

**Amiodarone (PM101), Lidocaine or Neither for Out-Of-Hospital Cardiac Arrest Due to Ventricular Fibrillation or Tachycardia**  
**(ALPS: Amiodarone, Lidocaine or Placebo Study)**

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<b>SUMMARY</b> .....	<b>6</b>
<b>1. SPECIFIC AIMS</b> .....	<b>8</b>
<b>1.1 Primary Endpoint</b> .....	<b>8</b>
<b>1.1.1 Primary Aim</b> .....	<b>8</b>
<b>1.1.2 Secondary Aims</b> .....	<b>8</b>
<b>1.2 Secondary Endpoint</b> .....	<b>8</b>
<b>2. BACKGROUND</b> .....	<b>9</b>
<b>2.1 Conceptual Framework</b> .....	<b>9</b>
<b>2.2 Prior and Preliminary Studies</b> .....	<b>11</b>
<b>2.2.1 Possible Mechanisms</b> .....	<b>11</b>
<b>2.2.2 Lidocaine</b> .....	<b>11</b>
<b>2.2.3 Amiodarone</b> .....	<b>12</b>
<b>2.2.4 Captisol-Enabled Amiodarone Hydrochloride (PM101)</b> .....	<b>14</b>
<b>2.2.5 Clinical Equipoise</b> .....	<b>17</b>
<b>2.3 Summary of Rationale</b> .....	<b>18</b>
<b>3. STUDY METHODS</b> .....	<b>20</b>
<b>3.1 Primary Endpoint</b> .....	<b>20</b>
<b>3.1.1 Primary Aim</b> .....	<b>20</b>
<b>3.1.2 Secondary Aims</b> .....	<b>20</b>
<b>3.2 Secondary Endpoint</b> .....	<b>20</b>
<b>3.3 Design</b> .....	<b>21</b>
<b>3.3.1 Inclusion Criteria</b> .....	<b>22</b>
<b>3.3.2 Exclusion Criteria</b> .....	<b>22</b>
<b>3.4 Study Population</b> .....	<b>23</b>
<b>3.4.1 Primary Analysis Population (Efficacy Population)</b> .....	<b>23</b>
<b>3.4.2 Patients with Noncardiac Causes for Cardiac Arrest</b> .....	<b>23</b>
<b>3.4.3 Patients with Initial Asystole or PEA</b> .....	<b>24</b>
<b>3.4.4 Confirmed Non-recipients of Study Drug</b> .....	<b>24</b>
<b>3.4.5 Safety population</b> .....	<b>24</b>
<b>3.5 Setting</b> .....	<b>25</b>
<b>3.6 Random Allocation</b> .....	<b>25</b>
<b>3.7 Intervention</b> .....	<b>25</b>

<b>3.8 Study Drug Kit .....</b>	<b>25</b>
<b>3.8.1 Study Drug.....</b>	<b>26</b>
<b>3.8.2 Rationale for Dosing Regimen .....</b>	<b>26</b>
<b>3.8.3 Weight Adjusted Study Drug Dosing.....</b>	<b>27</b>
<b>3.9 Initial and Concurrent Care .....</b>	<b>28</b>
<b>3.10 Administration of Study Drug (Figure 3) .....</b>	<b>28</b>
<b>3.10.1 Time-to-treatment.....</b>	<b>31</b>
<b>3.10.2 Vascular Access.....</b>	<b>32</b>
<b>3.11 Rationale for Absence of a “Rescue” Arm.....</b>	<b>33</b>
<b>3.12 Hospital After-Care.....</b>	<b>33</b>
<b>3.12.1 Monitoring and Diagnostic Procedures .....</b>	<b>34</b>
<b>3.12.2 Therapeutic Hypothermia .....</b>	<b>34</b>
<b>3.12.3 Ventilatory Support .....</b>	<b>35</b>
<b>3.12.4 Hemodynamic Support .....</b>	<b>35</b>
<b>3.12.5 Glucose Control .....</b>	<b>35</b>
<b>3.12.6 Cardiac Catheterization and/or Coronary Interventions .....</b>	<b>35</b>
<b>3.12.7 Ancillary Antiarrhythmic Therapies.....</b>	<b>36</b>
<b>3.12.8 Seizure Recognition.....</b>	<b>36</b>
<b>3.12.9 Implantable Cardioverter Defibrillator (ICD).....</b>	<b>36</b>
<b>3.12.10 Withdrawal of Care.....</b>	<b>36</b>
<b>3.12.11 Facilitating Improved Hospital Care .....</b>	<b>37</b>
<b>3.13 Antiarrhythmic Drug Administration after Hospitalization .....</b>	<b>37</b>
<b>3.14 Data Recording.....</b>	<b>38</b>
<b>3.15 ECG Rhythm Analysis .....</b>	<b>38</b>
<b>3.16 Training .....</b>	<b>38</b>
<b>3.17 CPR Process Monitoring .....</b>	<b>39</b>
<b>3.18 Study Monitoring Committee .....</b>	<b>39</b>
<b>3.19 Pre-enrollment Phase .....</b>	<b>39</b>
<b>3.20 Outcome.....</b>	<b>39</b>
<b>3.20.1 Primary Comparison .....</b>	<b>39</b>
<b>3.20.2 Secondary Comparisons .....</b>	<b>40</b>
<b>3.20.3 Secondary Endpoint .....</b>	<b>40</b>

<b>3.20.4 Prespecified Subgroups .....</b>	<b>40</b>
<b>3.20.5 Mechanistic Outcomes .....</b>	<b>41</b>
<b>3.21 Adverse Events .....</b>	<b>41</b>
<b>3.21.1 Unexpected Serious Adverse Events (USAE).....</b>	<b>41</b>
<b>3.21.2 Expected Adverse Events: .....</b>	<b>41</b>
<b>3.21.3 Possible Drug-Related Adverse Events .....</b>	<b>42</b>
<b>3.22 Analyses .....</b>	<b>42</b>
<b>3.22.1 Primary Comparison .....</b>	<b>42</b>
<b>3.22.2 Secondary Comparisons .....</b>	<b>42</b>
<b>3.22.3 Secondary Endpoint .....</b>	<b>42</b>
<b>3.22.4 Safety Analyses.....</b>	<b>43</b>
<b>3.22.5 Prespecified Subgroup Analyses .....</b>	<b>43</b>
<b>3.22.6 Mechanistic Outcomes .....</b>	<b>43</b>
<b>3.22.7 Supplementary Analyses.....</b>	<b>43</b>
<b>3.23 Sample Size .....</b>	<b>44</b>
<b>3.24 Interim Analyses.....</b>	<b>44</b>
<b>3.24.1 Study plan based on differing interim outcome scenarios.....</b>	<b>47</b>
<b>3.25 Expected Duration of Enrollment.....</b>	<b>49</b>
<b>3.26 Safety Monitoring .....</b>	<b>50</b>
<b>3.27 Data Management.....</b>	<b>50</b>
<b>3.27.1 Data Entry .....</b>	<b>50</b>
<b>3.27.2 Database Management .....</b>	<b>50</b>
<b>3.28 Human Subjects Research .....</b>	<b>50</b>
<b>3.28.1 Population.....</b>	<b>50</b>
<b>3.28.2 Source of Data Collection.....</b>	<b>51</b>
<b>3.28.3 Potential Risks.....</b>	<b>51</b>
<b>3.28.4 Protection Against Risks .....</b>	<b>51</b>
<b>3.28.5 Recruitment and Consent.....</b>	<b>51</b>
<b>3.29 Budget.....</b>	<b>52</b>
<b>3.30 Anticipated Clinical Impact.....</b>	<b>52</b>
<b>References .....</b>	<b>54</b>
<b>Appendix 1: Exception from Consent for Emergency Research .....</b>	<b>61</b>

**Appendix 2: Overview of ROC Notification and Consent Procedures.....67**  
**Appendix 3: Suggested Templates for Notification Documents .....79**  
**Appendix 4: Communication with FDA Regarding the Interpretation of  
Subject Withdrawal .....87**  
**Appendix 5: CPR Process Monitoring.....88**  
**Appendix 6: Criteria for EMS Agency Data Compliance.....100**  
**Appendix 7: PM101 and Epinephrine Compatibility .....92**  
**Appendix 8: Lidocaine and Epinephrine Compatibility .....97**  
**Appendix 9: Compatibility of PM101 and Lidocaine with Vasopressin .....100**  
**Appendix 10: 2010 American Heart Association Advanced Cardiac Life Support  
Treatment Algorithm .....110**  
**Appendix 11: Suggested Script for Prehospital Provider to Family LAR.....107**  
**Appendix 12: Suggested Written Script Provided to Hospitals at the Time of  
Patient Admission .....108**  
**Appendix 13: Communications with the FDA Regarding Syringe Compatibility  
Issue .....112**

## **SUMMARY**

Amiodarone (PM101), lidocaine or neither for out-of-hospital cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia (VF/VT).

### **Primary Endpoint**

The primary endpoint of the trial is survival to hospital discharge, which will be analyzed in context of the following aims (and corresponding hypotheses):

#### **Primary Aim**

The primary objective of the trial is to determine if survival to hospital discharge is improved with early therapeutic administration of a new Captisol-Enabled formulation of IV amiodarone (PM101) compared to placebo.

The corresponding null hypothesis is that survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with PM101 or placebo.

#### **Secondary Aims**

The secondary objectives of the trial are to determine if survival to hospital discharge is improved with early therapeutic administration of:

- a) Lidocaine compared to placebo
- b) PM101 compared to lidocaine

The corresponding null hypotheses are that survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with lidocaine as compared with placebo; and with PM101 as compared with lidocaine.

#### **Secondary endpoint**

The trial's secondary endpoint is functionally favorable survival to hospital discharge (defined as Modified Rankin Score (MRS)  $\leq 3$ ) and will be compared in recipients of:

- a) PM101 as compared with placebo
- b) Lidocaine as compared with placebo
- c) PM101 as compared with lidocaine

The corresponding null hypothesis for the secondary endpoint is that functionally favorable survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with PM101, placebo or lidocaine.

#### **Inclusion Criteria**

Adult patients with nontraumatic out-of-hospital cardiac arrest and VF/VT, treated by ROC Emergency Medical Services (EMS) with Advanced Life Support (ALS) capability are eligible for randomization.

#### **Exclusion Criteria**

Patients with an written advance directive (DNAR); blunt, penetrating or burn-related injury; exsanguination, protected populations; non-ROC EMS; BLS-only capable EMS; prior receipt of open label IV lidocaine or amiodarone during resuscitation, or persons with known hypersensitivity or allergy to amiodarone or lidocaine are ineligible for randomization.

## **Study Design**

Randomized, double-blind, placebo-controlled.

## **Serious Adverse Events to Be Followed**

Local thrombophlebitis, drug allergy, seizures, bradyarrhythmias requiring temporary pacing.

## **Randomization Scheme**

1:1:1 (placebo:lidocaine:PM101); based on permuted blocks of concealed size within strata defined by participating site and within site by participating agency. Contents of the study drug kit for a given case will reflect the subject's randomization assignment and not require in-field randomization efforts by EMS personnel.

## **Statistical Analysis**

The trial's primary analysis population (efficacy population) will be comprised of eligible randomized recipients of study drug (irrespective of dose) whose presenting arrest rhythm is VF/VT. The trial is designed with a power of 90% and a one-sided alpha of 0.025 to detect a 6.3% absolute difference (27% relative difference, 29.7 vs. 23.4%) in survival to hospital discharge in recipients of PM101 versus placebo (the primary aim), which will require enrollment of approximately 3000 patients in the efficacy population (1000 per study arm) over 3 years. All analyses will also be performed in a corresponding safety population comprised of all patients in whom a study kit is opened, regardless of whether they were eligible for enrollment or received study drug.

## **Human Subjects Protection**

Exception from informed consent for emergency research.

## **1. SPECIFIC AIMS**

Although antiarrhythmics are commonly used in attempted resuscitation of ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) arrest (collectively referred to as VF/VT), the survival effects of these pharmacological treatments are not well-established. Using a randomized double-blinded, 3-arm trial design, we will compare rates of survival to hospital discharge after treatment with a new formulation of amiodarone (PM101), lidocaine or placebo for treatment of out-of-hospital VF or VT cardiac arrest. The trial will integrate advances in our scientific understanding of VF resuscitation and incorporate important improvements in study-drug formulation and delivery, while preserving clinical compatibility with current “protocolized” approaches of out-of-hospital resuscitation. Thus the trial will test a scientific approach in a clinically-relevant manner, so that the results will have direct and widespread generalizability and in turn address a substantial public health challenge.

### **1.1 Primary Endpoint**

In its statistical design, the trial has one primary endpoint, survival to hospital discharge. This outcome will be analyzed in the context of the following aims (and corresponding hypotheses):

#### **1.1.1 Primary Aim**

The primary objective of the trial is to determine if survival to hospital discharge is improved with early therapeutic administration of a new Captisol-Enabled formulation of IV amiodarone (PM101) compared to placebo.

The corresponding null hypothesis is that survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with PM101 or placebo.

#### **1.1.2 Secondary Aims**

The secondary objectives of the trial are to determine if survival to hospital discharge is improved with early therapeutic administration of:

- a) Lidocaine compared to placebo
- b) PM101 compared to lidocaine

The corresponding null hypotheses are that survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with lidocaine as compared with placebo, and with PM101 as compared with lidocaine.

### **1.2 Secondary Endpoint**

The secondary endpoint of the trial is functionally favorable survival to hospital discharge (defined as Modified Rankin Score (MRS)  $\leq 3$ ) which will be compared in recipients of:

- a) PM101 as compared with placebo
- b) Lidocaine as compared with placebo
- c) PM101 as compared with lidocaine

The corresponding null hypothesis for the secondary endpoint is that functionally favorable survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with PM101, placebo, or lidocaine.



## 2. BACKGROUND

### 2.1 Conceptual Framework

Almost a hundred thousand persons suffer out-of-hospital cardiac arrest due to VF or VT each year in the US and Canada. Although VF is the most viable cardiac arrest dysrhythmia, only about 20% of victims of out-of-hospital or in-hospital VF arrest survive to be discharged from the hospital.<sup>1</sup> Thus advances in VF resuscitation provide important opportunities to improve public health.

Successful resuscitation of patients with cardiac arrest due to VF or VT involves a sequence of interventions including external chest compression with ventilation (CPR), defibrillation, and advanced care. Antiarrhythmic medications are frequently used as part of advanced care to treat ventricular arrhythmias that persist or recur after shocks from an external defibrillator. Although much is known about the pharmacological effects of these drugs, there is a considerable gap in knowledge between our understanding of their mechanisms of action and whether their use actually improves survival after cardiac arrest.<sup>2</sup> Establishing the survival effects of antiarrhythmic drugs during VF cardiac arrest is important for a number of reasons. First, survival in VF cardiac arrest remains poor despite early deployment of CPR and defibrillation in many communities, supporting a need to refine or improve current approaches including treatment with antiarrhythmic drugs.<sup>3</sup> Second, surrogate measures of resuscitation outcome such as return of spontaneous circulation or admission alive to hospital may be important starting points for assessing the merits of an antiarrhythmic drug, but have not as yet distinguished treatments that truly save lives from those that may only forestall death or lead to poor neurologic outcome.<sup>4</sup> Third, cardiac arrest is a brief illness whose narrow time-sensitive therapeutic window affords little margin for the inclusion of interventions that are not essential for successful resuscitation. If the administration of antiarrhythmic drugs does not improve survival, the practice misdirects care and potentially deprives victims of alternative life-saving therapies.

Collectively, the relevant questions regarding antiarrhythmic drug treatment are not just which therapy is best but also whether drug treatment itself is beneficial. To adequately address these questions requires not only a comparison of the most promising available drug therapies, but the inclusion of a placebo control. Inclusion of placebo is both scientifically necessary and ethically justifiable. In its absence, proof of one agent's apparent superiority over another might only mean that one drug is less harmful than the other, not necessarily that either is truly beneficial. The fact that no pharmacologic agent has ever been demonstrated to improve survival to hospital discharge after cardiac arrest means that study patients assigned to placebo would not necessarily be deprived of a known lifesaving treatment. To the contrary, the recognized adverse effects of antiarrhythmic drugs (including hypotension, proarrhythmia and bradycardia) may worsen rather than improve outcome from cardiac arrest. Furthermore, if ineffective, the deployment of antiarrhythmic drug treatments in an illness of such short temporal duration and limited treatment opportunity as cardiac arrest potentially deprives patients of timely administration of alternate and perhaps more beneficial therapies.

Preliminary results from a recent randomized prehospital trial which compared resuscitation from cardiac arrest using standard medications with their absence further supports the existence of clinical equipoise in comparing active drug treatments with a placebo arm in cardiac arrest.<sup>5</sup> Indeed, lessons gleaned from randomized placebo-controlled trials within a number of disciplines, including the suppression of premature ventricular ectopy following myocardial infarction,<sup>6</sup> the use of estrogen therapy for primary prevention of cardiovascular disease,<sup>7</sup> vitamin supplements for secondary prevention of cardiovascular disease,<sup>8</sup> and even

surgical procedures such as ligation of internal mammary arteries for refractory angina,<sup>9</sup> have challenged the efficacy of once widely used therapies and taught the valuable lesson (despite biases to the contrary at the time these trials were conducted), that placebo in some cases may actually be the preferred treatment. In addition to these, 3 recent randomized trials of dispatch-assisted resuscitation of adult cardiac arrest in which a core feature of CPR (rescue breathing) was withheld found chest compression only CPR to be just as effective (and in some subgroups perhaps even better) and more easily implemented by laypersons than traditional CPR. What had been regarded by many as a life-saving component of lay-resuscitation was found to be nonessential. This resulted in a major change in Guideline recommendations and arguably a wider dissemination of citizen CPR than would have been possible had the necessity for and tradition of rescue breathing not been challenged by randomized clinical trials.<sup>10 11-13</sup> From an ethical perspective, the October 2000 revision of the Declaration of Helsinki states: “The benefit, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, where no proven prophylactic, diagnostic or therapeutic method exists,”<sup>14</sup> as is the case for antiarrhythmic drugs in cardiac arrest. Thus comparison of active treatments and placebo is not only imperative to address future treatment strategies in cardiac arrest, but scientifically and ethically justified.

To optimally evaluate the survival effects of antiarrhythmic treatments, study design should incorporate developments in the understanding of VF arrest pathophysiology and its relationship to treatment. Increasing evidence indicates that the heart is not static during arrest but rather progresses through dynamic, time-dependent, physiologic phases – starting in the electrical phase, then progressing to the circulatory phase, and finally to the metabolic phase. These phases help identify the relevant pathology and in turn may guide therapies. For example, treatments directed at the electrical abnormalities such as defibrillation are required for successful resuscitation during the electrical phase. During the circulatory phase, essential treatments include hemodynamic support with CPR in combination with treatments for the electrical phase. By the metabolic phase, the patient is more refractory to treatment and consequently more difficult to resuscitate despite therapies aimed at the electrical and circulatory phases. Antiarrhythmic medications are designed to correct underlying electrical abnormalities, and yet trials of antiarrhythmic medication for out-of-hospital cardiac arrest have typically delayed study drug administration (as part of study protocol and/or drug formulation) too late in the course of resuscitation, often when the patient had progressed well into the metabolic phase. Given the phased pathophysiology of VF arrest, a more optimal approach may be to deliver the antiarrhythmic medication earlier in the course of resuscitation, so that the beneficial electrical effects will more closely correspond to the electrical and circulatory phases where treatment may be most effective.

A study to evaluate the survival effects of antiarrhythmic therapies would ideally be able to test the best formulation and dose of clinically-relevant medications in a practical manner so that the results of the trial would have direct implications for community-based care. Optimal formulations would maximize the favorable antiarrhythmic profile while limiting any potential adverse aspects of the drug or its diluent. The integration of the study drug should strive to be seamless with other components of care – specifically CPR and defibrillation. Evidence indicates that interruptions or distractions in CPR can adversely affect survival. Hence, the administration of study treatment should be simple, ideally administered in a bolus form through a variety of access modes. The trial should strive to evaluate study drug for indications that correspond to clinical practice.

## 2.2 Prior and Preliminary Studies

### 2.2.1 Possible Mechanisms

Antiarrhythmic agents such as lidocaine and amiodarone exert their effects by altering excitatory, conduction and/or refractory properties of cardiac tissue via alteration of ion flow across cellular channels. This can result in direct pharmacologic termination of some organized arrhythmias, alteration of the defibrillation threshold in a manner that facilitates termination of the arrhythmia by shock, and/or prevention of the re-emergence (recurrence) of arrhythmias after their successful termination by electrical therapies. That some supraventricular arrhythmias and ventricular tachycardia can be pharmacologically terminated is well recognized. However, no data support the ability of an antiarrhythmic agent to directly (pharmacologically) terminate ventricular fibrillation, the far more common precipitating cause of out-of-hospital cardiac arrest. Furthermore, the effect of antiarrhythmic agents on the ventricular defibrillation threshold is variable. Lidocaine, for example, may increase the defibrillation threshold;<sup>15-19</sup> whereas amiodarone may increase or decrease this threshold.<sup>20, 21</sup> Given the unlikely prospect that an antiarrhythmic agent can pharmacologically terminate VF, it is more plausible that the therapeutic benefit of antiarrhythmic drugs in cardiac arrest stems from their alteration of substrate in a manner that facilitates the maintenance of an organized rhythm, and minimizes arrhythmia recurrences, once an organized rhythm is restored by other means such as shock. This effect is partly supported by data from two recent cardiac arrest trials (ARREST and ALIVE), in which the magnitude of benefit from IV amiodarone was greater in the subgroup of patients in whom VF/VT transiently terminated but continued to recur following shocks.<sup>22, 23</sup>

### 2.2.2 Lidocaine

For more than 3 decades, lidocaine has represented the “standard of care” in the pharmacological treatment of acute ventricular tachyarrhythmias. In the past, lidocaine was also used for prevention of VF in the setting of acute myocardial infarction,<sup>24</sup> a practice now largely abandoned because of an uncertain risk to benefit ratio.<sup>25, 26</sup> Despite lidocaine’s traditional place in treatment guidelines and frequent use in clinical practice, few clinical trials have specifically addressed its efficacy in cardiac arrest. In a retrospective study of 116 patients with shock-refractory VF, lidocaine was associated with a numerically but not statistically significant increase in the likelihood of admission alive to hospital (13/62 (21%) versus 9/54 (17%)), or survival to hospital discharge (7/62 (11%) versus 1/54 (2%)) compared to patients who did not receive such treatment.<sup>27</sup> In another retrospective report of 1360 patients with out-of-hospital VF, prehospital treatment with lidocaine that depended on the availability of nursing personnel for its administration was associated with a greater return of spontaneous circulation (45% vs. 24%,  $p < 0.001$ ), admission alive to hospital (38% vs. 18%,  $p < 0.05$ ), but not a statistically significant difference in survival to hospital discharge (7.6% in both groups). However, this study was confounded by the potential influence of added nursing personnel on-scene assisting in the resuscitation when lidocaine was administered.<sup>28</sup> A prospective randomized trial comparing lidocaine against epinephrine in out-of-hospital shock-resistant VF found a significantly higher incidence of asystole following defibrillation among lidocaine recipients. In addition, hospital admission and survival rates tended to be worse in the lidocaine than epinephrine group (42% versus 51% and 15% versus 18%) respectively, although these differences were not statistically significant. Notably, the use of either drug during resuscitation was associated with a lower survival to hospital discharge when compared to a matched historical cohort that did not receive lidocaine or epinephrine (15% vs. 30% respectively),  $p < 0.03$ .<sup>29</sup>

Two randomized trials that prospectively compared lidocaine to bretylium found no significant differences between the two drugs in the proportion of patients admitted to or discharged alive

from the hospital, but (in the absence of a placebo control) could not address what absolute effect, if any, either drug had on outcome.<sup>30, 31</sup> Studies of in-hospital cardiac arrest have also found no clear evidence of either intermediate or survival benefit associated with lidocaine therapy.<sup>32, 33</sup> In summary, while in vitro and animal studies suggest lidocaine may be effective for the treatment of VF cardiac arrest, there are no clinical data to indicate that it improves survival. And yet lidocaine is the traditional cornerstone of antiarrhythmic therapies for VF arrest.

### 2.2.3 Amiodarone

Amiodarone is a complex drug with blocking effects on sodium, potassium, and calcium channels, as well as alpha- and non-competitive beta-adrenergic and thyroid blocking properties.<sup>34, 35</sup> Its potential mechanism of benefit in cardiac arrest may be attributable to 3 or more mechanisms. First, when administered during ongoing VF/VT, amiodarone may facilitate electrical defibrillation as a result of its class III antiarrhythmic properties. Second, once rhythm and circulation are restored, amiodarone may prevent recurrence of VF/VT as a result of its beta blocking and class III antiarrhythmic properties. Third, amiodarone may have a non-specific salutary effect on cardiac function in the aftermath of cardiac arrest resulting from protective effects from calcium channel blockade, beta adrenergic blockade, or positive inotropic effects resulting from prolongation of the action potential (class III antiarrhythmic effect).

Three randomized clinical trials have evaluated IV amiodarone in out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation. Two of the trials showed significant improvement in the proportion of patients admitted alive to hospital when treated with amiodarone as compared with lidocaine; and one trial demonstrated such benefit when amiodarone was compared against placebo.<sup>22</sup> The smallest of these three prospective trials was an open label, single center study of 20 patients with out of hospital VF/VT cardiac arrest. Recipients of IV amiodarone required fewer shocks to restore and maintain a perfusing rhythm than lidocaine (mean 4.6 vs. 6.7 shocks,  $p < 0.05$ ) and were more likely to be admitted alive to hospital (80% vs. 20%,  $p = 0.05$ ).<sup>36</sup> ALIVE, a single-center double-blind prospective randomized comparison of amiodarone and lidocaine in 347 patients with out-of-hospital cardiac arrest, found amiodarone recipients were significantly more likely to be admitted alive to hospital (23% vs. 12%,  $p = 0.009$ ).<sup>23</sup> ARREST, a single center double-blind prospective randomized placebo-controlled evaluation of amiodarone in 504 patients with out-of-hospital VF/VT cardiac arrest, observed a significant improvement in admission alive to hospital in amiodarone recipients (44% vs. 34%,  $p = 0.03$ ).<sup>22</sup> None of the trials were designed nor statistically powered to evaluate survival.

ALIVE and ARREST each demonstrated a small but not statistically significant improvement in survival to hospital discharge with amiodarone. There were some consistencies across the trials with regard to design, intervention, and results. None was powered sufficiently to evaluate amiodarone's long-term survival effects so that it is unclear whether amiodarone's short-term resuscitation advantage will translate to long-term survival benefits with a sufficiently-powered trial. The trials were also conducted in an era when there was a lesser emphasis on high quality CPR, and frequently long pauses transpired without CPR for rhythm analysis and "stacked" shock delivery, pulse checks and other interventions. Thus, the state of circulation at the time of drug administration may have compromised its effects, or the severity of organ damage sustained because of the poor circulatory state may have not permitted the benefits of an antiarrhythmic drug upon survival to be manifested. Furthermore, in the 2 trials where time to treatment was reported, amiodarone was given late in the course of resuscitation, an average of 21 and 25 minutes after EMS dispatch, respectively. Importantly, IV access was available in these studies on average  $13 \pm 4$  minutes after EMS dispatch, but the study drug was not administered for approximately 10 additional minutes. This delay was in part attributable to the

study design of these trials, which assessed study drug (amiodarone) only after failing repeated defibrillation and receipt of epinephrine. In addition, the drug required aspiration from glass ampules and dilution prior to administration, a process lengthened further by the tendency of the drug, as then formulated, to foam upon aspiration (see below). Hence, with a different trial design that encourages earlier drug administration, a different drug formulation (see below) that is packaged in a manner that facilitates rapid administration, earlier drug delivery is logistically feasible.

Unpublished results from the subset of patients in the ARREST trial (comparing amiodarone and placebo) in whom time-to-drug treatment was available, suggest that survival to hospital discharge tended to be better after amiodarone when administered earlier (23% vs. 16%, (p=0.20) as compared with 8% vs. 4% when amiodarone or placebo respectively were administered relatively late),(Table 1), although the overall difference in survival between amiodarone and placebo in this subset was not statistically significant (17% vs. 12%, respectively).

Notably in ARREST, only patients whose initial cardiac arrest rhythm was VF or VT survived to hospital discharge, suggesting that patients presenting with asystole or pulseless electrical activity (PEA) are unlikely to benefit from this intervention, even if later developing VF or VT. In ASPIRE, a trial that evaluated mechanical CPR, similarly poor survival was observed among patients who developed VF later in the course of resuscitation.<sup>37, 38</sup> Arguably, patients in whom cardiac arrest is initially associated with asystole or PEA typically have a protracted period of pulselessness prior to receipt of antiarrhythmic therapy for late-occurring VF/VT, at which time no therapy is likely to be beneficial. Conversely, an emphasis on earlier drug therapy in patients with a more treatment-responsive rhythm (VF/VT), coupled with a strong emphasis on high quality minimally interrupted CPR during resuscitation, the potential for a drug effect that extends to influence survival is now more conceivable.

**Table 1:** Unpublished Post Hoc Observational Analyses from the ARREST Trial

<i>Median time to drug administration</i>	<i>≤19 minutes</i>		<i>&gt; 19 minutes</i>	
	<i>Amiodarone</i> <i>n=79</i>	<i>Placebo</i> <i>n=73</i>	<i>Amiodarone</i> <i>n= 76</i>	<i>Placebo</i> <i>n=73</i>
<i>Admitted alive to hospital</i> <i>n, (%)</i>	46 (58%)	28 (38%)	27 (36%)	19 (26%)
<i>Survival to hospital discharge</i> <i>n, (%)</i>	18 (23%)	12 (16%)	6 (8%)	3 (4%)

The formulation of amiodarone used in past trials may have offset some of the drug's benefits. Because amiodarone is insoluble in water, a detergent (polysorbate 80) is used as a diluent in both the branded formulation of amiodarone, Cordarone®, and in its generic equivalents. This diluent makes the drug difficult to administer. With this formulation, amiodarone must be aspirated from glass ampules and then filtered and diluted before use, a process that is time-consuming. Administration of the drug may be further hindered by its tendency to foam when agitated or aspirated too rapidly, a characteristic that can compromise proper dosing. The current formulation of amiodarone also poses problems with respect to its adsorption to plastics and rubber, limiting its ability to be “packaged” in a manner that would facilitate its rapid use

under emergency conditions (such as a prefilled syringe). It is also incompatible with electrolyte solutions other than dextrose in water (D5W). These formulation issues further delay and complicate drug administration. Furthermore, the diluent polysorbate has adverse hemodynamic effects, particularly hypotension. This adverse result could have impeded an adequate return of organ perfusion after termination of VF and potentially compromised survival. Evidence suggests that this hypotensive effect was largely due to polysorbate 80 rather than to amiodarone itself.<sup>39, 40</sup> When solubilized in another diluent, amiodarone appears to have much more modest effects on blood pressure and left ventricular function.<sup>40</sup>

## **2.2.4 Captisol-Enabled Amiodarone Hydrochloride (PM101)**

Recently, amiodarone has been successfully solubilized in a medium different from the previously approved formulation (polysorbate 80). This newly FDA-approved Captisol-enabled formulation of amiodarone (PM101, branded as Nexterone®) (Prism Pharmaceuticals Inc, King of Prussia, PA) is a sterile, clear dispersion that allows for blinding against lidocaine and placebo, and has been shown to be bioequivalent to the approved formulation of amiodarone. The diluent (Captisol, a sulfobutyl ether  $\beta$ -cyclodextrin) is an FDA-approved excipient, has been demonstrated itself to be hemodynamically and electrophysiologically inert, well tolerated with no known organ toxicity in humans,<sup>41</sup> and is currently used for intravenous administration of other FDA-approved drugs (voriconazole (Vfend®), ziprasidone (Geodon®), and aripiprazole (Abilify®)). Captisol is a donut-shaped molecule that complexes water insoluble active drugs like amiodarone in its central cavity. When given by injection, a Captisol-enabled formulation helps carry a drug into the patient's bloodstream, where Captisol and the drug disassociate, allowing the active ingredient to become biologically available and able to produce its desired pharmacological effect. This formulation of amiodarone seems likely to avoid many of the problems associated with the current formulation. It is compatible with ionic solutions besides D5W, does not adsorb to plastics, and can be packaged in pre-filled syringes that may be administered as an intravenous push immediately after establishing IV access. This formulation offers the practical and important advantage of easy administration, making it an ideal preparation for emergency use in the prehospital setting. The formulation has been shown to be stable over 12 months at temperatures ranging from 5-40° C, and has a shelf life of 60 months at room temperature. This formulation of amiodarone administered as a rapid IV bolus (150 mg) and as an infusion at a variety of doses has undergone extensive testing in animals and in more than 500 normal human volunteers. It has been observed to be bioequivalent to the previously approved formulation of amiodarone,<sup>42</sup> with identical electrophysiologic effects after bolus dosing<sup>43</sup> and, most importantly, without accompanying hypotensive effects particularly after a 150 mg bolus intravenous administration.<sup>44</sup>

In cardiac arrest, the previously approved formulation of amiodarone (Cordarone®) is recommended by the American Heart Association for administration as a bolus dose of 300 mg, and was administered at this dose in the ARREST trial (in which it was compared against placebo) and up to 450 mg (300 mg followed by an additional 150 mg bolus, if required) in ALIVE (where it was compared against lidocaine). In ARREST, recipients of amiodarone at this dose who had a return of spontaneous circulation were more likely to require prehospital treatment for hypotension or bradycardia, and had a lower mean heart rate (90±26 versus 101±25 beats/minute) and systolic blood pressure (104±41 versus 117±36 mm Hg) upon hospital arrival. In ALIVE, there were no statistically significant differences in the requirement for treatment of bradycardia or hypotension between recipients of up to 450 mg (7.5 mg/kg) of amiodarone as compared with up to 3 mg/kg of lidocaine. Given the similarity in electrophysiologic effects of Cordarone® and PM101 at 150 mg, it is expected that the effects of both drugs at 300 mg or higher doses would be electrophysiologically comparable.

Thrombophlebitis is a known adverse effect of intravenous amiodarone. The incidence of peripheral phlebitis observed with the new formulation of amiodarone is comparable to the approved formulation of amiodarone, and is likely due to irritant effects of amiodarone itself upon the vessel wall, upon its dissociation from its excipient when diluted by blood. Notably, the incidence of infusion site reactions (including thrombophlebitis) appears to be time-dependent, associated with the continuous infusion of amiodarone over 24 hours, and has a lower incidence after shorter term administration, particularly as a short-term bolus injection (see Table 2<sup>45</sup>) which compares the Captisol-enabled amiodarone (PM101), with the previously FDA-approved formulation of amiodarone (Cordarone®). For example, when 150 mg was given as a single dilute infusion over 10 minutes (Study 101 in Table 2), the incidence of infusion site reactions at 24 hours with both amiodarone formulations was similarly low (< 5%). When given as a 150 mg undiluted bolus followed by a 24 hour infusion (Study 102 in Table 2), the incidence of infusion site reactions with the previously approved formulation of amiodarone (Cordarone®) was 49.1%, as compared with 29.5% with the newly approved formulation (PM101). At 5 minutes as well as 1 hour after bolus administration of undiluted drug followed by a continuous infusion for 24 hours, the incidence of peripheral infusion site reactions ranged from 2.7-6.4% in the Captisol-enabled amiodarone group.

**Table 2:** Incidence of peripheral vein Injection site reactions comparing placebo with two formulations of amiodarone (Captisol-enabled amiodarone (PM101) and Cordarone®)

Variable <sup>a</sup>	Number (%) of Subjects			
	Placebo	PM101 <sup>b</sup>	CORDARONE® IV 10-min <sup>d</sup>	Cordarone® IV 15-sec <sup>e</sup>
Study 101, number of subjects <sup>c</sup>	---	82	87	---
Injection Site Reaction	---			---
1 hour	---	2 (2.4)	1 (1.2)	---
24 hours	---	3 (3.7)	3 (3.4)	---
Study 102, number of subjects <sup>c</sup>	112	112	57	57
Injection Site Reaction				
5 minutes	0	3 (2.7)	0	0
1 hour	0	7 (6.4)	1 (1.8)	0
24 hours	5 (4.5)	33 (29.5)	22 (38.6)	28 (49.1)

Data source: Study 101 CSR supportive table 14.3.1.9 and Study 102 CSR supportive table 14.3.6. Branded names are provided in this table to minimize confusion over the formulations of amiodarone being compared.

- a) Injection site reaction was used to record those reactions identified by clinic staff following both a visual examination of the infusion site and questioning of the subject at the times indicated after the start of the infusion. These included injection site pain, erythema, swelling, rash, coldness, warmth, pruritis, hemorrhage, phlebitis or other reaction.
- b) PM101 was given as a 10-minute 150 mg amiodarone infusion/100 cc D5W in Study 101 and initially as a 3 cc (50 mg/cc) bolus push (150 mg) in Study 102.
- c) Study drug was administered for 10 minutes in Study 101 and for 24 hours in Study 102.
- d) 150 mg/100 ml amiodarone
- e) 150 mg/3ml amiodarone

Notably, when given as an undiluted bolus 150 mg followed by a continuous infusion over 24 hours, the incidence of infusion site reactions sufficient to require withdrawal from the study was relatively low, and lower in Captisol-enabled amiodarone than conventional amiodarone formulation groups. (Table 3)<sup>45</sup> In all cases where phlebitis or infusion site pain led to study withdrawal, the intensity of the problem was judged to be mild-moderate, with full recovery among treated patients. Taken together, these data suggest that Captisol-enabled amiodarone has a similar thrombophlebitis profile as the previously approved formulation of amiodarone and indicates a low risk associated with transient infusion that would be used in the proposed trial.



**Table 3: Adverse events leading to withdrawal of subjects from study**

Study 102 Variable	Placebo (N=112) n (%)	PM101 (N=112) n (%)	CORDARONE®IV 10-minute (N=57) n (%)	CORDARONE®I V 15-second (N=57) n (%)
Subjects with at least 1 infusion site AE leading to withdrawal	0	4 (3.6)	1 (1.8)	6 (10.5)
Infusion site phlebitis <sup>a</sup>	0	2 (1.8)	1 (1.8)	5 (8.8)
Infusion site pain	0	1 (0.9)	0	1 (1.8)
Dyspnea	0	1 (0.9)	0	0

Data source: Study 102 CSR supportive table 14.3.2.2 and table 14.3.2.5 and appendix 16.2, Listing 16.2.7.1. Branded names are provided in this table to minimize confusion over the formulations of amiodarone being compared.

<sup>a</sup> Infusion site phlebitis was defined as the presence of two or more of the following signs: palpable cord, induration, pain, warmth, or redness and/or signs along the course of the infusion vein for a significant amount of time (>24 hours).

Amiodarone, as an iodinated moiety, also has the potential for, but has only rarely been reported as a cause of anaphylaxis.<sup>46</sup> To our knowledge, there have been no reports of anaphylaxis in association with Captisol, and none identified in the animal and human studies conducted to date with PM101.

In December 2008, the US Food and Drug Administration (FDA) approved the Captisol-enabled formulation of amiodarone (PM101, branded Nexterone®), with the same label indications as the previously approved formulation of amiodarone (Cordarone®). Nonetheless, because of the planned off-label use of the drug as a bolus dose for cardiac arrest in a prehospital federally-funded trial using exception from informed consent for emergency research, the drug will require Investigational New Drug (IND) exemption in accordance with federal regulations. The manufacturer supports the proposed study, including provision of study drug (matching syringes of PM101 lidocaine, and placebo) to the Consortium without cost.

### 2.2.5 Clinical Equipoise

The preponderance of evidence supports the existence of clinical equipoise between amiodarone, lidocaine, and placebo for treatment of cardiac arrest. This may be attributable to the fact that these antiarrhythmic drugs are truly not life-saving. Alternatively, the absence of any clinical trials that were adequately designed or powered to demonstrate improved survival to hospital discharge may contribute, in part, to the current state of clinical equipoise with respect to this endpoint. While it is acknowledged that some of the previously cited studies evaluating antiarrhythmic drug therapies in cardiac arrest have observed improvement in short-term surrogate outcomes, such as return of spontaneous circulation and admission alive to hospital, none demonstrated improved survival to hospital discharge. The large majority of patients who were resuscitated and admitted to hospital in these studies were comatose; the persistent comatose status was particularly the case for those who subsequently died in the hospital. In fact, in the drug trials in which a higher hospital admission rate was observed, subsequent hospital mortality in admitted patients was higher in treatment groups than in

controls, such that overall survival among all patients enrolled in both groups did not differ. This is best illustrated by the ARREST trial in which 108 of 246 (44%) patients treated with amiodarone were admitted alive to hospital as compared with 89 of 258 (34%) treated with placebo. However, overall 33 of 246 patients (13.4%) in the amiodarone group as compared with 34 of 258 (13.2%) survived to hospital discharge. That is, among drug treatment as compared with placebo recipients who were admitted alive to hospital, more drug-treated patients subsequently died in-hospital than recipients of placebo, such that in the end, overall survival was comparable in the two treatment groups. Thus it is unlikely that the surrogate endpoint of admission alive to hospital would have ethical significance in this population. Rather, this finding raises valid concerns about the value of interventions which may improve short-term (surrogate) outcomes, but because they do not ultimately effect a change in hospital survival, arguably only foster an added healthcare burden and cost. Indeed, a widely voiced criticism of the ARREST and ALIVE trials was that these trials only proved that drug therapy could change the location of death from field to hospital, its ultimate cost, but not its inevitability. Furthermore, were an improvement in admission rates alive to hospital to be taken as a reason for suppression or elimination of equipoise, one could conclude that any study resulting in improvement in the surrogate endpoint of admission alive (as opposed to neurologically intact discharge from hospital) should result in a change in practice and no further studies in out of hospital cardiac arrest for any treatment showing such intermediate benefit would be required or permitted.

Given this uncertainty as to whether antiarrhythmic drugs improve outcome after cardiac arrest, current AHA Resuscitation Guidelines classify lidocaine as “class indeterminate” (indicating there is insufficient information to recommend for or against) and amiodarone as class IIb (indicating benefit may or may not exceed its risk), consistent with a state of equipoise. Notably, a recent randomized clinical trial found no significant differences in survival when pharmacologic treatments (including antiarrhythmic drugs) were provided or withheld entirely during the resuscitation phase of out-of-hospital cardiac arrest. Such a finding lends further support to the presence of clinical equipoise with respect to the question under study.<sup>5</sup> Indeed, the recognized shortcomings of surrogate outcomes such as return of spontaneous circulation and admission alive to hospital in predicting ultimate survival from cardiac arrest is what spurred the creation and specific charge to the Resuscitation Outcomes Consortium: to identify treatment strategies that will improve survival. For these reasons, and given the absence of definitive evidence that antiarrhythmic medications improve survival outcome in cardiac arrest, we believe that clinical equipoise indeed exists for each of the hypotheses proposed in this trial.

### **2.3 Summary of Rationale**

Antiarrhythmic drugs are frequently used in the management of out-of-hospital VF or pulseless VT arrest. However, none has been appropriately assessed for its impact on survival to hospital discharge. Prior studies suggest that these medications may help organize the electrical rhythm and restore circulation, but a true long-term survival benefit from their use remains in question. A well-designed trial to assess the potential survival benefits of an antiarrhythmic drug should evaluate the most promising of all available agents, include standard care practice to assure clinical relevance, provide for a placebo control to assure scientific merit, as well as incorporate scientific and technical advances in an effort to optimize potential benefits of study therapy. The trial should be adequately powered for testing its primary hypothesis, recognizing that the statistical corrections required for testing additional hypotheses (i.e. for multiple primary hypotheses) can compromise the ability to establish statistical significance for any of them.

In its statistical design, this trial will have one primary endpoint, survival to hospital discharge. This outcome will be analyzed in the context of a primary aim (comparing amiodarone with placebo), and two secondary aims (comparing lidocaine with placebo, and amiodarone with lidocaine). As a secondary endpoint, the trial will compare functionally favorable survival (Modified Rankin Score  $\leq 3$  at hospital discharge) between the 3 treatment arms.

Amiodarone is regarded as potentially the most promising of antiarrhythmic agents for improving survival after cardiac arrest. Amiodarone produces significantly better intermediate outcomes than lidocaine or placebo, and as such affords the greatest hope of benefit. However, it has not been proven to improve survival, begging the critical question of its impact on this outcome.<sup>22, 23</sup> In previous trials, amiodarone's effectiveness may have been hampered by its relatively late administration, limited dosing, and potentially by adverse effects related to its formulation. Accordingly this trial will be designed to potentially enhance the likelihood of effective antiarrhythmic drug treatment by its early initiation (during the predominant electrical phase of the arrest if possible), repeat dosing if required, and use a more optimal formulation (in the case of amiodarone, PM101) that facilitates such administration with less concern over adverse hemodynamic effects.

The primary aim of this trial is to compare the effectiveness of amiodarone against placebo for improving survival after out-of-hospital cardiac arrest. Without such comparison against placebo, it would be impossible to determine amiodarone's absolute effect on survival; that is whether such therapy as compared with its absence has no effect on survival or may even adversely affect it. If not beneficial, antiarrhythmic drugs like amiodarone are used at a substantial cost of lost clinical opportunity to provide alternative interventions in the time-critical scenario of cardiac arrest. Thus even a drug with a "neutral" effect on outcome could be considered indirectly detrimental if it prevents or delays receipt of another more beneficial intervention. The use of placebo is not without precedent, or merit in establishing (or refuting) the potential benefit of active drug therapies. For example, a recent randomized clinical trial found no significant differences in survival when pharmacologic treatments were provided or withheld entirely during the resuscitation phase of out-of-hospital cardiac arrest. This finding supports the importance of comparing active treatments against their absence (or placebo) as well as the presence of clinical equipoise when drugs are evaluated alongside of placebo.<sup>5</sup>

As secondary aims, this trial will also evaluate whether lidocaine improves survival after cardiac arrest compared to placebo, and compared to amiodarone. Lidocaine remains the traditional standard and still contemporary antiarrhythmic choice although, based on existing data, not as promising as amiodarone. Nonetheless, the EMS systems with the highest cardiac arrest survival rates in ROC continue to use lidocaine or both lidocaine and amiodarone rather than only amiodarone-based drug treatment protocols. Thus the hypothesis that lidocaine may be a potentially effective antiarrhythmic agent in cardiac arrest is worthy of consideration. Establishing lidocaine's effectiveness both in an absolute (compared to placebo) as well as relative sense (compared to amiodarone) is also important from a cost containment perspective, given that it is a relatively inexpensive drug.

In summary, the design of the proposed trial permits a more comprehensive evaluation of these clinically relevant alternatives regarding the choice of antiarrhythmic agents in cardiac arrest. Given its promising attributes as an antiarrhythmic agent, this trial evaluates the potential benefit of amiodarone over placebo as its primary aim. Acknowledging lidocaine's traditional place in resuscitation, the trial also evaluates the benefit of lidocaine over placebo as a secondary aim; and given the possibility of a differential benefit between the two antiarrhythmic agents, the trial additionally compares the effectiveness of amiodarone against lidocaine as another secondary aim. It thereby comprehensively addresses both the absolute and relative worth (if any) of the

most promising and most commonly used antiarrhythmic agents in cardiac arrest. Finally, recognizing the importance of functional outcome in survivors of cardiac arrest, as a secondary endpoint the trial will compare functionally favorable survival between the 3 treatment arms.

In the following discussion, reference to PM101 applies to Captisol-enabled amiodarone (PM101 or Nexterone®), and refers to the specific formulation of amiodarone used in this trial.

### **3. STUDY METHODS**

#### **3.1 Primary Endpoint**

The primary endpoint of the trial is survival to hospital discharge. This outcome will be analyzed in the context of the following aims (and corresponding hypotheses):

##### **3.1.1 Primary Aim**

The primary aim of the study is to determine whether PM101 as compared with placebo will improve survival to hospital discharge in patients with out-of-hospital cardiac arrest due to VF or pulseless VT.

The corresponding null hypothesis is that survival to hospital discharge is identically distributed when out-of-hospital VF or pulseless VT arrest is treated with PM101 compared to placebo administered under comparable circumstances.

##### **3.1.2 Secondary Aims**

The secondary aims of the trial are to determine if survival to hospital discharge is improved with early therapeutic administration of:

- a) Lidocaine compared to placebo
- b) PM101 compared to lidocaine

The corresponding null hypotheses are that survival to hospital discharge is identically distributed when out-of-hospital VF or pulseless VT arrest is treated with lidocaine compared to placebo administered under comparable circumstances; and with PM101 as compared with lidocaine administered under comparable circumstances.

Prioritizing aims and their corresponding hypotheses in this manner (as primary and secondary) acknowledges where differences in outcome are most likely to be identified based on existing data. We acknowledge that these aims entertain potentially mutually exclusive study outcomes. Nonetheless each represents a clinically plausible scenario based on existing literature and a presumed differential effect between treatments that is worthy of investigation. As to be discussed subsequently in the statistical section, we have hypothesized an absolute 6.3% absolute difference (27% relative difference) in survival for the primary outcome. While the previously reviewed studies provide some guidance for this estimate, the range in the reported literature is wide, such that our hypothesized difference is also partly based on what might be regarded as a potentially clinically significant and achievable improvement in outcome within the constraints of the time, subjects and resources available to a clinical trial.

#### **3.2 Secondary Endpoint**

The secondary endpoint of the trial is functionally favorable survival to hospital discharge (defined as Modified Rankin Score (MRS)  $\leq 3$ ) which will be compared in recipients of:

- a) PM101 as compared with placebo
- b) Lidocaine as compared with placebo

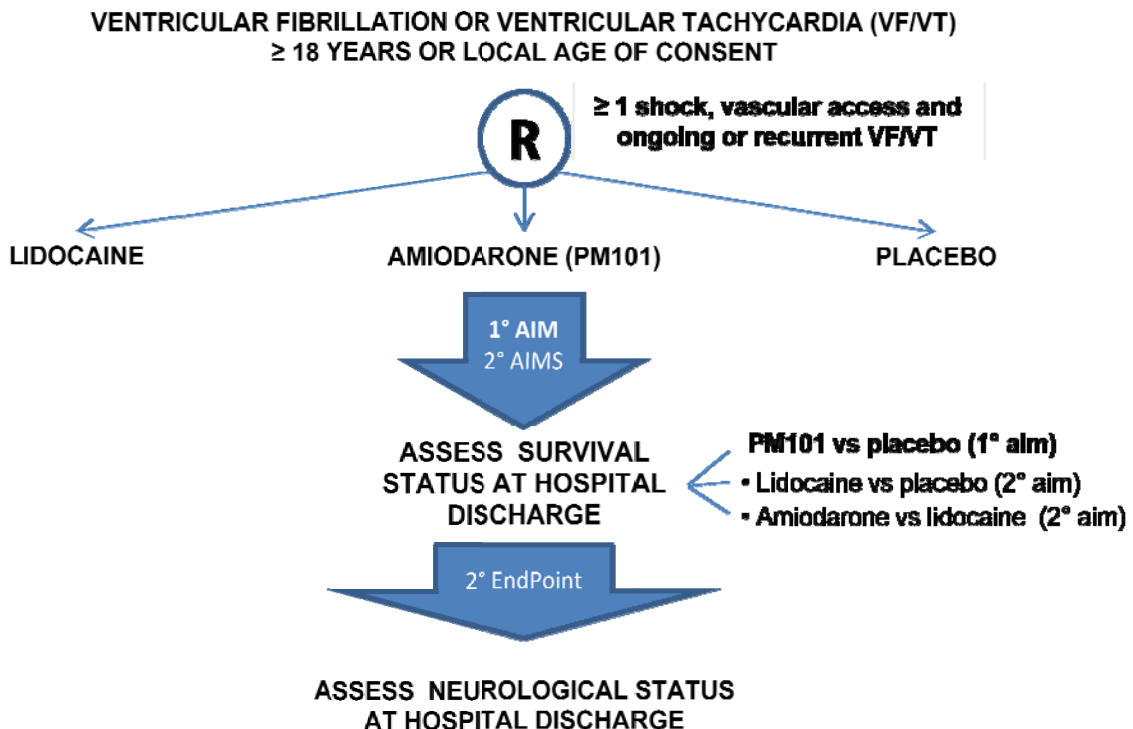
c) PM101 as compared with lidocaine

The corresponding null hypothesis for the secondary endpoint of the study is that functionally favorable survival to hospital discharge is identically distributed when out-of-hospital VF/VT arrest is treated with PM101, placebo or lidocaine.

### 3.3 Design

This individually randomized trial will compare IV PM101, lidocaine and placebo in nontraumatic out-of-hospital cardiac arrest due to VF or pulseless VT (or deemed shockable by an automated external defibrillator (AED)) (Figure 1). The study provides for therapeutic antiarrhythmic drug intervention, repeated, if necessary, to maximum recommended doses. Subjects who develop VF or VT as a secondary rather than primary arrhythmia during the course of resuscitation, will be treated in identical fashion as those with VF or VT as their primary presenting arrhythmia. However, patients who develop VF or VT secondarily (in whom, as previously discussed, survival regardless of treatment is anticipated to be poor) will be included in the trial's safety population, but excluded from the efficacy population which as defined below is comprised of eligible recipients of study drug whose presenting arrest rhythm is VF or pulseless VT. This distinction between a safety and efficacy population is made in recognition of the importance of including all patients randomized to drug treatment in analyses for the purpose of evaluating the safety of drug therapy (i.e. the trial's safety population), as compared with those in whom there is expectation of benefit from antiarrhythmic drug therapy and in whom such therapy would likely be beneficial when given under comparable clinical circumstances (i.e. the trial's efficacy population). A major challenge in prehospital research under emergency conditions is the optimal approach to the analysis of outcome among patients in whom there may be little hope of benefit from antiarrhythmic therapy but in whom the logistics of prehospital trial conduct precludes their exclusion from randomization.

**Figure 1:** Overall study design



### **3.3.1 Inclusion Criteria**

Patients eligible for randomization will be comprised of those with:

- a) Age at least 18 years or local age of consent
- b) Non-traumatic out-of-hospital cardiac arrest treated by ROC EMS with advanced life support capability
- c) VF or pulseless VT presenting as the initial arrest arrhythmia or results from conversion of another arrhythmia (such as transient asystole or pulseless electrical activity)
- d) Incessant or recurrent VF/VT after receipt of  $\geq 1$  shocks
- e) Established vascular access

### **3.3.2 Exclusion Criteria**

Patients ineligible for randomization will be comprised of those with:

- a) Asystole or PEA as the initial arrest rhythm who never transition to VF or pulseless VT
- b) Written advance directive to not attempt resuscitation (DNAR)
- c) Blunt, penetrating, or burn-related injury
- d) Exsanguination
- e) Protected populations (prisoners, pregnancy, children under local age of consent)
- f) Treated exclusively by non-ROC EMS agency/provider, or by basic life support-only capable ROC EMS providers
- g) Prior receipt of open label lidocaine or amiodarone during resuscitation
- h) Known hypersensitivity or allergy to amiodarone or lidocaine

### **3.3.3 Broken study drug syringes exclusion**

The design of this trial presumes the possibility that a patient may need all doses of study (ALPS) drug for optimal effectiveness. Accordingly, if one or more unused syringes is found to be broken (unusable) upon initial opening of the ALPS kit and before any ALPS drug has been administered, the patient will be excluded from ALPS, and treated with open label antiarrhythmic agents at customary doses, as required, during resuscitation. No ALPS drug should be given to such patients. For purposes of analysis, such patients will be included in the safety population, but excluded from the primary efficacy population.

Should one or more unused study (ALPS) drug syringes become broken (or rendered unusable) after some ALPS drug has already administered, such that the patient is unable to receive 3 full doses of study drug if required, the patient will be excluded from further treatment with ALPS drug. In such instances, the patient may be treated with open label antiarrhythmic agents such as lidocaine or amiodarone. However, if required, open label lidocaine should be limited to a total dose of no more than 200 mg for safety purposes (bearing in mind the possibility that the patient may have already received up to 120 mg of lidocaine as study drug). Amiodarone has a wider allowable dosing range than lidocaine. Therefore if open label amiodarone is required, it may be administered at customary doses under such circumstances (bearing in mind the possibility that the patient may have already received up to 300 mg of amiodarone as study drug). For purposes of analysis, such patients who received any part of a

dose of ALPS drug will be included in both the safety population and primary efficacy population.

EMS providers should promptly alert the study coordinator should either of these described scenarios occur.

### **3.4 Study Population**

Out-of-hospital cardiac arrest is a condition of high lethality that must be managed rapidly under relatively uncontrolled circumstances. Accordingly, treatment of such patients requires that any screening procedures and interventions be minimally complicated, and designed in a manner that facilitates their implementation in a time-sensitive manner by providers who, though highly skilled, are not expected to function as physicians. A unique challenge in performing prehospital research under emergency conditions within this environment is the optimal approach to the analysis of outcome among patients in whom existing data suggest there is little hope of a treatment benefit (in this instance from an antiarrhythmic drug) but whose physical exclusion from such treatment requires more complicated screening procedures which, under the duress of the situation may only serve to confuse providers and impede care. To accommodate this challenge, outcomes will be evaluated in two populations, a safety population and a primary analysis (or efficacy) population. The safety population will consist of all randomized patients by intention to treat in whom a study drug kit is opened during resuscitation, even if the patient is considered ineligible or the study drug is not administered. The primary analysis (efficacy) population will consist of all eligible randomized drug recipients by intention to treat, but exclude, a priori, those in whom there is little or no expectation of benefit from antiarrhythmic therapy. This distinction between a safety and efficacy population allows for inclusion of all patients randomized to drug treatment for evaluation of the overall safety and effectiveness of drug therapy, but with respect to the primary analysis, excludes those in whom existing data indicate the intervention is unlikely to be beneficial.

#### **3.4.1 Primary Analysis Population (Efficacy Population)**

The trial's primary analysis population (efficacy population) will be comprised of eligible randomized recipients of any dose of study drug whose initial presenting arrest rhythm is VF or pulseless VT, in accordance with their randomized treatment assignment by intention to treat. Based on a number of scientific and practical considerations (discussed in the subsequent subsections (3.4.2-3.4.4) below), the efficacy population will include randomized patients with cardiac as well as noncardiac causes for their arrest, but will exclude randomized patients in whom the initial cardiac arrest rhythm is asystole or PEA, and those in whom there is evidence that study drug was never administered.

#### **3.4.2 Patients with Noncardiac Causes for Cardiac Arrest**

VF/VT may occasionally occur in patients with cardiac arrest associated with an obvious noncardiac cause such as drowning, strangulation, hanging, or electrocution; circumstances in which treatment and outcome may not necessarily apply to those in whom the arrest results from a cardiac (or presumed cardiac) cause. Although their number is expected to be small, the added screening procedures required to exclude such patients from randomization may distract prehospital providers and interfere with on-going resuscitation efforts. Conversely, to later exclude such patients from the efficacy population based on the presumed cause of the arrest, particularly if ascertained from information only known after the fact, introduces the potential risk of the post hoc selection bias. Accordingly, to obviate these concerns, and because their relatively small number is unlikely to substantially influence results, we will regard these patients

as eligible for randomization and included in the efficacy population in whom the primary endpoint will be assessed.

### **3.4.3 Patients with Initial Asystole or PEA**

It is not uncommon for patients whose initial presenting cardiac arrest rhythm is asystole or PEA to later develop VF/VT during the course of resuscitation. Survival among such patients is poor. In the ARREST and ASPIRE trials, virtually no patients with late occurring VF/VT survived to hospital discharge.<sup>22, 37, 47</sup> That antiarrhythmic therapy does not appear to improve outcome in such patients may be attributable to the protracted ischemic period of pulselessness before its receipt. Though there was no evidence of harm from antiarrhythmic drug treatment among such patients in the placebo-controlled ARREST trial, that antiarrhythmic therapy was not found to be beneficial argues for their exclusion from the current trial as their inclusion in significant number is more likely to dilute findings than provide meaningful results. However, doing so requires giving potentially confusing directives to prehospital providers as to when to treat and when not to treat VF/VT, which can complicate in-field screening procedures and compromise patient care. In addition, because such patients may continue to be treated with antiarrhythmic drugs clinically, their exclusion from the trial would sacrifice opportunity to collect further valuable information about the safety of drug therapies that may be given under such circumstances in clinical practice. Thus there is reason to include such patients for the purpose of evaluating the safety of drug therapy (i.e. in the trial's safety population), but to exclude them for the purpose of evaluating drug effectiveness (i.e. in the trial's efficacy population). Accordingly, such patients will be eligible for randomization and included in the trial's safety analysis, but excluded from the efficacy population. Their exclusion from the efficacy population can be accomplished without risk of post-hoc selection bias because it will be determined strictly by the initial cardiac arrest rhythm, a prespecified, objective pre-randomization variable that is ascertained in all patients at the onset of resuscitation efforts.

### **3.4.4 Confirmed Non-recipients of Study Drug**

A pharmacologic effect from study drug cannot necessarily be ascribed to patients in whom study drug may have been accessed (kit opened) in anticipation of use but never administered because of a subsequent change in clinical eligibility for drug treatment (e.g. conversion of VF/VT to sustained PEA or asystole), or mistakenly accessed. Accordingly, such patients in whom the drug kit was opened but its contents confirmed to not have been given (e.g. all study drug syringes returned unused) will be included in the safety population but excluded from the primary analysis.

### **3.4.5 Safety population**

The trial's safety population will encompass all randomized patients, defined as those in whom a study drug kit is opened during resuscitation, even if the patient is considered ineligible or the study drug is not administered. Excepted from this policy (as discussed in Appendix I) are persons from protected populations including known pregnant women (excluded due to the unknown effects of PM101 administered as a bolus on fetal development), recognized minors (excluded because of the absence of data on use of bolus PM101 in children) and known prisoners (who are excluded in accordance with Health and Human Service regulations, as defined in 45 CFR part 46 303 (c)).

In addition to unexpected serious adverse events, the safety population will be assessed for the same primary outcome (survival to hospital discharge) and secondary endpoint (functionally favorable survival, defined as MRS  $\leq$  3) as the efficacy population, in accordance with their



randomized treatment assignment by intention to treat. With respect to these analyses, the safety population will be additionally stratified by those in whom drug was administered, and those in whom the drug kit was opened but confirmed not to have been given (Drug Kit Opened but Not Given (KONG)). Outcomes will also be specifically evaluated among randomized patients in the safety population who present with asystole or PEA and have late-occurring VF/VT.

### **3.5 Setting**

The trial will be conducted among the communities served by the emergency medical services (EMS) systems participating in the Resuscitation Outcomes Consortium.

### **3.6 Random Allocation**

Eligible patients will be randomly allocated to lidocaine:placebo:PM101 in a proportion of 1:1:1, respectively, with distribution determined by the Data Coordinating Center (DCC) based on permuted blocks of concealed size within strata defined by participating site and within site by participating agency or subagency. The contents of the study drug kit for a given case will reflect the subject's randomization assignment and not require any randomization efforts in the field by EMS personnel. As described in the preceding section (3.4.5), a patient will be considered randomized and included in the safety population if the study kit is opened during the event even if the patient is considered ineligible or the study drug was not administered.

### **3.7 Intervention**

Victims of cardiac arrest will be treated by EMS providers who will initiate BLS measures including CPR and the delivery of shocks with an automated or manual external defibrillator. After CPR and defibrillation are initiated by EMS, paramedics with advanced life support capability will establish vascular access. EMS providers will be instructed to establish intravenous (IV) vascular access whenever feasible. If placement of an IV is not feasible in a timely manner, and requires intraosseous (IO) vascular access, administration of study drug IO will be permitted (if this route of administration is permitted by FDA), recognizing that this may be the only feasible vascular access in the patient (see section 3.10.2). After vascular access has been established, patients meeting the eligibility criteria will be allocated to 1 of 3 study arms as determined by the study drug kit. Separate use of open label lidocaine or amiodarone will not be permitted in randomized patients. All care providers will be blinded to study assignment. Initial antiarrhythmic drug therapy during resuscitation will be limited to the contents of the study kit. Patients with recurrent or refractory VF/VT after study drug has been exhausted will be eligible for standard ALS procedures and interventions, including receipt of additional vasopressors, magnesium, beta blockers, procainamide, if required and available, but not open label lidocaine or amiodarone. Upon allocation to therapy, an adhesive study identification label will be taken from the kit and applied to EMS forms, and/or the study identification number manually entered on the electronic patient care record. Paramedics will account for all syringes that were used during resuscitation. The time of first administration of study drug will be recorded and synchronized with the time clock on the defibrillator. After resuscitation, there will be independent confirmation and accounting for of spent and unspent study drug syringes, which will be systematically tracked by the local site investigators.

### **3.8 Study Drug Kit**

Each study kit will consist of a customized light-protected receptacle containing 3 ready to administer, pre-filled syringes designated as "study drug" that may be directly injected (undiluted) via established vascular access (as defined below) using a proprietary adapter (Baxter Clearlink) to insure compatibility with all needleless administration sets, as further

described in Appendix 13. Medics will be instructed to administer syringes as a bolus via established vascular access using the described adapter followed by at least 20-30 cc flush. The specific drug content for each kit for the 3 study arms is shown in Table 4. The physical appearance of the contents of syringes in kits pertaining to PM101, lidocaine and placebo will be indistinguishable from one another, and the identity of their actual contents identifiable only by a numerical code known only by the DCC. Study drug will be stored and maintained at agency sites of practice in accordance with local agency policies and environmental precautions pertaining to other drugs (e.g. lidocaine, epinephrine etc.) used during resuscitation.

**Figure 2:** Study Drug Kit



**Study Drug Kit Contents (Treatment Assignment)**

<u>Amiodarone (PM101) Arm</u>	<u>Lidocaine Arm</u>	<u>Placebo Arm</u>
PM101 150 mg (3cc)	Lidocaine 60 mg (3 cc)	Placebo (3cc)
PM101 150 mg (3cc)	Lidocaine 60 mg (3cc)	Placebo (3cc)
PM101 150 mg (3cc)	Lidocaine 60 mg (3cc)	Placebo (3cc)

**Figure 2 Legend:** Appearance of study drug kit, showing three primary treatment 5 cc syringes (each containing 3 cc of study drug). The table describes the content of syringes, depending on whether randomization is to PM101, lidocaine or placebo.

**3.8.1 Study Drug**

Eligible subjects will be randomized to one kit (containing PM101, lidocaine, or placebo) which will be used throughout the resuscitation. In the PM101 kit, each of 3 syringes will each contain 150 mg of PM101 (amiodarone) (3cc at 50 mg/cc), permitting use of a maximum field dose of 450 mg of PM101 (amiodarone). In the lidocaine kit, each of 3 syringes will each contain 60 mg of lidocaine (3cc at 20 mg/cc); permitting a maximum field dose of 180 mg of lidocaine. In the placebo kit, each of 3 syringes will contain placebo (3 cc normal saline).

**3.8.2 Rationale for Dosing Regimen**

The proposed dosing regimen (mg and volume per syringe) is envisioned to: (a) take advantage of the available FDA-approved concentrations of PM101 (50 mg/ml) and lidocaine (20 mg/ml), (b) provide opportunity for therapeutically appropriate initial and subsequent drug dosing within recommended guidelines and (c) maintain the study double blind.

PM101 is only available at a concentration of 50 mg/cc; lidocaine is available at 1% (10 mg/cc) and 2% (20 mg/cc) concentrations. To permit use of available drug concentrations, administer safe and effective doses for cardiac arrest, and, importantly, to maintain the double blind, each preloaded syringe will contain 3 cc of study drug. This volume corresponds to 150 mg of amiodarone, or 60 mg of 2% lidocaine or 3 cc of saline placebo.

PM101 (amiodarone) is currently FDA-approved for acute infusion at a dose of 150 mg in patients with life-threatening ventricular tachyarrhythmias, and has been safely administered acutely at bolus doses of 300 mg, with a follow-up dose of 150 mg (450 mg total) during cardiac arrest in the ARREST and ALIVE trials, respectively. While higher doses of amiodarone may be safe and effective, such acutely administered doses have not been sufficiently tested in human cardiac arrest to be utilized in a trial involving exception to informed consent. Thus the maximum cumulative dose of the PM101 to be administered in this trial will be limited to 450 mg. There are at present no weight-adjusted dosing recommendations for amiodarone in adults.

Current standard dosing recommendations for lidocaine in cardiac arrest call for an initial dose of 1-1.5 mg/kg, repeated, if required, at 0.5-0.75 mg/kg, up to a total dose of 3 mg/kg during a 1 hour period. Three syringes, each containing 60 mg of lidocaine will fulfill these dosing requirements in average-sized patients when the drug is administered per study protocol of 120 mg (initial dose), followed by an additional 60 mg (if required), to a maximum total dose of 180 mg. These doses fall within currently prescribed ranges for lidocaine in cardiac arrest, and permit achievement of higher therapeutic concentrations, if required, that are within the accepted upper dosing range.

As discussed below, the first therapeutic dose of study drug in average-sized patients will consist of two syringes (containing 300 mg of PM101, or 120 mg lidocaine, or placebo), doses which fall within studied and recommended parameters for initial dosing of these drugs in cardiac arrest. Thereafter, ongoing or recurrent VF/VT will be treated with additional single syringe doses of drugs until all study drug syringes (if required) are exhausted. Apart from study drug, use of open label lidocaine or amiodarone will not be permitted. The configuration of the syringes and protocol design permits patients to receive appropriate therapeutic cumulative doses of study drug of up to 450 mg of PM101 and/or up to 180 mg of lidocaine during resuscitation, if required. Thus PM101 or lidocaine will be administered in doses that permit achievement of higher therapeutic concentrations, if required, and are within the accepted upper dosing range for each drug. While achieving therapeutic dosing in the field, the protocol will also enable administration of supplemental doses of these medications, if clinically required, after hospitalization.

### **3.8.3 Weight Adjusted Study Drug Dosing**

Cardiac arrest due to VF/VT is uncommon in pediatric patients, who will be excluded from the current trial as a protected population. Most adult victims of out-of-hospital cardiac arrest are of average body habitus or more (> 80 kg in weight) and typically receive a standard non-weight adjusted dosing regimen of antiarrhythmic drugs during cardiac arrest (e.g. 100-200 mg of lidocaine, or 300-450 mg of amiodarone). These doses may be excessive in the occasional patient with a smaller body habitus. In such circumstances, prehospital providers are generally confident of their ability to identify those weighing less than 100 pounds (45 kg) and commonly reduce doses of medications. Accordingly, in this trial, patients judged to weigh <100 pounds (45 kg) will initially receive a single (rather than two) syringes of study drug, corresponding to 60 mg of lidocaine, or 150 mg of PM101, or placebo. For lidocaine, this falls within the initial recommended weight-adjusted dose of 1-1.5 mg/kg (e.g. 45-67.5mg for a 45 kg patient). Subsequent dosing of study drug for refractory or recurrent VF/VT in such patients will be limited to one additional syringe, corresponding to a total cumulative dose of 120 mg lidocaine, or 300 mg PM101 or placebo. For lidocaine, this falls within the within the maximum recommended weight-adjusted dose of up to 3 mg/kg (e.g. 135 mg for a 45 kg patient). Although there are no analogous weight adjusted dosing guidelines for administration of amiodarone in adults, the anticipated initial and total dose of amiodarone would fall within the

recommended pediatric dose range (5-15 mg/kg), suggesting this represents a reasonable adjusted dosing schedule in the occasional small sized patient.

### **3.9 Initial and Concurrent Care**

Upon arrival of EMS providers at a patient with cardiac arrest, CPR will be initiated. Defibrillation will be performed consistent with local practice. Subjects will be ventilated in accordance with local practice (with bag-mask or advanced airway (e.g., Combitube, King or other supraglottic airway, laryngeal mask airway [LMA], or endotracheal tube)) and receive chest compressions with minimal hands-off time. Vascular access will be established as soon as feasible. Resuscitative measures will follow local EMS treatment protocols. Patients with recurrent or refractory VF/VT after study drug has been exhausted will be eligible for standard ALS procedures and interventions, including receipt of additional vasopressors, magnesium, beta blockers, procainamide, if required, but not open label lidocaine or amiodarone.

### **3.10 Administration of Study Drug (Figure 3)**

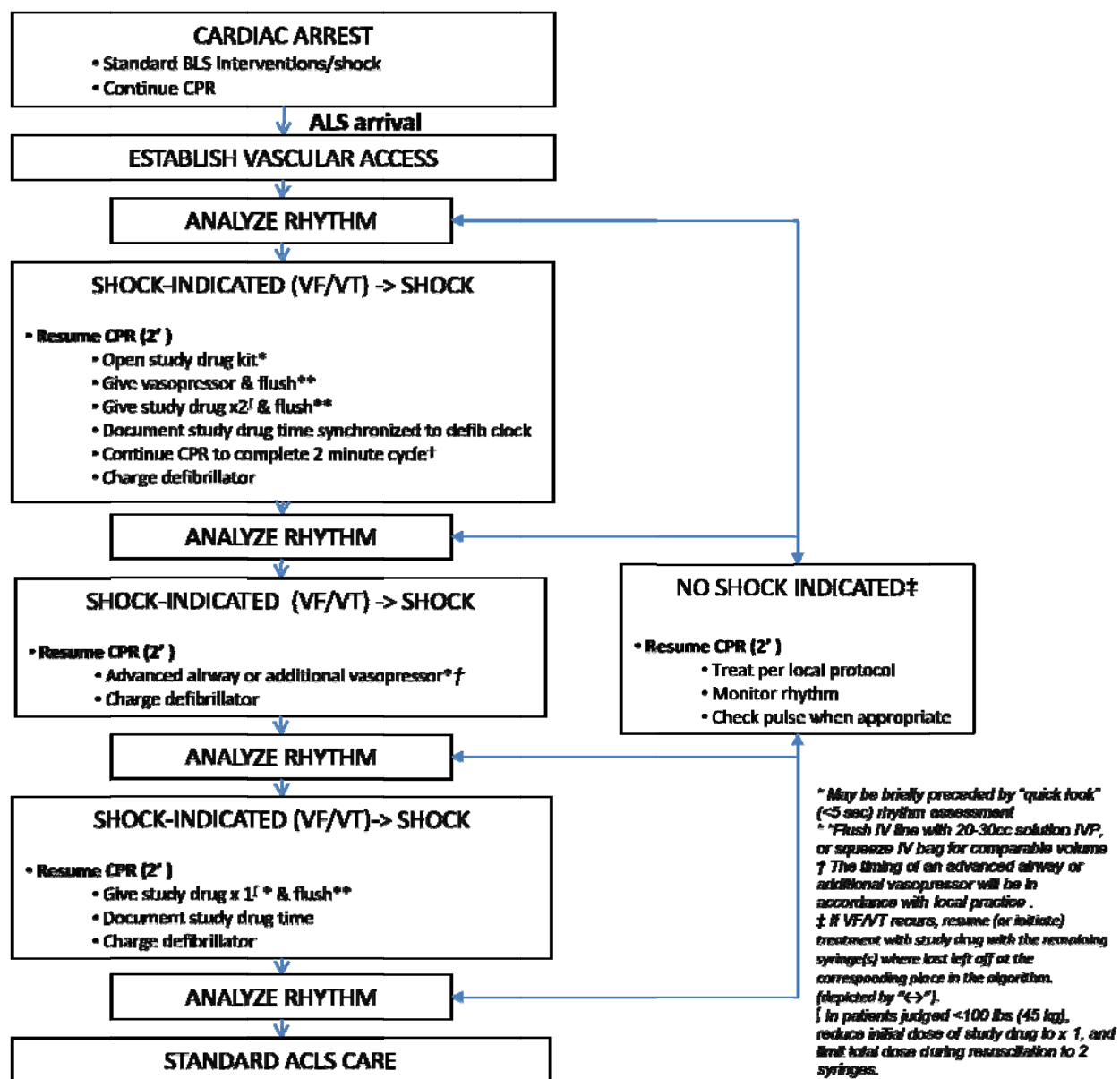
Eligible subjects of average size (who have received at least one shock for VF or pulseless VT) with ongoing or recurring VF/VT will receive a vasoactive drug (epinephrine or vasopressin) flushed and immediately followed (back-to-back) by their first dose of study drug administered as two syringes in rapid succession during ongoing CPR, followed by shock. Study drug will be given for refractory/recurrent VF/VT after 1 or more shocks that is either seen or presumed to be present/recurrent at the actual time of drug receipt. Accordingly, study drug will be administered in as close a temporal proximity as possible to when VF/VT was last identified and/or the rhythm deemed unstable due to refractory or recurrent VF/VT, but no longer than approximately 2 minutes from when VF/VT was last confirmed to be present. The subsequent dose of study drug (if required for ongoing or recurring VF/VT meeting these same criteria after initial receipt of study drug and subsequent shock(s)), will be administered as a single syringe dose, with other ALS measures (such as intubation, etc.) interposed as required. Study drug will be administered in as close a temporal proximity as possible to when VF/VT was last identified and/or the rhythm deemed unstable due to refractory or recurrent VF/VT after 1 or more shocks. The subsequent dose of study drug, if required for ongoing or recurring VF/VT, will be administered as a single syringe dose, with other ALS measures (such as intubation, etc.) interposed as required. Thus, depending upon randomized assignment, an average sized subject in ongoing VF/VT will receive an initial therapeutic dose of 300 mg of PM101, or 120 mg lidocaine or placebo (two syringes in each instance). For ongoing refractory or recurrent VF, single doses of study drug will subsequently be administered, up to a total of up to 450 mg of PM101, or 180 mg lidocaine, or placebo. The sequence of vasoactive drugs, study drug, shock and other ALS interventions will follow local EMS treatment protocols for pulseless cardiac arrest. As described in the preceding section (3.8.3) patients judged to be <100 lbs (45 kg) in size will receive a weight-adjusted initial dose of study drug (1 syringe), and a maximum cumulative dose of two syringes. Although vasoactive drug will be flushed into the circulation before administration of study drug, it is possible that a small amount of diluted drug may still remain in the line resulting in a potential admixture. In such an event, both PM 101 and lidocaine are chemically compatible with either epinephrine or vasopressin<sup>48</sup> when administered in the same line at the concentrations to be used in this trial (Appendix 7-9), and no compatibility issues are therefore anticipated from a more dilute admixture.

Current ACLS Guidelines (Appendix 10) suggest that vasopressors and antiarrhythmic drugs be administered during the 2 minute period of CPR that follows administration of shock, without specifying whether CPR should be briefly paused to confirm the rhythm diagnosis at the actual time when these drugs are given. In the current trial protocol, a brief pause for rhythm

confirmation is permitted immediately prior to administration of study drug according to local EMS practice. The importance of high quality, minimally interrupted CPR will be stressed and monitored throughout the course of this study. If a pause immediately prior to drug administration is prescribed under local EMS practice, providers will be instructed and trained that any interruption in CPR for rhythm analysis be as brief as possible (5 seconds or less; i.e. a “quick look”), which will be monitored as part of the study’s ongoing analysis of CPR process.

An example of standing orders for EMS providers pertaining to how the trial might be orchestrated in the field is shown in Table 4.

**Figure 3:** Possible (illustrative) treatment scenario



**Figure 3 Legend:** In this scenario, it is presumed that at least 1 shock has been administered for VT/VF, vascular access has been established, and upon subsequent evaluation the patient is found to remain in or have recurrent VT/VF. In eligible patients, the study drug kit is opened, and a vasopressor drug (epinephrine or vasopressin, in accordance with local practice) is administered immediately followed by two syringes of study drug during ongoing CPR. Upon completion of the 2 minute period of CPR, the rhythm is reanalyzed and shocked if appropriate. CPR is thereafter resumed during which time, depending upon local protocol, either an additional dose of a vasopressor is administered or an advanced airway may be placed. Upon completion of the 2 minute period of CPR, rhythm is reanalyzed and if indicated shock is delivered. CPR is resumed, whereupon if required the remaining syringe of study drug is administered. Upon completion of the 2 minute period of CPR, the rhythm is reanalyzed and shocked, if appropriate. Thereafter, standard ACLS treatment measures are provided, as

required. If at any time a nonshockable rhythm is identified, the patient is assessed for evidence of perfusion and treated accordingly. Should VF/VT recur in such patients, treatment with study drug is resumed (or initiated) with the remaining syringe(s) of study drug where last left off at the corresponding place in the algorithm (depicted by “↔”).

**Table 4:** Example of standing EMS orders for study drug

<p>Sample Standing Orders for Ongoing or Recurrent VF/VT</p> <ol style="list-style-type: none"> <li>1. Upon ID of cardiac arrest, begin CPR followed by rhythm analysis and shock (if required). Resume CPR*</li> <li>2. Analyze rhythm. If VF/VT → shock, resume CPR* and establish vascular access (IV/IO). Charge defibrillator.</li> <li>3. Analyze rhythm. If VF/VT → shock, resume CPR*, open study drug kit** and</li> <li>4. Give vasopressor IV Push, flush, † and immediately follow with 2‡ study drug syringes IV Push, flush. † Document drug time, synchronized to defibrillator clock. Continue CPR* to complete 2 minutes. Charge defibrillator.</li> <li>5. Analyze rhythm. If VF/VT → shock, resume CPR* and establish advanced airway or give additional vasopressor§**. Charge defibrillator.</li> <li>6. Analyze rhythm. If VF/VT → shock, resume CPR* and give one study drug syringe IV Push**, flush†. Document drug time. Charge defibrillator.</li> <li>7. Analyze rhythm, resume CPR* and follow standard procedures for refractory cardiac arrest.</li> <li>8. Anytime a nonshockable rhythm is identified, assess pulse (after appropriate period of CPR) and treat accordingly. Should VF/VT recur in such patients, resume (or start) treatment with study drug where last left off (i.e. at steps 4 or 6 above), using the remaining syringe(s)‡.</li> <li>9. Return study drug kit with any spent/unspent syringes.</li> </ol> <p>* All CPR sequences are for a period of 2 minutes</p> <p>** May be briefly preceded by “quick look” (&lt;5 seconds) rhythm assessment</p> <p>† Flush IV line with 20-30cc solution IVP, or squeeze IV bag for comparable volume</p> <p>‡ In patients judged to be &lt; 100 lbs (45 kg), reduce initial dose of study drug to 1 syringe, and limit total dose during resuscitation to 2 doses.</p> <p>§ The timing and sequence of these ALS interventions will be in accordance with local practice and protocols; one of the other may be deferred to a later point in the treatment protocol.</p>
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### 3.10.1 Time-to-treatment

The study will prioritize establishing intravenous access and administering study drug as soon as possible to eligible patients. The time of study drug administration will be documented in a variety of ways, depending upon local EMS agency practice, such as an audible announcement (“study drug in”) on the audio channel of the electronic defibrillator recording, activation of an electronic marker on the electronic defibrillator recording, and/or documentation in the patient care record, each synchronized to the defibrillator clock. A pre-enrollment phase using our

cardiac arrest registry (prior to start of the trial itself) will soon be initiated in order to demonstrate an agency's ability and reliability in capturing the precise time of drug administration. During this phase, EMS providers will be asked to document the time of first administration of epinephrine (which will be nearly simultaneous with the administration of study drug under the proposed protocol) as an exercise in demonstrating their ability to capture the time to study drug administration and to ascertain this time interval from dispatch. All EMS agencies will be required to demonstrate a reliable method for capturing drug administration time prior to beginning the enrollment phase of the trial.

The aim is for study drug to be administered within 10 minutes of paramedic (ALS) arrival. A pre-specified efficacy analysis will evaluate the impact of earlier versus later treatment based upon the actual median time-to-study drug achieved. We anticipate that earlier treatment will result in improved outcomes; though we acknowledge that the greater emphasis upon high quality CPR may extend the window of beneficial drug effect. Given this uncertainty and practical and important operational considerations related to performing excessive screening procedures in the field (which would complicate care and potentially detract from the resuscitation effort) treatment with study drug will not be precluded based upon a particular time interval from EMS arrival to its potential receipt.

### **3.10.2 Vascular Access**

The study protocol calls for obtaining vascular access as soon as possible, and administering study drug as soon as possible thereafter. EMS providers will be instructed to establish vascular access which may be intravenous (IV) or intraosseous (IO), in accordance with local clinical practice.

IO fluid and drug administration has historical precedent for use in children.<sup>49</sup> In animal models of cardiac arrest, administration of epinephrine and bicarbonate IO achieved comparable concentrations and effects as when given IV.<sup>50-52</sup> A recent observational analysis was performed by the San Diego ROC site to evaluate the effect of IV versus IO administered sodium bicarbonate on measures of end tidal CO<sub>2</sub> (EtCO<sub>2</sub>) during human resuscitation from out-of-hospital cardiac arrest. EtCO<sub>2</sub> reflects endogenous carbon dioxide levels, and as such serves as a marker of ventilation in patients with normal circulatory status, can serve as a marker of returning circulation in patients in cardiac arrest, and, importantly, is also increased after administration of sodium bicarbonate, which is almost immediately converted to carbon dioxide ( $\text{NaHCO}_3 + \text{H}^+ \rightarrow \text{Na}^+ + \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$ ). Thus a surrogate for how rapidly sodium bicarbonate enters the circulation after its administration is the timing of the subsequent rise in EtCO<sub>2</sub>. In the San Diego analysis, the median time interval from administration of IV as compared with IO bicarbonate to a sharp ( $\geq 2$  mm Hg) absolute increment in EtCO<sub>2</sub> from a comparable and relatively stable baseline was 12 and 14 seconds, respectively, suggesting a comparable systemic effect from the drug by either vascular route.<sup>53</sup> While this does not specifically address whether other drugs may behave similarly, it provisionally suggests such a possibility.

The 2005 American Heart Association Guidelines recommended IO access as "safe and effective for fluid resuscitation, drug delivery and blood sampling for laboratory evaluation and is attainable in all age groups,"<sup>54</sup> a practice that was affirmed in the 2010 Guidelines (Class IIa, LOE C).<sup>55</sup> A growing minority of EMS agencies now administer Advanced Cardiac Life Support (ACLS) drugs IO during cardiac arrest when IV access is not readily available, or as primary means of vascular access in order to assure their successful and expeditious receipt.



Approximately 5-10% of ROC EMS agencies administer ACLS drugs IO at the present time. While there are reports of virtually all ACLS drugs, including amiodarone, being given IO during cardiac arrest, admittedly this is an area that requires further study.<sup>56</sup> Recognizing these concerns, we will carefully track IO drug administration with respect to, safety and outcome during the trial.

### **3.11 Rationale for Absence of a “Rescue” Arm**

In average-sized adults, the study protocol calls for administration of 3 syringes of study drug in serial fashion for incessant or recurrent VF/VT to maximum doses. Should VF/VT persist or recur after study drug is completed, the protocol does not allow for cross-over to open label amiodarone or lidocaine. The rationale for this approach is:

- a) receipt of open label amiodarone or lidocaine in patients who have already received the same drug may risk toxicity due to over dosage or require immediate unblinding (which is not feasible in the acute resuscitation setting) to prevent re-treating with the same drug;
- b) at present, neither amiodarone or lidocaine has been proven to improve survival from cardiac arrest and use of either medication is at best only weakly recommended (Class IIb or class indeterminate, respectively) in American Heart Association/ILCOR Guidelines, such that neither drug is deemed essential (Class I) during resuscitation;
- c) there is provision in the study protocol for subjects who fail study drug to receive other standard ALS treatment measures including additional vasoactive drugs, magnesium, beta blockers or procainamide, if required;
- d) provision of cross-over may render it difficult to ascribe outcome to a specific treatment, rendering the study more difficult or impossible to interpret.

### **3.12 Hospital After-Care**

Optimizing and standardizing hospital care after cardiac arrest is desirable, in light of recent randomized and observational studies. However, while the use of hypothermia in comatose patients who are resuscitated from ventricular fibrillation is supported by evidence from randomized trials and included in AHA/ILCOR guidelines, the role of other therapies is drawn from observational studies and is less certain.<sup>57</sup> With this in mind, the prelude to the 2005 AHA Resuscitation Guidelines stated “post resuscitation treatment is now receiving greater emphasis in emergency cardiovascular care, but there is little evidence to support specific therapies,”<sup>58</sup> and was affirmed in the 2010 Guidelines which stated “the best hospital care for patients with ROSC after cardiac arrest is not completely known, but there is increasing interest in identifying and optimizing practices that are likely to improve outcomes.”<sup>59</sup> In the absence of such high-level evidence, it would be challenging to obtain consensus on what constitutes an optimal post resuscitation treatment plan and to apply it uniformly across the numerous participating communities and hospitals. Arguably, establishing the specific components of such standardized care might itself require a separate in-hospital randomized trial. Alternatively, providing individual hospitals with an assessment of their care of cardiac arrest patients, (as proposed below) could be taken as the next and necessary step to fostering greater standardization of hospital care, analogous to how assessment of EMS care in the ROC Cardiac Arrest Epistry prompted improvements in its delivery.

Currently there is evidence to suggest a reasonable existing measure of systematized care for cardiac arrest patients after hospitalization, as exemplified by hospital treatment and survival

rates in the ROC PRIMED trial. In ROC PRIMED, more than half of patients (approximately 52%) admitted to hospital after cardiac arrest due to ventricular fibrillation (VF) survived to hospital discharge and 52% received hypothermia (a value that may underestimate the actual proportion of patients considered for such therapy, given that an additional 10-20% of admitted patients may not require hypothermia because of early signs of responsiveness). Thus while affording room for improvement; these data suggest that a reasonable foundation of post-resuscitation care is already provided by hospitals within ROC. Arguably, the requirement for more rigorous trial-regulated control of hospital care may also be more relevant to trials assessing treatment efficacy (whether the interventions work under ideal conditions) than to effectiveness trials, whose intent is to determine the benefit of interventions under usual practice conditions. In fact, FDA regulations governing exception from informed consent for emergency research require that such studies assess effectiveness rather than efficacy (21 CFR 50.24), that is, be performed under usual practice circumstances.

Recognizing these challenges, the proposed study includes a strategy to encourage greater uniformity in post resuscitation hospital care, within the constraints of conducting an effectiveness trial whose principal focus is on prehospital interventions. Receiving hospitals will be provided with AHA recommendations for post resuscitation care<sup>60</sup>, and encouraged to practice in accordance with these guidelines, which include hemodynamic and respiratory support, control of temperature (particularly prevention or treatment of hyperthermia) and glucose concentration. Importantly, because as indicated above many patients in the efficacy population (study drug recipients with initial VF/VT) are likely to receive hypothermia interventions during the initial days of their hospital course (an intervention that requires close monitoring of other vital parameters during the initial phases of hospitalization), it is anticipated that this practice will assure a relatively comparable level of care and attention to other components during the initial days of hospitalization. In addition, while not formally prescribing hospital therapies for the reasons cited above, the trial will afford a unique opportunity to capture, characterize and systematically evaluate the potential impact of current post-resuscitation care practices across ROC communities. The specific therapeutic strategies to be surveyed are listed below, along with a brief commentary as to their importance and limitations, excerpted directly or adapted from the AHA post resuscitation care recommendations<sup>60</sup> and other references.

Because the proposed trial is randomized and blinded, it is expected that the treatments described below subsequent to the receipt of study drug, will be balanced across treatment groups. Treatment imbalances, if any, will be identified through this detailed assessment of hospital care, and used in secondary analyses to explore treatment mechanisms.

### **3.12.1 Monitoring and Diagnostic Procedures**

Post-cardiac arrest patients generally require intensive monitoring and may receive a variety of diagnostic procedures for evaluation of their hemodynamic status, cardiac function and possible etiology of their arrest. This may include pulmonary artery catheterization, echocardiography, and other diagnostic studies. Although the impact of these specific procedures on post cardiac arrest outcome has not been proven, their obtainment during hospitalization will be tracked during the trial. Other procedures to be tracked are mentioned under their specific subsections below (e.g. cardiac catheterization, EEG, etc.).

### **3.12.2 Therapeutic Hypothermia**

The American Heart Association regards therapeutic hypothermia as a part of the treatment strategy for comatose survivors of cardiac arrest. 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.<sup>61</sup> Two randomized trials demonstrated that mild hypothermia (32° to 34°C) via external cooling methods for 12-24 hours is safe and improves neurologic outcomes significantly in comatose survivors of out-of-hospital cardiac arrest in whom the initial rhythm was ventricular fibrillation.<sup>62 63</sup> Another trial demonstrated that mild hypothermia (32° to 34°C) is safe and tends to improve neurologic outcomes in comatose survivors of out of hospital cardiac arrest in whom the initial rhythm was not VF.<sup>64</sup> Animal data suggest that hypothermia should be initiated as soon as possible during resuscitation.<sup>65,66</sup> A case-control study of patients without restoration of circulation after out of hospital cardiac arrest 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.<sup>67</sup> If therapeutic hypothermia is not feasible or contraindicated, it is recommended that at a minimum hyperpyrexia should be prevented.<sup>68</sup> Given these considerations, use of therapeutic hypothermia in the hospital setting will be monitored during this trial.

### **3.12.3 Ventilatory Support**

Provision of oxygen and ventilation support are essential components of care in comatose survivors of cardiac arrest. Although no data exist to support the targeting of a specific PaCO<sub>2</sub> or PaO<sub>2</sub> after resuscitation,<sup>69 70</sup> the duration of initial continuous ventilator support in the hospital setting can be an indicator of an overall commitment to the patient's post resuscitation care, and will be monitored during this trial.

### **3.12.4 Hemodynamic Support**

Myocardial dysfunction is commonly observed after resuscitation from cardiac arrest and is associated with poor prognosis compared to normal cardiac function.<sup>71</sup> This hemodynamic instability responds to fluid administration and vasoactive support, but may also require mechanical support (e.g. intra-aortic balloon pump). Both cardiac arrest and sepsis are thought to involve multi-organ ischemic injury and microcirculatory dysfunction.<sup>72</sup> Goal-directed therapy, with volume and vasoactive drug administration, has been effective in improving survival from sepsis.<sup>73</sup> 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. Accordingly use of hemodynamic support in the hospital setting will be monitored in this ROC trial.

### **3.12.5 Glucose Control**

Hyperglycemia after resuscitation from cardiac arrest is associated with a poor prognosis compared to normoglycemia.<sup>74,75</sup> 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.<sup>76,77</sup> but did not improve outcomes in patients undergoing cardiac surgery.<sup>78</sup> Although there is inconsistent evidence regarding the effectiveness of insulin therapy in resuscitated victims of cardiac arrest, early use of insulin therapy will be monitored during this trial.

### **3.12.6 Cardiac Catheterization and/or Coronary Interventions**

Up to 71% of patients with cardiac arrest have coronary artery disease, and nearly half have an acute coronary occlusion.<sup>79-81</sup> 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; 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.<sup>79</sup> 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.<sup>82</sup> 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. 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.<sup>83</sup> 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.<sup>60, 79, 84-89</sup> 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.<sup>86, 90, 91</sup> Accordingly, early cardiac catheterization and use of PCI will be monitored in this ROC trial.

### **3.12.7 Ancillary Antiarrhythmic Therapies**

There are limited data on the use and efficacy of antiarrhythmic drugs in-hospital after out-of-hospital cardiac arrest. Although presumably administered to treat and/or prevent recurrent arrhythmias, observational data has not established a benefit of such treatment on survival.<sup>92</sup> Accordingly, early use of intravenous antiarrhythmic drugs during hospitalization will be monitored in this trial. Such use, particularly during the early phase of hospitalization, will be of particular interest, as discussed in section 3.13.

### **3.12.8 Seizure Recognition**

Seizures, myoclonus, or both occur in 5% to 15% of adult patients who achieve ROSC and 10% to 40% of those who remain comatose.<sup>93</sup> Seizures increase cerebral metabolism by up to 3-fold.<sup>94</sup> Prospective studies are needed to determine the benefit of EEG monitoring for seizures during the course of recovery from cardiac arrest, which will be tracked during this ROC trial.

### **3.12.9 Implantable Cardioverter Defibrillator (ICD)**

Patients who have been resuscitated from cardiac arrest are at risk of a recurrent arrhythmia event. Randomized trials demonstrate that the implantable cardioverter defibrillator decreases mortality in such patients.<sup>95</sup> Since implantable defibrillators may lack benefit in selected populations, patient preferences influence use of such devices, and the cognitive recovery status of patients may play an important role in decision-making, not all patients will necessarily be suitable candidates for implantable defibrillator during the initial hospitalization. In light of these concerns, receipt or referral for an ICD will be monitored in this ROC trial.

### **3.12.10 Withdrawal of Care**

The need for protracted high intensity care of survivors of cardiac arrest creates a burden for families, the healthcare system and society, if the ultimate outcome is likely to be poor. A recent study showed that prognostication based on the neurological examination and diagnostic modalities influenced the decision of physicians and families as to the timing of withdrawal of life-sustaining therapies.<sup>96</sup> The ideal timing and reliability of early prognostication in predicting neurological outcome after cardiac arrest remains limited. However, it is asserted that the time period beyond 3 days following arrest, considered the recovery phase, may demarcate the period of recovery when prognostication becomes more reliable and outcomes more predictable.<sup>97</sup> Both theoretical and evidence-based concerns suggest that the approach prognostication may need to be modified in recipients of therapeutic hypothermia, in whom hypothermia may mask the neurological examination, delay the clearance of drugs that

themselves mask neurological function. Accordingly, the duration of provision of active care, the time and circumstances surrounding instances where care is withdrawn, and the proximate cause of death will be monitored in this trial.

### **3.12.11 Facilitating Improved Hospital Care**

In addition to characterizing the post resuscitation care of study patients, we propose using this information to foster ongoing improvement in the treatment of patients after hospitalization. Recognizing that quality improvement is dependent upon altering current perceptions about hospital-based care, we will provide hospitals with an objective assessment of their performance in the surveyed areas as a first and requisite step toward facilitating greater standardization of such care. This information will be provided to the hospitals at the time of the regular required reports of trial progress to them. Each site PI will determine the appropriate recipient of such reports at each hospital, such as the local intensive care committee or its equivalent. Included in the report will be the local hospital's individual performance in the above surveyed areas of care, as compared with the aggregated data from other hospitals in the community and/or across the Consortium, to serve as the stimulus for changing practice in potentially deficient areas. In addition to the regular provision of these reports to the local hospitals, the ROC Study Monitoring Committee (SMC) will regularly monitor hospital performance in the surveyed areas. In instances where a local hospital's performance substantially deviates from the norm of the community or Consortium, if necessary the site PI will be encouraged by the SMC to work with the local intensive care committee or equivalent in these areas.

Finally, we propose to use the data acquired from our assessment of post resuscitation hospital care to determine what relationship, if any, specific care measures may have on survival outcome. Observations stemming from this exploratory analysis may provide a more informed basis for advising and better directing future post resuscitation care.

### **3.13 Antiarrhythmic Drug Administration after Hospitalization**

All receiving hospital emergency departments and intensive care departments will be informed in advance about the prehospital trial and its treatment components as part of the community notification plan for this study. Hospital care providers will be informed of the possibility that subjects may have already received up to 180 mg of lidocaine or up to 450 mg of amiodarone. This permits administration of supplemental doses of these medications as per current clinical dosing guidelines, if clinically required after hospitalization. For example, as per current clinical dosing guidelines, supplemental doses of lidocaine (an additional 100-120 mg or up to a total cumulative dose of 3 mg/kg over the first hour) or of amiodarone (up to 2 gms over the first 24 hours) may be administered within the initial hours of hospitalization. If needed, higher doses of lidocaine may be guided by measurement of plasma concentrations in accordance with current clinical practice. As per current clinical dosing guidelines (and in light of the waning plasma concentrations of prehospital-administered study medications), it is not anticipated that the prior use of medications will be a clinical consideration after the first 1-2 hours of hospitalization. It is also the current impression of the investigators that amiodarone (which has a higher therapeutic index for dosing than lidocaine) is more likely to be used preferentially over lidocaine for initial treatment of ventricular arrhythmias in hospitals, making it less likely that higher doses of lidocaine will be deployed after hospitalization. If unblinding is required for safety or treatment purposes during the course of the study, a mechanism will be in place by which the identity of study drug will be promptly disclosed. A suggested written script that can be provided to the hospital upon subject admission to the Emergency Department is provided in Appendix 12.

Although treatments, such as use of antiarrhythmic drugs, may vary from patient-to-patient after hospitalization, this is taken into account by the trial's randomized, blinded design, and analysis

of outcome by modified intention-to-treat. Given the randomized design, each prehospital treatment arm should be equally eligible for specific hospital treatments(s) including receipt of additional antiarrhythmic medications. Even if there were a disproportionate use of open label antiarrhythmic therapy (such as amiodarone) that corresponded to the randomization assignment, this finding may reflect the relative effectiveness of the specific prehospital antiarrhythmic treatment (manifested, for example, by the return of recurrent tachyarrhythmias once the effect of prehospital-administered therapy had waned). Thus the subsequent open-label use of antiarrhythmic therapy might even provide some insight into the mechanism by which one of the prehospital interventions exerted its effect and underscore rather than undermine the importance or validity of the study. Indeed, the content and design of the hospital study data abstraction will enable an evaluation of the potential mechanism by which the prehospital intervention produces outcome effects.

### **3.14 Data Recording**

Dispatch records, electronic (ECG) recordings, voice recordings and narrative data from the resuscitation will be obtained and analyzed. EMS providers will be asked to specifically document the time that each dose of study drug is administered, synchronized whenever possible to the defibrillator clock. This may be done verbally (for audio recorded resuscitations), by depressing a drug marker (time stamp) on the defibrillator and/or written recording of the time of administration synchronized to the defibrillator clock. Electronic records will be analyzed in relationship to these times that study drug was administered for its resulting effect on rhythm and hemodynamics. CPR process will be monitored in accordance with standard ROC procedures, extending, where feasible, throughout the entire period of resuscitation. Hospital records will be reviewed and abstracted.

### **3.15 ECG Rhythm Analysis**

The initial ECG tracing will be analyzed off-line for identification of the initial recorded arrest arrhythmia as well as subsequent rhythms during the course of resuscitation. Three possible ECG rhythms will be defined. Asystole will be defined as background electrical activity less than 0.2 mV in amplitude with an average rate of  $\leq 10$  beats/minute (e.g., a 6-second strip with at most one ventricular complex). 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 a PEA rhythm will also be recorded.

### **3.16 Training**

ALS EMS providers are already familiar with antiarrhythmic drug administration and little training is anticipated to be required for the technique of study drug administration. Rather, a greater emphasis will be placed on earlier establishment of vascular access during training, recognizing that this skill set (IV and/or IO placement) along with the skill set of IV and/or IO drug administration are already regularly practiced by EMS providers in a variety of circumstances. Accordingly, training will focus on the scientific basis for and review of study protocols, identification of appropriate patients for enrollment, prioritizing establishing IV access, serial administration of study drug, and review of optimal CPR performance. It is anticipated that approximately 1-2 hours of didactic instruction (including face-to-face and/or web-based instruction) and 30 minutes of practicum/"hands on" experience along with refresher training during the course of the study will be required, and will be adjusted depending on periodic assessment of performance and compliance. This requirement may vary from site-to-site and will be individualized as required. Notably two of the largest sites participating in the Consortium

have prior experience in performing a comparable drug trial, in having participated in the ARREST and ALIVE, which were successfully conducted with comparable training periods. EMS personnel will be retrained in study-related procedures in intervals and intensity according to local standards, and/or in the event that monitoring of study progress by the Study Monitoring Committee identifies the need for remedial action.

### **3.17 CPR Process Monitoring**

During the course of conducting the current cardiac arrest trials, ROC sites have acquired expertise in monitoring CPR process variables, including rates of chest compression and CPR fraction, ventilation, time to defibrillation and others. High quality CPR is the foundation of care in resuscitation. Accordingly, these variables will continue to be monitored and the quality of CPR optimized during this proposed drug trial, as described in Appendix 5.

### **3.18 Study Monitoring Committee**

A Study Monitoring Committee comprised of elected or appointed investigators and, representatives from the Data Coordinating Center (DCC) will assess site compliance with CPR Process (as described above), study procedures (including time to administration of study drug), provision of timely data (Appendix 6), and hospital performance parameters (as previously described). In instances where performance deviates from expectations, the site PI will be encouraged by the SMC to work with EMS and/or the local hospital(s) to remedy these concerns.

### **3.19 Pre-enrollment Phase**

A brief pre-enrollment phase prior to start of the trial itself is anticipated in order to demonstrate an agency's ability to assess the capture of time to drug administration. During this phase, EMS providers will be asked to document the time of first administration of epinephrine as an exercise to demonstrate their ability to capture the time to study drug administration. Since patients will not be randomized, nor study drug given during this phase, it is not anticipated to change the total number of patients projected to be enrolled in the trial.

### **3.20 Outcome**

The primary outcome of the trial is survival to hospital discharge. Patients who are transferred to another acute care facility for other nonelective treatments (e.g., for recurrent ventricular arrhythmias) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility (e.g. skilled nursing care or rehabilitation facility) will be considered discharged.

In order to minimize the need for complicated patient screening procedures by EMS providers in the field under emergent circumstances, all patients with VF/VT at anytime during resuscitation will be eligible to receive the study drug in this trial. However, as discussed above, the primary outcome analysis will be conducted in an efficacy population comprised of eligible randomized recipients of any dose of study drug whose presenting arrest rhythm is VF or pulseless VT.

As discussed below, the primary outcome will be analyzed in the context of a primary comparison (comparing PM101 with placebo), and two secondary comparisons (comparing lidocaine with placebo, and PM101 with lidocaine). As a secondary endpoint, the trial will compare functionally favorable survival (Modified Rankin Score  $\leq 3$  at hospital discharge) between the 3 treatment arms.

#### **3.20.1 Primary Comparison**

The primary comparison of the trial (corresponding to its primary aim) is survival to hospital discharge in patients who are randomized to PM101 versus placebo, which will be analyzed in

the efficacy population. Patients who are transferred to another acute care facility for other nonelective treatments (e.g., for recurrent ventricular arrhythmias) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility (e.g. skilled nursing care or rehabilitation facility) will be considered discharged.

### **3.20.2 Secondary Comparisons**

The secondary comparisons for the trial (corresponding to its secondary aims), are survival to hospital discharge in patients randomized to lidocaine versus placebo, and in those randomized to PM101 versus lidocaine, which will be analyzed in the efficacy population. Patients who are transferred to another acute care facility for other nonelective treatments (e.g., for recurrent ventricular arrhythmias) will be considered to be still hospitalized. Patients transferred to a non-acute ward or facility (e.g. skilled nursing care or rehabilitation facility) will be considered discharged.

### **3.20.3 Secondary Endpoint**

The secondary endpoint of the trial is survival to discharge with a Modified Rankin Score (MRS)  $\leq 3$  and will be compared in patients randomized to PM101 versus placebo, lidocaine versus placebo, and PM101 versus lidocaine in the efficacy population. The secondary endpoint in these respective groups will be assessed from the written medical record at hospital discharge. The MRS has face validity and can be determined via review of the clinical record, in person or over the telephone.<sup>98 99</sup> MRS has concurrent validity with other measures of neurological recovery after stroke and brain injury.<sup>100 101</sup> MRS has prior use in a cohort of neurosurgical patients with in-hospital cardiac arrest<sup>102</sup>, in a cohort of survivors of out-of-hospital cardiac arrest.<sup>103</sup>, and was the primary endpoint in the ROC PRIMED Trial<sup>104 105</sup>. It is scaled from zero (no symptoms) to six (death), with a score of  $\leq 3$  indicating a moderate functional disability or better and conventionally taken to be consistent with a good neurological outcome<sup>106</sup> Patients who die before hospital discharge will be assigned an MRS of 6.

### **3.20.4 Prespecified Subgroups**

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 of the efficacy population. The exact specifications of the sub-groups will be made in consultation with the DSMB and FDA prior to the initiation of the trial, and will likely include:

- a) Observational status of an arrest (EMS witnessed, bystander witnessed, unwitnessed);
- b) Bystander CPR vs. not;
- c) Location of arrest (private versus public);
- d) Time from dispatch to first administration of study drug by EMS treated as a continuous variable and also dichotomized (e.g.,  $<15$  minutes and  $\geq 15$  minutes).
- e) Site-specific survival rate in treatment groups
- f) Mode of vascular access – intravenous (IV) vs. intraosseous (IO)
- g) Subjects estimated to weigh less than 100 lb by enrolling medics; and
- h) Agency approach to rhythm evaluation (study drug given for presumed VT/VF during ongoing CPR following a shock versus rhythm evaluated and confirmed eligible [either via a brief pause and/or using see-through CPR technology] immediately prior to drug administration).



In addition, any potential interactions between other treatments such as differing CPR treatment protocols (e.g. continuous chest compression as compared with interrupted chest compression CPR) and post-resuscitation hypothermia with drug outcomes will be evaluated.

### **3.20.5 Mechanistic Outcomes**

Other outcomes will also be collected and used for descriptive purposes in the efficacy population, including:

- a) Number of defibrillation shocks delivered;
- b) Return of spontaneous circulation (ROSC), defined as the presence of both a measurable pulse and blood pressure upon hospital (Emergency Department) arrival;
- c) Survival time, defined as time interval from 911 call to time of patient death;
- d) Time of awakening, defined as the time from 911 call to the time a patient is able to obey verbal commands;
- e) Time of withdrawal of care, defined as time from 911 call to time care is withdrawn for those patients transferred to hospital;
- f) Length of hospital stay, for those patients admitted alive to hospital

### **3.21 Adverse Events**

Adverse events will be evaluated in both the efficacy and safety populations.

#### **3.21.1 Unexpected Serious Adverse Events (USAE)**

These events will be defined as any unexpected serious adverse effects on health or safety or any unexpected life-threatening problem caused by, or associated with the interventions if the effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan or application, or any unexpected serious problem that relates to the rights, safety, or welfare of subjects. Given the recognized high mortality and morbidity from cardiac arrest, the death or neurological impairment of an individual patient will not be considered an unexpected serious adverse event in this study

#### **3.21.2 Expected Adverse Events:**

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. These will be recorded as noted on the hospital discharge record, but not necessarily considered as adverse events related to study interventions.

- a) Hypotension requiring vasopressor support
- b) Pulmonary edema
- c) Pneumonia
- d) Sepsis
- e) Stroke
- f) Recurrence of cardiac arrest
- g) Chest wall injuries related to resuscitation efforts
- h) Abdominal injury
- i) Airway bleeding

### **3.21.3 Possible Drug-Related Adverse Events**

Given the potential association of some adverse events with study drug, the following will be considered possible drug-related adverse events and will be assessed in all patients in whom study drug was accessed:

- a) Thrombophlebitis in infusion limb (defined as the presence of two or more of the following reported signs: palpable cord, induration, pain, warmth, or redness and/or signs along the course of the infusion vein during the first 24 hours after study drug administration requiring medical or surgical intervention, as reported in the prehospital and/or hospital record).
- b) Severe drug allergy (defined as reported anaphylaxis during the first 24 hours after study drug administration, as reported in the prehospital and/or hospital record).
- c) Clinical seizure activity within the first 24 hours after study drug administration (which may signify potential lidocaine neurotoxicity, as reported in the prehospital and/or hospital record).
- d) Severe bradycardia and/or heart block defined as a rhythm requiring temporary pacing support during the first 24 hours after study drug administration in a patient not previously requiring pacing, as reported in the prehospital and/or hospital record.

### **3.22 Analyses**

The primary outcome is survival to hospital discharge, which will be analyzed in the efficacy population comprised of eligible randomized recipients of any dose of study drug whose presenting arrest rhythm is VF or pulseless VT. Survival outcome will be analyzed in the context of a primary comparison (comparing PM101 with placebo), and two secondary comparisons (comparing lidocaine with placebo, and PM101 with lidocaine). As a secondary endpoint, the trial will compare functionally favorable survival (Modified Rankin Score  $\leq 3$  at hospital discharge) between the 3 treatment arms.

#### **3.22.1 Primary Comparison**

This analysis will compare survival outcome in patients randomized to PM101 as compared with placebo in the efficacy population. This test will be performed using the Z-test for comparison of binomial proportions with pooled variance at a one-sided significance level of 0.025.

#### **3.22.2 Secondary Comparisons**

Secondary comparisons of survival outcome will be performed in lidocaine versus placebo and PM101 versus lidocaine groups comprising the efficacy population. As in the primary comparison, these comparisons will be based on a Z-test using the pooled variance. The comparison of lidocaine to placebo will be use a one-sided significance level of 0.025, and the comparison of PM101 to lidocaine a two-sided significance level of 0.05.

#### **3.22.3 Secondary Endpoint**

As with analysis of the primary and secondary outcomes, analysis of the secondary endpoint will compared between all treatment groups in the efficacy population. However, this analysis in the efficacy population will use functionally favorable survival (MRS 3 or less) as outcome rather than survival. This analysis will include the 3 treatment group comparisons using the Z-test for comparison of binomial proportions with pooled variance. In addition, exploratory analyses will compare MRS at hospital discharge as an ordinal outcome across treatment groups using the Wilcoxon rank-sum test and proportional odds regression.<sup>107</sup> Treatment effects

in this analysis will be summarized using the estimate of the common odds-ratio for comparing probabilities of superior scores between two treatment groups obtained from the proportional odds model and 95% confidence intervals for the odds-ratio will be obtained. The proportional odds regression models will include the stratification factors (site and agency or subagency within site) as covariates. For the purposes of the secondary endpoint of MRS, patients dying before admission to the hospital will be treated in the same manner as admitted patients dying before hospital discharge and will be assigned an MRS of 6.

#### **3.22.4 Safety Analyses**

Evaluation of the safety of the study drugs will be performed in the efficacy population and in the safety population using all data from all patients who were randomized to treatment with study drug regardless of eligibility, presenting rhythm or actual receipt of treatment. In addition, safety outcomes will be specifically evaluated among patients in the safety population who presented with initial asystole or PEA and had late-occurring VF/VT. The safety population will be further stratified by those in whom drug was administered, and those in whom the drug kit was opened but confirmed not to have been given (Drug Kit Opened but Not Given (KONG)).

Safety will focus on:

- a) the incidence of severe drug allergy, seizures, or thrombophlebitis requiring medical or surgical intervention arising within the first 24 hours after study drug administration;
- b) marked differences between treatment groups in the incidence of bradyarrhythmias requiring temporary pacing arising within the first 24 hours after study drug administration.

#### **3.22.5 Prespecified Subgroup Analyses**

Modification of the effect of treatment in the efficacy population by the presence or absence of prognostic factors will be performed separately in subgroups as described in the previous section (3.20.4). Tests for interactions (different treatment effects between these subgroups) will also be performed. However, it is recognized that this study is not powered adequately to detect interactions and thus all subgroup analyses will be considered exploratory and not used as the basis for treatment recommendations.

#### **3.22.6 Mechanistic Outcomes**

Due to the large number of outcomes and potential analyses, results of analyses of these outcomes (specified in the previous section (3.20.5)) will be treated as exploratory or hypothesis-generating and will not be used to make treatment recommendations. These will be summarized descriptively and will be analyzed using the same methods as for secondary outcomes in order to give insight into the mechanism(s) underlying the observed treatment effect. Results will be reported using point estimates and 95% confidence intervals rather than p values.

#### **3.22.7 Supplementary Analyses**

In addition to these analyses, we propose to use the data acquired from our assessment of post resuscitation hospital care to determine what relationship, if any, specific care measures may have on survival outcome. Observations stemming from this exploratory analysis may provide a more informed basis for advising and better directing future post resuscitation care.

### **3.23 Sample Size**

All patients achieving a VF/VT rhythm will be eligible to be enrolled in the trial. However, as noted above, the benefits of drug treatment are expected to be limited to drug recipients who have an initial rhythm of VF/VT refractory to a single shock; in fact, based on results from the ARREST and ASPIRE trials, it is anticipated that survival rates in patients achieving late VF/VT rhythms will be close to 0 regardless of subsequent treatment. Thus, the primary analysis will use an efficacy population restricted to eligible randomized recipients of study drug (irrespective of dose) whose presenting arrest rhythm is VF/VT. Based on the frequency of presenting arrhythmias in the ARREST and ALIVE trials, it is anticipated that 85% of the enrolled patients will have initial VF/VT rhythms, whereas the remaining 15% will have initial asystole or PEA but with later development of VF/VT. If, as expected, patients with a late rhythm of VF/VT have close to 0 survival in all three treatment arms, an analysis focused on patients with initial VF/VT will have higher power than the one that included all randomized subjects as a result of restricting the analysis to the subpopulation in which the greatest treatment effect resides. In addition to the efficacy population, analyses will also be performed in all enrolled subjects, so that an unanticipated benefit of drug treatment even in the “late VF” population would be discoverable.

A target sample size of 3000 in the efficacy population will provide 90% power for each of the primary group comparisons to detect an increase in survival from 23.4% to 29.7% (a relative increase of 27%). This baseline survival rate was estimated using the PRIMED subjects with a first recorded rhythm of VT/ VF who received at least two shocks, a group expected to be representative of the subjects in the efficacy population.

### **3.24 Interim Analyses**

The trial will be monitored by a Data and Safety Monitoring Board using a sequential design to guide decisions regarding stopping the trial as soon as sufficient evidence is available to establish benefit or lack of significant benefit of the active treatments. The stopping boundaries for the comparisons of active drug to placebo are asymmetric, one-sided designs from the unified family of group sequential stopping rules using  $P=0.8$  for the superiority boundary and  $P=0.5$  for the futility boundary. The boundaries for monitoring the difference between the two active drugs is based on  $P=0.8$ . These are depicted in Tables 5-7.

**Table 5: Monitoring boundaries for Amiodarone vs. Placebo**

Analysis	Sample Size (total)	Prop. Max Stat Info	Lower stopping boundary (Amio not meaningfully better – drop Amio)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	600	0.2	-0.068	-0.055	(-0.120, 0.016)	0.117
2	1200	0.4	-0.038	-0.026	(-0.080, 0.027)	0.286
3	1800	0.6	-0.025	-0.014	(-0.060, 0.031)	0.461
4	2400	0.8	-0.017	-0.008	(-0.050, 0.033)	0.612
5	3000	1.0	-	-	-	-

Analysis	Sample Size (total)	Prop. Max Stat Info	Upper stopping boundary (Amio better – drop placebo)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	600	0.2	0.145	0.136	(0.061, 0.197)	0.001
2	1200	0.4	0.083	0.074	(0.023, 0.127)	0.006
3	1800	0.6	0.060	0.053	(0.010, 0.098)	0.018
4	2400	0.8	0.048	0.043	(0.003, 0.082)	0.035
5	3000	1.0	0.040	0.036	(0.000, 0.076)	0.050

**Table 6:** Monitoring boundaries for Lidocaine vs. Placebo

Analysis	Sample Size (total)	Prop. Max Stat Info	Lower stopping boundary (Lido not meaningfully better – drop Lido)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	600	0.2	-0.068	-0.055	(-0.120, 0.016)	0.117
2	1200	0.4	-0.038	-0.026	(-0.080, 0.027)	0.286
3	1800	0.6	-0.025	-0.014	(-0.060, 0.031)	0.461
4	2400	0.8	-0.017	-0.008	(-0.050, 0.033)	0.612
5	3000	1.0	-	-	-	-

Analysis	Sample Size (total)	Prop. Max Stat Info	Upper stopping boundary (Lido better – drop placebo)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	600	0.2	0.145	0.136	(0.061, 0.197)	0.001
2	1200	0.4	0.083	0.074	(0.023, 0.127)	0.006
3	1800	0.6	0.060	0.053	(0.010, 0.098)	0.018
4	2400	0.8	0.048	0.043	(0.003, 0.082)	0.035
5	3000	1.0	0.040	0.036	(0.000, 0.076)	0.050

**Table 7: Monitoring boundaries for Amiodarone vs. Lidocaine**

Analysis	Sample Size (total)	Prop. Max Stat Info	Lower stopping boundary (Lido better – drop Amio)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	600	0.2	-0.151	-0.141	(-0.206, -0.064)	0.001
2	1200	0.4	-0.087	-0.078	(-0.132, -0.024)	0.006
3	1800	0.6	-0.063	-0.055	(-0.102, -0.010)	0.018
4	2400	0.8	-0.050	-0.044	(-0.085, -0.003)	0.035
5	3000	1.0	-0.042	-0.037	(-0.079, 0.000)	0.050

Analysis	Sample Size (total)	Prop. Max Stat Info	Upper stopping boundary (Amio better – drop Lido)			
			Abs. Diff.	Adj. Diff	CI	P-value
1	600	0.2	0.151	0.141	(0.064, 0.206)	0.001
2	1200	0.4	0.087	0.078	(0.024, 0.132)	0.006
3	1800	0.6	0.063	0.055	(0.010, 0.102)	0.018
4	2400	0.8	0.050	0.044	(0.003, 0.085)	0.035
5	3000	1.0	0.042	0.037	(0.000, 0.079)	0.050

### 3.24.1 Study plan based on differing interim outcome scenarios

A variety of outcome scenarios can be envisioned on interim analysis, for which specific action may be required by the DSMB. These include:

- a) Should amiodarone be found superior to placebo, but other trial comparisons unresolved, the DSMB will be asked to rule on whether treatment with placebo should be discontinued and whether there are apparent emerging differences between amiodarone and lidocaine such that their continuation as the sole remaining treatment arms of the study is justified.
- b) Conversely, should amiodarone be found to be inferior to placebo, but other trial comparisons unresolved, the DSMB will be asked to rule on whether treatment with amiodarone should be discontinued, and whether there are apparent emerging differences between lidocaine and placebo such that their continuation as the sole remaining treatment arms of the study is justified.
- c) Should lidocaine, be found superior to placebo, but differences between amiodarone and placebo remain unresolved, the DSMB will be asked to rule on whether the placebo arm will be discontinued and whether there are apparent emerging differences between

lidocaine and amiodarone such that their continuation as the sole remaining treatment arms of the study is justified.

- d) Conversely, should lidocaine be found inferior to placebo, but differences between amiodarone and placebo remain unresolved, the DSMB will be asked to rule on whether the lidocaine arm should be discontinued and whether there are apparent emerging differences between amiodarone and placebo such that their continuation as the sole remaining treatment arms of the study is justified.
- e) Should amiodarone be found superior to lidocaine, but differences between amiodarone and placebo remain unresolved, the DSMB will be asked to rule on whether the lidocaine arm should be discontinued. Given that superiority of amiodarone to lidocaine will have been established, the remaining issue is whether amiodarone is superior to placebo, whereas the need to compare lidocaine against placebo (if already known to be inferior to amiodarone) is moot. In this instance the DSMB will be asked whether there are apparent emerging differences between amiodarone and placebo such that their continuation as the sole remaining treatment arms of the study is justified.
- f) Conversely, should amiodarone be found inferior to lidocaine, but differences between lidocaine and placebo remain unresolved, the DSMB will be asked to rule on whether the amiodarone arm should be discontinued. Given that superiority of lidocaine to amiodarone will have been established, the remaining issue is whether lidocaine is superior to placebo, whereas the need to compare amiodarone against placebo (if already known to be inferior to lidocaine) is moot. In this instance the DSMB will be asked whether there are apparent emerging differences between lidocaine and placebo such that their continuation as the sole remaining treatment arms of the study is justified.

These various interim analysis scenarios are summarized in Table 8.



**Table 8: Interim Analysis Scenarios and Proposed Treatment Plan**

Interim Trial Outcome	Disposition of other Treatment Arms			Comment
	Amiodarone (PM101)	Lidocaine	Placebo	
Amiodarone > placebo; other differences unresolved	Continue*	Continue*	Consider Stop	*If there are apparent emerging differences between these remaining treatment arms such that their continuation is justified
Amiodarone < placebo; other differences unresolved	Consider Stop	Continue*	Continue*	
Lidocaine > placebo; other differences unresolved	Continue*	Continue*	Consider Stop	
Lidocaine < placebo; other differences unresolved	Continue*	Consider Stop	Continue*	
Amiodarone > lidocaine; other differences unresolved	Continue*	Consider Stop	Continue*	
Amiodarone < lidocaine; other differences unresolved	Consider Stop	Continue*	Continue*	

> refers to “shown superior to”; < refers to “shown inferior to”

### 3.25 Expected Duration of Enrollment

The number of patients with cardiac arrest due to VF or pulseless VT consortium-wide is estimated to be approximately 2200 per year, based on the ROC cardiac arrest Epistry. From a recent randomized trial evaluating defibrillation therapy in patients with out-of-hospital cardiac arrest due to VF in Seattle (TIMBER), only approximately 20% of patients had return of circulation that was sustained to hospitalization in response to the first defibrillation shock. Conversely, approximately 70% of patients presenting with VF required a second shock, and approximately 50% required 3 or more shocks for ongoing or recurrent VF/VT.<sup>108</sup> It is anticipated that approximately 1100 (50% of 2200) patients per year would be eligible for enrollment in this trial. Allowing for the exclusion of up to about 10% of patients with IO, rather than IV, access (should IO administration not be permitted by FDA), it would require up to 3 years to complete enrollment if the trial is not stopped prior to reaching the maximum target sample size of 3000 patients in the efficacy population. It is estimated that were the trial to be powered for neurologically-intact survival (defined as having a Modified Rankin Score 3 or less at hospital discharge) as the primary (rather than secondary) endpoint, and as few as 80% of survivors had MRS of 3 or less, this would require over 4000 patients in the primary analysis, or a trial duration of about 4 years. A trial of such long duration, while feasible, could pose potential challenges with respect to its timely completion and analysis within the allotted funding cycle, as well as maintaining sufficient enthusiasm for ongoing enrollment among local EMS providers. Thus, the primary and secondary endpoints for this trial represent a pragmatic balance between valid scientific inquiry and what is believed can be feasibly accomplished within the framework of time, resources, and the prehospital care environment.

### **3.26 Safety Monitoring**

Clinical staff will report all potential adverse events to the Data Coordinating Center (DCC) as soon as possible. These will be collected in both a structured (standard form) and open (describing any difficulties encountered) form. All potentially serious adverse events will be classified by: a) Severity (life-threatening (such as anaphylaxis)), serious (such as thrombophlebitis requiring medical or surgical intervention), or non-serious; and b) Expected vs. unexpected; and c) Relation to study drug, as identified in the field prior to hospitalization, through contact with hospital care providers or upon review of the hospital record, and presented to the Data Safety Monitoring Committee. For serious unexpected 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 (DSMB) will help ensure the safety of the trial by monitoring adverse outcomes throughout the trial and by reviewing outcome data for possible harm. In addition, the committee will review the results of the interim analyses. The committee will review and approve the protocol before the study can commence. The DSMB will evaluate the rate of adverse events between the treatment and control arms at intervals to be determined by the DSMB, expected to be approximately semi-annually. The DSMB will also monitor primary and secondary study outcomes between the treatment and control groups. The coordinating center will forward DSMB reports to study investigators, the Institutional Research Boards, the Food and Drug Administration, and the sponsor in accordance with federal regulations 45 CFR Part 46 Subpart A and 21 CFR 312 and the Investigational New Drug Exemption regulations, as is our current practice.

### **3.27 Data Management**

Data will be collected by individual sites and provided to the DCC in the manner described below.

#### **3.27.1 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. Additional features of the web entry forms will include: forms transmission history, access to past forms, tracking of data corrections, and the capability to save and re-load incomplete forms.

#### **3.27.2 Database Management**

The DCC will use a two-tiered database system. A front-end database serves the web entry needs, using a database management system well-suited to handling updates from multiple interactive users. The data from this database will be transferred periodically (e.g. weekly) to a data format that can be utilized by statistical software packages. These will be the basis for queries, analyses and monitoring reports. Various versions of the database are kept as needed, e.g. for quarterly performance reports. Backups of data and programs will be performed regularly. Access to data is limited to those who need access to perform their tasks.

### **3.28 Human Subjects Research**

#### **3.28.1 Population**

This study calls for the enrollment of approximately 3000 patients who have sustained an out-of-hospital nontraumatic cardiac arrest and require treatment for ventricular fibrillation or pulseless

ventricular tachycardia. Review of cardiac arrest registry data suggest that these patients will be >60 years of age, the majority of whom will be men, with an anticipated mortality of approximately 80%. Enrollment will be restricted to patients of apparent legal consenting age who do not represent a protected population (that is, exclusive of pregnant women, prisoners and children). No other subgroups (based on gender, ethnicity or age) will be excluded.

### **3.28.2 Source of Data Collection**

Data will be collected prospectively from prehospital and subsequent hospital medical records, as well as electronic data from the resuscitation, including rhythm waveforms and CPR process information acquired from the defibrillators used during resuscitation.

### **3.28.3 Potential Risks**

The safety of IV PM101 administered as a bolus compares favorably with the previously approved formulation of amiodarone (Cordarone®), as reviewed elsewhere in this proposal. Both bolus IV lidocaine and amiodarone (Cordarone®) are regarded as standard of care in the resuscitation of cardiac arrest. Potential adverse effects related to their use, for lidocaine, include neurological toxicity and seizures, hypersensitivity, hypotension, bradycardia, heart block and local thrombophlebitis. For amiodarone (Cordarone®), potential adverse effects include hypotension, bradycardia, heart block, hypersensitivity, and local thrombophlebitis. The incidence of hypotension is anticipated to be less with PM101 than with Cordarone® given the difference in the excipient, as discussed in detail elsewhere. In this cardiac arrest population, it is expected that approximately 80% of patients will die with the majority of deaths occurring early in the hospital course. Therefore death in and of itself is not an adverse event. If the death is felt to be directly related to study treatments, it will receive expedited reporting. Other events such as acute myocardial infarction, pneumonia, and heart failure are expected in this population. Any unexpected events will be collected and reported to the FDA, NIH, IRB and DSMB in their semiannual review of data in aggregate and by treatment arm along with standard mortality data.

### **3.28.4 Protection Against Risks**

In accordance with the FDA, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. In accordance with the regulations 21 CFR 312.32, we have outlined the expected serious and non-serious adverse events. These will be reported according to the regulatory requirements. An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. In addition, subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location.

### **3.28.5 Recruitment and Consent**

This study qualifies for the “Exception from informed consent required for emergency research” outlined in FDA regulation 21CFR50.24. Because of the likely highly time-dependent benefit from treatment, the study drug needs to be administered as the first antiarrhythmic drug therapy as soon as possible following out-of-hospital cardiac arrest. In this uncontrolled setting, the patient will be unconscious secondary to pulselessness, and unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the arrest scene, or are sufficiently distraught so as to not be approachable for obtaining informed consent; nor is it practical for the pre-hospital provider to explain the study and receive consent while caring for

the patient. Cardiac arrest is a short-lived illness, for which immediate interventions cannot be delayed without irreparable harm to the patient. Taken together, these issues provide sufficient support for an emergency medicine exception from informed consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. We have outlined in Appendix 1 each criteria stipulated in the regulations for this exception and how our study design applies to these criteria.

Accordingly, this research will operate under exception from consent for emergency research through exception of consent regulations, with local community consultation and public disclosure as well as patient or family notification (with opportunity to withdraw from ongoing participation) at the earliest feasible opportunity after admission to the hospital, as further described in Appendix 2 (III.E.3e-f), and Appendix 3 (Suggested Notification Documents). PM101 has been approved by the FDA. Although this new formulation of amiodarone would be used in cardiac arrest in identical manner as the previously approved formulation of amiodarone (300 mg IV, followed by additional 150 mg if required), use of amiodarone regardless of formulation in this manner as a bolus is defined as off-label use within a trial using exception from informed consent for emergency research. For these reasons, an Investigational New Drug application (IND) for PM101 is required. In addition, at the time of IND submission to FDA, we will request permission to administer study drugs by IV or IO route under the IND, and carefully track such use and any resulting adverse effects during the course of the trial.

### **3.29 Budget**

The main costs entailed in this study pertain to supply of study drug, training of EMS personnel, as well as local and centralized study management. The study protocol is designed to be operationally straight forward (identification of an eligible patient, administration of two syringes of study drug, followed by standard resuscitation measures with subsequent administration of the remaining syringe, if required, until all supplies are exhausted). Paramedic personnel are already trained in obtaining vascular access and in administration of drugs. Study drug will be provided in prefilled syringes that require no additional skills or precautions in administration. Active and placebo drugs will be provided to the Consortium without cost by the manufacturer. The existing infrastructure at Consortium sites would provide for assurance of quality control, acquisition of data, and maintenance of drug inventory.

### **3.30 Anticipated Clinical Impact**

The results will provide important information about the choice and the value of antiarrhythmic therapy in cardiac arrest. From the perspective of its primary comparison, if PM101 is found to be superior to placebo, this will beg the precise questions posed by the trial's secondary comparisons. That is, how does PM101 then compare against lidocaine and how does lidocaine, in turn, compare against placebo? If, for example, PM101 but not lidocaine were found to be superior to placebo, or PM101 were found to be superior to both placebo and lidocaine, this result would define PM101's role as the antiarrhythmic drug of choice for VF/VT cardiac arrest.

Conversely, if PM101 is not found to be superior to placebo, the trial's secondary comparisons will address whether lidocaine is a more effective agent when compared against placebo and PM101. If, for example, neither PM101 nor lidocaine were found to be more effective than placebo, the trial results would challenge the antiarrhythmic drug hypothesis itself in cardiac arrest, and support refocusing resuscitative efforts on other interventions and avoid the use of either drug (and by inference, perhaps any antiarrhythmic drug).

Other possibilities could also emerge from these comparisons. For example, if amiodarone and lidocaine were both found to be better than placebo but each no better than the other, the results would support using either drug during resuscitation. Given the known higher intermediate efficacy of amiodarone as compared with placebo or lidocaine, a scenario in which

lidocaine would prove superior to placebo and PM101 is not anticipated. However, were this to be the case, lidocaine could emerge as the antiarrhythmic drug of choice in cardiac arrest, although the fact that this outcome represented a secondary, not primary, comparison of the trial would need to be taken into consideration, and accordingly qualified.

It is recognized that the frequency of cardiac arrest due to VF or pulseless VT is declining, and that therapies directed at this subgroup of victims of cardiac arrest excludes the majority of patients in whom the presentation of cardiac arrest is with a nonshockable arrhythmia. However, a significant minority of such patients may evolve from a nonshockable to shockable rhythm, and in whom the utility of antiarrhythmic therapy is unknown. Though not the primary focus of this study, outcomes will be evaluated in these patients who will be included in the trial's safety population. Finally, irrespective of their minority status, patients who present with cardiac arrest due to VF/VT currently represent the most salvageable group of patients with cardiac arrest, in whom acute therapies may afford the greatest impact on outcome, making the aims of this trial well worthy of study.

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## **Appendix 1: Exception from Consent for Emergency Research**

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

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

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

The proposed trial is a randomized trial of PM101, lidocaine or placebo to be administered as the first antiarrhythmic drug intervention to victims of cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia. These patients are in an immediate life threatening situation. Although VF is the most viable cardiac arrest dysrhythmia, only about 20% of victims of out-of-hospital or in-hospital VF arrest survive to be discharged from the hospital with the current standard of care. Standard of care for pre-hospital management of these patients includes CPR, defibrillation, use of vasoactive drugs (epinephrine and vasopressin) and use of antiarrhythmic medications (primarily lidocaine and/or amiodarone, depending upon the EMS system). Currently, no antiarrhythmic medication has been demonstrated to improve survival to hospital discharge after out-of-hospital cardiac arrest due to VF/VT. Amiodarone has shown promise in improving the short-term outcome of admission alive to hospital as compared with placebo or lidocaine, as reviewed elsewhere in this proposal and there is reason to believe it may improve survival after cardiac arrest, although whether any antiarrhythmic medication can achieve this outcome, as compared with the absence of antiarrhythmic medications, remains unproven.

Collectively, the relevant questions regarding antiarrhythmic drug treatment are not just which therapy is best but also whether drug treatment itself is beneficial. To adequately address these questions requires not only a comparison of the best available drug therapies, but the inclusion of a placebo control. Inclusion of placebo is both scientifically necessary and ethically justifiable. In its absence, proof of one agent's apparent superiority over another might only mean that one drug is less harmful than the other, not necessarily that either is truly beneficial. The fact that no pharmacologic agent has ever been demonstrated to improve survival to hospital discharge after cardiac arrest means that no study patient is necessarily being deprived of lifesaving treatment by receipt of placebo. Furthermore, if ineffective, the deployment of antiarrhythmic drug treatments in an illness of such short temporal duration as cardiac arrest may themselves potentially deprive patients of timely administration of alternate more beneficial therapies.

The proposed clinical trial will have sufficient statistical power to detect a clinically important difference in survival outcome. Furthermore, an emphasis on both survival (as primary endpoint) and neurological morbidity (as a secondary endpoint) will define the clinical utility of this resuscitation strategy 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.**

Because of the likely highly time-dependent benefit from treatment (as suggested by previous clinical trials), the study drug needs to be administered as the first antiarrhythmic drug therapy as soon as possible following out-of-hospital cardiac arrest. In this uncontrolled setting, the patient will be unconscious secondary to pulselessness, and unable to provide consent for study

enrollment. Legal next-of-kin are often not immediately available at the arrest scene, or are sufficiently distraught so as to not be approachable for obtaining informed consent; nor is it practical for the pre-hospital provider to explain the study and receive consent while caring for the patient. Cardiac arrest is a short-lived illness, for which immediate interventions cannot be delayed without irreparable harm to the patient. Taken together, these issues provide sufficient support for an emergency medicine exception from informed consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. Because of the unpredictable nature of cardiac arrest, it is not possible 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) Without immediate intervention, patients in pulseless cardiac arrest are facing imminent death.

(ii) Previous clinical studies have been conducted which suggest survival may be improved with receipt of the proposed intervention, with potentially significant direct benefit to individual patients with cardiac arrest.

(iii) With current therapies, victims of out-of-hospital cardiac arrest are overwhelmingly more likely to die of this acute illness than to survive. Antiarrhythmic drug therapy, though of unproven effectiveness, is the standard of care in present resuscitation from cardiac arrest, the potential life-saving benefits from which are believed to outweigh the known risks. Amiodarone and lidocaine have been routinely used in patients with cardiac arrest for number of years. Preliminary evidence suggests that amiodarone may be superior to lidocaine, and its use entails no greater risk to the patient than lidocaine. The inclusion of placebo in this evaluation is also necessary and justifiable. The fact that no pharmacologic agent has ever been demonstrated to improve survival to hospital discharge after cardiac arrest means that no study patient is necessarily being deprived of life-saving treatment by receipt of placebo rather than amiodarone or lidocaine. Furthermore, if ineffective, the deployment of antiarrhythmic drug treatments in an illness of such short temporal duration as cardiac arrest may themselves potentially deprive patients of timely administration of alternate more beneficial therapies. Thus there is clinical equipoise between the use of the three proposed interventions in this trial.

**(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 study drug as the first antiarrhythmic drug as soon as possible by EMS providers to these critically ill patients for whom any delay to treatment would be life-threatening.

**(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.**

Based on known data, the therapeutic window for the use of antiarrhythmic agents in shock-refractory cardiac arrest begins as soon as possible during resuscitation, and does not afford opportunity to obtain consent prior to or at the actual time of treatment. A script describing the study will be provided to a recognized LAR on-scene, when feasible, but it is acknowledged that the acute circumstances may only rarely if ever afford such opportunity. Accordingly, every effort will be made to contact legal representatives as soon as feasible after admission to the hospital to notify them that the patient was enrolled in a randomized trial. If legal representatives are not immediately available, research personnel will attempt to contact the subject's legal representative as soon as feasible and a summary of these efforts will be documented. If the subject becomes competent during the study period then he/she will be provided with the same information for notification of enrollment. These activities will be systematically tracked, documented and reported regularly to the IRB.

We propose to use exception from informed consent for emergency consent for participation in the study including review of records, with public notification, community consultation, and patient notification of enrollment, in keeping with FDA guidelines during the currently conducted ROC trials. However, when notified of study enrollment, the patient or their legal representative will be given the opportunity to withdraw from further study participation. If the patient or LAR withdraws, only the data up to the point of withdrawal will be accessed for study purposes. Our previous experience suggests that refusals of this nature are uncommon. During the notification process, the details of the study will be reviewed along with potential risks and benefits, the endpoints of interest and the process by which these endpoints are evaluated.

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

All procedures and notification documents (referred to as "consent documents") will be approved by the regional study site IRBs (Canadian Research Ethics Boards, REBs) 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 notification and consultation in accordance with local IRB and REB policies will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions, it will not be possible to target specific individuals although the local IRB may suggest targeting specific groups such as older citizens. The community consultation plan for each study site will be individualized to fit the IRB requirements. The ROC sites have considerable experience conducting community consultation and have published these experiences.<sup>109, 110</sup> A variety of methods are employed including consultation with community leaders and targeted community groups, random telephone surveys, and community meetings. Most sites provide opt out bracelets to individuals who do not want to be enrolled. Prehospital personnel will be trained to check for these bracelets prior to enrolling any patient.

(ii) & (iii) Public disclosures will be performed both prior to study enrollment (with opportunity and a mechanism for the community to contact the investigators with their response) and at the completion of the study in the form of multimedia press releases organized by the Resuscitation Outcomes Consortium and by local sites, at the direction of the local IRB/REB. 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, other means of providing such information such as advertisements placed in local papers describing the study may be performed, at the discretion of the local IRB/REB. Information regarding the study will also be available on the ROC website.

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

(v) We expect that all patients who meet the enrollment criteria will be unconscious, and thus will not be in a position to provide informed consent in the pre-hospital setting. In addition, any delay in medical care that would be required for EMS providers attempt to obtain consent from others on-scene would itself add to the acute life threatening circumstances. Accordingly, it is rarely, if ever, feasible to attempt to obtain informed consent during the therapeutic window. However, a brief written script describing the study (Appendix 11) will be developed for presentation to a LAR on-scene by the prehospital provider, when feasible, giving opportunity to exclude the subject from the study. Because the acute circumstances of cardiac arrest rarely if ever afford even such a limited opportunity without compromising patient care in process, determining if or when presenting this script is feasible, in light of these safety considerations, will be left to the clinical discretion of the provider.

The study staff will attempt to notify patients/families as soon as feasible after enrollment and will allow for an opportunity to withdraw from the research. In the event that a patient or their family withdraws from ongoing participation in this study and we are thereby unable to ascertain the primary outcome from the clinical record, we shall seek vital status information from our separate, ongoing cardiac arrest registry by using confidentiality agreements to protect patient privacy.

*Protection Against Risks*

In accordance with the FDA, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. In accordance with the regulations 21 CFR 312.32, we have outlined below the expected serious and non-serious adverse events. These will be reported according to the regulatory requirements.



### *Serious Adverse Events*

The safety of IV PM101 administered as a bolus compares favorably with the previously approved formulation of amiodarone (Cordarone®), as reviewed elsewhere in this proposal. Both bolus IV lidocaine and amiodarone (Cordarone®) are regarded as standard of care in the resuscitation of cardiac arrest. Potential adverse effects related to their use, for lidocaine, include neurological toxicity and seizures, hypersensitivity, hypotension, bradycardia, and heart blocks. For amiodarone (Cordarone®), potential adverse effects include hypotension, bradycardia, and heart block. The incidence of hypotension is anticipated to be less with PM101 than with Cordarone® given the difference in the excipient, as discussed in detail elsewhere.

### *Other Adverse Events*

Local thrombophlebitis has been reported with administration of lidocaine and PM101. The incidence of thrombophlebitis with PM101 is expected to be no greater than that reported for Cordarone®, but will be specifically monitored in the prehospital and hospital setting for the first 24 hours after study drug administration.

Hospital emergency department care providers will be given a local contact number by which they can direct any questions or concerns to the investigators, as well as an emergency contact number whereby treatment may be expeditiously unblinded upon request. In addition, all pre-hospital providers will be advised as to the potential adverse effects from treatment, and will be surveyed after each treatment incident to report any such problems. In this cardiac arrest population, it is expected that approximately 80% of patients will die with the majority of deaths occurring early in the hospital course. Therefore death in and of itself is not an adverse event. If the death is felt to be directly related to study treatments, it will receive expedited reporting. Other events such as acute myocardial infarction, pneumonia, and heart failure are expected in this population. Any unexpected events will be collected and reported to the FDA, NIH, IRB and DSMB in their semiannual review of data in aggregate and by treatment arm along with standard mortality data. Any unexpected or more serious than expected adverse event will be reported to the FDA, NIH, DSMB and IRB according to the regulations (within 10 working days or 7 days if fatal/life threatening).

All other potential adverse events will be reported to the DSMB and reviewed at the interim analyses and included in a safety report to the FDA. At the interim analyses, all adverse events will be reviewed and mortality will be compared between the groups. The chair of the DSMB can convene additional meetings as necessary to investigate adverse events.

An additional risk to subjects in this proposal pertains to the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis will be required to sign a confidentiality agreement as required by the institutional review board. In addition, subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location.

### *Potential Benefits to Subjects and Society*

Due to the Hawthorne Effect, patients in both arms of the study may anticipate improved outcomes because of the additional training and focusing of interest on them by pre-hospital personnel. The potential benefit to society involves a critical evaluation of antiarrhythmic therapy in a patient population that is most likely to benefit from this intervention. Results from this study could result in a significant change in the resuscitation strategy for cardiac arrest patients worldwide in the very near future.

### *Inclusion of Women*

There will be no exclusion on the basis of gender. Known pregnant women will be excluded due to the unknown effects of PM101 administered as a bolus on fetal development. In the unlikely

event that a pregnant woman and is inadvertently enrolled in the trial, his/her safety data will be evaluated for evidence of any harm resulting from treatment, but will otherwise be excluded from the trial.

#### *Inclusion of Minorities*

There will be no exclusion on the basis of race or ethnicity.

#### *Exclusion of Children*

Cardiac arrest is a rare occurrence in children. There is insufficient information on the use of PM101 in children to recommend its use in this population. For these reasons, children will be excluded from study. In the unlikely event that an adult-sized child is mistaken for an adult and is inadvertently enrolled in the trial, his/her safety data will be evaluated for evidence of any harm resulting from treatment, but will otherwise be excluded from the trial.

#### *Exclusion of Prisoners*

Prisoners will be excluded in accordance with Health and Human Services regulations. HHS regulations at 45 CFR part 46.303(c) defines prisoner as “any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.”

#### *Data Safety and Monitoring Plan*

This study will be monitored by an independent Data Safety Monitoring Board (DSMB) established by NHLBI. All adverse events will be reported to the DSMB as described. The DSMB will review the protocol in advance and develop a plan for monitoring in collaboration with the Resuscitation Outcomes Consortium Steering Committee.

## **Appendix 2: Overview of ROC Notification and Consent Procedures**

### **I. Introduction**

The intent of this document is to provide an overview of the approach to Institutional Review Board (IRB) oversight, subject notification and consent for the Resuscitation Outcomes Consortium's (ROC) anticipated trial entitled "Amiodarone (PM101), Lidocaine or Neither for Out-of-Hospital Cardiac Arrest due to Ventricular Fibrillation or Tachycardia," which will be referred to as the Amiodarone, Lidocaine or Placebo Study (ALPS) in this document.

The information is provided here to provide clarifying detail about the general principles of the ALPS notification/consent process and to serve as a reference for reviewers of the notification/consent process. It should be noted that the exact details regarding the implementation of these principles (e.g., consent documents) will be specific to the individual geographic sites.

### **II. Overview of Prehospital Emergency Research**

Conduct of prehospital emergency research differs from conduct of other research as follows:

- A. Interventions must be administered in a short therapeutic window;
- B. Interventions are administered to patients who are often not capable of advising on or consenting to the therapies (whether standard or experimental) that they will receive;
- C. Interventions are administered in the prehospital setting, where there is not access to as wide a range of diagnostic and therapeutic options;
- D. Interventions are administered by Emergency Medical Service (EMS) providers who are not as highly trained as physicians and whose number on scene is limited;
- E. There is a definite break in the continuity of care: Providers administering the intervention are not involved in the long term (i.e. hospital and post-discharge) follow-up of the patient, and the physicians administering follow-up care were typically not involved in specifying the prehospital treatments administered to the patient population.
- F. Furthermore, in research directed solely toward assessing the safety and effectiveness of prehospital therapeutic strategies:
  1. Research interventions are most likely completed prior to hospital admission, and staff of the receiving hospitals are not frequently directly engaged in the research.
  2. Hospital activities related to subjects may be entirely passive: Subjects are notified about their participation in the research, and medical records are reviewed, but no further research-related therapies or diagnostic studies are administered in the hospital. In this way, the effectiveness of the experimental prehospital therapeutic strategy can be assessed in the context of current in-hospital medical practice.

ALPS is being conducted under an exception from informed consent, which invokes a number of regulatory requirements both during the design and conduct of the clinical trial. Below is a brief description of the features of the clinical trial and the consortium of investigators that impact the implementation of the clinical trial.

### **III. Overview of ALPS**

ALPS is a randomized clinical trial conducted in the prehospital emergency setting by the Resuscitation Outcomes Consortium (ROC). ROC is a government sponsored consortium of 10

geographic centers in North America (7 US, 3 Canadian) encompassing more than 200 EMS agencies that serve a catchment population of more than 20 million people. Surviving patients will be treated at more than 250 receiving hospitals.

The ultimate goal of ALPS is to improve the clinical outcomes of patients who experience an out of hospital cardiac arrest (OOHCA). The mission of ROC is to investigate therapeutic strategies administered by Emergency Medical Technicians (EMTs) and/or paramedics involved in the organized EMS response to a call to 911.

ALPS employs a design to compare the effectiveness of antiarrhythmic drug treatments for OOHCA. The trial will have one primary endpoint, survival to hospital discharge. This outcome will be analyzed in the context of a primary hypothesis (comparing amiodarone with placebo), and two secondary hypotheses (comparing lidocaine with placebo, and amiodarone with lidocaine). As a secondary endpoint, the trial will compare functionally favorable survival (Modified Rankin Score  $\leq 3$  at hospital discharge) between the 3 treatment arms.

#### **A. Co-Enrollment**

ALPS will be conducted in concert with a second (non-FDA regulated) ROC trial, in which patients will be co-enrolled, in a partial factorial design. This second ROC study (referred to here as the "ROC CPR Trial") will evaluate two forms of CPR before intubation: one in which chest compressions are interrupted for ventilations (in a ratio of 30 compressions to 2 ventilations) vs. CPR in which continuous chest compressions are not interrupted for ventilation, both of which are within the scope of currently accepted emergency medical practice. ALPS and the ROC CPR Trial will be conducted at two distinctly different phases of resuscitation, for which there is likely to be minimal overlap. That is, the ROC CPR Trial will be conducted by EMTs during the initial provision of basic life support interventions before intubation, whereas ALPS will be conducted by paramedics during the later provision of advanced life support interventions when in all likelihood the patient will have been intubated and ROC CPR Trial interventions completed. Not all patients will be co-enrolled in both trials; this will depend upon their eligibility for each trial and whether respective EMS agencies are participating in either trial. It is likely, for example, that many of the patients enrolled in the ROC CPR Trial will not be eligible for randomization in ALPS. There are not expected to be any interactions between ALPS and the ROC CPR Trial, but this will be carefully monitored by the same Data Safety Monitoring Board (DSMB) which will oversee both trials. Both trials will be conducted under Exception from Informed Consent Requirements for Emergency Research, and the notification process for coenrolled patients will be melded into a single notification, covering the specifics of both trials, and with identical notification procedures, as outlined below for ALPS. Single notification in this instance refers to a single contact with the subject and/or LAR (either in person, or in a single mailing) during which notification for each study in which they may have been enrolled (with opportunity to withdraw from ongoing participation in either or both) will be provided. The notification documents themselves that will be provided during such an encounter will be separate for each respective study. Thus, for example, the subject and/or LAR would be notified by study personnel of their enrollment in ALPS and a separate CPR study, and provided separate notification documents describing each respective study. Each notification form will also state the possibility that the subject may be co-enrolled in a separate study, whether or not this actually occurs.

#### **B. Exception from Informed Consent**

ALPS will be conducted in the U.S. under the Exception from Informed Consent Requirements for Emergency Research as regulated under 21 CFR 50.24.because:

1. The patients are in a life threatening situation in which available treatments are unproven or unsatisfactory and collection of valid scientific evidence is necessary;
2. There is a body of animal and pilot clinical data suggesting that the participants involved in the clinical trial might directly benefit from the investigational therapies with an acceptable risk/benefit ratio;
3. Obtaining informed consent is not feasible due to the short therapeutic window after the onset of OOHCA
4. It is not feasible to conduct the study by prospectively identifying and obtaining consent from subjects at high risk for the need for the intervention; and
5. The safety and effectiveness of the treatments investigated in this clinical trial when used in the prehospital emergency setting could not be inferred from studies conducted in the absence of an exception from informed consent.

Participation of the Canadian sites under the Exception from Informed Consent is governed by Article 2.8 of the Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans. The above justification for the Exception from Informed Consent satisfies those Canadian regulations, as well.

### **C. Overview of Oversight of ALPS**

The trial will be conducted with the approval and oversight of Institutional Review Boards (IRBs) and Regional Ethics Boards (REBs) in the US and Canada, respectively. The IRBs / REBs will affirm that the study adheres to the above requirements of 21 CFR 50.24 (in the US) or Article 2.8 of the Tri-Council Policy Statement (in Canada). These will include:

1. At the earliest feasible opportunity, subjects or their legally authorized representatives (LARs) will be informed of their participation in this study and be provided with information about the study consistent with the level of information that would normally be included in an informed consent process; and
2. At this earliest feasible opportunity, subjects or their LARs will also be informed of their right to withdraw from ongoing participation in the clinical trial and be informed of the process by which they may make their desires for study discontinuation known to the investigators.
3. If the information regarding the clinical trial was initially provided to an LAR due to the inability of the patient to process such information, the investigators will again provide the information to the participant as soon as he/she becomes competent.

### **D. Subject Enrollment**

The process of notifying a patient, family member or LAR of his/her participation in ALPS including providing an opportunity to withdraw from ongoing participation will vary, depending upon his/her vital status (alive versus dead).

#### **1. ROC Epistry Characterization of Vital Status**

ROC Epistry, a registry including all out of hospital cardiac arrest (OOHCA) or severe trauma events having EMS response by any of the participating ground ROC EMS agencies. The following table provides Epistry data related to OOHCA for each geographic site in ROC (the SDG data are incomplete):

- a. The number of 911 calls for OOHCA that were reported as having an EMS response in calendar year 2006,

- b. Among all those 911 OOHCA calls, the percentage that received some amount of treatment by the EMS providers, the percentage that were transported to the hospital, and the percentage that led to a discharge alive from the hospital,
- c. Among all EMS treated episodes of OOHCA during 2006, the percentage that were transported to the hospital and the percentage that led to a discharge alive from the hospital, and
- d. Among all patients transported to hospital for OOHCA during 2006, the percentage that were discharged alive from the hospital.

**Table 1: Outcomes after OOHCA As Reported to ROC Epistry**

Site	Number of Reported OOHCA		Proportions					
			Among All Reported OOHCA			Among EMS Treated OOHCA		Among Transport to hospital
	All 911 Calls	EMS Treated	Treated	Transport to hospital	Survive to Hosp D/C	Transport to hospital	Survive to Hosp D/C	Survive to Hosp D/C
ARC	697	272	0.390	0.344	0.011	0.882	0.027	0.031
DAL	2052	1058	0.516	0.495	0.019	0.960	0.037	0.039
MLW	798	708	0.887	0.358	0.086	0.404	0.097	0.241
OTT	2980	1856	0.623	0.393	0.031	0.631	0.049	0.078
PGH	1168	534	0.457	0.336	0.042	0.736	0.093	0.126
PTL	1229	751	0.611	0.355	0.076	0.581	0.125	0.215
SDG <sub>1</sub>	453	354	0.781	0.263	--- <sup>1</sup>	0.336	--- <sup>1</sup>	--- <sup>1</sup>
SKC	2283	1163	0.509	0.245	0.078	0.482	0.154	0.320
TOR	3948	2399	0.608	0.313	0.027	0.516	0.044	0.086
VAN	2359	1596	0.677	0.365	0.056	0.539	0.083	0.153
TOT	17967	10691	0.595	0.352	0.044	0.591	0.074	0.125

<sup>1</sup> Epistry data for SDG is incomplete.

Site to site variation in the proportion of OOHCA patients who are EMS treated, who are transported to hospital, or who survive to hospital discharge may reflect variation across sites in patient characteristics, in the incidence of bystander witnessed arrest with bystander administered CPR, in the response time following 911 calls due to urban vs. rural EMS coverage, in the legal authority of EMS providers to withhold treatment or to declare death in the field, and/or in the effectiveness of the treatments routinely administered by particular EMS agencies.

Collectively these data demonstrate that a high proportion of patients die in the field; and a minority of patients survive to discharge. The recognition of these low survival rates led the

ROC investigators to generally adopt a notification/consent process that would place the least burden on the participants by permitting their personal notification or legally authorized representative (LAR) as soon as feasible after hospital admission, or by mail in the event of death before such notification was possible. (Exact procedures at each site will, however, vary according to local IRB oversight.)

### **E. Phases of ALPS**

In order to best address the medical, ethical, and logistical issues involved in the conduct of the clinical trial and the consent process, the ROC investigators find it useful to view the implementation of the clinical trial as comprised of three distinct phases:

- *Pre-implementation phase*: The study protocol is reviewed and approved by oversight and regulatory bodies; community consultation and notification activities are conducted as directed by IRBs.
- *Intervention phase*: The treatments are administered out of hospital. This is the active treatment phase of the research activity.
- *Hospitalization phase*: Those patients whose condition warrants transport and admission to the Emergency Department and Hospital are monitored for clinical outcome. This phase of the research activity is passive, in that no further research related interventions are performed in the hospital. Instead, during this phase, subjects are notified of their participation in the trial and given an opportunity to withdraw from ongoing participation. Ongoing participation refers to the review of medical records related to the current hospitalization. In the event they do not decline further participation, their clinical outcome is passively monitored by the researchers. In this phase, hospital staff provides strictly routine clinical care to patients, and are not engaged in any study-related research activities.

The study activities ongoing during each of these phases are described briefly below.

#### *1. Pre-implementation phase*

- a. NIH Protocol Review Committee, and Data Safety Monitoring Board review and approval of the ALPS protocol
- b. FDA review and approval of the ALPS protocol, with approval of IND
- c. IRB of record review and approval of community consultation, notification, and components of a priori “opt out” plan:
  - During the course of notification/consultation, including public advertising of the study, individuals in the community not wishing to be enrolled in the trial will be provided opportunity to “opt out” in advance of treatment via provision of a mailing address and/or telephone number to which such a request can be made.
  - Those requesting a priori exclusion from trial enrolment should they sustain a cardiac arrest will be provided, without cost, with a bracelet or its equivalent which, when displayed, signifies ineligibility for the study.
  - A letter will accompany the bracelet/item indicating that it must be displayed on person in a recognizable manner (i.e. as a bracelet) in order to be identified by prehospital providers.
  - Prehospital providers will be trained to recognize such bracelets or their equivalent, and that the identification of such an item will exclude the patient from trial enrollment and study-related procedures.

- Because all study procedures are completed prior to hospital arrival, the bracelet and opt-out procedures are only relevant to this time period and are not relevant to events that transpire upon or after hospital arrival and therefore do not require training of hospital personnel with respect to their significance.
- If, during the onset or course of resuscitation, a family member of LAR learns of or expresses concern that the subject may receive research-related treatments, and objects to such treatment, this will be regarded as an “opt out” and prehospital providers will exclude the patient from study-related treatments.
- IRB of record final approval of ALPS protocol in light of community notification/consultation reported findings
- IRB approval from receiving hospitals for access to admitted subjects for notification and for access to medical records

## 2. Intervention Phase

- a. Within the first few minutes of a ROC EMS agency arriving on the scene, an eligible patient should receive standard basic life support treatments including analysis of cardiac rhythm (with administration of defibrillatory shock as appropriate).
- b. As soon as feasible after an advanced life support (ALS) ROC EMS agency arrives on the scene with study drug, vascular access will be established and eligible patients with ongoing or recurrent ventricular fibrillation or pulseless ventricular tachycardia will receive treatment with study drug. Treatment with study drug will be limited exclusively to the prehospital setting as an intravenous or intraosseous rapid bolus, and will not be administered after hospital arrival.
- c. All other aspects of the resuscitation efforts by the EMS providers should proceed according to the prevailing standard of care as determined by the Medical Director of the EMS agency.
- d. Data regarding the prehospital treatment of the participant will be abstracted from the Patient Care Report (PCR) or Ambulance Care Report (ACR) as routinely completed by the ROC EMS providers.
- e. The experimental interventions (treatment with study drug) is administered under an exception to consent in emergency research:
  - In OOHCA, the patients are unconscious, and thus unable to provide consent, and
  - If the LAR or family member is already aware (as a result of prior community notification activities or by other means) or becomes aware of and objects to a research intervention during the course of resuscitation, such a request will be honored insofar as possible, and the subject excluded from such treatment.
  - When feasible, a LAR or family member will be afforded opportunity to object to the subject’s enrollment in a clinical trial by means of a brief written script presented by the prehospital provider (Appendix 11). However, it is recognized that the provision of study-related



information at the scene of an ongoing cardiac arrest is rarely if ever feasible without redirecting limited on-scene resources and attention away from the immediate care of a pulseless patient, thereby potentially compromising care. Accordingly determining if or when such action is feasible, in light of these safety considerations, will be left to the clinical discretion of the provider.

- f. Ethical oversight of the study protocol and the EMS providers administering the intervention will be provided by one or more “main IRBs/REBs” for the geographical site.

### 3. Hospitalization Phase

- a. Once a ROC Drug Trial patient arrives at the receiving hospital, all experimental therapies dictated by the study have been completed. Patients are transferred to the care of the receiving hospital medical staff, and ALPS protocol dictates that the patients should receive usual medical care.
- b. Typically on arrival to the hospital, the ALPS patient is comatose as a consequence of the cardiac arrest, and will remain neurologically impaired and critically ill during the initial days of hospitalization. The majority of such patients will not survive to hospital discharge. In addition, families are usually in process of dealing with the sudden and catastrophic proportion of their loved one’s illness and uncertain prognosis for recovery during the early hospitalization phase.
- c. The ALPS protocol calls for hospitalization safety and effectiveness outcomes to be collected through passive review of medical records for such study defined adverse events as pulmonary edema, other serious adverse events noted in the discharge summary, vital status at discharge, and neurological status at discharge. There are no ROC Drug Trial specified therapeutic or diagnostic procedures administered in the hospital.
- d. This data abstraction and collection process is conducted by study staff who review the medical records under data sharing agreements with the receiving hospitals. Ethical oversight of the data abstraction process is primarily provided by the “main IRBs/REBs” at each site. Some receiving hospitals use their individual IRBs to review the data sharing agreements.
- e. Subject notification: In concert with the requirements of 21 CFR 50.24 and Article 2.8 of the Tri Council Policy Agreement, at the earliest feasible opportunity after admission to the hospital, ROC Drug Trial study staff will attempt to notify (inform) the subject or, if the subject is unconscious or otherwise incapacitated, the participant’s LAR of the patient’s inclusion in ALPS. This disclosure will be provided in person and/or by mail, at the discretion of the IRB/REB. The provisions of this notification, as reviewed with and approved by FDA (see Appendix 4), and subject to IRB/REB approval, will include:
  - An overall description of the trial, its objectives, including the specific treatments under study and their potential risks and benefits
  - Notification of inclusion in the study under the exception to informed consent;

- Information regarding the nature of the intervention(s) and the study procedures up to that point;
  - Information that additional study procedures during the hospital phase are limited to review of medical records related to the current hospitalization; no other study procedures or contact with study personnel are required
  - Notification of the right of each participant to decline further participation without such a decision impacting their future treatment, penalty or loss of benefits to which the subject is otherwise entitled and that such withdrawal means no further information will be collected about the subject from their medical record but that information collected thus far would be retained,
  - Data up to the time of a subject's withdrawal may be reported in aggregate at the time of trial publication
- 
- Notification of the means by which the participant can make any desire to decline further participation known, and the opportunity provided for such withdrawal from the study.
  - The ROC site study staff will maintain written records of the notification to each patient or LAR of his/her participation in the clinical trial. Such documentation will include the date and people involved in the notification.
- f. Notification of family or LAR of deceased subjects
- Family members or LAR of enrolled subjects who die prior to hospital arrival, or before a LAR or family member can feasibly be contacted before death in the hospital will receive an IRB-approved condolence letter along with a copy of a notification document identical to that provided to surviving subjects or families, but whose wording will be adapted to a deceased patient.
  - A physical address and telephone number for the investigators will be included in the notification form to address questions or to receive notice of withdrawal if requested.
  - Letters and notification documents will be mailed as soon as feasible, usually once an address and LAR recipient can be confirmed. Some IRBs, at their discretion, may recommended delaying such mailings for a variable time period after death, in the belief that permitting time for bereavement, funeral arrangements, and settling of local affairs, affords greater likelihood that the mailed materials would be received and actually read than if sent sooner
  - Of note, in instances cases of out-of-hospital cardiac arrest, either the name (e.g. John Doe) and/or address of residence (e.g. arrest occurred in a public location) for the deceased subject may not be known. In such instances other reasonable sources of information for LAR contact will be sought, such as a reverse telephone directory (if a telephone number is available), internet web search, or other good faith efforts to establish a contact for notification. These may not always be successful, in which case evidence of good faith effort will be documented.

- Notification mailings will be tracked and reported to IRBs at the time of study renewal.
  - Information provided in written notification documents to family members or LAR of deceased subjects will contain the same information and include the same provisions described in the preceding section E3e above, as reviewed with and approved by FDA (see Appendix 4), and subject to IRB/REB approval.
- g. Inadvertent enrollment of persons from a protected population
- Inadvertent enrollment of persons from a protected population will be reported to the IRB/REB
  - Notification procedures for subjects who were inadvertently enrolled in the trial will be identical to those specified in sections E3e and E3f above for all surviving and deceased subjects.
  - Records of inadvertently enrolled protected populations, in accordance with FDA regulations and as clarified with FDA, “may be accessed for purposes of evaluating safety and treatment efficacy in the following circumstances:
    - Subject recovers capacity and is able to consent to an on-going review of medical records describing clinical follow-up, or
    - LAR provides consent for the review of medical records, or
    - An IRB approves a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in §46.116 or waives the requirements to obtain informed consent for medical record review under 45 CFR 46.116(d). For this waiver provision to be satisfied, the IRB would have to find and document that:
      - The research involves no more than minimal risk to the subjects;
      - The waiver or alteration will not adversely affect the rights and welfare of the subjects;
      - The research could not practicably be carried out without the waiver or alterations; and
      - Whenever appropriate, the subjects will be provided with additional pertinent information after participation."
  - Under such conditions, information from "protected population subjects" (up to the time of their withdrawal from continued participation, if applicable) can be included in the study database, reviewed for safety, and reported in aggregate at the time of trial publication (see Appendix 4)
- h. Ethical oversight of the notification process will be provided by the “main IRBs / REBs” for each of the sites, who will be provided with the guidance provided by FDA pertaining to obtaining written informed consent under these circumstances. Specifically, that *“obtaining informed consent for access to medical records and collection of hospital data is not required since FDA*

*regulations do not require that written informed consent be obtained from the subject or the subject's LAR in order to continue that subject's participation in emergency research with the exception from informed consent. The investigator would have access to all of the records that are generated and maintained from enrollment until discharge or death, unless the subject or the subject's LAR or family member discontinues the subject's participation in the study."*

- i. ROC investigators will summarize efforts made to contact the subject's LAR [or family member] and make this information available to the IRBs at the time of continuing review in compliance with 21 CFR 50.24(a)(5) and (a)(7)(v).
- j. If the patient or his/her LAR indicate an unwillingness to continue participation in the study, whether orally or in writing, that directive will be binding on the investigators with respect to information documented in the medical record subsequent to the date and time of withdrawal of continued participation.
- k. In keeping with the recommendations of the FDA Consultative Body (as communicated to the ROC investigators on Dec 4, 2006), if a patient withdraws from further participation:
  - The study staff will have no further contact (neither in person, by telephone, nor in writing) with the patient or his/her LAR;
  - The medical record of the patient's hospitalization past the time of withdrawal may not be available for review (data pertaining to that patients' clinical outcomes prior to opting out can be retained); and
  - The ALPS investigators will instead have to rely on vital status as determined from our ongoing registry for cardiac arrest (in such a setting, safety and other outcome data will not be available for time periods following the patient/LAR withdrawal) and/or from public records.

#### **IV. Organization of ROC Research**

The mission of the Resuscitation Outcomes Consortium is to investigate the safety and effectiveness of therapeutic strategies administered by EMS providers (paramedics and EMTs) in the prehospital setting. The primary focus of currently implemented studies is the effectiveness of prehospital interventions in the context of current standards of in-hospital medical care. Hence,

- A. Research interventions are completed prior to hospital admission, and hospital staff of the receiving hospitals may not be directly engaged in the research.
- B. Hospital activities related to subjects are primarily passive: Subjects are notified about their participation in the research, and medical records are reviewed, but no further research-related therapies are administered. Furthermore, to the extent that the requirements of monitoring for safety will allow it, the study protocol does not prescribe diagnostic studies during hospitalization beyond those consistent with current standards of in-hospital medical practice.

The administrative structure of ROC and the ethical oversight of the ROC studies reflects the prehospital nature of the interventional trials. In the case of ALPS, the intervention is completed in the prehospital setting, and the hospital phase of the research involves contact between the participants and the study personnel only for the purposes of informing the patients of their participation in the clinical trial and their right to decline further participation. Collection of outcome data for safety and primary measures of effectiveness relies primarily on review of the

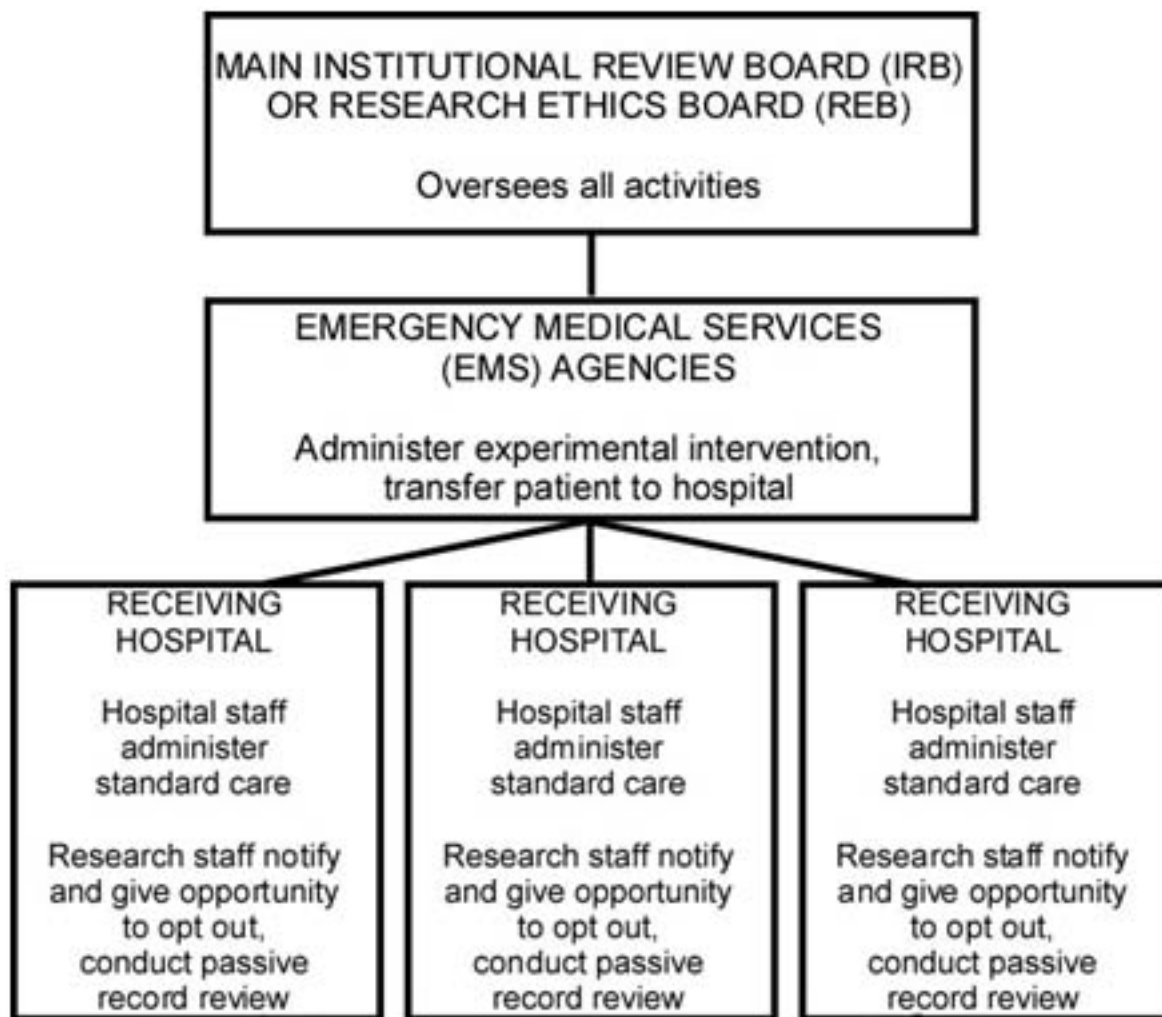
routine medical care received by the patient in the hospital, providing the patient has not declined further participation in the study.

The remainder of this document describes the general framework for the ethical oversight of ALPS.

## V. Main IRB Oversight

In each ROC site, one main institution (and IRB / REB) is responsible for oversight of the entire study including administration of the intervention by the EMS agencies, the notification of the patients, and collection of the study data in the prehospital and hospital setting.. The study staff in most cases is associated with the main institution. The **main IRB / REB** determines the notification process, notification materials, the community consultation process, etc.

Figure 1: Organization



### A. EMS agencies

The site investigators and the main IRB / REB in collaboration with the individual EMS agency medical directors oversee the training and adherence to the study protocol. The EMS transports the patient to various hospitals as dictated by their local requirement which are not altered due to the study. The EMS agency notifies the investigators of patient enrollment and forwards patient records for the collection of data for the study.

## **B. Receiving Hospitals**

Patients who are enrolled in a study that is conducted in the out-of-hospital setting with exception from consent for emergency research are taken to any of many different hospitals for care after their resuscitation in the field. Once the patient reaches the emergency department of such a receiving hospital, no further study-related intervention is conducted in the hospital; only standard of care is provided. However, the ROC investigators need to apply to the hospital for access to the patient for notification and to review hospital records. The hospital personnel in these receiving hospitals are NOT engaged in the research but merely allowing access to the patient for notification and to the patients' records by ALPS researchers. Thus there is no reason nor requirement that they separately approve the policies and procedures pertaining to the prehospital interventions themselves, if these have already been approved by the main IRB / REB that is providing such oversight for the trial's actual conduct. Many receiving hospitals choose to have their own IRB review and approve the protocol and study procedures specific to data abstraction from the hospital record, recognizing that the main IRB is providing oversight for and has approved the prehospital trial itself, including policies and procedures related to subject notification. Other receiving hospitals do not have their own IRB, and choose to approve access to the patient and the records by other means such as data sharing agreements, administrative approval to review records, etc., recognizing that the main IRB is providing oversight for the prehospital trial itself. Participation by these receiving hospitals is passive, that is, limited to review of the medical records and allowing the investigators access to the patient to notify them of study enrollment.

## **VI. Similarities and Differences between U. S. and Canadian Regulatory Requirements**

- A. Canadian sites are obligated to act according to the principles and guidance of the Canadian Tri-Council Policy Statement for Ethical Conduct for Research Involving Humans (December 2010)  
[http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS\\_2\\_FINAL\\_Web.pdf](http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf).
- B. The three Canadian Government Councils are; the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada.
  - 1. The policy states: "This Policy expresses the Agencies' continuing commitment to the people of Canada to promote the ethical conduct of research involving humans. It has been informed, in part, by leading inter- national ethics norms, all of which may help, in some measure, to guide Canadian researchers, in Canada and abroad, in the conduct of research involving humans."
- C. Canadian researchers, funded through Canadian Government Agencies, are bound by the following statement from the Policy:

1. "As a condition of funding, the Agencies require that researchers and their institutions apply the ethical principles and the articles of this Policy and be guided by the application sections of the articles."
2. The components of this policy statement are the guiding principles used by local Research Ethics Boards (REB) when approving studies in their jurisdiction.

#### D. Canadian waiver of consent guidelines

##### 1. Article 3.8

"Subject to all applicable legal and regulatory requirements, research involving medical emergencies shall be conducted only if it addresses the emergency needs of the individuals involved, and then only in accordance with criteria established in advance of such research by the REB. The REB may allow research that involves medical emergencies to be carried out without the consent of participants, or of their authorized third party, if all of the following apply:

- a. a serious threat to the prospective participant requires immediate intervention;
- b. either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care;
- c. either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant;
- d. the prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project;
- e. third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so; and
- f. no relevant prior directive by the participant is known to exist.

When a previously incapacitated participant regains capacity, or when an authorized third party is found, consent shall be sought promptly for continuation in the project, and for subsequent examinations or tests related to the research project."

2. The following paragraph defines the special obligations to those who cannot consent:

"Because their incapacity to exercise consent makes them vulnerable, prospective participants for emergency research are owed special ethical obligations and protection commensurate with the risks involved. Their welfare should be protected by additional safeguards, where feasible and appropriate. These might include: additional scientific, medical or REB consultation; procedures to identify prospective participants in advance so that consent may be sought prior to the occurrence of the emergency situation; consultation with former and prospective participants; and special monitoring procedures to be followed by data safety and monitoring boards."

3. In previous ROC trials (as approved by the FDA), Canadian Research Ethics Boards have always required the following: Consent for follow-up if there is to be further patient contact after the opportunity for the patient or legal representative to consent. This issue is not applicable to ALPS, which has no provision for subject follow-up.

4. In previous ROC trials, some but not all Canadian Research Ethics Boards, at their discretion, have required the following:

Notification by mail to all patients enrolled in the trial (or their legal representative) if the patient is deceased or if personal contact is not required for other reasons (such as to explain additional research activities that require written informed consent (which is not applicable to ALPS)). This mail notification describes how a patient can contact the researchers and object to collection of any more information on outcomes. REBs in Canada recognize that the waiver of informed consent includes collection of hospital information in order to carefully track any potential safety issues related to the experimental therapy.

5. In Canada, there is no uniform REB consensus regarding community consultation and notification. However, in compliance with FDA IND requirements, Canadian sites participating in ALPS will perform community notification and consultation activities in advance of the trial and at its conclusion the components of which will be at the discretion of the local REB.



## Appendix 3: Suggested Templates for Notification Documents

### **3A: Notification of Enrollment in a Research Study** **Amiodarone, Lidocaine, or Neither in Cardiac Arrest**

*(Insert Investigator list and phone numbers here)*

#### **Surviving Subjects**

##### **Purpose and Benefits of the Research**

*You/Your family member had a cardiac arrest and survived. The Emergency Medical System (EMS) providers quickly started cardiopulmonary resuscitation (CPR). This includes breathing for you and pumping on your chest. They may have applied electricity to your heart, often referred to as defibrillation, to try and restore a normal heart beat.*

The EMS providers who cared for *(you/your family member)* when *(you/he/she)* had *(your/his/her)* cardiac arrest are participating in a research study to see how to best treat cardiac arrests. Because of the seriousness of *(your/his/her)* illness and the immediate need for treatment, the providers were unable to ask *(your/his/her)* permission to participate in the study. However, we told the public about this study before it started. Also, the Food and Drug Administration (FDA) and the *Name of Institution* Institutional Review Board reviewed this study before it started and gave us permission to enroll subjects without their consent. The study is being supervised locally by Dr. *XXX of XXX*.

EMS providers treat cardiac arrest by performing cardiopulmonary resuscitation (CPR). This includes pushing on the chest with the heel of their hands to help the blood move, and helping a person breathe. By giving chest compressions during CPR, blood is circulated throughout the body to the important organs. The EMS providers also give medications intended to stabilize the heart beat (called heart rhythm medications) but these medications have not been shown to increase the number of people who survive from a cardiac arrest.

##### **Purpose**

The purpose of the study is to determine whether the use of heart rhythm medications will improve the likelihood of patients surviving to hospital discharge following a cardiac arrest outside of the hospital. The study will also look at whether more patients are discharged alive from the hospital when given the heart rhythm medication amiodarone compared to lidocaine (another drug used for an irregular heart beat) or neither medication, that is, what is called a placebo (made up of salt water).

*You/your family member was/were* randomized (like the flip of a coin) to receive amiodarone, lidocaine or neither medication (a placebo made up of salt water), in addition to all other standard treatment measures for cardiac arrest. When admitted to the hospital, you received standard medical care there.

Several studies have been done looking at giving heart rhythm medications to persons who suffer a cardiac arrest outside of the hospital. Some have been promising in showing that more patients may reach the hospital alive, but none have shown an improvement in the number of patients who are discharged alive from the hospital. The purpose of this study is to find whether the most commonly used heart rhythm medications (amiodarone or lidocaine) can improve such survival, or whether neither is beneficial in treating patients with cardiac arrest. In this study, one-third of the patients in cardiac arrest will receive amiodarone, one-third will receive lidocaine and one third will receive a placebo made up of salt water rather than either medication. All patients will receive all other standard treatments for cardiac arrest.

This study is being conducted in 10 different areas throughout the United States and Canada by the Resuscitation Outcomes Consortium (ROC). Approximately 3,000 patients will be enrolled in this research. About XXX patients will be enrolled in our local area.

Cardiac arrest is an extreme emergency during which the patient will die within a few minutes if treatment is not begun immediately. Patients in cardiac arrest are unconscious and unable to discuss their treatment, and any time taken to discuss their treatment with family robs the patient of immediately starting life-saving measures. Because of this and because medications may have greater benefit if used quickly after a cardiac arrest, *(you/your family member)* was/were entered into the study at the scene of the event. In this situation, oversight groups who are responsible for supervising and regulating such studies, including the U.S. Food and Drug Administration (FDA) have allowed us to enter people into the study without first obtaining written consent. This permission was granted only after informing and seeking input from the local community as required by an oversight group. These requirements may have included household surveys, press releases, and lectures to the medical and lay public.

There are also other safeguards in place for this research. First, the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) which is supporting this research, had an independent group of experts to review the research to make sure it was scientifically sound. Next, another independent group of experts, a Data Safety Monitoring Board, was chosen to monitor the results of the research during the course of the study to be sure of patient safety. Finally, a local group associated with the University of XXXX is also monitoring the research.

If there is any benefit to you of being in the study, it has already occurred. You will receive no further benefit from being in this study. However, your participation in this study will benefit society if we are able to show whether an antiarrhythmic drug such as amiodarone provides more or less benefit than lidocaine or neither (a placebo made up of salt water).

## **Risks and Benefits of the Research**

Patient safety is carefully monitored and recorded for any complications of study treatments. As is possible with any new treatment, there are risks involved. Possible reactions to the study drugs are seizures, a severe drug allergy, or a slow heart beat that may require a pacemaker (a small device placed under your skin to speed up your heart beat). *(You/your family member)* may also experience a reaction to the drug that causes redness, warmth, tenderness or a hard swelling under your skin where the drug entered the body. However, you have already experienced these risks.

Also, there are risks associated with traditional CPR done by emergency medical providers. These risks are possible rib fractures, pneumothorax (collapse of part of the lung), laceration of the liver (internal cut of liver) or abdominal injury or pulmonary edema (fluid in the lungs). However *you/your family member* would have experienced these risks regardless of whether *you/he/she* was/were enrolled in this research.

After you were admitted to the hospital, all of the treatments for your cardiac condition were determined by your physicians, and this study did not interfere with such treatment in any way. The only treatment being evaluated was the use of the antiarrhythmic drugs under study (amiodarone and lidocaine) or neither (a placebo made up of a salt solution) given during the resuscitation.

Because all other treatments, tests, and procedures are part of routine care and not a part of this study, this study will not pay for any part of your medical care. Any tests, procedures, or treatment will be determined by your doctors as necessary for your care.

In the event of physical injury or complication which results directly from the study, treatment will be available immediately from the investigating team or referred for appropriate treatment at no cost to you within the limits of the institution's compensation plan. However, all physician, hospital, and laboratory bills will be charged to you and/or your insurance company. If you think that an adverse event has occurred, call one of the investigators at the top of this form.

There were no alternative treatments to treat the victims of cardiac arrest in the location that you had a cardiac arrest. The best known treatments were given.

Medical records will be reviewed and kept by the investigators for at least 2 years after the FDA is notified that the study is stopped or the drug is approved, and if it forms any part of a medical or scientific report, your identity will not be disclosed. Your records (including an electronic recording of your heart rhythm), which will not contain your name, address, phone number, or other personal identifying information, will be sent to the Data Coordinating Center at the University of Washington. The information gathered for this study will be used to try to determine better treatment for you and other patients with heart rhythm problems. As in all studies which evaluate new medical treatments, site information including medical records (which may contain identifying information such as your name and social security number) might be reviewed by the United States Food and Drug Administration, the National Institutes of Health, Health Canada (if applicable), the University of Washington Data Coordinating Center, PRISM (the company that manufacturers Amiodarone) and (*insert site IRB name*).

### **Treatment in other Studies**

It is possible that you may have also received treatment during your cardiac arrest as part of another research study that is unrelated to this drug study. If this was the case, you will receive similar information about this other study as that which has been provided to you here about this drug study.

### **Withdrawal from the study**

You may withdraw (*you may withdraw your relative*) from further participation in this study at any time after receiving this notification without penalty or loss of benefits to which you are otherwise entitled by telling us or by contacting the investigators at (*address, phone number*).

Withdrawing from the study means that information about your treatment that transpired up to the date and time of your withdrawal will be collected, but no further information will be collected about your treatment that occurs after this date and time.

### **Further Information**

If you have further questions concerning this study at any time you are free to contact the investigators listed at the top of this sheet. If you have questions about your rights as a research participant you may contact (*insert IRB name and contact number*).

### **3B: Notification of Enrollment in a Research Study** **Amiodarone, Lidocaine, or Neither in Cardiac Arrest**

*(Insert Investigator list and phone numbers here)*

#### **(Deceased Subjects)**

##### **Purpose and Benefits of the Research**

*Your family member had a cardiac arrest. The Emergency Medical System (EMS) providers quickly started cardiopulmonary resuscitation (CPR). This includes breathing for (him/her) and pumping on (his/her) chest. They may have applied electricity to (his/her) heart, often referred to as defibrillation, to try and restore a normal heart beat. Unfortunately, (he/she) did not survive.*

The EMS providers who cared for *(your family member)* when *(he/she)* had *(his/her)* cardiac arrest are participating in a research study to see how to best treat cardiac arrests. Because of the seriousness of *(his/her)* illness and the immediate need for treatment, the providers were unable to ask *(his/her)* permission to participate in the study. However, we told the public about this study before it started. Also, the Food and Drug Administration (FDA) and the *Name of Institution* Institutional Review Board reviewed this study before it started and gave us permission to enroll subjects without their consent. The study is being supervised locally by Dr. *XXX of XXX*.

EMS providers treat cardiac arrest by performing cardiopulmonary resuscitation (CPR). This includes pushing on the chest with the heel of their hands to help the blood move, and helping a person breathe. By giving chest compressions during CPR, blood is circulated throughout the body to the important organs. The EMS providers also give medications intended to stabilize the heart beat (called heart rhythm medications) but these medications have not been shown to increase the number of people who survive from a cardiac arrest.

##### **Purpose**

The purpose of the study is to determine whether the use of heart rhythm medications will improve the likelihood of patients surviving to hospital discharge following a cardiac arrest outside of the hospital. The study will also look at whether more patients are discharged alive from the hospital when given the heart rhythm medication amiodarone compared to lidocaine (another drug used for an irregular heart beat) or neither medication, that is, what is called a placebo (made up of salt water).

*Your family member was/were* randomized (like the flip of a coin) to receive amiodarone, lidocaine or neither medication (a placebo made up of salt water), in addition to all other standard treatment measures for cardiac arrest. If admitted to the hospital, your family member received standard medical care there.

Several studies have been done looking at giving heart rhythm medications to persons who suffer a cardiac arrest outside of the hospital. Some have been promising in showing that more patients may reach the hospital alive, but none have shown an improvement in the number of patients who are discharged alive from the hospital. The purpose of this study is to find whether the most commonly used heart rhythm medications (amiodarone or lidocaine) can improve such survival, or whether neither is beneficial in treating patients with cardiac arrest. In this study, one-third of the patients in cardiac arrest will receive amiodarone, one-third will receive lidocaine and one third will receive a placebo made up of salt water rather than either medication. All patients will receive all other standard treatments for cardiac arrest..

This study is being conducted in 10 different areas throughout the United States and Canada by the Resuscitation Outcomes Consortium (ROC). Approximately 3,000 patients will be enrolled in this research. About XXX patients will be enrolled in our local area.

Cardiac arrest is an extreme emergency during which the patient will die within a few minutes if treatment is not begun immediately. Patients in cardiac arrest are unconscious and unable to discuss their treatment, and any time taken to discuss their treatment with family robs the patient of immediately starting life-saving measures. Because of this and because medications may have greater benefit if used quickly after a cardiac arrest, *your family member* was entered into the study at the scene of the event. In this situation, oversight groups who are responsible for supervising and regulating such studies, including the U.S. Food and Drug Administration (FDA) have allowed us to enter people into the study without first obtaining written consent. This permission was granted only after informing and seeking input from the local community as required by an oversight group. These requirements may have included household surveys, press releases, and lectures to the medical and lay public.

There are also other safeguards in place for this research. First, the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) which is supporting this research, had an independent group of experts to review the research to make sure it was scientifically sound. Next, another independent group of experts, a Data Safety Monitoring Board, was chosen to monitor the results of the research during the course of the study to be sure of patient safety. Finally, a local group associated with the University of XXXX is also monitoring the research.

Your family member's participation in this study will benefit society if we are able to show whether an antiarrhythmic drug such as amiodarone provides more or less benefit than lidocaine or neither (a placebo made up of salt water).

## **Risks and Benefits of the Research**

Patient safety is carefully monitored and recorded for any complications of study treatments. As is possible with any new treatment, there are risks involved. Possible reactions to the study drugs are seizures, a severe drug allergy, or a slow heart beat. that may have required a pacemaker (a small device placed under the skin to speed up the heart beat). (*Your family member*) may also have experienced a reaction to the drug that causes redness, warmth, tenderness or a hard swelling under the skin where the drug entered the body.

Also, there are risks associated with traditional CPR done by emergency medical providers. These risks are possible rib fractures, pneumothorax (collapse of part of the lung), laceration of the liver (internal cut of liver) or abdominal injury or pulmonary edema (fluid in the lungs). However *your family member* would have experienced these risks regardless of whether *he/she* was/were enrolled in this research.

If admitted to the hospital, all of the treatments for your family member's cardiac condition were determined by your physicians, and this study did not interfere with such treatment in any way. The only treatment being evaluated was the use of the antiarrhythmic drugs under study (amiodarone and lidocaine) or neither (a placebo made up of a salt solution) given during the resuscitation.

Because all other treatments, tests, and procedures are part of routine care and not a part of this study, this study will not pay for any part of your family member's medical care. Any tests, procedures, or treatment were determined by your family member's doctors as necessary for his/her care.

In the event of physical injury or complication which resulted directly from the study, treatment was available immediately at no cost to them within the limits of the institution's compensation plan.

There were no alternative treatments to treat the victims of cardiac arrest in the location that your relative had a cardiac arrest. The best known treatments were given.

Medical records will be reviewed and kept by the investigators for at least 2 years after the FDA is notified that the study is stopped or the drug is approved, and if it forms any part of a medical or scientific report, your family member's identity will not be disclosed. Your family member's records (including an electronic recording of heart rhythm), which will not contain his/her name, address, phone number, or other personal identifying information, will be sent to the Data Coordinating Center at the University of Washington. The information gathered for this study will be used to try to determine better treatment for you and other patients with heart rhythm problems. As in all studies which evaluate new medical treatments, site information including medical records (which may contain identifying information such as your name and social security number) might be reviewed by the United States Food and Drug Administration, the National Institutes of Health, Health Canada (if applicable), the University of Washington Data Coordinating Center PRISM (the manufacturer of Amiodarone) and (*insert site IRB name*).

### **Treatment in other Studies**

It is possible that your relative may have also received treatment during your cardiac arrest as part of another research study that is unrelated to this drug study. If this was the case, you will receive similar information about this other study on his/her behalf as that which has been provided to you here about this drug study.

### **Withdrawal from the Study**

You may withdraw your family member from further participation in this study at any time after receiving this notification without penalty or loss of benefits to which they are otherwise entitled by telling us or by contacting the investigators at (*address, phone number*). Withdrawing from the study means that information about your family member's treatment that transpired up to the date and time of their withdrawal will be collected, but no further information will be collected about their treatment that occurred after this date and time.

### **Further Information**

If you have further questions concerning this study at any time you are free to contact the investigators listed at the top of this sheet. If you have questions about your family member's rights as a research participant you may contact (*insert IRB name and contact number*).

### **3C: Sample Condolence Letter (to be included with Information sheet for families of deceased subjects)**

To the Family of (Insert patient's name)

Address

Dear Family Member:

We understand this letter may come at a time that is difficult for your family and we offer our condolences for your loss. We are aware a death is often an unexpected event and may have devastating personal consequences.

We want to inform you of the treatment **your family member** received by (insert ambulance service) when they recently suffered a cardiac arrest. We want to assure you that **your family member** received the best medical care currently practiced for the treatment of cardiac arrest. In addition to the standard treatments for cardiac arrest, they were entered into a research study, in hope of finding the best medicines to treat cardiac arrest, and we are writing to inform you that this has occurred. This was done without their prior consent because they were unconscious and without a pulse at the time, and immediate treatment for this was necessary. No further action on your part is required. As part of this study, we will look at the medical records from the emergency response team and for the time **your family member** was hospitalized for the cardiac arrest. Additional information about the study is attached including the opportunity for you to withdraw your family member from ongoing participation in the study.

**Your family member's** having participated in this study will contribute a great deal to better understanding how we can improve the treatment of patients that have a cardiac arrest.

Additional Information about this study may be found at the following web address:

<http://www.xxxxxx.xxx>

**You** may withdraw your family member from ongoing participation in this study at any time after receiving this notification by calling (xxx) yyy-yyyy, or contacting us at the address provided below.

Apart from our sharing this information, you will receive no further contact from study personnel. If you have any questions about the study, please feel free to contact us at the number provided below.

We apologize for this intrusion. We appreciate how difficult this situation may be for you and your family and offer you our sincere condolences.

Kindest regards,

### **3D: Sample Letter (to be included with Information sheet for subjects/families of surviving subjects)**

Dear (insert subject's name)

We want to inform you of the treatment [you \(or your family member\)](#) received by (insert ambulance service) when you (or your family member) recently suffered a cardiac arrest. We want to assure you that [you \(or your family member\)](#) received the best medical care currently practiced for the treatment of cardiac arrest. In addition to the standard treatments for cardiac arrest, [you \(or your relative\)](#) were entered into a research study, in hope of finding the best medicines to treat cardiac arrest, and we are writing to inform you that this has occurred. This was done without your (or your family member's) prior consent because you were unconscious and without a pulse at the time, and immediate treatment for this was necessary. No further action on your part is required. As part of this study, we will look at the medical records from the emergency response team and for the time [you \(or your family member\)](#) were hospitalized for the cardiac arrest. Additional information about the study is attached including the opportunity for you to withdraw from ongoing participation in the study.

[Your \(or your family member's\)](#) having participated in this study will contribute a great deal to better understanding how we can improve the treatment of patients that have a cardiac arrest. Additional Information about this study may be found at the following web address:

<http://www.xxxxxx.xxx>

[You \(or your family member\)](#) may withdraw your ongoing participation in this study at any time after receiving this notification by calling (xxx) yyy-yyyy, or contacting us at the address provided below.

Apart from our sharing this information, you will receive no further contact from study personnel. If you have any questions about the study, please feel free to contact us at the number provided below.

We apologize for this intrusion. We appreciate how difficult this situation may be for you and your family and offer you our best wishes for your full recovery.

Kindest regards,



## Appendix 4: Communications with FDA Regarding the Interpretation of Subject Withdrawal

A:

-----Original Message-----

From: Fortney, Russell [<mailto:Russell.Fortney@fda.hhs.gov>]

Sent: Thursday, February 24, 2011 11:40 AM

To: 'Amy Gest'

Subject: RE: IND 110280 Clinical Hold Response-Data Retention/IO Access

Amy,

Our answer for each question is YES.

-Russell

-----Original Message-----

From: Amy Gest [<mailto:agest@uw.edu>]

Sent: Friday, February 18, 2011 7:54 PM

To: Fortney, Russell

Cc: 'Brown, Siobhan'; 'Powell, Judy'; 'Kudenchuk, Peter'; 'Lois Van Ottingham'; 'ctcAMY'

Subject: IND 110280 Clinical Hold Response-Data Retention/IO Access

Hi Russell,

Our data retention and IO Access clarification questions are below:

1. For living patients who withdraw we understand the regulations allow us to keep the data up to the time of withdrawal which can be used for publication in aggregate form. Is our understanding correct?

2. For patients who die prior to notification we understand that, as with living patients, the notification wording must contain the information about withdrawing from the research. The difference in this instance is that if a family member requests withdrawal there will not be further data to collect. Our understanding is that, as with living patients, the regulations in this instance also allow us to keep the data up to the time of withdrawal which can be used for publication in aggregate form. That is, the acquired data from withdrawn patients, whether living or deceased, may stay in the database and can be used in aggregate form for publication. Is this correct?

3. We understand that access to records of inadvertently enrolled protected populations is permitted by IRBs under the terms iterated by FDA. That is, for such subjects, "records may be accessed for purposes of evaluating safety and treatment efficacy in the following circumstances:  
\* Subject recovers capacity and is able to consent to an on-going review of medical records describing clinical follow-up, or

\* LAR provides consent for the review of medical records, or  
\* An IRB approves a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in §46.116 or waives the requirements to obtain informed consent for medical record review under 45 CFR 46.116(d). For this waiver provision to be satisfied, the IRB would have to find and document that:  
O The research involves no more than minimal risk to the subjects; O The waiver or alteration will not adversely affect the rights and welfare of the subjects; O The research could not practicably be carried out without the waiver or alterations; and O Whenever appropriate, the subjects will be provided with additional pertinent information after participation."

... Under such conditions, we understand the information from such "protected population subjects" can be included in the study database and reviewed for safety. Although such subjects are formally excluded from enrollment in the trial, in instances where such a subject has been inadvertently enrolled and with IRB approval under the conditions described above, the subjects will be included in aggregate form along with other enrolled patients when the trial is published. Is this correct?'

4. We had previously indicated to FDA that IO access for ALPS drug would be used when vascular access was otherwise infeasible (i.e. IO would serve as a second line vascular access approach). We have since learned that some EMS agencies have adopted IO as their primary (first line) method of vascular access for clinical purposes and are administering medications in this manner at present. Given this evolving practice, would FDA permit administration of study drug IO as a first line vascular access approach when this is the standard clinical approach for initial vascular access by an EMS agency? We would, of course, track all IO use of study drugs.

Please don't hesitate to contact us if you need any other information to respond to our questions. If need be, we can also schedule another conference call.

Thank you!  
Amy Gest

B:

>> \_\_\_\_\_  
>>  
>> From: Hillebrenner, Matthew  
> [mailto:matthew.hillebrenner@fda.hhs.gov]  
>> Sent: Wednesday, August 01, 2007 2:01 PM  
>> To: Graham; Wentz, Catherine P.  
>> Subject: RE:  
>>  
>>  
>>  
>> This is consistent with our interpretation.  
>>  
>>  
>>  
>> Sincerely,  
>>  
>> Matt  
>>  
>>  
>>  
>>  
>>  
>> \_\_\_\_\_  
>>  
>>  
>> From: Graham [mailto:grahamnichol@spamarrest.com]  
>> Sent: Wednesday, August 01, 2007 11:59 AM  
>> To: Hillebrenner, Matthew ; Wentz, Catherine P.  
>> Subject:  
>>  
>> Catherine  
>>  
>>  
>>  
>> Thanks for talking to me by telephone today. We discussed  
> whether and  
>> how researchers will be able to access the clinical record  
> of patients  
>> who opt out of ongoing participation at the time of notification in  
>> the Seattle King County site. Recall that access to the clinical  
>> record has been granted to the researchers by the UW IRB as part of  
>> the exception from consent for emergency research. Notification and  
>> provision of an opportunity to opt out will occur as soon  
> as feasible  
>> after enrollment. In the event that a patient opts out at  
> the time of  
>> notification, researchers will be able to access the  
> clinical record  
>> and abstract information contained in that refers to events  
> up to the  
>> time and date that the patient opted out.  
>>  
>>  
>>  
>> Please confirm that I have interpreted our conversation correctly.  
>>  
>>  
>>  
>> Thanks again.  
>>  
>> Graham  
>>  
>>

## **Appendix 5: 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 measure chest compression calculates CPR fraction. A separate impedance channel and audio recording are 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 an 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
<b>ALS Devices</b>							
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 in development	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
<b>BLS Devices</b>							
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 semiautomated 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 <sup>a</sup>	80	120	Above maximum or below minimum parameters in > 20% of resuscitations
CPR fraction <sup>b</sup>	0.85	0.6	-	Below minimum parameter in >20% of resuscitations

- a. refers to speed of compressions (i.e. the instantaneous compression rate) rather than actual number of compressions per minute
- b. CPR fraction will be defined as = (Total seconds with chest compressions) ÷ (Total seconds with interpretable signal and no evidence of spontaneous circulation).

### 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., ETCO<sub>2</sub> 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, 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.

## Appendix 6: Criteria for EMS Agency Data Compliance

Participation in the trial requires meeting all of the following performance measures during its conduct. (The corresponding percentages are working criteria that may be modified in the future at the discretion of the Study Monitoring Committee (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:

- Less than 2% missing/unknown data (unless otherwise specified) for the following data points:
  - <5% missing time of first vasopressor and of first study drug 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 among patients with VF/VT.
- 100% of Study Drug Kits accounted for; >95% of opened Study Drug Kits having a confirmed physical count of used and nonused study syringes performed by site

## Appendix 7: PM101 and Epinephrine Compatibility

Visual Compatibility of Nexterone injection and Epinephrine Injection

**Study Date:** August 12, 2009

**Completed by:** Paul Souney (on behalf of Prism Pharmaceuticals, Inc.)

**Purpose:** To evaluate visual compatibility of PM101 (NEXTERONE Injection) and epinephrine injection during simulated Y-site administration.

### Method:

Equipment: PM101, 50 mg/mL, 3 mL vial (7074); PM101, 1.5 mg/mL 100 mL bag (47967); epinephrine 0.1 mg/mL (IMS lot S1034F9, EXP 5/11), epinephrine (Hospira NDC004909-7241-01) 1 mg/mL

Allen et al.<sup>1</sup> demonstrated that the mixing of an i.v. fluid in the administration set with a secondary additive from the Y-injection site to the needle tip occurs in a 1:1 ratio. To simulate this situation, a 1-mL sample of each test solution of PM101 was mixed with a 1 mL sample of each epinephrine solution. The solutions were added to sterile empty glass vials. Duplicate samples of each solution containing PM101 and epinephrine were evaluated. Visual examinations were performed against a black and white background with the aid of a magnifying lens (2X) just after mixing (T0) and at 5 and 30 minutes, and at 4 and 24 hours. Solutions were examined for the presence of haze, precipitate, color change, and evolution of gas.

**Results:** No evidence of precipitate, color change or gas evolution in any study sample

	T0	5 minutes	30 minutes	4 hours	24 hours
N 50/Epi 0.1	C/C	C/C	C/C	C/C	C/C
N50/Epi 1.0	C/C	C/C	C/C	C/C	C/C
N1.5/Epi 0.1	C/C	C/C	C/C	C/C	C/C
N1.5/Epi 1.0	C/C	C/C	C/C	C/C	C/C

N50= Nexterone injection 50mg/mL; N1.5= Nexterone Premixed Injection 1.5 mg/mL

E0.1= epinephrine 0.1 mg/mL; E1.0 = epinephrine 1.0 mg/mL

Conclusion: Nexterone Injection 50 mg/mL and 1.5 mg/mL were each visually compatible with epinephrine injection 1 mg/mL and 0.1 mg/mL.

<sup>1</sup>Allen LV Jr, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets. Am J Hosp Pharm 1977;34:939-43.



# Appendix 8: Lidocaine and Epinephrine Compatibility

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## IV Compatibility Report

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Click result icon for detailed study information.

ND = No Data Available

---

From Trissel's™ Clinical Pharmaceutics Database

**YSite**

	Epinephrine hydrochloride	Lidocaine hydrochloride
Epinephrine hydrochloride	-	
Lidocaine hydrochloride		-

**Legend**      = Compatible      = Incompatible      = Results uncertain, variable or dependent

Click result icon for detailed study information.

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**Compatibility Chart**

- Indicates compatibility for this method.
- Uncertain or variable for this method.
- Indicates incompatibility for this method.
- No data for any method.

**Drugs**

Epinephrine hydrochloride

Lidocaine hydrochloride

Epinephrine hydrochloride

Lidocaine hydrochloride

Y-Site

Y-Site

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<http://online.factsandcomparisons.com/IVH/compatibilityChartDisplayPrint.aspx?&drugs...> 7/20/2009

**Additional Compatibility Information**

**Alkalies and Oxidizing Agents** — Epinephrine hydrochloride is rapidly destroyed by alkalies or oxidizing agents including sodium bicarbonate, halogens, permanganates, chromates, nitrates, nitrites, and salts of easily reducible metals such as iron, copper, and zinc. (4)

Drugs known to be alkali labile such as epinephrine should not be mixed in aminophylline-containing solutions because of the alkalinity of these solutions. (6)

**Color Changes** — Visual inspection for color changes may be inadequate to assess compatibility of admixtures. In one evaluation with aminophylline stored at 25 °C, a color change was not noted until eight hours had elapsed. However, only 40% of the initial epinephrine hydrochloride was still present in the admixture at 24 hours. (527)

**Bupivacaine and Fentanyl** — A solution composed of bupivacaine hydrochloride (Winthrop) 0.44 mg/mL, fentanyl citrate (Janssen) 1.25 mcg/mL, and epinephrine hydrochloride (Abbott) 0.69 mcg/mL was stored in 100-mL portable infusion pump reservoirs (Pharmacia Del-

tec) for 30 days at 3 and 23 °C. The samples were then delivered through the infusion pumps over 48 hours at near-body temperature (30 °C). The samples were visually compatible throughout, and bupivacaine hydrochloride and fentanyl citrate exhibited no loss by HPLC analysis. Epinephrine hydrochloride sustained about a 5 to 6% loss by HPLC analysis after 20 days of storage at both temperatures and about a 9 to 10% loss after 30 days of storage and subsequent pump delivery. The authors recommended restricting storage before administration to only 20 days. (1627)

**Lidocaine Hydrochloride** — When lidocaine hydrochloride is mixed with epinephrine hydrochloride, the buffering capacity of the lidocaine hydrochloride may raise the pH of intravenous admixtures above 5.5, the maximum necessary for stability of epinephrine hydrochloride. The final pH is usually about 6. Epinephrine hydrochloride will begin to deteriorate within several hours. Therefore, admixtures should be used promptly after preparation or the separate administration of the epinephrine hydrochloride should be considered. This restriction does not apply to commercial lidocaine-epinephrine combinations that have had the pH adjusted to retain the maximum epinephrine potency. (24)

**EPIRUBICIN HYDROCHLORIDE**  
**AHFS 10:00**

**Products** — Epirubicin hydrochloride is available as a 2-mg/mL, preservative-free, ready-to-use solution in single-use polypropylene vials of 25 and 100 mL containing 50 and 200 mg of drug, respectively. The solution also contains sodium chloride and water for injection. The pH has been adjusted with hydrochloric acid. (1-5/05)

**pH** — The solution pH has been adjusted to 3. (1-5/05)

**Trade Names** — Ellence.

**Administration** — Epirubicin hydrochloride is administered by intravenous infusion over three to five minutes; infusion into the tubing of a freely running intravenous infusion of sodium chloride 0.9% or dextrose 5% is recommended. Administration by direct push is not recommended because of the risk of extravasation. Extravasation may cause pain, severe tissue lesions, and necrosis and should be avoided. Burning or stinging may indicate extravasation, requiring immediate termination of the infusion and restarting in another vein. Epirubicin hydrochloride must *not* be given by intramuscular or subcutaneous injection. (1-5/05)

Personnel preparing and administering this drug should take protective measures to avoid contact with the solution, including use of disposable gloves, gowns, masks, and eye goggles. Dose preparation should be performed in a suitable laminar airflow device on a work surface protected by plastic-backed absorbent paper. All equipment and materials used in preparing and administering doses should be disposed of safely using high-temperature incineration. (1-5/05) See Inactivation below.

**Stability** — Epirubicin hydrochloride in intact vials should be stored under refrigeration at 2 to 8 °C and protected from freezing and exposure to light. The manufacturer recommends discarding any unused solution from the single-dose vials within 24 hours after initial puncture of the vial stopper. (1-5/05)

Beijnen et al. examined the stability of epirubicin hydrochloride infusions. In solutions containing 100 mg/L in dextrose 5% (pH 4.35), the drug was stable for 28 days at 25 °C when protected from light. Epirubicin hydrochloride was less stable in sodium chloride 0.9% or Ringer's injection, lactated, with a 10% loss in eight or three days, respectively, under the same conditions. (1007)

Wood et al. assessed the stability of epirubicin hydrochloride 100 mg/L in sodium chloride 0.9% (pH 6.47) when stored in PVC bags at 4 and 25 °C in the dark. Epirubicin hydrochloride was stable for at least 43 and 20 days at 4 and 25 °C, respectively. The drug admixed in dextrose 5% (pH 4.36) also was stable for at least 43 days at 4 °C. (1460)

Epirubicin hydrochloride was cultured with human lymphoblasts to determine whether its cytotoxic activity was retained. The solution retained cytotoxicity for 24 hours at 4 °C and room temperature. (1575)

**pH Effects** — Epirubicin hydrochloride stability is pH dependent. It becomes progressively more stable at acid pH. Maximum stability is obtained at pH 4 to 5. (1007; 1460) Prolonged contact of epirubicin hydrochloride with any solution having an alkaline pH should be avoided because of the resulting hydrolysis of the drug. (1-5/05)

**Freezing Solutions** — Epirubicin hydrochloride was stable for at least 43 days when stored at -20 °C at a concentration of 100 mg/L in sodium chloride 0.9% or dextrose 5% in PVC bags (Travenol). (1460)

## Appendix 9: Compatibility of PM101 and Lidocaine with Vasopressin

Thank you for your Inquiry regarding the compatibility of Nexterone Injection 50 mg/mL with vasopressin injection when administered through a common intravenous access.

Prism has completed a study designed to evaluate the visual compatibility of Nexterone injection and Vasopressin injection during simulated Y-site administration using the method of Allen<sup>1,2</sup>. We tested concentrations of vasopressin injection previously tested by Feedema<sup>3</sup>, which included vasopressin 2U/mL and 4u/mL (each dilution in 0.9% sodium chloride) and also included vasopressin 20U/mL (undiluted). Each concentration was mixed with NEXTERONE injection 50mg/mL (prefilled syringe) and observed for 24 hours. We repeated the process with NEXTERONE injection 1.25 mg/mL and 1.8 mg/mL, each from premixed bags.

NEXTERONE injections 50 mg/mL, 1.8 mg/mL and 1.5 mg/mL were each visually compatible with vasopressin injection concentrations of 2 U/mL and 4 U/mL in sodium chloride injection when mixed in ratios of 1:1. Solutions remained clear, colorless and free of particulates for the 24 hour observation period.

Vasopressin 20 U/mL mixtures with NEXTERONE injection 50 mg/mL, 1.8 mg/mL, and 1.5 mg/mL resulted in immediate white cloudy appearance and are therefore visually incompatible.

We believe that the observed incompatibility with the Vasopressin injection at the 20 U/mL concentration is due to the presence of chlorobutanol 0.5% included as a preservative. Captisol, used to solubilized amiodarone in NEXTERONE injection, binds quite well to chlorobutanol<sup>4</sup> and the chlorobutanol may be displacing amiodarone, resulting in the precipitation of amiodarone.

To avoid the incompatibility, the intravenous access should be flushed with a volume of DSW or 0.9% sodium chloride injection sufficient to clear the line prior to administration of the second drug when concentrations of vasopressin other than 2 U/mL or 4 U/mL are utilized.

Please review the enclosed prescribing information for approved indications and complete prescribing and safety information. We hope the provided information is useful to you.

This information has been sent to you in response to your request.

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1) Allen LV Jr, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y-injections sites of intravenous administration sets. Am J Hosp Pharm 1977;34:939-43.

2) Souney PF. Visual compatibility of NEXTERONE injection and vasopressin injection. Prism Pharmaceuticals, Inc. July 19, 2010.

3) Feddema S, Rusho WJ, Tyler LS, Barker B. Physical compatibility and vasopressin with medications commonly used in cardiac arrest. Am J Hosp Pharm 2003;60:1271-2.

4) Fulk C, Gayed A, Lund B, et al. Preserved formulations containing Captisol® sulfobutylether-beta-cyclodextrin. Cydex, Inc. Lenexa, KS.

Note: DSW above refers to D5W

# Compatibility of various admixtures with secondary additives at Y-injection sites of intravenous administration sets

Loyd V. Allen, Jr., R. Saul Levinson and Daranee Phisutsinhop

The compatibility of various secondary additives with selected intravenous admixtures at the Y-injection site of an intravenous administration set was studied.

The mixing volume of the secondary additive and the i.v. admixture at the Y-injection site to the needle tip was found to occur approximately in a 1:1 ratio. For convenience in observing the results, 1 ml of secondary additive and 1 ml of i.v. admixture were drawn in sterile disposable syringes under aseptic conditions and mixed in a clean test tube. Visual (macroscopic) and microscopic observations were performed on each mixture immediately after preparation and four hours later. The i.v. fluids used were dextrose 5% in water, sodium chloride 0.9%, and lactated Ringer's solution. The primary additives were: (1) vitamin B complex with C, (2) potassium chloride, and (3) heparin sodium and hydrocortisone sodium succinate. The secondary additives tested (in usual clinical concentrations) were: aminophylline, ampicillin sodium (four concentrations), calcium gluconate, cephalothin sodium, dexamethasone sodium phosphate, diazepam, digitoxin, digoxin, conjugated estrogens, ethacrynate sodium, insulin, kanamycin sulfate, lidocaine hydrochloride, methylprednisolone sodium succinate, phenytoin sodium, penicillin G potassium, prednisolone sodium phosphate, sodium bicarbonate, succinylcholine chloride, and sterile water for injection.

Most of the drugs studied were found to be physically compatible. Incompatibilities of secondary additives observed included phenytoin sodium, diazepam and methylprednisolone sodium succinate.

Some of the factors a pharmacist should be concerned with in additives at Y-injection sites are pH, solubility and the specific formulations of the additives. It is suggested that the pharmacist should monitor the addition of any drug at a Y-injection site of an i.v. admixture administration set.

**Key words:** Additives; Incompatibilities; Stability; Surgical supplies

It is generally accepted that the addition of only one drug to an intravenous fluid presents little problem. But when more drugs are added to the same infusion fluid, the problem becomes more complicated.<sup>1</sup> An alternative technique that can be used in treating a variety of conditions and in reducing the number of venipunctures is to inject the drugs individually into the gum rubber injection site of an

administration set of an i.v. solution being administered to a patient. The advantages of this technique include the avoidance of making additional venipunctures, and the separation of the additives from the large-volume solution as much as possible. This reduces the contact time between the solution and the drug, minimizes the absorption of certain drugs onto the surface of the tubing and containers which leads to inaccurate and insufficient doses, and may also minimize the occurrence of incompatibilities.<sup>2,3</sup>

It was the purpose of this investigation to determine the physical compatibility of selected individual drug additives injected at the Y-sites of administration sets using various i.v. admixtures. Further objectives were to investigate the presence of particulate matter microscopically in the event that visual observations was not sufficiently sensitive.

Loyd V. Allen, Jr., Ph.D., is Assistant Professor of Pharmacy, and R. Saul Levinson, Ph.D., is Assistant Professor of Physical Pharmacy and Biopharmaceutics, College of Pharmacy, Health Sciences Center, University of Oklahoma, Oklahoma City 73190. Daranee Phisutsinhop, M.S., is a pharmacist in Bangkok, Thailand.

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## Materials and Methods

All the infusion fluids (Table 1), primary additives (Table 2) and secondary additives (Table 3) studied in this project were selected because they are commonly used injectable medications. The secondary additives were also selected because of some special requirement with respect to administration, i.e., they should be diluted and given as an infusion as in the case of primary additives,<sup>4,5</sup> or they should not be mixed with infusion fluids, or they should be given through a Y-tube administration set as in the case of secondary additives.<sup>4,6,7</sup> The concentrations were selected on the basis of their usual therapeutic doses.

The samples were aseptically prepared in a laminar flow hood<sup>a</sup> using sterile disposable syringes. Only freshly prepared solutions were used, and any i.v. admixture or solution remaining after 24 hours was discarded. Proper storage temperatures of reconstituted medicaments and multiple-dose solutions were maintained for a period of time as indicated in the product information inserts, and they were returned to room temperature prior to use.

The study was designed to simulate the actual conditions in a hospital intravenous admixture program, therefore syringes were used to transfer the drugs for the admixtures and

for the secondary additives. The mixing of the i.v. fluid in the administration set with the secondary additive from the Y-injection site to the needle tip was found by a dye dilution technique to occur approximately in a 1:1 ratio (Figure 1). Therefore, any volume of secondary additive and i.v. admixture in a 1:1 ratio could be used in this investigation. The volume that was used was 1 ml of i.v. admixture, drawn by disposable syringes and mixed in a precleaned test tube for convenience in observing the results. The test tubes were thoroughly washed, rinsed with distilled water filtered through a 0.45- $\mu$ m membrane filter in a pressure-rinser and dried.

The admixtures were prepared in duplicate and stored at room temperature and under constant light conditions for the duration of the study.

Visual observations were performed on each mixture, using a black and white background, immediately after preparation and again four hours later. A microscopic<sup>b</sup> examination was also performed at the same intervals. Photographs<sup>c</sup> of uniformly distributed particles found in each microslide were taken at magnifications of 100X, 200X and 430X, and the size of the particles was determined.

## Results and Discussion

From the results (Table 4) obtained both visually and microscopically, three drugs resulted in physical incompatibilities. These were phenytoin sodium, diazepam and methylprednisolone sodium succinate.

The probable cause for the phenytoin crystallization (see Figure 2) was the low pH of the admixture. Because of the phenytoin insolubility in water, it must be dissolved in a special diluent which contains propylene glycol, alcohol and water, adjusted to a pH of 12 with sodium hydroxide. When a solution of phenytoin sodium is mixed with an acidic fluid, the pH may be shifted below the optimum range for solubility. Free phenytoin will precipitate out at a pH of 11.5 or below.<sup>8</sup> Although precipitates were not visually detectable, microscopic examination showed them to be formed immediately following admixture. These precipitates were visually discernible within four hours of admixture. The crystals of phenytoin that occurred in each mixture were larger at four hours observation than at time zero. They became thicker and longer as they grew relative to the length of time. We believe that phenytoin sodium should not be added to any i.v. admixture or even injected through a Y-injection site of an administration set. Infused particles might block blood vessels, cause thrombus or embolus formation or result in local granulomas.<sup>9</sup>

Diazepam is incompatible with all the admixtures used in this study; the haziness (Figure 3) occurred immediately, probably because of its poor solubility. Diazepam is slightly soluble in water, therefore commercially it is dissolved in a suitable medium containing 40% propylene glycol, 10% ethyl

<sup>a</sup> Abbott Clean Air System Model HC-4, manufactured by Dexon, Inc., Minneapolis, MN 55401.

Table 1. Large-volume Intravenous Solutions Used

Name	Manufacturer	Lot Number
Dextrose 5% in water	Abbott Laboratories <sup>a</sup>	60-682-DE-1
Sodium chloride solution 0.9%	Abbott Laboratories <sup>a</sup>	61-988-DM-04
Lactated Ringer's solution	Abbott Laboratories <sup>a</sup>	64-407-DM-03

<sup>a</sup> North Chicago, IL 60064.

Table 2. Primary Additives Studied

Generic Name	Proprietary Name	Manufacturer	Lot Number	Quantity Added per Liter
Vitamin B complex with C	Berocca-C	Roche Laboratories <sup>a</sup>	0311,0318	1 ampul
Potassium chloride	—	Eli Lilly and Co. <sup>b</sup>	9TT59B 0AR90B	40 mEq
Heparin sodium and Hydrocortisone sodium succinate	Lipo-Hepin	Riker Laboratories <sup>c</sup> Upjohn Company <sup>d</sup>	56763A 560DX, 682ED	1000 units 100 mg

<sup>a</sup> Nutley, NJ 07110.

<sup>b</sup> Indianapolis, IN 46206.

<sup>c</sup> Northridge, CA 91324.

<sup>d</sup> Kalamazoo, MI 49002.

<sup>b</sup> Bausch and Lomb Company Limited.

<sup>c</sup> Polaroid Automatic Land camera—440 film, 3000 speed, black and white, Polaroid Corporation.

# Physical compatibility of vasopressin with medications commonly used in cardiac arrest

SARAH FEDDEMA, WILLIAM J. RUSHO, LINDA S. TYLER,  
AND BRIAN BARKER

*Am J Health-Syst Pharm.* 2003; 60:1271-2

**R**ecent advanced cardiac life support (ACLS) guidelines include vasopressin as an alternative to epinephrine in the algorithm for persistent or recurrent ventricular fibrillation or ventricular tachycardia.<sup>1</sup> Vasopressin, a naturally occurring antidiuretic hormone, becomes a powerful vasoconstrictor when used in quantities much higher than those normally occurring in the body. Vasopressin produces the same positive effects as epinephrine in terms of vasoconstriction and increased blood flow to the brain and heart during cardiopulmonary resuscitation, but it does not have the adverse effects that epinephrine does on the heart, such as increased ischemia, irritability, and the propensity for ventricular fibrillation.<sup>1-3</sup>

Many other medications are administered during cardiac arrest. Vasopressin should be administered by i.v. push, using Y-site delivery if another infusion is being administered. The medical literature lacks information about vasopressin's compatibility with other drugs, making it difficult to ensure the best care for patients in cardiac arrest. The purpose of this study was to determine the physical compatibility of vasopressin with routinely used medications in cardiac arrest.

**Materials and methods.** Similar methods of testing drug compati-

ty have been previously described.<sup>4,6</sup> The medications to be tested were determined by interviewing pharmacists who routinely respond when patients are in cardiac arrest and by reviewing ACLS guidelines. Vasopressin was supplied in vials containing 20 units/mL.<sup>a</sup> Twenty or 40 units of vasopressin was drawn into a 10-mL syringe and then diluted to 10 mL with 0.9% sodium chloride injection.<sup>b</sup> All other medications were prepared in infusion bags in commonly used concentrations (Table 1) and delivered by a standard infusion pump.<sup>c</sup>

Vasopressin was injected over five seconds at the Y injection site on the polyvinyl chloride (PVC) i.v. tubing set<sup>d</sup> while each other drug solution was running through the set (into a container). The tubing in each test setup included a filter system<sup>e</sup> with a 0.8- $\mu$ m filter disk.<sup>f</sup> Each drug combination was tested in triplicate. Each medication was passed separately (without mixing with other medica-

tion solutions) through a filter disk to provide baseline information. After the fluid finished running, the filter was "bubble-point" tested<sup>g</sup> to ensure its integrity and remove residual solution. The Y injection site and i.v. tubing were visually examined continuously during the experiment for precipitate and color change and for at least 10 minutes after the vasopressin injection to ensure all the vasopressin passed through the filter. The filter was inspected under a microscope<sup>h</sup> at 51 $\times$  magnification to detect precipitate or crystals indicating incompatibility.

Drug combinations were considered incompatible if (1) a color change visible to the naked eye was observed during filtration, (2) a precipitate was visible to the unaided eye, or (3) the number of particles observed under the microscope exceeded the number stated in the *United States Pharmacopeia (USP)* guidelines for particulate levels of large-volume injections (i.v. fluid is considered impure if there are 12 or more particles of  $\geq 10 \mu\text{m}$  in diameter per milliliter of solution or 2 or more particles of  $\geq 25 \mu\text{m}$  in diameter per milliliter of solution).<sup>7</sup> A drug was considered compatible with vasopressin if there was no color change or precipitate visible to the unaided eye and the number of particles observed under the microscope did not exceed that stated in the *USP* guidelines.

SARAH FEDDEMA, PHARM.D., is Drug Information Specialty Resident; WILLIAM J. RUSHO, M.S., is Clinical Specialist, Intravenous Therapy; LINDA S. TYLER, PHARM.D., is Pharmacy Manager, Drug Information Services; and BRIAN BARKER, B.S.PHARM., is Clinical Specialist, Critical Care, Department of Pharmacy Services, University of Utah Hospitals and Clinics, Salt Lake City.

Address correspondence to Dr. Feddema at the Department of Pharmacy Services, Uni-

versity of Utah Hospitals and Clinics, Room A-050, 50 North Medical Drive, Salt Lake City, UT 84132.

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Table 1.

## Drugs Tested for Physical Compatibility with Vasopressin 20 and 40 Units/10 mL

Drug	Manufacturer and Lot	Concentration <sup>a</sup>	Rate
Amiodarone	Wyeth 100001 <sup>b</sup> and 31142 <sup>c</sup>	1.5 mg/mL in D5W <sup>d</sup>	0.5 mg/min
Diltiazem	Nova Plus 280383 <sup>b,c</sup>	1 mg/mL in NS <sup>e</sup>	5 mg/min
Dobutamine <sup>f</sup>	Abbott 80-651-DK <sup>g</sup> and 86-596-DK <sup>c</sup>	4.2 mg/mL in D5W <sup>d,g</sup>	350 µg/min
Dopamine hydrochloride	American Regent 2036 <sup>b,c</sup>	4.2 mg/mL in D5W <sup>d,g</sup>	350 µg/min
Epinephrine	American Regent 1645 <sup>b,c</sup>	4 µg/mL in NS <sup>h</sup>	1 µg/min
Heparin sodium	Baxter P5118232 <sup>b</sup> and P5117069 <sup>c</sup>	100 units/mL in D5W <sup>i</sup>	1000 units/hr
Lidocaine hydrochloride	Baxter P5113423 <sup>b,c</sup>	4 mg/mL in D5W <sup>i</sup>	1 mg/min
Milrinone <sup>j</sup>	Abbott 77-164-FJ <sup>b,c</sup>	200 µg/mL in D5W <sup>i</sup>	26 µg/min <sup>k</sup>
Nitroglycerin	Baxter G987628 <sup>b</sup> and G985820 <sup>c</sup>	200 µg/mL in D5W <sup>i</sup>	5 µg/min
Norepinephrine <sup>l</sup>	Abbott 624603A <sup>g</sup> and 74-024-DK <sup>c</sup>	4 µg/mL in NS <sup>e</sup>	8 µg/min
Phenylephrine hydrochloride	American Regent 1617 <sup>b</sup> and Baxter 02A123 <sup>c</sup>	40 µg/mL in NS <sup>m</sup>	40 µg/min
Procainamide hydrochloride	Abbott 68-533-DK <sup>g</sup> and 72-541-DK <sup>c</sup>	4 mg/mL in NS <sup>m</sup>	1 mg/min

<sup>a</sup>D5W = 5% dextrose injection, NS = 0.9% sodium chloride injection.

<sup>b</sup>Tested with vasopressin 20 units/10 mL.

<sup>c</sup>Tested with vasopressin 40 units/10 mL.

<sup>d</sup>D5W was Baxter lot P511608.

<sup>e</sup>NS was Baxter lot C520882.

<sup>f</sup>As the hydrochloride.

<sup>g</sup>Concentration calculated for 70-kg patient using "rule of 6," weight in kg × 6 = amount of drug in 100 mL of diluent.

<sup>h</sup>NS was Baxter lot C537164.

<sup>i</sup>Delivered premixed from manufacturer.

<sup>j</sup>As the lactate.

<sup>k</sup>Rate calculated for 70-kg patient (0.375 µg/kg/min).

<sup>l</sup>As the bitartrate.

<sup>m</sup>NS was Baxter lot C530287.

**Results.** All medications tested were compatible with 20 and 40 units of vasopressin.

**Discussion.** This study only evaluated vasopressin's physical compatibility when given via Y-site injection. These data cannot be extrapolated to chemical admixture compatibility (the stability or compatibility of two medications or solutions combined in one container). The concentrations of all other medications represent those commonly used at our institution. Other institutions may use different concentrations; however, most are likely to use these standard concentrations.

Because of the rapid administration and short mixing times, we believe that vasopressin can be administered by i.v. push via Y-site delivery with the medications studied.

**Conclusion.** No evidence of phys-

ical incompatibility appeared when vasopressin 20 units/10 mL or 40 units/10 mL in 0.9% sodium chloride solution was injected at the Y-site of i.v. tubing through which any of 12 other drugs was running.

<sup>a</sup>American Regent Laboratories, Shirley, NY, lots 0658, 110133, and 1692.

<sup>b</sup>Baxter Healthcare Corporation, Deerfield, IL, lots C531780 and PS119461.

<sup>c</sup>3M, 3000 modular infusion pump, St. Paul, MN.

<sup>d</sup>Primary i.v. administration set CC1201, Sims Deltec, Inc., St. Paul, MN.

<sup>e</sup>Swinnex, Millipore, Bedford, MA.

<sup>f</sup>Millipore.

<sup>g</sup>A 10-mL empty syringe was attached to the filter housing and used to force air through the filter disk until resistance was felt. The syringe was then removed from the filter housing.

<sup>h</sup>American Optical Spencer Lens Co., Buffalo, NY.

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## Materials and Methods

All the infusion fluids (Table 1), primary additives (Table 2) and secondary additives (Table 3) studied in this project were selected because they are commonly used injectable medications. The secondary additives were also selected because of some special requirement with respect to administration, i.e., they should be diluted and given as an infusion as in the case of primary additives,<sup>4,5</sup> or they should not be mixed with infusion fluids, or they should be given through a Y-tube administration set as in the case of secondary additives.<sup>4,6,7</sup> The concentrations were selected on the basis of their usual therapeutic doses.

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The admixtures were prepared in duplicate and stored at room temperature and under constant light conditions for the duration of the study.

Visual observations were performed on each mixture, using a black and white background, immediately after preparation and again four hours later. A microscopic<sup>b</sup> examination was also performed at the same intervals. Photographs<sup>c</sup> of uniformly distributed particles found in each microslide were taken at magnifications of 100X, 200X and 430X, and the size of the particles was determined.

## Results and Discussion

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The probable cause for the phenytoin crystallization (see Figure 2) was the low pH of the admixture. Because of the phenytoin insolubility in water, it must be dissolved in a special diluent which contains propylene glycol, alcohol and water, adjusted to a pH of 12 with sodium hydroxide. When a solution of phenytoin sodium is mixed with an acidic fluid, the pH may be shifted below the optimum range for solubility. Free phenytoin will precipitate out at a pH of 11.5 or below.<sup>8</sup> Although precipitates were not visually detectable, microscopic examination showed them to be formed immediately following admixture. These precipitates were visually discernible within four hours of admixture. The crystals of phenytoin that occurred in each mixture were larger at four hours observation than at time zero. They became thicker and longer as they grew relative to the length of time. We believe that phenytoin sodium should not be added to any i.v. admixture or even injected through a Y-injection site of an administration set. Infused particles might block blood vessels, cause thrombus or embolus formation or result in local granulomas.<sup>9</sup>

Diazepam is incompatible with all the admixtures used in this study; the haziness (Figure 3) occurred immediately, probably because of its poor solubility. Diazepam is slightly soluble in water, therefore commercially it is dissolved in a suitable medium containing 40% propylene glycol, 10% ethyl

<sup>a</sup> Abbott Clean Air System Model HC-4, manufactured by Dexon, Inc., Minneapolis, MN 55401.

**Table 1. Large-volume Intravenous Solutions Used**

Name	Manufacturer	Lot Number
Dextrose 5% in water	Abbott Laboratories <sup>a</sup>	60-682-DE-1
Sodium chloride solution 0.9%	Abbott Laboratories <sup>a</sup>	61-988-DM-04
Lactated Ringer's solution	Abbott Laboratories <sup>a</sup>	64-407-DM-03

<sup>a</sup> North Chicago, IL 60064.

**Table 2. Primary Additives Studied**

Generic Name	Proprietary Name	Manufacturer	Lot Number	Quantity Added per Liter
Vitamin B complex with C	Berocca-C	Roche Laboratories <sup>a</sup>	0311,0318	1 ampul
Potassium chloride	—	Eli Lilly and Co. <sup>b</sup>	9TT59B 0AR90B	40 mEq
Heparin sodium and	Lipo-Hepin	Riker Laboratories <sup>c</sup>	56763A	1000 units
Hydrocortisone sodium succinate	Solu-Cortef	Upjohn Company <sup>d</sup>	560DX, 682ED	100 mg

<sup>a</sup> Nutley, NJ 07110.

<sup>b</sup> Indianapolis, IN 46206.

<sup>c</sup> Northridge, CA 91324.

<sup>d</sup> Kalamazoo, MI 49002.

<sup>b</sup> Bausch and Lomb Company Limited.

<sup>c</sup> Polaroid Automatic Land camera—440 film, 3000 speed, black and white, Polaroid Corporation.

Figure 1. The injection of a secondary additive through the Y-site of the administration set; the inset shows the mixing area between the primary solution and the secondary additives

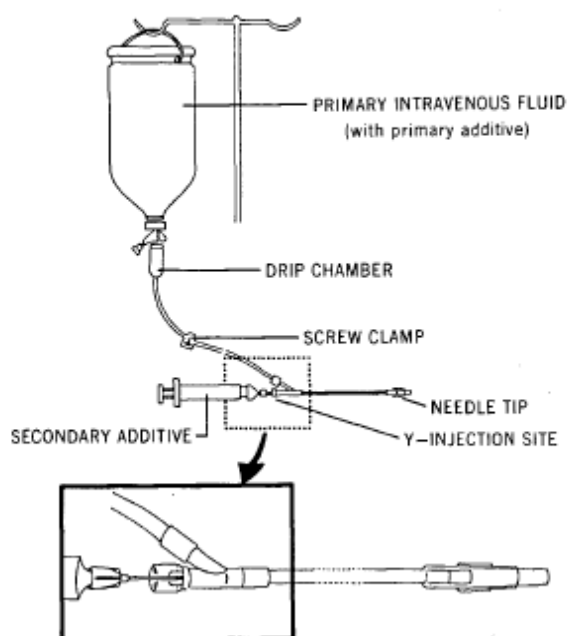


Figure 2. Photomicrograph of phenytoin crystals that formed immediately upon the addition of phenytoin to a primary solution consisting of vitamin B complex with C in dextrose 5% in water (200 X)

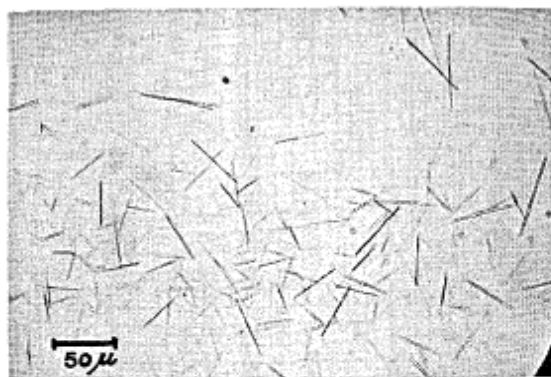


Figure 3. Photomicrograph of globules that formed immediately when diazepam was added to a primary solution consisting of vitamin B complex with C in lactated Ringer's solution (100 X)

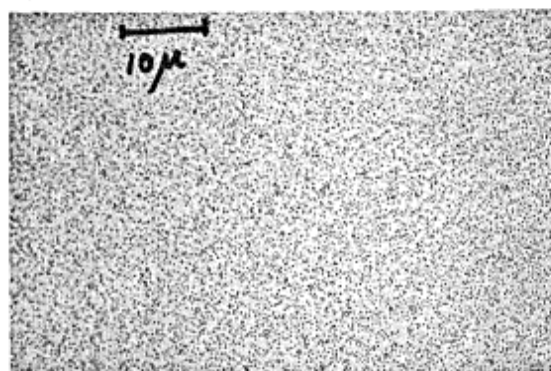


Table 4. Results of Compatibility Testing of Various Secondary Additives with Primary Admixtures at Room Temperature<sup>a</sup>

Intravenous Fluid and Secondary Additive	Berocca-C <sup>b</sup>				Potassium Chloride <sup>c</sup>				Heparin Sodium <sup>d</sup> and Hydrocortisone Sodium Succinate <sup>e</sup>				
	0 hour		4 hours		0 hour		4 hours		0 hour		4 hours		
	Visual	Micro.	Visual	Micro.	Visual	Micro.	Visual	Micro.	Visual	Micro.	Visual	Micro.	
Dextrose 5% in water													
Diazepam	hazy	globules	droplets	globules	hazy	globules	hazy	globules	hazy	globules	hazy	globules	
Phenytoin sodium	crystals	crystals	crystals	crystals	—	crystals	crystals	crystals	—	crystals	—	crystals	
Sodium chloride solution													
Diazepam	hazy	globules	droplets	globules	hazy	globules	hazy	globules	hazy	globules	hazy	globules	
Methylprednisolone sodium succinate	—	—	—	—	—	—	hazy particles	—	—	—	hazy	—	
Phenytoin sodium	—	crystals	—	crystals	—	—	—	crystals	—	crystals	—	crystals	
Lactated Ringer's solution													
Diazepam	hazy	globules	hazy	globules	hazy	globules	hazy	globules	hazy	globules	hazy	globules	
Methylprednisolone sodium succinate	—	—	hazy	± <sup>f</sup>	hazy	—	hazy	±	—	—	hazy	±	
Phenytoin sodium	—	—	—	crystals	—	—	crystals	crystals	—	crystals	—	crystals	

<sup>a</sup> All secondary additives listed in Table 2 were tested; only those that demonstrated incompatibilities are shown in this table.

<sup>b</sup> 1 10-ml ampul/liter of i.v. fluid.

<sup>c</sup> 40 mEq/liter of i.v. fluid.

<sup>d</sup> 1000 units/liter of i.v. fluid.

<sup>e</sup> 100 mg/liter of i.v. fluid.

<sup>f</sup> A questionable change is designated by ±.

alcohol and water. When this solvent was diluted, as mixing with infusion fluids, a haziness resulted.

Regarding methylprednisolone, it could be a salting out effect from the primary additives that produced the haze, in addition to the pH effect.

#### Conclusion

The majority of the drugs added at the Y-injection site were found to be physically compatible. Incompatibilities of secondary additives that were observed in this investigation included phenytoin sodium, diazepam and methylprednisolone sodium succinate.

Some of the factors a pharmacist needs to be concerned with regarding additives at Y-injection sites are pH, solubility and the specific formulations of the additives. Perhaps the pharmacist should monitor the addition of any drug at a Y-injection site of an i.v. admixture.

#### References

1. Engle G: Addition of drugs to intravenous fluids, *Drug Intell Clin Pharm* 6:145-147 (Apr) 1972.
2. Jacobs J: The clinical use of infusion for drug administration, *J Hosp Pharm* 31:254-257 (Dec) 1973.
3. Turco S and King RE: Sterile dosage forms, 1st ed, Lea & Febiger, Philadelphia, Pennsylvania, 1974, p 145-146.
4. Gahart BL: Intravenous medications, 1st ed, The C.V. Mosby Co., St. Louis, Missouri, 1968.
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6. Trissel LA, Grimes CR and Gallelli JF: Parenteral drug information guide, American Society of Hospital Pharmacists, Washington, D.C., 1974, p 60.
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8. Reilly MJ (ed): American hospital formulary service, American Society of Hospital Pharmacists, Washington, D.C.
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### Visual Compatibility of Nexterone injection and Vasopressin Injection

Study Date: July 18, 2010

Completed by: Paul Souney

Purpose: To evaluate visual compatibility of PM101(NEXTERONE Injection) and Vasopressin injection during simulated Y-site administration.

#### Method:

Materials: PM101, 50 mg/mL, 3 mL prefilled syringe(908265); PM101, 1.5 mg/mL 100 mL premixed bag (49198); Nexterone 1.8 mg/mL 200 mL premixed bag (49177); vasopressin injection 20 U/mL, 1 mL vial, American Reagent Inc. (Lot 0273 exp Oct11);0.9% sodium chloride injection, USP 10 mL vial, Hospira (lot67-330-DK, exp 7/2010)

Allen et al.<sup>1</sup> demonstrated that the mixing of an i.v. fluid in the administration set with a secondary additive from the Y-injection site to the needle tip occurs in a 1:1 ratio. To simulate this situation, a 1-mL sample of each test solution of PM101 was mixed with a 1 mL sample of each vasopressin solution. The solutions were added to sterile empty glass vials. Duplicate samples of each solution containing PM101 and vasopressin were evaluated. Visual examinations were performed against a black and white background with the aid of a magnifying lens (2X) just after mixing (T0) and at 5 and 30 minutes, and at 4 and 24 hours. Solutions were examined for the presence of haze, precipitate, color change, and evolution of gas.

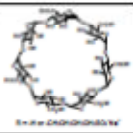
Results: 1:1 mixtures of various concentrations of Nexterone and vasopressin

	T0	5 minutes	30 minutes	4 hours	24 hours
N 50/Vaso2 U/mL	C/C	C/C	C/C	C/C	C/C
N50/Vaso 4 U/ML	C/C	C/C	C/C	C/C	C/C
N50/Vaso 20 U/mL	Cloudy/white	Cloudy/white	Cloudy/white	Cloudy	Cloudy
N 1.5/Vaso 2 U/ML	C/C	C/C	C/C	C/C	C/C
N1.5/Vaso 4 U/mL	C/C	C/C	C/C	C/C	C/C
N1.5/Vaso 20 U/mL	Cloudy/white	Cloudy/white	Cloudy/white	Cloudy	Cloudy
N1.8/Vaso 2	C/C	C/C	C/C	C/C	C/C



Preserved Formulations Containing Captisol® Brand of Sulfobutylether-Beta-Cyclodextrin  
C. Fuhr<sup>1</sup>, A. Gayed<sup>2</sup>, B. Lind<sup>3</sup>, G.L. Mosher<sup>4</sup>, D. Thompson<sup>5</sup>, and R. Wedel<sup>6</sup> (CyDex, Inc., <sup>1</sup>Aventis Pharmaceuticals, <sup>2</sup>Beckhoff & Associates)

Cyclodextrin	Captisol®
Other (NMEs)	substituted ether propyl- butyl
Preservative	WFA acid
MSD	2140 (20mg/1)
Water Solubility	1000 mg/ml
Supplier	CyDex, Inc. Linn, KS
Use	Injection, ointment, and tableting



Introduction

Cyclodextrins and their derivatives are widely used in liquid formulations to enhance the aqueous solubility and stability of hydrophobic compounds (1). They provide these benefits by forming inclusion complexes whereby a portion of the active compound is inserted into the hydrophobic cavity of the cyclodextrin. The complex is stabilized by hydrophobic interactions and does not involve the formation of covalent bonds. Captisol® (sulfobutylether-beta-cyclodextrin) is a chemically modified cyclodextrin containing sulfobutyl groups attached to an average of 7 of the hydroxyls of beta-cyclodextrin. It was rationally designed to increase drug solubility, yet utilize neutral cyclodextrins to be biologically biocompatible in injectable formulations. Captisol® and one liquid pharmaceutical product typically need antiseptic agents to protect the product from accidental microbial contamination during their use. However, including an antimicrobial preservative agent in a cyclodextrin containing formulation is often a formulation challenge. Published studies have shown that preservative molecules can displace the drug molecule from the cyclodextrin cavity, thus reducing the solubilizing capacity of the cyclodextrin in relation to the active pharmaceutical ingredient. The antimicrobial activity of the preservative can also be reduced by the formation of preservative-cyclodextrin inclusion complexes (2).

Objective

The present studies investigated the preservation of Captisol containing formulations in several forms by evaluating:

- 1) antimicrobial preservative activity of Captisol alone
- 2) the interaction of Captisol with preservatives through phase solubility (relative preservative/competitive binding (relative preservative/stable, etc))
- 3) antimicrobial preservative activity of drug formulations containing Captisol and trace preservatives.

Materials and Methods

API	Propolis	Hexadecane HCl	Berberine HCl
Other (NMEs)	2,6-Diisopropylphenol	(9- <i>n</i> -1)-hydroxy-4-(4-dihydroxyphenylmethyl)-1-piperidinol(methyl), 4'-dimethyl tetraacetate acid/hydrochloride	(7S)-6-(4'-O-4',4'-dihydroxyphenyl)-1,2,3,4-tetrahydropyridin-1-yl-methyl-1-naphthalene sulfonate hydrochloride
Formule	CyDex®	CyDex®/HCl	CyDex®/HCl
MSD	176.3	558.12	342.7
Current dosage form	IV emulsion (10 mg/ml) and capsules (180 mg)	Tablets (25, 50, 100 mg) & non-injectable oral suspension (25 mg/ml)	Tablets (25, 50, 100 mg) & non-injectable oral suspension (25 mg/ml)
Indication	Anesthetic	Antibacterial	Antibacterial
Water Solubility	<0.2 mg/ml	<0 mg/ml @ pH 3	<0.2 mg/ml
Stability @ 25°C w/ Captisol	<13 mg/ml	<0 mg/ml @ pH 3	<30 mg/ml
Stability Increase	85x	14x	5x
Structure			

API = Active Pharmaceutical Ingredient

Methods

Self Preservation Evaluation

Captisol solutions (60-500 mg/ml) were evaluated for their inherent self-preservation properties against *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*, and *A. niger* by determining the log reduction of each microbe at 0, 14, 40, and 70 hours post- $t=1$  at 10<sup>7</sup> CFU/ml inoculation and inoculation based upon USP <61>.

Phase Solubility

Phase solubility studies with methylparaben and propylparaben were performed at ambient conditions by the method of Higuchi and Connors (3) over a Captisol concentration range of <math>0-50.0\text{ mg/ml}</math>. The solubility studies were carried out by adding excess preservative into glass vials containing Captisol solutions of increasing strength. The vials were gently agitated for 24 hours, centrifuged, and the supernatant was cleared and analyzed by HPLC.

Antimicrobial Studies

The activity of propolis, hexadecane HCl, and berberine HCl in Captisol was independently determined by adding excess API to a vial containing a solution of Captisol at the targeted formulation concentration. The vials were mixed with gentle agitation for <math>24\text{ hours}</math>, then an aliquot removed for viable count and subsequent API activity determination. A known concentration of preservative was then added directly to each vial. The vials were allowed to mix for an additional <math>24\text{ hours}</math> and then re-analyzed by viable count for concentration of soluble API. The percent recovery of soluble API and preservative addition versus that of initial API solubility was calculated and is indicative of the extent of cyclodextrin cavity displacement that the preservative substituent has on the API.

Antimicrobial Effectiveness Studies

Analysis of Captisol/Emulsion® propolis, hexadecane HCl, and berberine HCl formulated products was performed according to USP <61>, categories 1 (propolis) and 3 (one product with an aqueous base) to determine the survival time of *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*, and *A. niger*. Aliquots of each formulation were inoculated with  $1 \times 10^7$  CFU/ml microbes, then incubated for a total of 28 days. At 0, 7, 14, and 28-day time intervals, sample aliquots were removed, plated, and the log reduction of each microbe reported.

Results and Discussion

Method and Development Phase Solubility

The activity profiles of the poorly soluble preservatives methylparaben and propylparaben in Captisol solutions are illustrated in Figure 1. The profiles show Type A, linear behavior in which the complex has that order dependence on the cyclodextrin concentration. The resulting 1.01 and 0.83 slopes of the respective linear solubility curves indicate that both preservatives have substantial propensity to complex with the cyclodextrin.

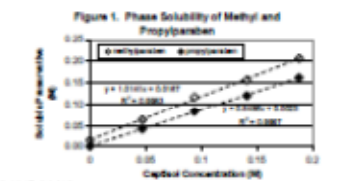
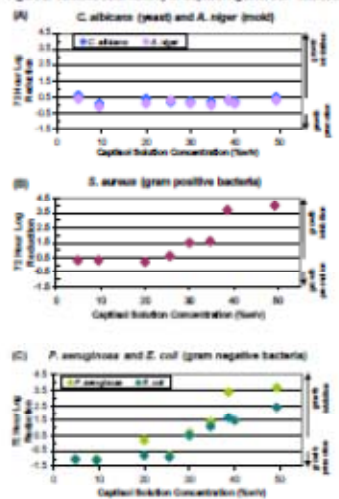


Figure 1. Phase Solubility of Methyl and Propylparaben

Self Preservation

The preservative properties of Captisol are shown in Figures 2A, 2B, and 2C. Up through 70 hours, Captisol solutions >4.6% w/v did not provide the growth of yeast, mold, and gram-positive bacteria and Captisol solutions >3% w/v did not provide the growth of gram-negative bacteria.

Figure 2. Antimicrobial Activity of Captisol Against USP Microbes



Antimicrobial Effectiveness Studies

As shown in Figures 2A and 2B, various degrees of competition for cyclodextrin binding resulted when preservatives were introduced at concentrations levels typically used for parenteral products, 1% Captisol solutions saturated with propolis.

Recovery of Soluble Propolis in Captisol

The recovery of soluble propolis in Captisol solutions saturated with propolis is shown in Figure 3.

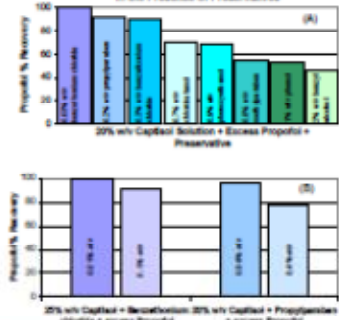


Figure 3. Recovery of Soluble Propolis in Captisol

When acetic acid or benzoic acid were introduced at concentrations greater than their intrinsic solubility (>4.0 mg/ml and 0.45%, respectively) into Captisol solutions saturated with API, the API activity was less with acetic acid (Figures 4 and 5).

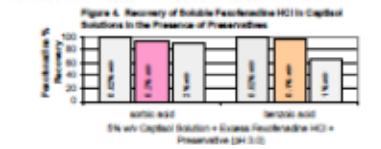


Figure 4. Recovery of Soluble Hexadecane HCl in Captisol Solutions in the Presence of Preservatives

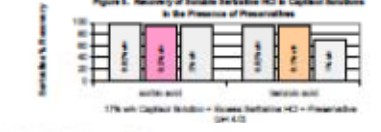


Figure 5. Recovery of Soluble Berberine HCl in Captisol Solutions in the Presence of Preservatives

Antimicrobial Effectiveness Studies

The three Captisol/Emulsion® (3%) formulations passed the USP <61> criteria for self-preservation effectiveness when preservatives were present.

Formulation	Composition	USP <61>
(1) Propolis for aqueous solution	10 mg/ml propolis + 20% w/v Captisol + 2.2% w/v hexadecane HCl + buffer	PASS
(2) Hexadecane for emulsion	8 mg/ml hexadecane + 2% w/v Captisol + 2.2% w/v acetic acid + buffer + emulsifiers	PASS
(3) Berberine HCl solution	20 mg/ml berberine + 17% Captisol + 0.2% w/v acetic acid + buffer + emulsifiers	PASS

Formulation	<i>S. aureus</i> (log 10 CFU/ml)	<i>P. aeruginosa</i> (log 10 CFU/ml)	<i>E. coli</i> (log 10 CFU/ml)	<i>C. albicans</i> (log 10 CFU/ml)	<i>A. niger</i> (log 10 CFU/ml)
1	No increase	No increase	<math>-1.2\text{ log}</math>	<math>-1.2\text{ log}</math>	<math>-1.2\text{ log}</math>
2	No increase	No increase	<math>-1.2\text{ log}</math>	<math>-1.2\text{ log}</math>	<math>-1.2\text{ log}</math>
3	No increase	No increase	No increase	No increase	No increase

Captisol 3.0. One product with an aqueous base

Conclusions

New Captisol solutions can provide antimicrobial activity depending on their concentration. For Captisol-related products containing lower Captisol concentrations, an added preservative may be required to pass preservative effectiveness testing. Selection of an appropriate preservative must include an evaluation of the extent of competitive binding to ensure preservative activity as well as solubilization of the drug. Although most preservatives tend to complex with cyclodextrins to some degree, the following preserved Captisol emulsion formulations were successfully prepared:

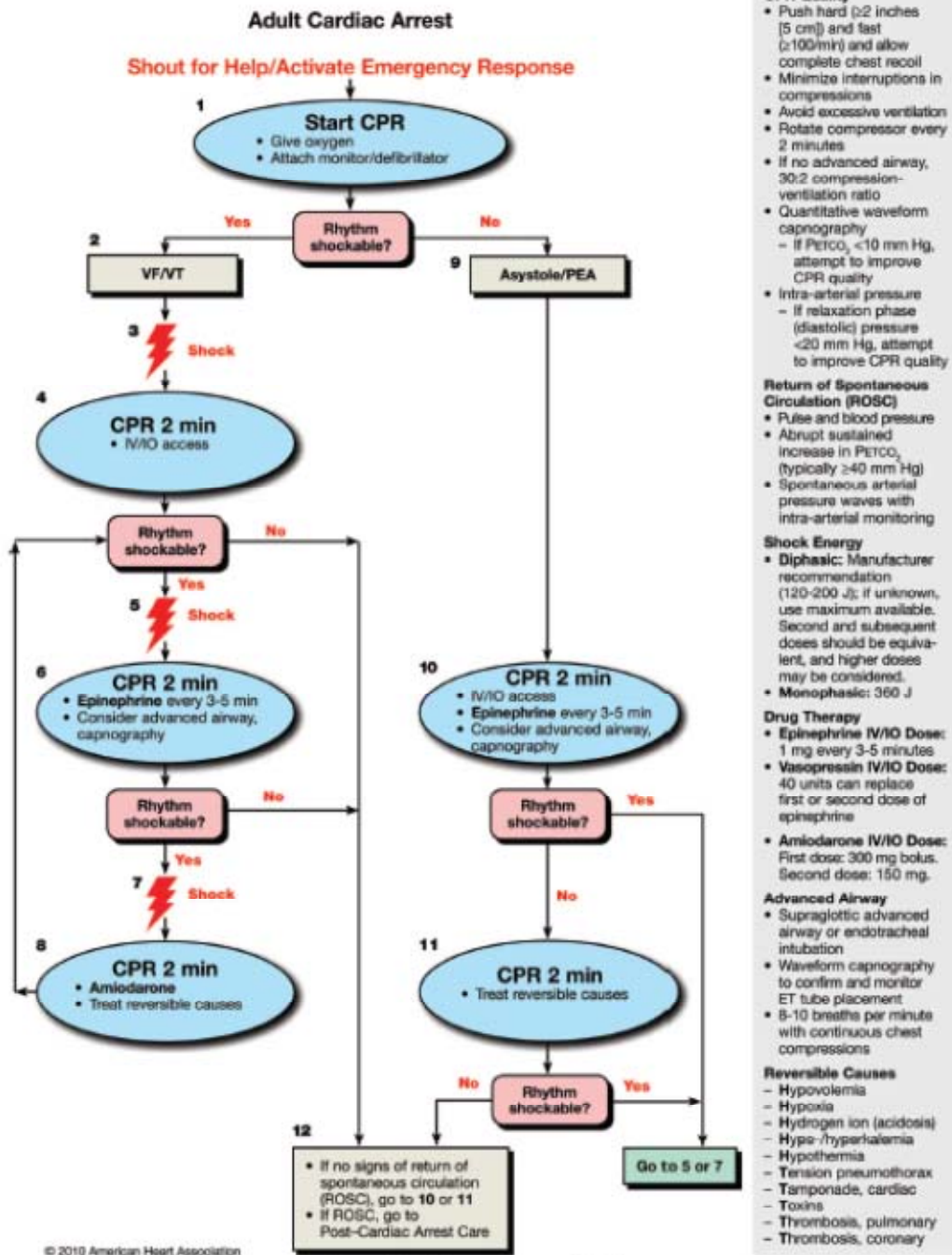
- 10-propolis 10 mg/ml, IV multiple solution containing hexadecane HCl
- 10-hexadecane 8 mg/ml, oral solution containing benzoic or acetic acid
- 10-berberine 20 mg/ml, oral solution containing benzoic or acetic acid

References

1. Loffman, T., and Brewster, M. (1990) "Pharmaceutical Applications of Cyclodextrins. I. Drug Solubilization and Encapsulation." *J. Pharm. Sci.* 79(12), 1027-1034.
2. Loffman, T., et al. (1992) "Interactions between Preservatives and 2-Hydroxypropyl-β-Cyclodextrin." *Drug Development and Industrial Pharmacy* 18(12), 1477-1484.
3. Higuchi, T.; Connors, K.A. (1965) *Advances in Analytical Chemistry and Instrumentation* 3(5), 211-270.



# Appendix 10: 2010 American Heart Association Advanced Cardiac Life Support Treatment Algorithm



From: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. *Circulation* 2010; 122:S736.

## **Appendix 11: Suggested Script for Prehospital Provider to Family LAR**

*“Your family member is having a cardiac arrest due to a very dangerous heart rhythm. We will do everything possible to save his/her life. [Local Ambulance Service] is also performing an important study to find the best heart rhythm medication to use for this condition, in hope of saving more lives. Unless you say no, we will give this treatment, in addition to all other standard treatments for your family member. You will receive more information about this later, and a chance to ask questions.”*

When feasible, this written script (or its facsimile) will be presented to a LAR by the prehospital provider, recognizing that the acute circumstances of cardiac arrest may rarely if ever afford such opportunity on-scene without compromising patient care in process (see Appendix 1). Accordingly determining if or when presenting this script on-scene is feasible, in light of these considerations, will be left to the clinical discretion of the provider.

## **Appendix 12: Suggested Written Script Provided to Hospitals at the Time of Patient Admission**

*“This patient was enrolled in an NIH-supported prehospital trial of antiarrhythmic drugs in cardiac arrest (ROC-ALPS). He/she may have received up to 450 mg of amiodarone, or up to 180 mg of lidocaine, or neither during the course of prehospital treatment. All trial interventions have been completed. All standard hospital treatments may be given now, including additional amiodarone or lidocaine, if required. Because this patient may have already received up to 180 mg of lidocaine in the field, it is suggested to limit additional bolus doses of lidocaine if required over the next 2 hours to at most 100-120 mg such that the total cumulative dose received by their patient over the past 1-2 hours does not exceed the clinically recommended maximum of 3 mg/kg (300 mg); thereafter standard doses of lidocaine can be given if required. Amiodarone or other drugs, if required, can be given at standard doses now. If you have any questions or concerns please contact Dr. xxxxxxx at xxx-xxx-xxxx.”*

### **Alternative suggested wording:**

*“This patient was enrolled in an NIH-supported prehospital trial of antiarrhythmic drugs in cardiac arrest (ROC-ALPS). He/she may have received up to 450 mg of amiodarone, or up to 180 mg of lidocaine, or neither during the course of prehospital treatment. All trial interventions have been completed. All standard hospital treatments may be given now, including additional amiodarone or lidocaine, if required. Because this patient may have already received up to 180 mg of lidocaine in the field, it is suggested to follow current clinical guidelines to limit additional bolus doses of lidocaine if required to at most 100-120 mg such that the total cumulative dose received by their patient over the past 1-2 hours does not exceed the clinically recommended maximum of 3 mg/kg (300 mg). Thereafter standard doses of lidocaine can be given if required. Again, amiodarone or other drugs, if required, can be given at standard doses now. If you have any questions or concerns please contact Dr. xxxxxxx at xxx-xxx-xxxx. If emergency unblinding of the identity of the study drug is required for this patient, please call the ROC study nurse coordinator in Seattle, WA at yyy-yyy-yyyy. Please note that this is a dedicated line to request UNBLINDING ONLY. Requests for information should instead be directed to the local investigators at the local number xxx-xxx-xxx.”*



## Appendix 13: Communications with the FDA Regarding Syringe Compatibility Issue

### Email approval from the FDA:

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**From:** Fortney, Russell [mailto:Russell.Fortney@fda.hhs.gov]  
**Sent:** Thursday, July 14, 2011 12:25 PM  
**To:** 'Kudenchuk, Peter'  
**Cc:** 'Judy Powell'; 'Lois Van Ottingham'; 'May, Susanne'; 'Nichol, Graham'; 'Amy Gest'  
**Subject:** IND 110280 Amiodarone/Lidocaine/Placebo in BD Glass Syringes

Dr. Kudenchuk,

We have reviewed your submissions regarding your proposal to deal with the incompatibility of BD glass syringes with certain needleless access devices. You have proposed using a Baxter Clearlink adapter between the glass syringe and the needleless access device, which would prevent the glass syringe from being connected to an incompatible access device. You plan to include a Clearlink adapter with each syringe in the drug kit, train EMS providers to use them in each instance of study drug administration, and track any issues related to drug administration.

We agree that your proposal is acceptable and that your trial may go forward with the BD glass syringes.

Russell Fortney  
Senior Project Manager  
Division of Cardiovascular and Renal Products  
Food and Drug Administration  
301-796-1068

**Letter to the FDA:**

July 13, 2011

Food and Drug Administration  
Center for Drug Evaluation and Research  
Therapeutic Biological Products Documents Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Re: IND 110280 Serial 0006

We are writing to formally propose our approach to address the reported compatibility issues between BD Hypak glass syringes and certain needleless administration sets to be used in ROC-ALPS.

As FDA is aware, at issue is the “proboscis” (pin-like structure) on the female side of some needleless administration sets that is too large to fit into the lumen of the nipple of the glass syringe, and results in occlusion or breakage of the nipple. Figure 1 below illustrates the design of the Hypak glass syringe, depicting the central lumen of the glass nipple which is the source of the incompatibility issue. The smaller diameter of this central lumen makes the male connector of the glass syringe potentially incompatible with administration sets having a female connector (on the patient side) that has such a “proboscis”, also variably referred to as an acrylic conduit or “pin” (e.g. the Clave design). Figure 2 below illustrates the design of the Clave-type connector with such a design. This figure is derived and annotated from the commercial brochure for this connector.

Our proposed plan to circumvent the incompatibility problem is to use a female to male adapter (Baxter Clearlink) that does not have a “proboscis”. Figure 3 below describes this adapter in detail (the figure is derived and annotated from the commercial brochure for this adapter). In brief, at the time of intended administration of ALPS drug, the glass nipple (male end) of the Hypak syringe will be connected to the female end of the Clearlink adapter; and the male portion of the Clearlink adapter to the patient side of the needleless administration set. BD Medical Pharmaceutical Systems has specified that “BD Hypak syringes are compatible with ISO 594 compliant conical fittings except the ones containing a pin” (see attached letter from BD Medical Pharmaceutical Systems). Baxter Healthcare Corporation, in turn, has specified that the Clearlink adapter is “designed to be compatible with both male and female ISO compliant Leurs; one (male or female) on each end of the device” (see attached letter Baxter Healthcare Corporation). That is, the glass male nipple of the Hypak syringe is ISO compatible with the “pin-less” female portion of the Baxter Clearlink adapter, and in turn, the male portion of the Clearlink adapter is ISO compatible with all ISO compliant Leurs.

If our adapter approach is acceptable to FDA, we would hope to proceed with our original plan to include an adapter with each syringe in the kit and train EMS providers to use them in each instance of study drug administration. Please refer to the U-tube video in two different formats, Flash Video (flv) and Windows Media Video (wmv), on the attached CD as to how we envision this occurring. We have a reporting system in place that would track any issues related to drug administration reported by paramedics in the field.

At present, most ROC sites have submitted IRB applications for this study. However, many IRBs are aware of the FDA warning about the syringes and in light of this concern, are requesting written approval from FDA for the trial specific to using the glass syringes under our proposed adapter plan.

We hope this proposed resolution to the compatibility problem is acceptable to FDA and appreciate your patience as we have ironed out the details regarding documentation of ISO compatibility. Thank you for your consideration.

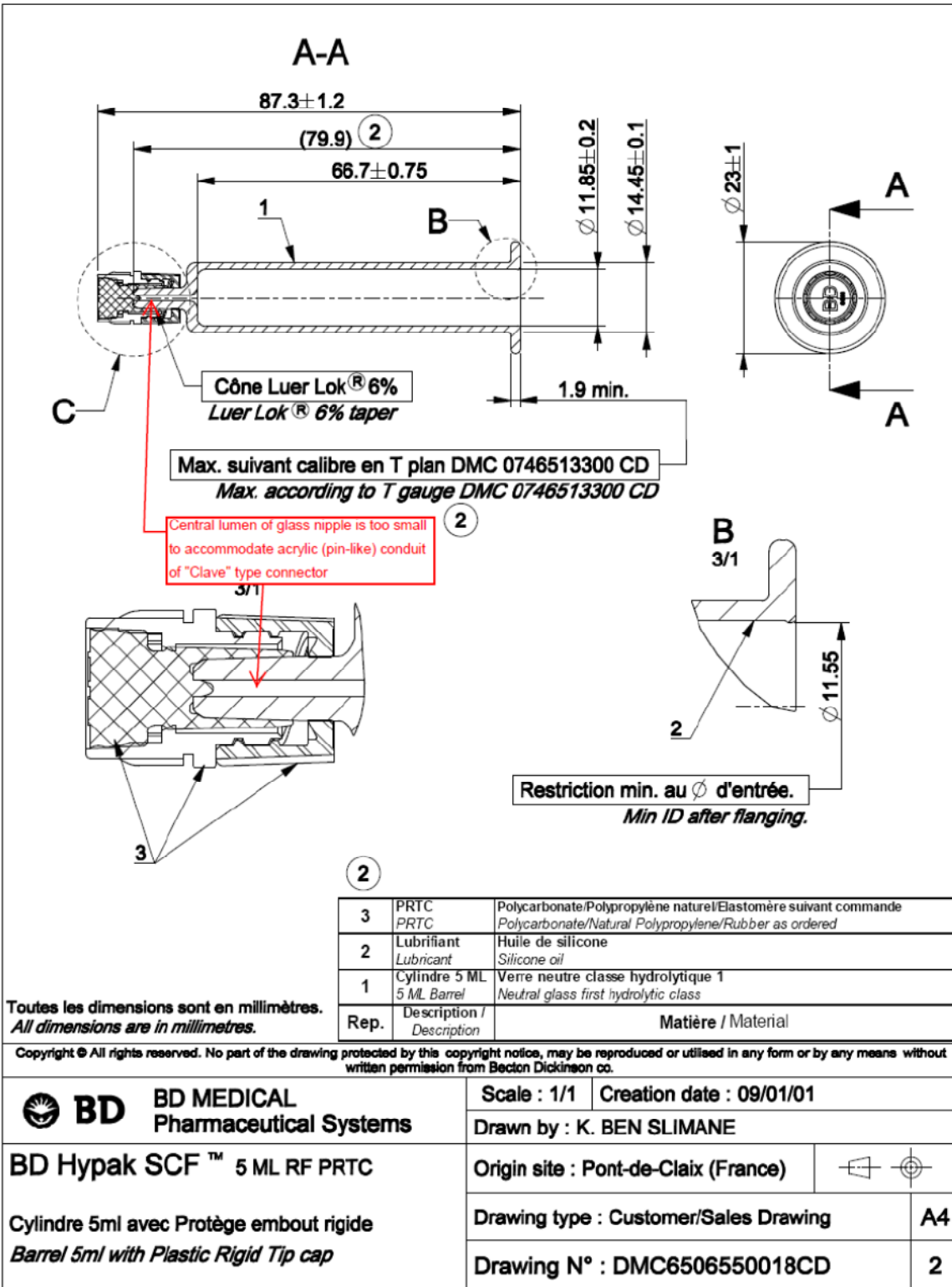
Sincerely,

Susanne May, Ph.D.

Principal Investigator for the Data Coordinating Center

For the ROC Investigators

Figure 1:



Print Date: 12/17/2009  
Release Date: 08/11/2009

Version: 2.0

Status: Released  
Releasing ECO: ECO107333

Design of Hypak glass syringe.

# MicroCLAVE<sup>®</sup> Needle Free IV S... Accessories

Maximizing Safety and Innovation through

Note "pin"-like or acrylic conduit in Clave adapter that inserts into male "nipple" of the Hypak syringe. This "pin"-like conduit is what renders the Clave system incompatible with the BD Hypak syringe, because the narrow internal lumen of the glass nipple of the Hypak syringe cannot accommodate this pin without risk of clogging or breakage. The male nipple on plastic syringes has a larger internal luminal diameter that accommodates this conduit.

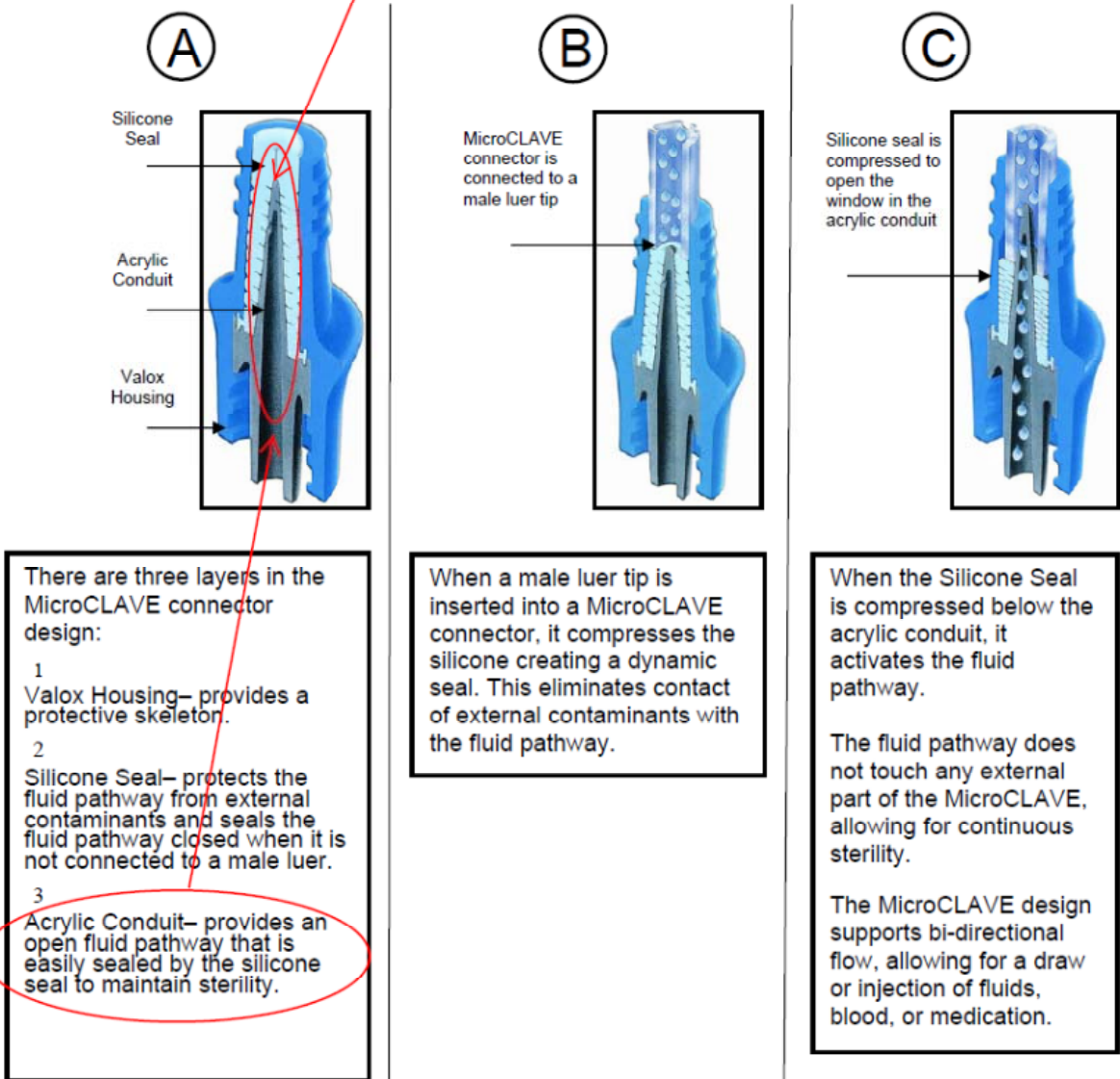


Figure 2: Abbot Clave connector, with central acrylic conduit ("pin") that creates compatibility issue with the BD Hypak glass syringe nipple.

## Rigorous Design Test Patient Care Safety

Elements Tested	Result
Microbial Barrier	Microbiologically up to 20 years over a period of 20 years
Fluid Leakage, Visual, Air Aspiration	Qualified

\* Following disinfection with sterile 70% alcohol, a CLEARLINK Valve should remain at room temperature for 24 hours before use. See the label copy for specific instructions. Do not use if the valve is damaged.

Note: While these tests have established the safety of the product, the clinician will need to maintain aseptic technique. A CLEARLINK Valve should remain at room temperature for 24 hours before use. See the labeling and how frequently it will be accessed.

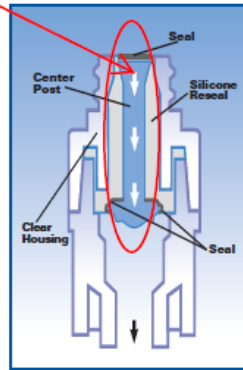
### Ordering Information:

Contact your Baxter Medication Delivery Sales Representative or call 1-800-933-0303 for more information.

Note no "pin"-like (acrylic) conduit within the lumen of the Clearlink adapter. Absence of this conduit (or "pin") renders this adapter compatible with the BD Hypak syringe because no "pin"-like conduit inserts into the lumen of the male nipple of the glass syringe when it is placed onto the adapter. The opposite (male) end of the Clearlink adapter is plastic, and accordingly has a larger internal lumen which can accommodate adapter systems using either a "pin"-like conduit (Clave) or not.

## See for Yourself

The dual seal design and clear housing is readily apparent in this cross-section drawing of the CLEARLINK Valve.



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Figure 3: Baxter Clearlink Adapter (planned for use in ROC-ALPS), which lacks an internal acrylic conduit ("pin"), making it compatible with the BD Hypak glass syringe