    - 75% of episodes with compression fraction >0.60 for 3 of first 5 minutes

At least 80% of the following 12 items must be achieved for participation in the CCC trial:

- Less than 2% missing/unknown data for the following data points
    - <5% missing time of Epinephrine administration
    - Bystander CPR
    - Witnessed Status
    - First EMS cardiac arrest rhythm
    - Location of arrest
    - Time from call received at dispatch to first vehicle arrival
    - Pre-hospital disposition including ROSC status at ED arrival
- Timeliness of Data
    - 85% of treated episodes entered within 3 days of episode date
    - 75% of Enrollment and Pre-Hospital forms completed within 20 days of episode date
    - 75% of Time-Record and CPR Process forms completed within 45 days of episode date
    - 75% of episodes must have a 30-day vital status within 60 days of episode date
- Case Enrollment
    - Treated enrollment should not be consistently below the lower bound based on the agency's estimated enrollment rate from the PRIMED trial or from prior Epistry reporting.

These criteria may be modified in the future at the discretion of the SMC.

13. Appendix 5: Criteria to Enter Evaluable Phase of the CCC Trial

The SMC will monitor the data of EMS agencies in the run-in phase of the CCC trial on a monthly basis. These agencies will be progressed to the Evaluable Phase after a period of two to six months if they meet the following benchmarks.

a) ECG Download and CPR Process data (at least one minute of CPR Fraction) available for 75% of cases within 30 days of episode date

b) Continuous Compressions Arm - 75% of episodes with CPR fraction >0.75 for 3 of first 5 minutes

c) 30:2 Arm - 75% of episodes with available CPR Process with CPR fraction >0.55 for 3 of first 5 minutes

d) >75% of pre-shock pause <20 seconds for all shocks given within the first 5 minutes

e) Adherence to Medical Director authorized ventilation strategy

f) <5% of Advanced Airways placed <5 minutes after arrival of first EMS provider for non-EMS witnessed episodes

g) <5% of administration of 1st dose Epinephrine or pressor >10 minutes after arrival of first ALS provider

h) Less than 2% missing/unknown data for the following data points:
    i. First EMS cardiac arrest rhythm
    ii. Time of Epinephrine or pressor administration, if given
    iii. Time of airway placement (other than bag/mask), if placed

i) 85% of episodes entered within 3 days of episode date; 95% within 7 days

These performance standards may be modified periodically upon the recommendation of the SMC.