

**PAD Protocol
Working Version**

**Revision 1.2
(5/8/2000)**

**Early Access to Defibrillation for Victims
of Out-of-Hospital Cardiac Arrest (OOH-CA)**

ABSTRACT

Sudden out-of-hospital cardiac arrest (OOH-CA) remains a significant cause of death, in spite of recent declines in overall mortality from cardiovascular disease. Existing methods of emergency resuscitation are inadequate due to time delays inherent in the transport of a trained responder with defibrillation capabilities to the side of the OOH-CA victim.

This is a study of a comprehensive, integrated community approach in which volunteer non-medical responders (lay volunteers without a traditional responsibility to take charge in medical emergencies as their primary job description) are trained to use automated external defibrillators (AEDs). This approach is called Public Access Defibrillation (PAD). The **hypothesis** to be investigated is that PAD will significantly increase survival in OOH-CA by reducing the time interval from collapse to defibrillation. The **specific aim** of this randomized, controlled trial is to measure survival to hospital discharge following OOH-CA in community units trained and equipped to provide PAD in addition to optimal standard care, compared to community units trained to provide optimal standard care (recognition of OOH-CA, 911 access, cardiopulmonary resuscitation [CPR]). **Secondary aims** include the comparison of Utstein criteria, neurological status, quality of life, cost, and cost-effectiveness between the two groups.

Participating research sites have identified 1,000 units (e.g., public areas, gated communities, shopping malls, airport terminals, casinos, business parks) within their service area that anticipate at least 0.6 *treatable* OOH-CAs within a 15 month period. Each unit will be randomized to serve as either an intervention or control group, with comparative episode data collected for a 15 month period following a short preliminary data collection period (~ 2 months to evaluate the ability for the site to capture event data) after training. Within each site, units will be sub-randomized to a retraining strategy. Performance at retraining will be monitored, and strategies modified if indicated.

Volunteer non-medical responders (e.g., office staff, bank tellers, merchants, and neighborhood volunteers) in both the intervention and control groups will be trained to provide the optimal standard of care: a) recognize OOH-CA, b) access 911 or its equivalent, and c) administer CPR. Volunteers in the intervention group will also be taught to use an AED promptly while awaiting arrival of the first public safety emergency medical team. The criteria for number and location of trained volunteers and devices will be a maximum 3-minute “walk through” to have the AED at the patient’s side.

OOH-CA victims in each of the two groups will be compared over the 15 month intervention period with respect to their: a) survival to hospital discharge (primary outcome); b) neurological status, c) quality of life, and d) resource use/costs. The incremental cost-effectiveness of volunteer non-medical responder defibrillation will be calculated.

This study will allow us to develop informed public policy regarding the use of AEDs by volunteer non-medical persons.

BACKGROUND AND RATIONALE

There has been a steady decline in morbidity and mortality from most cardiovascular diseases over the last 30 years.^{1,2,3,4} More than 90% of this reduction has been attributed to risk factor modification.⁵ Unfortunately, there has been little improvement in survival from sudden OOH-CA. Approximately 60% of the 489,171 deaths attributable to coronary heart disease in 1990 were thought to be due to sudden OOH-CA.⁶ Furthermore, the incidence of OOH-CA appears to be increasing in some populations,⁷ particularly in certain geographic areas.⁸

The true incidence of sudden OOH-CA is an elusive figure. Most sources state it as about 1,000 Americans per day.^{9,10} A recent phone survey of investigators in the field worldwide suggests that approximately 60% (range: 50%-82%) of events are witnessed and thus may be treatable.

Introduction

Existing Emergency Medical Services (EMS) systems typically combine paramedic and EMT services with some level of community involvement, such as bystander cardiopulmonary resuscitation (CPR) training. Some communities include automated external defibrillators (AEDs) at isolated sites or in mobile police or fire vehicles. Such an approach typically varies in effectiveness, with an incremental improvement in effectiveness seen in communities that organize and integrate services with the existing EMS. However, optimal improvement in survival from sudden out-of-hospital cardiac arrest (OOH-CA) may require a program that utilizes volunteer non-medical responders (who may not have a traditional duty to respond to an emergency) who are successfully trained to use AEDs. A comprehensive, integrated community approach to treatment with AEDs would have community units served by these volunteer non-medical responders who can quickly identify and treat a patient with OOH-CA. Such an approach is termed Public Access Defibrillation (PAD).

Some observational studies suggest support for the PAD approach. These studies have targeted traditional public safety responders such as police and firefighters or other laypersons in leadership positions who are trained and regularly called upon to take command in an emergency (e.g., airline flight attendants, security officers in Las Vegas casinos). Other studies, both randomized and observational, where trainees have been spouses or family members of at-risk patients, suggest that not all laypersons can effectively utilize AEDs in the setting of OOH-CA, even with extensive training. **This study differs from those conducted previously by focusing on an intermediate group, namely, volunteer non-medical responders (e.g., merchants, bank tellers, building superintendents, and co-workers).**

The **primary aim** of this randomized, controlled community trial is to compare survival to hospital discharge of patients with OOH-CA in community units (e.g., apartment or office buildings, gated communities, sports venues, senior centers, shopping malls) served by trained non-medical responders using automated external defibrillators (AEDs) with units receiving the traditional optimum community standard of care (i.e., rescuers trained to recognize a cardiac emergency, call 911, and initiate CPR). **Secondary aims** include the comparison of neurological status, health-related quality of life (HRQL), cost, and cost-effectiveness between the two groups.

In this study, approximately 25 sites will enroll a total of 1,000 units, each of which will collect data over a 15 month period following a few months of baseline data collection.

A high density of AED placement in the intervention arm and saturation of trained volunteers in both arms will be emphasized to maximize our ability to see an increase in survival. Our study will provide insight into the approach that is most effective and efficient in involving a community in the effort of providing public access to defibrillation.

This study is timely and important. AEDs are proliferating rapidly in public places. Commercial and charter aircraft increasingly carry the devices and train their personnel in using them, and

they are deployed in public spaces such as gambling casinos. Legislation is being drafted and passed to ease the requirements for their use. This scientific study will help to determine whether public policy and private behavior should encourage the deployment of AEDs outside of traditional settings in which users have a duty to respond. The PAD study is a randomized controlled clinical trial of a delivery system, not of a specific medical device. AEDs work well, and defibrillation is generally recognized as the most effective strategy for treating sudden cardiac arrest. But where AEDs should be deployed, how they should be deployed, how many of them should be deployed, whether the public can use them effectively, and the cost to society of broad dissemination of these devices are not sufficiently understood. Good science, ultimately, makes possible good public policy.

Treatment of OOH-CA

The optimal strategy to treat sudden OOH-CA should be primary prevention of the event. However, this approach is currently limited by our inability to identify prospectively the majority of potential sudden OOH-CA victims. We also do not yet have a safe, effective, and inexpensive preventive drug or device for the majority of potential victims.

Another, more pragmatic approach to sudden, unexpected OOH-CA is to provide rapid defibrillation to OOH-CA victims.¹¹ A ventricular tachyarrhythmia is responsible for the majority of OOH-CAs in adults. Electrical defibrillation by AEDs is very effective at terminating these arrhythmias, but the effectiveness of the defibrillation procedure is highly time-dependent. If defibrillation can be accomplished in the first minute of the OOH-CA due to ventricular fibrillation, survival is as high as 90%.¹¹ With each passing minute, the likelihood of survival without neurological deficit decreases by about 10%. By 10 minutes after the arrest, defibrillation results in long-term survival without neurological deficit in less than 10% of victims. That is, more than 90% of victims do not survive or do not survive neurologically intact.

A recent meta-analysis of 10 studies demonstrated a 9.2% absolute increase in survival when basic emergency medical technicians (EMTs) used AEDs in the field.¹² Another meta-analysis of 43 defibrillator-capable EMS systems demonstrated that median survival for all rhythm groups to hospital discharge was 6.4% (interquartile range: 3.7,10.3), and that a one minute decrease in time to defibrillation is associated with a 0.7% to 2.1% absolute increase in survival. (Personal communication, G Nichol, November 1, 1998) If survival were increased nationwide from 5% to 10% of events, the premature death of approximately 30,000 persons would be prevented in America annually.

The American Heart Association (AHA) has developed a ***chain of survival*** strategy that is designed to optimize a patient's chance for survival of OOH-CA.¹¹ There are four links in the chain: early access, early CPR, early defibrillation, and early advanced cardiac life support (ACLS). Early access means that citizens have been trained to recognize OOH-CA quickly and that a system of communications and emergency medical dispatch is in place to send trained emergency medical personnel and equipment quickly to the scene. Early CPR by bystanders provides ventilation and circulation, buying precious minutes for emergency medical teams to arrive with a defibrillator and other advanced life support equipment.

Only a few communities have developed a strong chain of survival that is yielding significantly improved survival from OOH-CA. For example, 27% of patients with witnessed OOH-CA in Seattle, Washington, survived to leave the hospital when bystanders performed CPR; only 13% survived without bystander CPR.¹³ In rural areas where emergency vehicles are nonexistent or remote and travel time is long, survival rates are extremely low. Similarly, in many urban areas, there are very few survivors of OOH-CA. For example, Becker and colleagues reported an overall 2% survival rate from OOH-CA in Chicago in 1987.¹⁴ Similar results were demonstrated in 1991 in New York City, where only 1.4% survived to leave the hospital.¹⁵ In New York City, as in Seattle, bystander CPR improved outcome, but only modestly. Survival was 2.9% among

victims who received bystander CPR, compared with 0.8% in those who received no bystander CPR. These rates are consistent with those reported by other investigators.

Cities that have low rates of survival have unacceptably long delays from the recognition of OOH-CA to defibrillation. In New York City the median time to first shock was 12.4 minutes in 1991. In Seattle, the majority of OOH-CA victims receive defibrillation within 5 to 7 minutes after the recognition of OOH-CA. No city has thus far been able to provide defibrillation for the majority of OOH-CA victims within five minutes of the recognition of the event. If defibrillation could be provided within 3-4 minutes, survival might be doubled.

Automated external defibrillators (AEDs), devices capable of automatically detecting and treating ventricular fibrillation, now make it possible for public safety personnel, e.g., EMT-Basics, police, and firefighters, to defibrillate safely. Clinical trials of AEDs used by EMT-Basics have shown, with few exceptions, that this technology is safe and saves lives. These devices defibrillate the heart with a high degree of sensitivity and specificity. However, about 24% of EMS systems in the United States still lack defibrillation capability.¹⁶

Five levels of potential AED users have been identified: (1) first responders (trained persons who have a duty to respond to medical emergencies, e.g., EMS personnel); (2) traditional targeted responders (trained individuals with a duty to respond to emergencies and are likely to react to a medical emergency, e.g., police, firefighters); (3) volunteer non-medical responders (trained individuals without a duty to respond to medical emergencies as their primary job description who desire to be trained and assume that duty, e.g., foremen, store managers, office clerks, building superintendents, and other members of the general public); (4) untrained members of the lay public (e.g., passers-by); and (5) family members of individuals known to be at risk for OOH-CA.

This study addresses level (3): volunteer non-medical responders.

Preliminary Studies

Studies of first responders clearly demonstrate that paramedics can safely and effectively defibrillate in the field.¹⁷ Targeted responders (e.g., police) have effectively increased survival to hospital discharge to between 14% and 58% by significantly decreasing the time to defibrillation.¹⁷ Pilot data in isolated populations suggest that volunteer non-medical responders can defibrillate safely and effectively, although no large scale trials of such an approach have been conducted. For patients with ventricular fibrillation or ventricular tachycardia at a large recreational facility in Australia, defibrillation by volunteer first aid personnel was associated with 67% survival to hospital discharge (Unpublished data, J Wassertheil, April 17, 1997). For patients with sudden OOH-CA in casinos, defibrillation by security guards was associated with 35% survival to discharge (Unpublished data, T Valenzuela, October 1, 1998).

The results have not been as striking when true lay persons have been trained to use AEDs, although existing studies are over a decade old and were conducted at a time when the technology was much less mature and devices were more difficult to use. Chadda and Kammerer trained a heterogeneous group of responders who subsequently saved 2 of 5 OOH-CA victims.¹⁸ Weaver and colleagues trained security personnel who successfully resuscitated 2 people in ventricular fibrillation.¹⁹ However, in a true lay population of trainees, Cummins et al. documented: 1) a trend toward lower performance scores in persons more than 60 years of age, 2) a 50% increase in the time required to deliver the first shock a year after initial training, and 3) failure to resuscitate the only 3 arrest victims attended in the field.²⁰ Presumably, strong community support will be needed to maximize survival when trained lay persons assume responsibility for defibrillation.

The need to improve defibrillation capabilities to the public is not universally acknowledged. Two major arguments against this approach revolve around issues of health-related quality of life (HRQL) and cost-effectiveness of this approach.

Health-Related Quality of Life of Survivors of OOH-CA

Use of AEDs by volunteer non-medical responders could actually **increase** the time to defibrillation if time were lost as the volunteer retrieved the AED and attempted to use it **prior** to calling 911. Confusion could also result in failure to provide prompt CPR. These delays could result in lower survival rates and/or worse neurologic status amongst survivors.

Several investigators have evaluated the HRQL of survivors of OOH-CA. Callicot et al. documented good to excellent HRQL among 32 persons administered the Health Status Survey (MOS Short Form-36) an average of 2.5 years (range, 0.02 to 5.5 years) following the event.²¹ Among 28 survivors interviewed an average of 18 months after arrest, 21 (75%) rated their HRQL as at least as good as before the arrest. Hsu et al. used the Functional Status Questionnaire to assess the HRQL of 35 patients who survived OOH-CA.²² Of those interviewed, 20 (57%) rated their quality of life as at least as good as before the arrest; 19 (54%) reported no impairment in HRQL.

Recently, Nichol et al. assessed the HRQL of survivors of OOH-CA by using the Health Utilities Index Mark 2 and Mark 3 system²³ Eligible patients had survived to hospital discharge after sudden CA. Of 126 patients discharged alive, 30 died before they could be interviewed. Of the 96 patients remaining, 86 (68% of survivors to discharge) completed the interview. Mean utility was 0.72 (SD=0.22) on a scale from 0 (dead) to 1 (perfect health), suggesting an acceptable HRQL. There was a significant association between HRQL and pre-discharge Cerebral Performance Category (CPC) and Minimal Status Exam (MMSE) score ($p=0.005$ and 0.0007 , Spearman $r^2=-0.29$ and 0.37 , respectively). This suggests that subsequent HRQL may be predicted from objective data on mental status that is collected prior to hospital discharge.

In summary, since most survivors have acceptable HRQL, concerns about poor quality of life are not a valid reason to abandon efforts to improve the health care system's response to victims of sudden OOH-CA.

Economic Impact

The direct costs of nationwide implementation of PAD may be large. If survivors are neurologically impaired, then the subsequent costs of care will also be large. Nichols used decision analysis to estimate the potential cost-effectiveness of PAD in another study.²⁴ Input data were derived from published data or fiscal databases. Compared to standard EMS, PAD using lay responders had a median incremental cost of \$44,000 per additional quality-adjusted life year (IQR=29,000 - 68,900). Since an incremental cost-effectiveness ratio of less than \$50,000 is usually considered to be economically attractive,²⁵ he concluded that implementation of PAD in the United States might be potentially useful. However, the cost-effectiveness of health care interventions must be demonstrated definitively if claims of their public health benefit are to have scientific credibility.²⁶ In addition, evaluation of the cost-effectiveness of a new treatment may boost early adoption of a beneficial intervention.²⁷ Therefore, a randomized controlled trial is necessary to evaluate the effectiveness and cost-effectiveness of expanded use of defibrillation in OOH-CA.

STUDY DESIGN

Rationale and basic approach

There are two clearly different locations for OOH-CA with regard to strategy of a layperson's use of AEDs: public and single-family home, with apartment residences and gated community residences intermediary.

Interventions for in-the-home cardiac arrest could include deployment and training in AEDs for family members, the defibrillator vest currently under trial, or even inexpensive "simple" implantable defibrillators. On the other hand, only deployment of the AED would appear to be an option for the public setting.

Although the percentage of OOH-CAs that occur in public places is only 25% of all OOH-CA events, it is 25% of a very large number (probably 250,000 or so per year). Moreover, the potential survival rates may be much greater in public places than in residences (27% vs 9% in Seattle), most likely relating to the event being witnessed more often in public places and/or collapse being associated with activity in public places.

There are two potentially viable PAD models. One is the **fire-extinguisher** model for which, at this time, there are many uncertainties.

The second model - the **directed training** model - aims to obtain a sufficient number of volunteers from a community unit and to train them in resuscitative measures. AEDs could be placed strategically so that in a “walk through,” the time to retrieve the AED and transport it to the victim requires no more than 3 minutes. This is the approach that we will test in this trial.

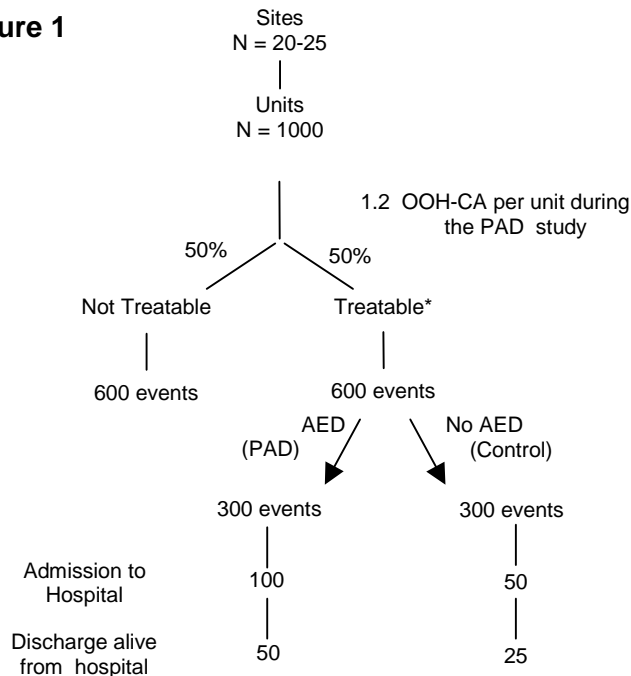
A key issue is whether to compare PAD versus usual care, or to test the incremental advantage of PAD against training that has been shown in Seattle and other areas to make an impact. If the PAD arm is not superior to the “optimal standard of care” arm and if both arms yield substantial improvement over historical controls, the implication would be that intensive citizen training needs to be implemented and that the additional expensive and potentially dangerous inclusion of AEDs is unnecessary. On the other hand, if the PAD arm is superior, then it will be clear that AEDs need to be employed, but we will not know if the “optimal standard of care” is also necessary. On the contrary, if PAD were to be compared to “usual care” and the PAD arm is found to be superior, it will be unknown whether that outcome is related to PAD or to the inclusion of known beneficial training (existing regulations do not permit deployment of AEDs without “optimal standard” training). The presumption is that testing PAD against “usual care” should provide a positive result since the PAD arm includes training which is known to be beneficial. *Thus, we will compare the PAD arm against “optimal standard care.”*

Study Sites

Across the USA and Canada about 25 sites, served by EMS systems that provide advanced life support, will participate. Based on the community units initially proposed by the prospective sites, 66% are urban, 31% suburban, and 3% rural.

Sites were evaluated on the basis of 1) characterization of the existing EMS, 2) data availability and accuracy, 3) leadership, 4) design, 5) organization, 6) probability of improvement in response time, 7) research or clinical experience, 8) cost of doing the study and availability of local logistical support, 9) evidence of community support, and 10) opportunity for minority enrollment.

Figure 1



*Treatable is essentially equivalent to witnessed or found shortly after collapse. The 50% split is across all types. In residential units there may be proportionately less treatable but absolutely more OOH-CA, while in public units there will be proportionately more treatable but absolutely fewer OOH-CA. Thus in both types of units we expect about 0.6 treatable OOH-CA.

individuals above 50 years of age with coronary artery disease and/or cardiomyopathy. At least 1,200 events are anticipated during the course of the trial (see Figure 1). We considered several possible age cutoffs for use of defibrillators by targeted responders. Defibrillation using an AED is recommended for anyone age 8 or greater by the AHA guidelines, and standard-sized adult defibrillation pads and paddles are recommended²⁸. An alternate age cutoff may lead to confusion among providers about who may receive defibrillation and would complicate use of the AHA training materials (most sites intend to use the AHA materials). Furthermore, setting of policy after the trial would be difficult if a nonstandard population were studied. Also, the incidence of cardiac arrest in persons under 21 is low - at most, only 1 or 2 episodes are likely to involve a victim under 21 in this study.

Patients with arrest and unconsciousness due to trauma or obvious drug overdose will be included.

Based on the proposed community units, we expect 25% of the OOH-CA will be in women and 31% in minorities.

Site exclusion criteria include: prior presence of a non-traditional targeted responder defibrillation program, inability to obtain IRB approval, unresolvable legal issues such as the absence of local Good Samaritan laws, problems associated with implementation of a volunteer responder defibrillation program, or lack of support from the EMS director.

Each research site will be expected to identify on average 40 distinct units sufficiently separated geographically to eliminate the possibility that there will be contamination of a control unit by rescuers bringing the AED from a nearby intervention unit.

At least 250,000 persons above age 50 will be "at risk" during the study.

Patient Population

The patient population of interest consists of persons (age ≥ 8) with OOH-CA (asystole, VT, VF, electromechanical dissociation [pulseless electrical activity]). The largest number of such events occur in

Volunteer Rescuer Population

The volunteer population of interest consists of lay-persons (without a responsibility to provide medical assistance in emergencies as their primary job description) who are willing (by signing an informed consent):

- (1) to be trained in recognition of OOH-CA, 911 access, CPR, and use of the AED, and
- (2) to assume a responsibility to respond.

Specifically excluded are police and firefighters. Following training, volunteers will be considered to be agents of the EMS.

Study Unit (Unit of Randomization)

The study will randomize approximately 1000 identifiable community units that are larger than single-family homes or individual offices and smaller than communities. The obvious candidates for study units are office buildings, shopping malls, airports, golf courses, gated communities, apartment buildings, etc. To enhance power and reduce cost, selected units are to have a substantial risk of OOH-CA by meeting a requirement of containing at least 250 persons over the age of 50 or documentation of a history of 0.6 treatable (i.e., witnessed or discovered shortly after collapse) OOH-CA over 1.25 years. This approach maximizes power (it approximates randomizing episodes) and is pragmatic for purposes of training, in that the participating centers' initial estimates are that such units would require from 4 to 6 AEDs and from 8 to 12 volunteers each. Currently identified units include 31% group residential, 18% workplace, and 51% other (airports, train stations, golf courses, entertainment facilities, malls, sports complexes).

Inclusion criteria for participation in the PAD trial are:

- The unit must have a clearly defined geographic boundary (note, however, that the unit could consist of several distinct contiguous areas, e.g., two or more apartment buildings might form a unit).
- The estimated EMS response time to defibrillation must be within 15 minutes at least 90% of the time so that the study results can be expected to apply to the vast majority of existing EMS systems.
- The volunteers must be able to deliver an AED to the victim within three minutes of notification of an event, if that unit is randomized to the intervention arm.
- There must be reasonable grounds to anticipate that at least 0.6 cases of treatable OOH-CA will occur within 1.25 years. Acceptable documentation of this assumption includes: 1) EMS documentation of at least one attempted resuscitation per 2 years, or 2) other data documenting at least one on-site cardiac arrest per 2 years, or 3) data showing that the population at risk contains at least 250 people aged 50 or more per 24 hour period of exposure (i.e., $N_{>50} * (\text{hours on site}/24) \geq 250$).
- There must be an existing identifiable group(s) of on-site volunteers who are not health care professionals (nurses, doctors) nor "traditional responders" (ambulance attendants, police, firefighters). Groups of other volunteers with first aid and/or CPR training are acceptable only if they do not have previous AED training. Examples of acceptable volunteers include lifeguards and workers trained in industrial first aid who expect to respond to emergencies but have no previous AED training.
- There must be easy access to the AED or CPR equipment.
- Consent must be obtained from the unit volunteers and from the unit residents or the community that will be participating in the trial.

Exclusion criteria are:

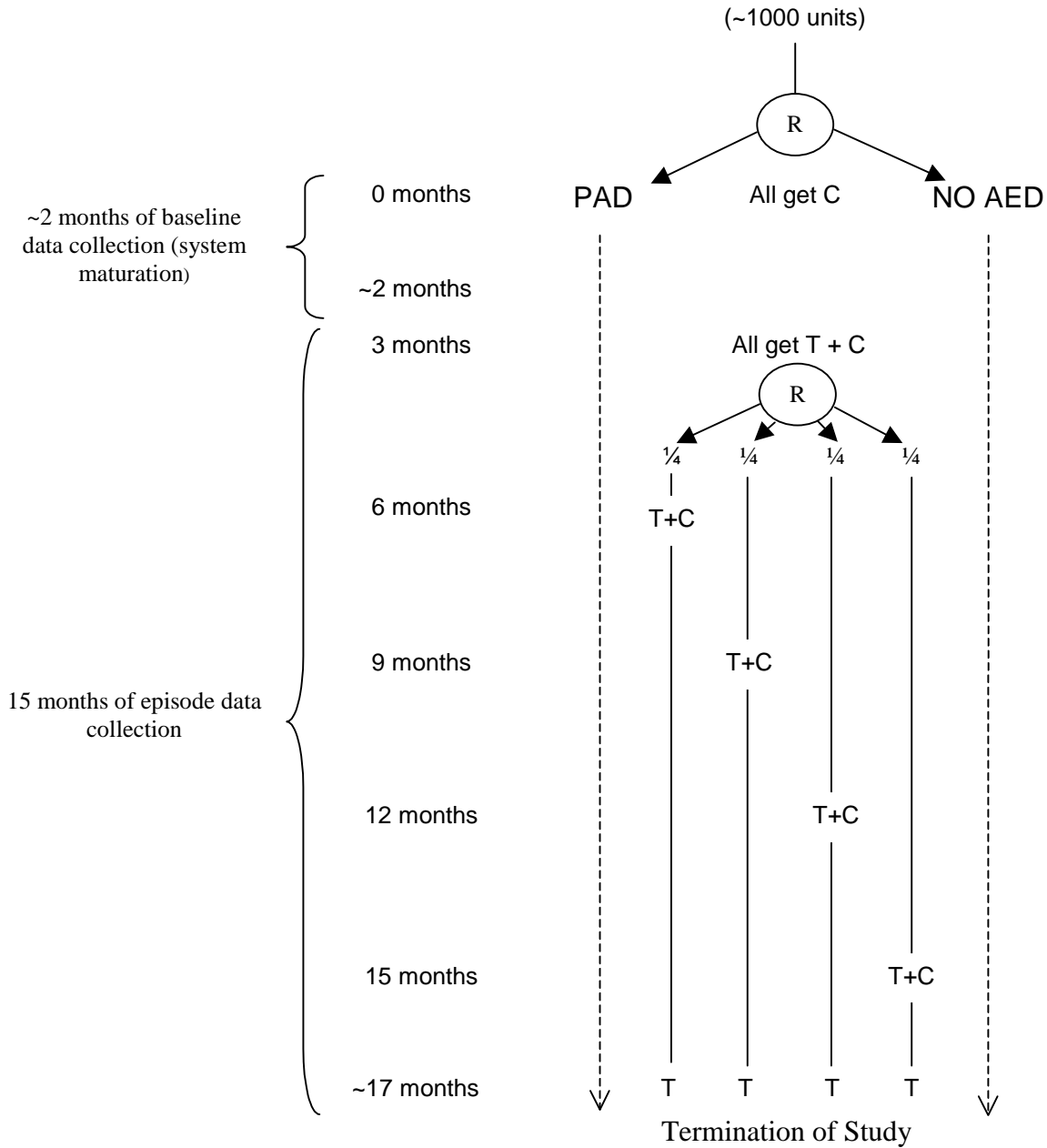
- A previous non-traditional defibrillation program in place.
- On-site medical or nursing personnel able to respond to the victim's side within three minutes of notification more than 10% of the time.
- The EMS is able to respond with a defibrillator to a victim's site within three minutes of notification more than 10% of the time.

The latter two exclusions should eliminate units with such excellent current response capabilities as to make any measurable impact of PAD problematic, e.g., units located next door to an EMS station.

Randomization

Study units will be randomized to **standard** or **PAD** resuscitation training in a parallel design (Figure 2), and will be subrandomized to a retraining schedule (Table 1). The subrandomization is described on page 13.

Figure 2
Randomization Scheme



Randomization will be stratified by site and within site by type of unit, residential or public. Sites will not be required to match units as pairs, but characteristics such as demographics will be monitored by the CTC. This information will be used to insure approximate balance of demographics between treatment arms. If there are large units with more than 4 expected treatable cardiac arrests, they will form a stratum across sites and be randomized to achieve balance. About 40 units will be randomized at each of approximately 25 sites, and the duration of the intervention will be 15 months. Accordingly, each stratum should have between 8 and 12 units.

Follow-up

After randomization, training, and baseline data collection (which may include “mock episodes” or practice training episodes of cardiac arrest), each unit will be followed for 1.25 years to identify all episodes related to study interests and to collect the appropriate data.

Contamination

Contamination is defined as use of an AED at a unit assigned to standard treatment, that is, CPR/no AED. Identified study units must be sufficiently separated physically as to avoid contamination between the units. The major issue is contamination due to aggressive marketing tactics of AED manufacturers or local implementations that cover an entire community, such as local Operation Heartbeat AHA activities. During the monthly Volunteer Log completion the coordinator will seek to identify any installation of an AED in a control unit. For certain types of units accounting for approximately half of the units identified (for example, low income apartment buildings), contamination from outside marketing will have little to no impact. Lack of funds would prohibit approval, funding, and implementation of AEDs through their agencies. In addition, the AED manufacturers have pledged to refrain from marketing in the study units.

INTERVENTION

Training

The study will compare the incremental effect of the AED in the PAD arm against “the optimal standard of care.”

All study units will receive an intervention – (1) CPR or (2) CPR + AED. Volunteer responders in both study arms will be trained to meet the following guidelines:

- **Assess unresponsiveness:**
The volunteer must have physical contact with the manikin and vocalize loud enough to awaken the victim, if possible.
- **Access 911 or other emergency numbers:**
The volunteer must send someone to call 911 (or call 911 himself/herself, if alone).
- **Use a barrier device for ventilation (site option):**
If a site chooses to test ventilations using a barrier device, the volunteer must apply the barrier device over the manikin’s mouth prior to the ventilation attempt.
- **Provide two ventilations:**
The volunteer must provide adequate ventilations to the manikin to achieve adequate chest rise, using the head tilt, chin lift maneuver necessary to open the airway.
- **Demonstrate proper hand placement for chest compressions:**
The volunteer must demonstrate the proper hand position over the sternum.
- **Provide adequate depth of chest compressions:**
The volunteer must depress the chest of the manikin approximately 1 1/2 to 2 inches.

In addition, volunteers in the AED arm will be required to demonstrate proficiency in the following skills:

- Bare the chest for pad placement:
The volunteer must remove all clothing over the chest prior to applying the AED pads.
- Attach pads correctly:
The volunteer must remove the protective backing and affix the AED pads to the manikin's bare chest. The volunteer must make an attempt to secure the AED pads to the contour of the manikin's chest. One pad is placed on the right upper chest to the right of the sternum, and the second pad is placed on the lower left chest, covering the anterior axillary line.
- Shock safely within 90 seconds from the time the AED arrives at victim's side:
The volunteer must remain clear of the manikin, manikin clothing, cables and AED from the time the AED begins analyzing. The volunteer must also be alert to potential contact by others in the situation and must clear everyone before pushing the shock button. The volunteer must call "all clear" before pushing the shock button. The 90-second interval begins when the volunteer places the AED at the side of the victim and ends when the volunteer pushes the shock button.

At the end of training volunteer competence in the above-mentioned skills will be assessed and documented using standardized checklists. No written test will be administered.

Since the purpose of the study is to assess the feasibility of broad implementation of PAD, the study training guidelines were developed to be versatile in order to accommodate different preferences among the sites. The goal is for volunteers to attain skill proficiency without requiring an undue investment of time and money by the volunteers and instructors. In addition, the training course must meet all criteria required by the specific state legislation and by the relevant device manufacturer.

All courses in both arms will teach the optimal standard of care: 1) recognition of an OOH-CA, 2) access to the community's emergency response number (in most communities, it will be 911), and 3) performance of CPR. In addition, volunteers in the AED arm will be trained in the operation of the specific AED model type that will be used by their unit/site. Laminated cards containing prompts for CPR/AED components and study contact information will be provided to each volunteer. Guidelines established for the training course are listed below:

- 3-4 hours in length
- student:instructor ratio of 4:1, not to exceed 6:1
- scenario-based training using case studies or real-life examples
- skills practice per trainee - 30 minutes optimal with a minimum of at least 20 minutes
- not more than 45 minutes total for instructor lecture/demonstration
- dispatcher assistance encouraged where available.
- minimum instructor requirements: BLS instructor certificate
- video recommended for CPR/AED training.

These guidelines are exemplified by the AHA HeartSaver AED course – a competency-based, performance-focused curriculum that has been carefully validated and refined prior to its public dissemination²⁹ - but they also allow some flexibility in instructor certification requirements .

“Do Not Attempt Resuscitation” Orders

Sites will be responsible for identifying their local state's method of identification of patients who have been legally designated as “Do Not Resuscitate.” The method of identification will vary from state to state, in some a bracelet, in some a necklace, and in others a legal document placed conspicuously in the patient's residence. Volunteers will be instructed to recognize them and must not attempt resuscitation on these patients.

“Mock” Cardiac Arrest Training Episode

As part of the training both for the volunteers and for the training coordinators, “mock episodes” or “episode dry runs” will be performed at each site. These episodes should be as realistic as possible within the bounds of reason. This episode should include full data collection, including debriefing of the volunteer(s), assessment of AED pad placement for the AED group, etc. The EMS could be involved in these practice episodes, if deemed appropriate by the site.

Retraining Schedule

Retention of skills is an important consideration for successful implementation of an effective PAD program. In addition, the cost of regular retraining of volunteers on a large scale can be substantial for both AED and CPR skills. All volunteers will be tested and retrained to proficiency at approximately 3 months after initial training. By random assignment of units ¼th of volunteers (approximately 2500) will be tested and retrained to proficiency at 6 months, 9 months, 12 months or 15 months after initial training. All volunteers will be tested at the end of the study (approximately 17 to 18 months after initial training). The retraining schedule would be intensified if the results of testing at 6 or 9 months indicated insufficient skill retention.

AED Devices

AEDs from two manufacturers will be used in the study (see attachment Devices). The devices currently on the market are essentially comparable with respect to ease of use, application technique, operating steps, safety, and known efficacy. No attempt will be made to make the device appearance, arrhythmia detection algorithms, or instructions more comparable.

Inclusion of AED devices with voice recording modules is desirable to facilitate interpretation of the sequence of events occurring during the resuscitation.

Flexible barrier mouth protection devices will be an option of the site. Bag masks or stiff ventilatory masks must not be used. Razors for use in shaving the chest for application of the AED electrode pads will also be an option of the site.

With the exception of New York City, AED model types will be randomly assigned to each site. Because of the larger number of community units in New York, both models will be used, stratified by unit type.

Device installation and maintenance will be carefully monitored (at least on a monthly schedule) according to manufacturers' guidelines.

Signs will be used throughout all units to remind the volunteer population of EMS access; CPR and, in the PAD units, of the location of the AED.

Volunteer Status

The site must recruit and train additional volunteers in the case of volunteer drop-out to maintain the 3 minute criterion.

Integration with the EMS

Technological integration with the local EMS will be determined at the site level. However, EMS's involvement in this project is essential for its success. In most systems, EMS keeps a log of all its runs and in many systems EMS personnel complete a special form for cardiac arrest. These data are important for the project.

A close working relationship with EMS is essential for the following reasons: 1) they are the people who respond to 911 calls and will be the only ones defibrillating cardiac arrest victims if

not already defibrillated by the PAD-AED; 2) they will transport all surviving cardiac arrest patients to the hospital, and 3) they will provide other definitive care such as endotracheal intubation, medications, etc.

The relationship between the EMS and the volunteer responder has to be developed carefully. EMS should consider itself an integral part of the study and work closely with the voluntary responder. The role of the voluntary responder should be respected by the EMS. A smooth working relationship between the two is important for the success of the project.

EVENTS AND ENDPOINTS

Primary and Secondary Endpoints

The basic **event** of interest is an OOH-CA. The **primary endpoint** of interest is survival through hospital discharge following OOH-CA. Secondary endpoints consist of: the cerebral function at discharge (CPC); neurologic status at 3 months post discharge (ALFI-MMSE); generic quality of life at 3 months post discharge (HUI); costs; and incremental cost-effectiveness.

Identification of Events

Events that will trigger data collection (the “episode net”, Figure 3) are defined as those for which

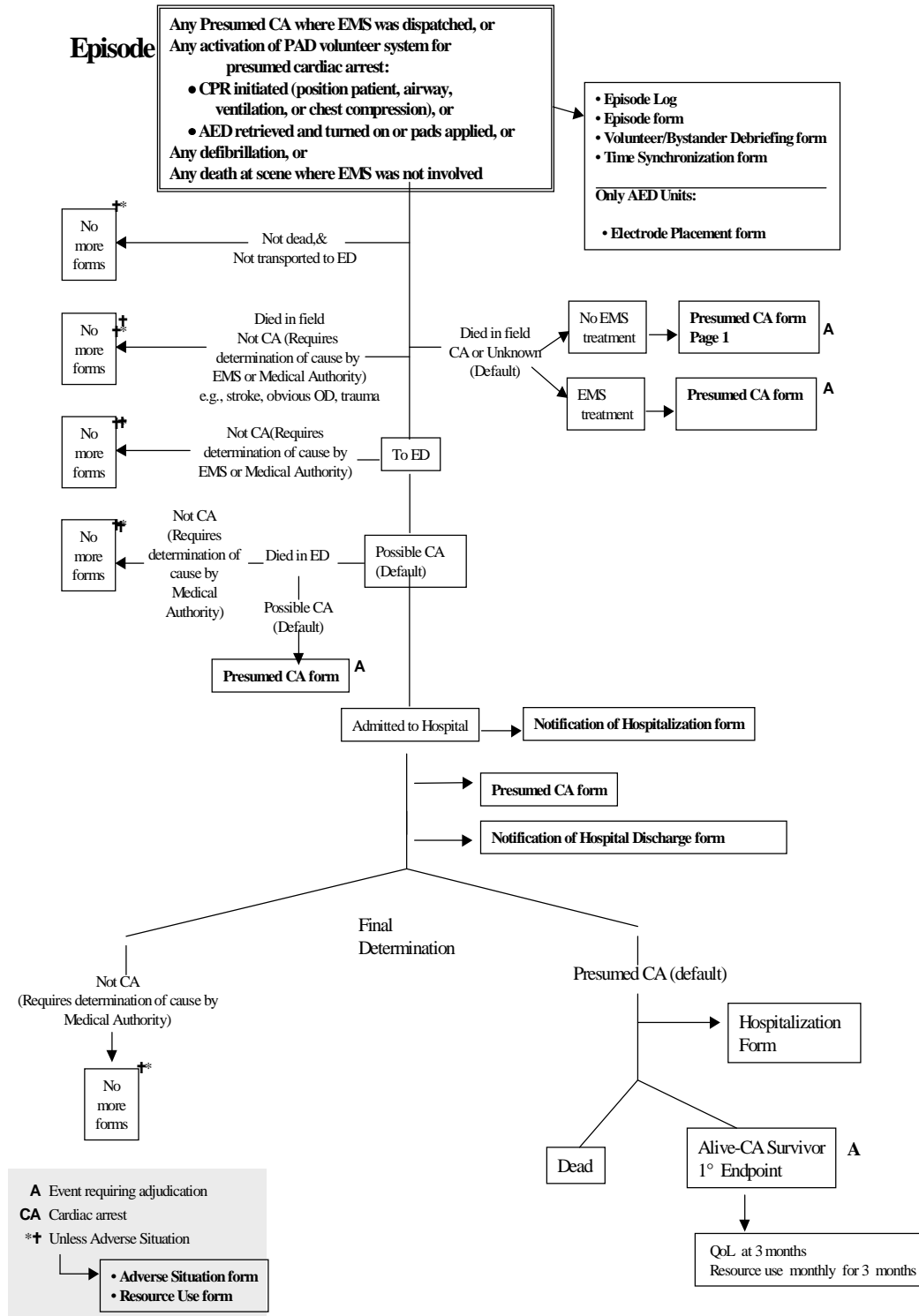
- (1) the EMS was dispatched for presumed OOH-CA, or
- (2) the PAD volunteer system was activated for presumed cardiac arrest:
 - any CPR was attempted (move or position patient flat and supine on the floor, and/or clear airway, and/or ventilate, and/or chest compression), or
 - the AED was retrieved and turned on or pads applied, or
- (3) any shock was delivered, or
- (4) the patient was found dead but the EMS not notified.

All cases that meet this definition will be logged onto the Episode Log and will have the Episode form (Attachment Forms) completed. If it is obvious that the patient was never in cardiac arrest after evaluation by EMS or the emergency department, then further data collection will not be necessary (except for adverse events and their associated costs), otherwise hospitalization and post-hospitalization data will be collected. Cases meeting the definition of cardiac arrest (defibrillatory shock, asystole, VT, VF, electromechanical dissociation [pulseless electrical activity]) will require completion of the Presumed Cardiac Arrest Form (Attachment Forms). While this strict definition may eliminate some cases which were truly arrhythmic cardiac arrests (patients found dead), it will not miss treatable cardiac arrests. A treatable arrest is defined as one that might benefit from CPR and/or defibrillation.

The Episode Log will be faxed to the CTC twice monthly.

Sites must develop the means to learn of all episodes through volunteer notification and EMS logs. The Episode and Volunteer/Bystander Debriefing forms must then be completed. These forms collect the necessary information for the initial branching in Figure 3. The Episode form includes data from the EMS report and the ED.

Figure 3



Each site must develop a strategy for ensuring that all episodes are captured at a given unit. Examples that might be employed are:

1. User of AED or CPR will use a 24-hour number (e.g., day pager or voice mail backup) to notify the site coordinator whenever an episode occurs in the unit.
2. EMS Dispatch will use 24-hour pager number whenever a suspected cardiac arrest occurs in a study unit. Most EMS dispatch computer systems will permit location-specific information to be entered that could be used to trigger this page.
3. Provide an incentive to the volunteer to make the call. AED replacement pads could be brought by the investigator or coordinator. A new pocket mask could be provided. Volunteer stress debriefing could be provided as needed.
4. Identify a lead volunteer at each site who would be responsible for device maintenance, backup for notification of arrest cases, loss of volunteers, asking for additional training, etc.
5. Capture all EMS responses at that location. Use geographic feature in the computer-aided dispatch system to capture 911 emergency calls at each unit.

Primary Outcome Measure

For any given OOH-CA incident, the endpoint of interest is survival through hospital discharge. If the survival rate within a unit is to be used as the outcome measure, these successes form the numerator. However, the logical denominator, all episodes of OOH-CA, is not easily measured. An arrest might go unrecorded in the conventional arm but be recorded in the PAD arm simply because the AED was applied, whether or not appropriately. To the extent that differential identification of cases occurs, an analysis that considers the proportion of arrests surviving would be biased. Another conceivable denominator is the sum of all successes and all deaths, irrespective of cause, that occur in the community unit. However, the EMS has no natural link with deaths that are not associated with a call to 911. Depending upon the nature of the community unit, capturing all deaths that occur in the unit might be extremely difficult and time consuming. Another potential denominator is the population size of the unit. Even if the population size could be obtained in sufficient detail to stratify by gender and age, the remaining inherent variability, after standardizing for age and gender, would probably introduce unwarranted variation in the outcome measure. Thus, the proportion of OOH-CA that survives would probably be more biased across arms than the number of successes.

Therefore, the primary outcome measure will be **the count of successes** in each unit. Moreover, the number of successes (without any denominator) is the appropriate outcome measure (incremental number of life-years saved) to assess the net effect for the cost-effectiveness analysis. It is this combined process that is the practical goal of this study.

If a patient experiences more than one cardiac arrest during the study, only the first episode will be counted, since the ability to resuscitate may be as much a patient function as a system function (e.g., a fast VT versus a VF rhythm). However, this is probably not likely to happen since almost all patients who survive an OOH-CA will receive an implanted defibrillator and hence be unlikely to need PAD when they experience a recurrent arrhythmia.

Cardiac Arrest Adjudication Committee

One definition of cardiac arrest is “no signs of life because of absent or diminished cardiac output that lasts for at least 30 seconds.” Some of these patients will not be in cardiac arrest. There may be events that do not meet this definition in which a well-meaning bystander starts chest compressions. For example, a patient might have severe hypotension (or bradycardia, or a vagal episode), and a pulse was not detected at the scene by the volunteer rescuer. Thus, a cardiac arrest might be suspected when none was present. There is also likely to be a problem with ascertainment bias in the patients who die and for whom we do not have any rhythm strip (e.g., dead on arrival of medics, or a rhythm strip not obtained for other reasons). Furthermore,

there may be cases in which a bystander puts an AED on a patient and it fires inappropriately (such an event should be rare, if it occurs at all, since devices are programmed conservatively to shock only VT or VF).

Thus, there may be episodes that appear to yield a survivor from OOH-CA when there was no actual cardiac arrest. Therefore, the Clinical Trial Center will develop an adjudication committee that is blinded to the intervention arm to classify all “presumed arrests” into four categories: 1) definite cardiac arrest; 2) probable cardiac arrest; 3) possible cardiac arrest, or 4) not a cardiac arrest. All purported cases of cardiac arrest will be adjudicated. All cases that could conceivably be cardiac arrests would be included. The site would obtain information for the adjudication committee. A blinded narrative, with information about type of unit and origin of defibrillator, will be developed by the CTC for the committee to review and will include rhythm strips and notation as appropriate. We recommend that there be some “sham blinding” of the cases that had an AED applied in the intervention arm so that the absence of an AED report does not flag a patient as being in the control group. For example, some AED rhythm strips could be “lost” and not included in the review, especially when there are other non-AED ECG rhythm records available with the same or similar information. Many patients captured by the episode net will not have received a shock. We anticipate approximately 1200 “presumed arrests.” Probably 600 of the untreatable cases will be dead and will receive no EMS therapy, thus not requiring adjudication. Most treatable (perhaps 80%) will be clear definite cardiac arrests that the committee can set criteria for and will not need individual committee review. Thus, there may be 200-300 that will require careful narration and full review, yielding a monthly Cardiac Arrest Adjudication Committee case load of 10 to 15. In addition, the CTC will renarrate and resubmit 5% of these cases to the Committee as a check on reliability.

The final definition of OOH-CA is crucial because the primary endpoint of the PAD Trial is OOH-CA survival to hospital discharge. Patients admitted to the hospital and subsequently discharged alive, but who never experienced a cardiac arrest, must be excluded. For purposes of analysis, the PAD Trial is unique. Most studies classify events based on etiology and mechanism:

- Cardiac
 - Arrhythmic
 - Nonarrhythmic (CHF or cardiogenic shock)
- Noncardiac
- Unknown

The important event of interest in the PAD Trial is a cardiac arrest, regardless of etiology. Underlying etiology of arrest is less important than mechanism of arrest. The AED would be expected to resuscitate VF, regardless of whether it was caused by ischemia, infarction, CHF, drowning, electrocution, etc. The PAD Trial is testing the additional benefit of the AED on survival, over and above the benefit of early recognition, early 911 access, and CPR. Thus, the net that captures possible episodes of OOH-CA is broad:

OOH-CA Episode Net

- Any EMS dispatch for presumed cardiac arrest, or
- Any presumed CA where the PAD volunteer system was activated:
 - In either the AED group or the control group, any CPR was initiated (any positioning of patient, clearing airway, ventilation, or chest compression), or
 - In the AED group, the AED was retrieved and turned on or pads applied, or
- Any defibrillation (prior to removal of the patient from the scene), or
- Any death at scene, even where the EMS was not involved.

All cases captured in the Episode Net will be reviewed locally to identify cases of presumed OOH-CA. Functionally, the local Principal Investigator will assign a diagnosis of presumed OOH-CA if CA cannot be excluded by other obvious causes:

Presumed OOH-CA

- Any case in the Episode Net where OOH-CA is not ruled out
- Any case included must either:
 - Be admitted to the hospital, or
 - Die in the field, en route, or in the ED

(Any case where CPR, VT/VF, asystole, or defibrillatory shock occurs only en route (after the paramedics begin to remove the patient from the scene) or only in the ED will be excluded.)

The Cardiac Arrest Adjudication Committee would then review all cases of presumed OOH-CA by the following scheme, which is independent of etiology (cardiac, non-cardiac [drowning, electrocution, metabolic/renal, overdose, trauma, pulmonary, hypothermia, anaphylaxis, cerebral, sepsis, exsanguination, and others]):

Classifications of Presumed OOH-CA

Definite OOH-CA

- Any defibrillatory shock is administered prior to departure from scene of event (i.e., prior to removal of patient from house/building/etc.), or
- First rhythm recorded by Medics
 - VF
 - VT
 - Asystole*, or
- First rhythm recorded by AED
 - VF
 - VT
 - Asystole*.

(*Asystole is defined as absence of any QRS complex $\geq 1\text{mm}$ @ 10 mm/mV for 6 seconds.)

Probable OOH-CA

- Found dead, no evidence for non-cardiac cause of death.

Possible OOH-CA

- Found without pulse or respiration, unresponsive, survived, only CPR administered, first recorded rhythm not VF/VT or asystole. No defibrillatory shock administered.
 - First rhythm severe bradycardia (11-50 bpm)
 - First rhythm PEA
 - First rhythm idioventricular rhythm
 - First rhythm sinus bradycardia (51-59 bpm)
 - First rhythm sinus rhythm or other supraventricular mechanism (60-100 bpm)
 - First rhythm sinus tachycardia (>100 bpm) or other supraventricular tachycardia (>100 bpm)
- Found without pulse or respiration, unresponsive, died, only CPR administered. First recorded rhythm not VF/VT or asystole. First rhythm PEA. No defibrillatory shock administered.

Not OOH-CA

- Was not admitted to hospital and did not die in field, en route, or in ED.
- DNAR – no CPR and no defibrillatory shock administered.
- Found dead, non-cardiac cause identified.
- Trauma, overdose, hypothermia, cerebral, metabolic, renal, electrocution, overdose, sequelae of seizure, drowning, anaphylaxis, or other cause where VF/VT or asystole not documented and defibrillatory shock not administered.
- CA with CPR or defibrillation begun only after removal of the patient from the scene, or en route, or in ED.
- Neither CPR nor defibrillatory shock ever administered.

Thus, these definitions, in general, outline the patient population in whom an AED might be expected to have a salutary effect on ultimate survival.

Further, the committee would judge etiology by previously published criteria:

- Cardiac
 - Arrhythmic
 - Non-arrhythmic
- Non-cardiac
- Unknown

The primary outcome for the PAD Trial will be survival to hospital discharge of patients with Definite OOH-CA. A secondary outcome will be survival to hospital discharge of patients with Definite-Probable-Possible OOH-CA.

Other Secondary Outcome Measures

General Health Status (Best Status Achieved By Hospital Discharge) The Cerebral Performance Category (CPC) will be completed by abstraction from hospital records. This is a five-point scale that measures global health from grade 1 (normal function) to 5 (brain dead).³¹ This scale is a standard element for uniform reporting of data from OOH-CA.³²

Neurological Status (3 mos. After OOH-CA Episode) Neurologic status will be collected on each survivor by using the Mini-Mental Status Exam (MMSE)³³. The Adult Lifestyle and Function (ALFI) MMSE is a modification of the MMSE that has been validated for telephone administration.³⁴ In the PAD trial, the ALFI MMSE will be used primarily to identify patients who are too cognitively impaired to be able to respond to the other questionnaires. For subjects with an ALFI MMSE score < 17, a proxy respondent will be used for the Health Utilities Index and health resource use questionnaires. Otherwise, the patient will be questioned.

Generic HRQoL (q 3 mos. After OOH-CA Episode) Generic HRQL will be measured by using the Health Utilities Index Mark 2 and 3 systems^{39,40}. The Health Utilities Index is one of the few measures that address cognition directly. Specifically, it assesses problems with memory, thinking, or problem solving. The HUI3 has construct validity because it correlates with more traditional functional scales such as Cerebral Performance Category or Mini Mental Status Exam.⁴¹ Others have demonstrated that the HUI3 discriminates among patients with Alzheimer's disease, stroke or brain tumors according to their severity of neurologic impairment.^{42,43,44} Both the HUI3 global score and HUI3 cognitive score correlate with the degree of cognitive impairment in patients with dementia. Finally, the HUI3 should have face validity in survivors of cardiac arrest because most of its attributes should be affected in patients with neurologic impairment.

Long-Term Survival and Morbidity (“SF-1” and “SOS”) status will be ascertained monthly to 3 months and then every 3 months after discharge for the duration of the study. The “SF-1” consists of the first question in the SF-36 “In the interval since your last follow-up, would you, in general, say your health is: excellent, very good, good, fair, or poor?” The “SOS” – (simple outcome screen) consists of 2 simple questions that have been used to assess outcome from stroke and found to be both reliable and valid measures⁴⁵. The long-term survival of control and intervention patients will be compared with standard survival analytic techniques.

Economic Impact Resource utilization will be obtained for overall Volunteer Training and EMS (from the yearly EMS resource/budget materials that each center will submit), for the initial Hospitalization (abstracted from the hospital billing data, if available, otherwise from the hospital record by the site coordinator), and for utilization to 3 months post discharge from the baseline hospitalization (1st, 2nd and 3rd months by structured interview from the CTC with the patient or appropriate responsible person-see Health Resource Use Questionnaire). In addition rehospitalization (how long and why) will be queried q 3 months to study end.

The discharge/post discharge measures and timing of collection are summarized in the table below:

	Months				
	Discharge	1	2	3	q3
CPC	X				
(ALFI) MMSE				X	
HUI				X	X
“SF-1”		X	X	X	X
“SOS”		X	X	X	X
Resource Use	X	X	X	X	X*
Vital Status	X	X	X	X	X

* Restricted to “Were you hospitalized? (yes, no, how long, why).”

Process Measures

Time to Defibrillation will be defined as the interval between receipt of the call to 911 and the first defibrillation applied to the patient. **We do not consider it feasible to try to collect time from collapse to defibrillation.** With the availability of clocks and event recording in AEDs, we will determine time from 911 call to defibrillation by synchronization (after the fact) with a common clock.

Volunteer Pre-tests at Retraining Volunteers will be pre-tested at the time of retraining to measure skills degradation using study defined criteria for evaluation. The results will be monitored during the study to help inform any decision about shortening retraining intervals.

Baseline and Ancillary Covariates Demographics and EMS response data will be collected for study units. Demographics and characteristics of volunteers will be collected. Wherever possible episode variables, including patient information collected by the EMS, will be collected in a manner consistent with the Utstein style of reporting.³² More extensive patient information will be collected for all consenting patients admitted to the hospital. In addition to episode data retrieved from devices, extensive data will be collected for any AED misuse or malfunction.

SAMPLE SIZE AND STATISTICAL DESIGN

Sample Size Estimates for Primary Outcome

The primary outcome for each unit is the number of successfully resuscitated cardiac arrests, and the primary analysis will compare PAD to control using a stratified t-test. The number of units needed depends on type I error rate and power, success rates of the control communities, effectiveness of stratification, and the improvement one wishes to detect. It also depends on the percentage of units contributed by New York City (NYC), which could be as high as 20%.

Table 1 presents power as a function of NYC's contribution, assuming stratification is not helpful at all. That is, the success rates of units within a stratum are no more similar to each other than those of randomly selected units from possibly different strata. This represents a pessimistic scenario.

Table 1: Power to detect various increases in the probability of successfully resuscitating a cardiac arrest for PAD units relative to controls. Sites outside New York City are expected to contribute approximately 40 units each, for a total of 24x40=960. Power is shown for different percentages of units contributed by New York.

	Percentage (No.) of Units Contributed By New York City			
	5% (50)	10% (107)	15% (170)	20% (240)
Total # Units	1010	1067	1130	1200
Power for 75% Increase	53%	53%	54%	54%
Power for 100% Increase	74%	74%	74%	75%
Power for 125% Increase	88%	88%	88%	88%

As Table 1 shows, power changes very little by adding more units because those extra units would have to come from New York, which has a very low cardiac arrest survival rate; doubling that rate would still produce very few successes. Power is good (88%) for detecting a 125%

increase in success probability, fair (about 74%) for a doubling, and poor (53%-54%) for a 75% increase.

The improvement in power due to successful stratification (small within-strata variability compared to between-strata variability) is a matter of speculation. Power is shown below under different assumptions about the effect of stratification on reducing the variability of the average difference between PAD and control.

Table 2: Power to detect various increases in the probability of successfully resuscitating a cardiac arrest for PAD units relative to controls, as a function of the reduction in variance from successful stratification. The Table assumes New York will contribute 10% (107) of the 1067 units.

	No Reduction in Variance from Strat.	10% Reduction in Variance from Strat.	20% Reduction in Variance from Strat.
Power for 75% Increase	53%	58%	63%
Power for 100% Increase	74%	78%	83%
Power for 125% Increase	88%	91%	94%

Table 2 shows that we have power in the 80%-95% range if stratification is quite effective (reducing variability of the average difference between PAD and control by 20%). Because other community randomized trials have not realized large gains from pairing or other stratification, it is safest not to assume much more than a 10% reduction in variance from stratification. This would yield close to 80% power for detecting a doubling of success probabilities. In fact, if we assume that stratification is about as effective as pairing in such a way that the control and PAD success probabilities of a given pair would be exactly the same if PAD had no effect, we get 80% power to detect a doubling of the success probability.

Details of the Calculations

Assumptions:

1. A two-tailed test at $\alpha=0.05$.
2. The number of cardiac arrests over the 15 month study in a unit follows a Poisson distribution with mean 0.6. This corresponds to a 45% chance of one or more cardiac arrests in a unit.
3. The control probability of successfully resuscitating a cardiac arrest varies from one unit to another as specified in the table in Appendix A of the application. Only summary information from the table is relevant. Specifically, the success rate in NYC (0.012), the average success rate outside NYC (0.072), the variance of success rates outside NYC (0.0023).
4. PAD improves the success probability by a factor of λ (e.g., $\lambda=2$ corresponds to doubling the success probability).

Assumption 2 implies that given a control unit's success probability c , the number of successes follows a Poisson distribution with mean $0.6c$. The number of successes in a PAD unit follows a Poisson distribution with mean $.6\lambda c$, where c is the success probability that unit would have had without PAD. Thus, the mean difference, δ , between PAD and control is

$$\delta = 0.6\mu(\lambda - 1),$$

where μ is the average success probability of control units, weighted to take into account that New York has a larger proportion, p , of units than other sites. The average success rates inside and outside NYC are $.012$ and $.072$, respectively. Thus,

$$\mu = 0.012p + 0.072(1 - p).$$

The variance of the number of successes in a unit can be obtained by conditioning on the unit's success rate, c , had it received no PAD, and using the familiar formula

$\text{var}(X) = E\{\text{var}(X|c)\} + \text{var}\{E(X|c)\}$. The variances in randomly selected control and PAD units are

$$0.6\mu + 0.36\sigma^2, 0.6\lambda\mu + 0.36\lambda^2\sigma^2$$

respectively, where σ^2 is the variance of the control success rates of the units, taking into account NYC's disproportionate share of units. Specifically,

$$\sigma^2 = 0.0023(1 - p) + (0.072 - 0.012)^2 p(1 - p).$$

Thus, the variance of the difference in sample means of the n PAD and n control units is

$$v = (0.6\mu + 0.36\sigma^2 + 0.6\lambda^2\sigma^2) / n.$$

Sample size/arm for 80% power is obtained by setting $\delta / v^{1/2} = 1.96 + 0.84$ and solving for n .

Power for given n is $\Phi(\delta / v^{1/2} - 1.96)$.

Sample Size for Retraining Comparisons

The sample size of each group in a comparison is at least 250 units. Assuming we use a pass/fail grading (based on data from A. Dougherty, personal communication, 1999) we might expect about an 83% pass rate with pass rates across units varying uniformly from 71% to 95%. If we assume 3 comparisons and use Bonferroni to set $\alpha = .05/3 = .017$, then $Z_{\alpha/2} = 2.12$ and if we want power 0.9, $Z_{\beta} = 1.28$. Then the Δ we can expect to observe is approximately 3%.

ANALYSIS

Primary Outcome

The primary analysis will use the stratified t-test on the number of successes in each stratum. Strata will consist of the site and unit type (i.e., residential or public). A secondary analysis, provided a test of the differences in counts of total OOH-CAs indicates little or no bias in counting (i.e., similar in intervention and control arms) will employ a loglinear multinomial model conditioning on the number of OOH-CAs.⁴⁶ The latter analysis will, of necessity, exclude units with no OOH-CA.

Secondary Outcomes

General Health Status The null hypothesis is that general health status at hospital discharge is identically distributed between survivors in the intervention and control arms. The CPC scores of **control** and **intervention** survivors of OOH-CA will be compared by using univariate and

multivariate ordinal regression. A CPC score of 1 or 2 has previously been defined as good cerebral functioning.³¹

Neurologic Status For the ALFI-MMSE, a score <17 has been defined as indicative of cognitive impairment.³⁴ Therefore, ALFI-MMSE scores will be transformed into a binary variable by using this cutoff. The neurologic status of **control** and **intervention** survivors of cardiac arrest will be compared by using multiple logistic regression with adjustment for significant covariates such as age and existing comorbidity.

Generic Quality of Life The utilities of **control** or **intervention** survivors of cardiac arrest will be compared with repeated measures analysis of variance over specific assessment points, by using generalized linear models to accommodate the unequal number of assessments. Goodness of fit will be assessed by evaluating the fraction of unexplained variance. Nonlinear transformations of the response (**HUI3**) will be considered such that an additive model is a good approximation for the data.

Economic Analyses We will evaluate the incremental cost and cost-effectiveness of the intervention by using the following steps: a) cost each component of care by measuring and valuing all resources used, b) compare the individual patient costs of control versus intervention by using statistical techniques, and c) estimate the incremental cost-effectiveness of the intervention by pooling the effectiveness and cost data in a **decision model**. Estimation of costs will adhere to current standards for health economic evaluation⁴⁷ All costs will be converted to year 2000 US dollars, using the medical care component of the Consumer Price Index as appropriate. Costs and effects will be discounted at a rate of 3%.⁴⁸

The primary cost analysis will compare the total per-patient cost of each intervention over the duration of the trial. If one intervention is both more costly and less effective than another, then the costs and outcomes will be reported separately.⁴⁹ Otherwise, an incremental cost-effectiveness ratio will be calculated (e.g. costs to the community per additional life saved).

Retraining Sequence We do not expect to have adequate power to compare survival by retraining strategy. Volunteer participation at an episode of OOH-CA (yes, no) will be compared by retraining strategy in each arm. In addition, each OOH-CA with volunteer participation will be reviewed and a qualitative assessment of volunteer performance made; good, adequate, inadequate, safety concern. Within each arm, the scores of each retraining strategy group will be compared by univariable and multivariable ordinal regression. ROSC (of at least 1 hour duration) will also be compared between retraining strategies by a loglinear multinomial model.

Observational Analyses

There are many analyses of interest that have no randomized basis for analysis.

Time to Defibrillation Since a basic premise for this trial is that shortening time to defibrillation will increase survival, it will be important to quantitate the relationship if there is a positive result or to explain any null result. **We will only collect time from 911 call to shock (or AED activation if sooner) since the time of collapse is notoriously difficult to verify for most cases.** The relationships between time to defibrillation and survival, hospital admission, and unit saturation (e.g., simulated response time, number of volunteer responders, number or density of AEDs) will be explored.

Volunteers The relationships between volunteer participation and performance and volunteer characteristics and system saturation will be explored. Since training costs will be a major component of any "directed training" PAD deployment, it will be important to note factors that distinguish between a trained volunteer who reacts appropriately and one who doesn't. Besides obvious factors such as physical handicaps (which will probably lead to self-deselection during or after training) there may be simple questions about interests or skills (e.g., Do you

have a driver's license?) that may be informative. We are currently seeking information about any studies or instruments developed in this area.

Two process measures of **effectiveness of training** are the user's willingness to use the AED and successful application of the AED. Willingness to use the AED will be measured as the number of volunteers who report at least seeking the AED when confronted by an apparent OOH-CA. Application of the AED will be assessed as "successful" if the AED is connected to the patient, turned on, and able to perform ECG analysis.

Volunteer non-medical responders who use an AED to resuscitate someone may experience psychological distress, commonly referred to as a "critical incident stress response." This response is thought to be self-limiting and typically relatively minor in intensity in this situation; however, the severity of the response will be assessed to validate this assumption. Volunteers who use an AED during a resuscitation will be interviewed within two weeks of the incident by the local Research Coordinator using questions designed to elicit the incidence and severity of the psychological impact on providers. Responses will be graded to determine the severity of stress responses. Volunteers indicating severe stress will be referred for counseling.

A Priori Subgroup and Covariate Analyses

We plan to conduct subgroup analyses with regard to two types of community units, those which are residential versus those which are more public, since we expect volunteers in the residential units to be true lay citizens, while volunteers in the more public units are likely to be "appointed" or to have work responsibilities that would make their participation more obvious.

DATA MANAGEMENT

Data Volume

If a site provides 40 units, it will be dealing with approximately 400 events captured in the episode net resulting in 48 OOH-CAs, 24 treated OOH-CA, 6 hospital admissions, 3 survivors, 200-400 volunteers, and 200 study AEDs. Although volunteers and AED checks will be simple, the latter, when a problem is discovered, will require additional documentation.

Forms Design/Collection/Entry

Data collection forms have been designed to guide the Coordinators and Investigators through the questions so that required sections are not missed, and all questions are unambiguous. A Manual of Operations will be developed to help guide the Research Sites through execution of the protocol, including day-to-day questions that come up regarding the trial. Initially the data will be collected on paper data forms, designed to minimize the chances for error or ambiguity on recording. Prior to the initiation of the study, the data forms will be field tested by 6 of the selected sites. Preliminary data forms are enclosed in the attachment Forms.

Forms will be grouped into packets. Although in community based studies, the urgency of individual patient data is diminished, it is important to establish tracking for immediate evaluation of episodes and serious adverse events. Notification forms for hospital admission, hospital discharge, and serious adverse events will be due by FAX at the CTC within 24 hours of the event. The remaining forms in the packet will be completed promptly, photocopied, and the originals mailed to the CTC. Packets not arriving 4 weeks after the event will be considered delinquent and the site will be pressed to complete the forms. See data forms collection table for schedule of data collection.

PAD SCHEDULE OF DATA FORMS COLLECTION									
Name of Form	Baseline	Monthly	Any Episode*	Presumed CA	Hospital-ization	Hosp D/C	Event **	Follow-up	Other
EMS Characteristics	X								X end of study
Unit Characteristics	X								
Entity Characteristics	X								
Final Entity Plan	X								
Potential Volunteer	X								
Volunteer Training –Initial	X								
Volunteer Log		X							
Volunteer Retrain Worksheet Volunteer Retraining Log								3 mo	6,9,12 or 15 per schedule
Initial AED Location Log	X								
AED Inspection Log		X							
AED Removal/Addition			±	±			±		
Episode Log *		X X							bi-weekly
Episode			X	X					
Presumed CA				X					
Time Synchronization				X					
Volunteer /Bystander Debriefing			X	X					
Electrode Pad Placement				X					
Notification of Hospitalization					X				
Notification of Hosp. Disch.						X			
Hospitalization					X				
Pt Information						X			
Follow-up								1,2,3 mos	qtrly
Health Resource Use								1,2,3 mos	
MMSE								3 mos	
Quality of Life Health Status								qtrly	
Adverse Situation Notification							X		
± as needed *Includes any presumed CA (where EMS was dispatched), anytime PAD volunteer system is activated, any AED retrieval, any attempted CPR, any death at scene where EMS was not involved. **Event includes non-PAD AED placement in unit; any volunteer/bystander or pt physical or emotional trauma due to PAD system activation; or AED misuse.									

All of the data will be collated at the CTC in Seattle, with the exception of each EMS's annual budget, which is collected for purposes of identifying incremental cost to the EMS system. Those data will be collated by the Economic Center in Ottawa. The data to be collected at the CTC in Washington will be collected through the site Coordinator. The exceptions are the quality of life and health resource use questionnaires which will be administered by telephone directly from the CTC. In some instances, data related to device problems will be obtained from the appropriate device manufacturer.

Beginning and ending EMS budgets and patient baseline hospital bills will be sent to the Economic Center at Ottawa for coding and entry.

Closeout

Sites must submit (complete and correct) all data within 2 months of termination of episode management. Final payment (which generally lags about 6 months at the University of Washington) will be withheld until data are complete.

Sites must maintain study materials in a secure accessible location for at least 2 years (longer if required by NHLBI or FDA).

AEDs must be disposed of according to instructions developed between the Steering Committee and manufacturers. *The study will attempt to have AEDs donated after the study for distribution to both intervention and control sites.*

PROTECTION OF HUMAN SUBJECTS

Institutional Review Board

Human Subjects IRB approval of the PAD Trial is necessary prior to beginning the study. Federal Regulation 21 CFR 50.24 outlines the requirements for obtaining informed consent for emergency research and the guidelines for obtaining waiver of consent. The key requirements and justification that PAD qualifies are in attachment Consent/Waiver.

Every effort will be made to recruit community units that will include a representative number of women and minorities as **volunteer** subjects. Women and minorities will be included to the extent that they contribute to the target population of **patients** with OOH CA. Although children comprise only a small percentage of this population, they will be included if they are at least eight years of age because the recommended lower limit for use of the AED is age 8. (see page 6).

All patients will be notified of this study as soon as they are conscious and able to understand the discussion. In the event of the patient's death or persistent impairment, the legal next-of-kin will be notified of the study as soon as the next-of-kin can be identified and located. In addition to notification, patients who survive to hospital admission and discharge will be asked to give informed consent for participation in the followup neurologic evaluations, quality-of-life measures, and economic surveys.

Waiver of consent must be approved by the appropriate IRB(s) at each site. Communities will be informed, and public disclosure of the nature of the PAD Trial will occur at each site, but the approaches to disclosure will vary from site to site. At sites where only discrete units are being recruited (e.g., gated residential communities) the public disclosure and communication will be much simpler than for units which have a large public access (e.g., shopping malls). Disclosure, communication, and consultation could be performed on a more localized level with meetings of the residents of these communities. Managers of residential and public units must also consent. However, for the sites with units which include extensive public access, (such as shopping malls), city-wide disclosure, communication, and consultation will be necessary by mass media techniques.

At each site or unit the local Principal Investigator will work intensely to inform the public of the purpose of the trial, the methodology, and the risks and benefits of the study. The Principal Investigator will facilitate public discussion about the trial and its acceptance in the community. This process will include public meetings wherein comment and consultation can be exchanged. Likewise, the Principal Investigator will communicate to other researchers in the field and other members of the medical community as well as educating the Emergency Medical Services system. After the study is completed, results will be made available to each community or unit.

The Clinical Trial Center (CTC) has obtained approval through the IRB of the University of Washington for the collection and analysis of data. **Each site will be responsible individually for its own IRB approval through accepted local mechanisms.** The CTC will facilitate national cooperation and communication among the sites, Principal Investigators, and Coordinators. In addition to providing a template for the informed consent for both the subject and the study volunteer responder, the CTC will develop a template for the following items:

1. Disclosure to representatives of the communities in which the clinical investigation will be conducted, including newspaper media, radio, and television.
2. Directions for community discussion and input.
3. Suggestions for community involvement, including public meetings to discuss the protocol.
4. Suggestions for establishing a separate panel of members of the community from which the subjects will be drawn (to include input from the IRB, as well as the investigators).
5. Suggestions for involvement of local government forums to establish the community's wishes and standards with respect to research of this type.
6. Assurance that a broad spectrum of each ethnic component of the community is represented in these community consultations, to include, but not be limited to, consultation with local leaders of community ethnic groups.

Each clinical investigation site IRB approval must be completed prior to beginning of baseline data collection and prior to contact with potential volunteer non-medical responders. Single project assurance will be obtained for sites without IRB. IRB renewal will be required yearly, and it will be the responsibility of the local site to assure such renewal. Notification of any withdrawal of IRB approval must be transmitted to the CTC by both phone and in writing within 5 working days, and the research activities must be halted immediately upon learning of withdrawal of IRB approval. The CTC will thereupon notify all appropriate parties.

IDE

In accordance with Federal regulations, the United States FDA determined that an Investigational Device Exemption (IDE) and a waiver of informed consent were both required for the PAD Trial. Based upon an earlier research grant proposal, an application for the IDE and waiver of consent were submitted to the FDA on March 19, 1998. The FDA responded by issuing IDE #G980067. This IDE was granted to the Emergency Care Research Institute (ECRI) in Plymouth Meeting, Pennsylvania. This organization subsequently transferred the IDE to the University of Washington on January 6, 1999. Upon completion of the development of the protocol, necessary supplements will be submitted to the FDA for approval.

DSMB

A Data and Safety Monitoring Board (DSMB) will be formed to provide independent review of the study progress, CTC and site performance, safety issues, and sequential monitoring and provide recommendations to the NHLBI. The NHLBI will form the Board following input from the CTC and Investigators. The Board will consist of a statistician, two physicians (one with EMS and the other with clinical trials experience), a paramedic, an expert on training, and an ethicist. The Board will meet annually, or more often if determined by Board members.

Safety

An important component of this study is the need to investigate and report on incidents involving an occurrence, unexpected within the framework of the study protocol, that involves harm to any individual involved in the study.

Criteria for adverse events include:

- Any criminal/prank use of an AED.
- Any AED malfunction during application, including any missing AED recording during a resuscitation.
- Any episode of an individual accessing an AED substantially before the placing of a call to 911.
- Any episode of an AED that does not shock a subject who was in ventricular fibrillation.
- Any shock to a subject not in OOH-CA or to a volunteer administering the AED.
- Any incident in which a bystander is injured.
- Any substantial emotional/mental or physical adverse complaint by a volunteer responder.
- Any injury to the victim due to chest compressions or rescue breathing resulting in hospitalization or prolongation of hospitalization.
- Any attempted resuscitation despite the presence of a valid “do not resuscitate” order.
- Any substantial community opposition to the PAD Trial .

The number and type of these events will be reviewed by the DSMB and reported to the FDA as appropriate.

Sequential Monitoring

The DSMB will continuously monitor safety (all serious adverse events will be reported immediately to the DSMB Chair). The DSMB will review accumulated adverse events on a quarterly basis via conference calls. In addition, the DSMB will also review recruitment, volunteer proficiency, volunteer dropout, and unit compliance on the same schedule.

The DSMB will monitor for efficacy only once, at the halfway point of randomized trial data collection, using a conservative statistical approach.

No formal rules for revising retraining intervals are planned, but the DSMB will monitor results and may propose revisions.

STUDY ORGANIZATION

Timeline

The timeline in Figure 5 outlines the major items that must be completed to accomplish the PAD Trial. Sentinel dates are:

IRB approval by 4/15/2000

Begin training of volunteers 5/1/2000

Begin baseline data collection 6/1/2000

Begin main trial cardiac arrest data 9/1/2000

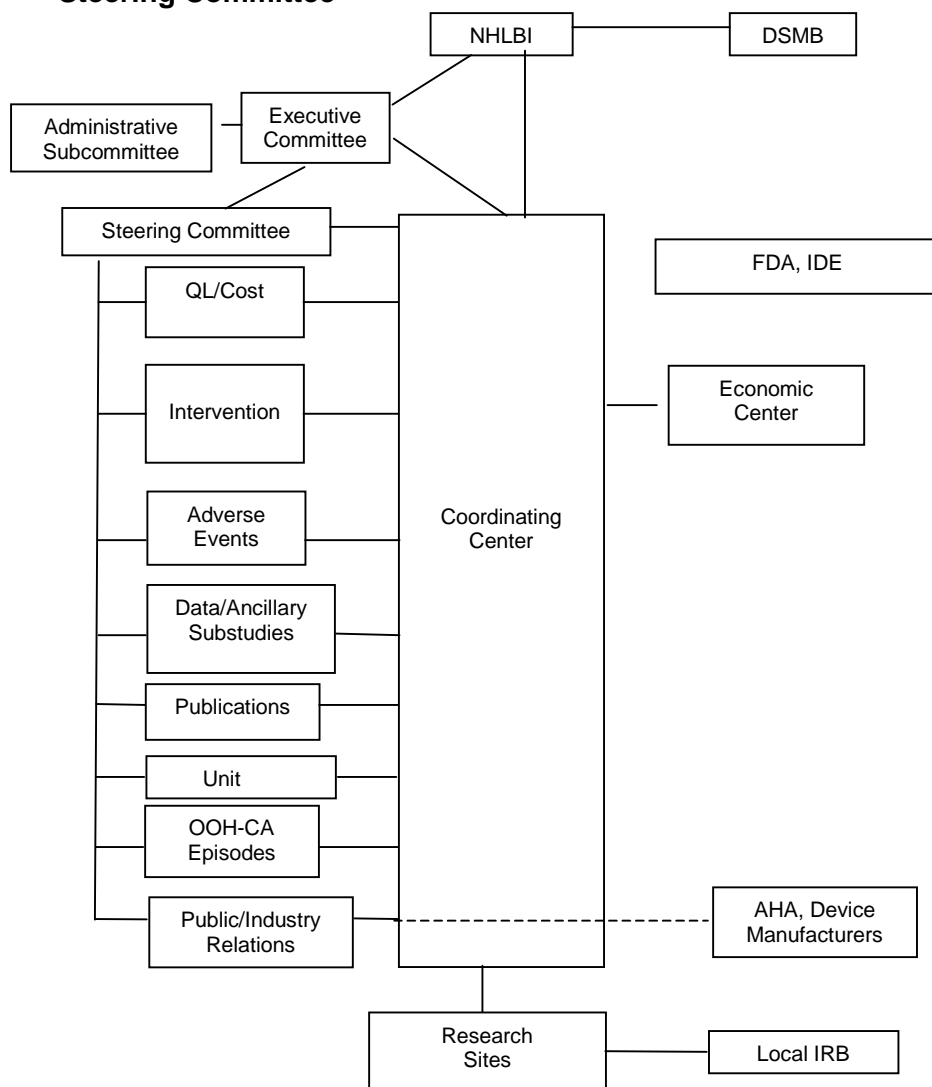
Figure 5: TIMELINE

CTC	NHLBI	SITES	TASK	DATE														
X	X		Timeline finalized	1/7/00														
		X	Begin unit enrollment negotiations	1/7/00														
X	X		Budget completed	1/7/00														
X	X		Protocol completed	1/7/00														
		X	Letter of Intent from PI		1/15/00													
X	X		Draft dataforms – Version 2		1/15/00													
X		X	IRB Packet to sites		1/15/00													
X		X	Draft community consent packet to PI		1/15/00													
X	X		DSMB meeting			1/25/00							9/15/00				7/1/01	
		X	IRB main site submission				2/1/00											
X	X		Submit OMB exemption					2/15/00										
X		X	Signed contract between UW and PI's Site						3/15/00									
X	X	X	Steering Committee - training							4/15/00 (approx.)								
		X	IRB main site approval							4/15/00								
		X	Begin volunteer enrollment							4/15/00								
		X	Begin community consent media process							4/15/00								
		X	Submit protocol to peripheral IRBs								5/1/00							
		X	Begin training units								5/1/00							
X		X	Begin baseline data collection									6/1/00						
		X	Approval from peripheral IRBs									6/1/00						
X		X	Begin main trial cardiac arrest data collection										9/1/00					
X	X	X	Steering Committee meeting											10/1/00 (approx.)				
X		X	Last unit begins collecting trial data												1/1/01			
		X	Enrollment ends													4/1/02		
X		X	Data cleanup															7/1/02
X		X	Followup ends															7/1/02
X	X	X	Data analysis ends															3/31/03

Units would be brought on-line for cardiac arrest main trial data from 9/1/00 through 1/1/01.
 Each unit reports main study cardiac arrest data for 15 months.

Duration of study: CTC = 3.5 years ; Sites = 2.5 years

**Committee Structure
Steering Committee**



The Steering Committee consists of the members of the Executive Committee (including consultants), the NHLBI representatives including the Project Officer, Deputy Project Officer, and the Contracting Officer, the Principal Investigator, Co-Investigator, and the Project Director of the CTC and the Principal Investigator and Principal Coordinator of each of the Research Sites. An ex-officio representative from the AHA, and from each manufacturer may also attend, if and when approved by the Steering Committee. The Steering Committee will meet as a group to complete planning, for purposes of training, and then approximately every 6 months to facilitate the study particularly through subcommittee work. Subcommittees will work closely with the CTC but

may also need to bring in as consultants members of the AHA or of the industry representatives. Membership on subcommittees will, in large part, depend upon the interests of the Steering Committee members. Chairs of subcommittees will be selected from members by the Executive Committee in collaboration with the Project Office and the CTC. Temporary committees will be appointed as needed and will remain in effect through the initial DSMB meeting.

The voting members of the steering committee will consist of the Principal Investigator (or appointee) at each site, the Principal Investigator (or appointee) at the CTC, the NHLBI Project Officer (or appointee) and the remaining members of the Executive Committee.

Executive Committee

The Executive Committee will be responsible for Steering Committee matters that arise between meetings of the Steering Committee and that need resolution before the next Steering Committee meeting. The Executive Committee will teleconference bi-monthly or more often if needed. Members of the Executive Committee are the Steering Committee chair, the NHLBI Project Officer and Deputy Project Officer, the CTC Principal and Co Investigator and Project Director, and all of the subcommittee chairs. An administrative team consisting of the Project

Officer or appointee, the Executive Committee Chair and the CTC Project Director will teleconference approximately every month to discuss meeting schedules and content, and other study logistics. The team will be responsible for scheduling Executive Committee teleconferences and will identify relevant topics for the agenda. The team will also identify, produce and distribute relevant materials to the Executive Committee members prior to calls.

Data Safety Monitoring Board

The Data Safety Monitoring Board is advisory to the NHLBI. It will initially to review this protocol and at least annually thereafter. At that time it will review extensive reports from the CTC. The Chair of the Steering Committee, the CTC Principal Investigator, and NHLBI staff will generally be expected to attend the first part of the meeting.

Subcommittees

Unit While the interactions between the EMS, the AED, and the volunteer non-medical responders will not be dictated by the study protocol and will be site-specific, we believe that the investigators who participate in this study can bring tremendous experience collectively to this issue. This subcommittee will specifically address the interaction issue with the goal of insuring maximum efficacy at all sites. This committee will also evaluate unit dropout due to adding non-study AEDs.

Intervention This committee will be involved with issues related to volunteer training, retraining, turnover, development of training guidelines, and criteria for training proficiency, as well as monitoring ongoing proficiency of training. This committee will also address issues specific to the AED including parameter settings, maintenance, unit location, and transference of event AED data to the CTC.

OOH-CA Episodes This committee will address the key issue in data ascertainment for this trial, namely methods of identifying all OOH-CAs, timely notification of the site Research Coordinator, and methods of ensuring that data are not lost nor misidentified in the delay inherent between the random occurrence of an OOH-CA. This committee will also adjudicate presumed cardiac arrests (see Figure 3).

Data, Substudies and Ancillary Studies This Committee will review all proposals for substudies, ancillary studies and database analyses and make recommendations to the Steering Committee regarding approval.

Publications This Committee will review manuscripts and abstracts prior to submission and make recommendations regarding approval. They will also propose authorship publication guidelines and (once approved by the Steering Committee) monitor their compliance.

Adverse Events For any presumed adverse event three members of the Adverse Events Committee will independently review the clinical data to evaluate whether or not an incident has occurred that requires reporting to the FDA, to local IRBs, and/or to the DSMB. The reports review will be prepared by the CTC and will include primary source material.

Public/Industry Relations This subcommittee will be responsible for dealing with public perception and industry relations, including AHA and Industry support and political support.

QL/Cost This subcommittee will review Quality of Life and Cost measures to be collected and will make recommendations regarding measures and time points for which QL/cost data should be collected. This subcommittee will also be responsible for QL/Cost data QC.

Site Management

Central oversight for the units within each site will be under the direction of the Principal Investigator and Coordinator at that site. The Coordinator is responsible for implementing training and follow-up, and it is anticipated that this Coordinator will visit each unit at least once each month. Coordinator time has been budgeted such that visiting each unit monthly is feasible. Central oversight of the 20 to 30 sites will be accomplished by the CTC at the

University of Washington. This oversight will involve all members of the CTC, from data acquisition to statistical analyses.

Individual sites will be responsible for the administrative and logistical oversight of their assembled units. One full-time Coordinator should be able to be responsible for 20 community units. The CTC's previous experience strongly suggests that full-time Coordinators are much more effective than part-time Coordinators and sites will be encouraged to structure their oversight through the use of full-time Coordinators. As the CTC monitors the performance of the sites, comparative site performance tables/charts will be useful in persuading those sites performing poorly to adopt the practices of those performing more effectively.

The DSMB will review any recommendation made by the CTC/Executive Committee to drop a site (or units within a site) for poor performance. The DSMB can also initiate any such recommendations. Decisions to drop a site must ensure that no bias is introduced in the primary comparison or unit.

Third Party Involvement

Third party involvement for this study has been obtained from the American Heart Association, Guidant Corporation, Agilent Technologies/Heartstream Operation, and Medtronic/Physio-Control Corporation. Corporate donations will either be made directly to the University of Washington or through the American Heart Association. These relationships will be consistent with the NHLBI memo entitled "Industry and Other Third Party Involvement in NHLBI-Sponsored Clinical Trials and Epidemiology Studies: Awardee-Third Party Related Issues," (dated 4/30/97). Specifically, the third party will have no influence upon study governance or conduct or interpretation of results, will have limited access to datasets (data for their specific device only), will not conflict with PHS grants policy, and will sign a contract with the University of Washington outlining any conditions of support and nature of the support.

Third party representatives will be invited to participate on the Steering Committee, particularly on certain subcommittees where their expertise may be especially helpful to the study. Device manufacturers and the American Heart Association may be useful to the Intervention Subcommittee.

Third parties will not have access to primary results prior to the public (except within 48 hours prior thereto) or access to more of the dataset than is the basis for reports that have been published or to which other qualified members of the scientific community have access, with the exception that device-specific information (the study is not powered to evaluate the 2 devices comparatively but may provide useful device-specific information), will be provided to the appropriate manufacturer on an ongoing basis. This is in the interests of the study in that, if this information leads to improvements in the device during the course of the study, it may also help to increase the likelihood of a positive result.

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