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Review article

## The Public Access Defibrillation (PAD) Trial Study design and rationale

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Dedicated to the memories of Thomas P. Holohan and Peter Frank, died 11 September, 2001, World Trade Center.

### Abstract

The PAD Trial is a prospective, multicenter, randomized clinical study testing whether volunteer, non-medical responders can improve survival from out-of-hospital cardiac arrest (OOH-CA) by using automated external defibrillators (AEDs). These lay volunteers, who have no traditional responsibility to respond to a medical emergency as part of their primary job description, will form part of a comprehensive, integrated community approach to the treatment of OOH-CA. The study is being conducted at 24 field centers in the United States and Canada. Approximately 1000 community units (e.g. apartment or office buildings, gated communities, sports facilities, senior centers, shopping malls, etc.) were randomized to treatment by trained laypersons who will provide either cardiopulmonary resuscitation (CPR) alone or CPR plus use of an AED, while awaiting arrival of the community's emergency medical services responders. The primary endpoint is the number of OOH-CA victims who survive to hospital discharge. Secondary endpoints include neurological status, health-related quality of life (HRQL), cost, and cost-effectiveness. Data collection will last approximately 15 months and is expected to be completed in September 2003.

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**Keywords:** Cardiopulmonary resuscitation (CPR); Automated external defibrillator (AED); Defibrillation; Emergency medical services (EMS); Ventricular fibrillation (VF); Out-of-hospital cardiac arrest (OOH-CA)

### Resumo

O Ensaio PAD é um estudo clínico prospectivo multicêntrico randomizado que pretende testar se voluntários não médicos podem melhorar a sobrevivência das paragens cardíacas extra-hospitalares (OOH-CA) através da utilização de Desfibriladores Automáticos Externos (AEDs). Estes voluntários leigos que não têm nenhuma responsabilidade tradicional na resposta à emergência médica como parte do seu trabalho, formarão parte de uma abordagem compreensiva integrada na comunidade ao tratamento de OOH-CA. Este estudo está a ser realizado no terreno em 24 centros nos Estados Unidos e Canadá. Foram randomizados cerca de 1000 unidades comunitárias (ex. Apartamentos de edifícios de escritórios, guardas de caminhos de ferro, instalações desportivas, centros comerciais, etc.) para serem tratadas por leigos treinados que fornecerão quer Reanimação Cardiorespiratória de forma isolada (CPR) quer CPR mais uso de um AED, enquanto aguardam a chegada dos serviços de emergência médica comunitários. O primeiro objectivo é saber o número de vítimas de OOH-CA que sobrevivem à alta hospitalar. O objectivo secundário inclui o estado neurológico, a qualidade de vida relacionada com a saúde (HRQL), custo, e custo-eficácia. A recolha de dados durará aproximadamente 15 meses e pretende-se que esteja concluída em Setembro de 2003.

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**Palavras chave:** Reanimação cardiorespiratória (RCR); Desfibrilhação automática externa (AED); Desfibrilhação; Serviços de emergência médica (EMS); Fibrilhação ventricular (FV); Paragem cardíaca fora do hospital (OOH-CA)

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## Resumen

El ensayo de desfibrilación de acceso público (PAD) es un estudio clínico prospectivo, multicéntrico, randomizado que investiga si acaso personal voluntario, no médico, puede mejorar la sobrevida del paro cardíaco extrahospitalario (OOHCA) con el uso de desfibriladores automáticos externos (AEDs). Estos voluntarios legos, que no tienen responsabilidad tradicional de responder a emergencias médicas como parte de la descripción de su labor primaria, formarán parte de esta aproximación comprensiva, integrada a la comunidad para el tratamiento del paro cardíaco extrahospitalario. El estudio está siendo conducido en 24 escenarios en los Estados Unidos y Canadá. Se randomizaron aproximadamente 1000 unidades comunitarias (por ejemplo edificios de oficinas o de departamentos, comunidades cerradas, centros deportivos, centros de tercera edad, centros comerciales, etc.) para que realizaran tratamiento por voluntarios entrenados quienes proporcionarán reanimación cardiopulmonar (RCP) solamente, o RCP mas el uso de desfibrilador automático externo, mientras llega la respuesta del servicio de emergencias médicas. La primera meta es el numero de víctimas de OOHCA que sobreviven al alta hospitalaria. Metas secundarias son la condición neurológica, la calidad de vida con relación a salud (HRQL), costo, y la relación costo/efectividad. La recolección de datos demorará aproximadamente 15 meses y se espera que esté completa en septiembre 2003.

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*Palabras clave:* Reanimación cardiopulmonar (RCP); Desfibrilador automático externo (DAE); Desfibrilación; Servicio de emergencias médicas (SEM); Fibrilación ventricular (FV); Paro cardíaco extrahospitalario.

## 1. Introduction

Sudden out-of-hospital cardiac arrest (OOH-CA) remains a leading cause of death in the United States, despite recent declines in morbidity and mortality from cardiovascular diseases [1–3]. Sudden OOH-CA claims the lives of 400 000–460 000 Americans each year [4]. Ventricular fibrillation (VF) is responsible for the majority of OOH-CAs in adults. Electrical defibrillation can be very effective at terminating these arrhythmias, but the effectiveness of the procedure is highly time-dependent. If defibrillation can be accomplished in the first minute of OOH-CA due to witnessed VF, survival is as high as 90%. With each passing minute, the likelihood of survival without neurological deficit decreases by about 10%. After a 10 min delay in defibrillation, more than 90% of victims either do not survive or survive with severe neurologic deficit [5]. It is estimated that only 5% of OOH-CA victims ultimately survive to hospital discharge [6]. Most patients with OOH-CA have no prior documented history of heart disease, and sudden death is the first manifestation of an underlying cardiovascular condition [7].

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. Furthermore, there is not yet a safe, effective, and inexpensive drug or device that prevents OOH-CA for the majority of potential victims. A more pragmatic approach for public health policy has been to provide rapid emergency medical care OOH-CA victims.

The American Heart Association's (AHA) Chain of Survival strategy (i.e. early recognition, early CPR, early defibrillation, and early advanced life support care) is designed to optimize a patient's chance for survival of

OOH-CA [5]. 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 due to VF in Seattle, Washington, survived to leave the hospital when bystanders performed CPR. Only 13% of similar cases survived without bystander CPR [8]. In Rochester, Minnesota, addition of a police defibrillation program to conventional emergency medical systems (EMS) services resulted in a 49% survival to discharge rate for patients in VF [9]. Such communities represent the exception rather than the rule.

In rural areas where emergency services are nonexistent or remote and travel time is long, survival rates are often extremely low. Stapczynski et al. reported an overall survival rate of only 6% among OOH-CA victims treated in 22 rural counties of Kentucky [10]. Similarly, there are very few survivors of OOH-CA in many densely populated urban areas. Becker et al. reported an overall 2% survival rate from OOH-CA in Chicago in 1987 [11]. Similar results were found in 1991 in New York City, where only 1.4% survived to leave the hospital [12]. 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.

Cities that have low rates of survival seem to have in common a long delay from the recognition of OOH-CA to the availability of defibrillation. In rural Kentucky, ambulance arrival in < 8 min from call receipt was a significant predictor of survival [10]. In New York City the median time to first shock was 12.4 min in 1991 [12]. In Seattle, the majority of OOH-CA victims receive defibrillation within 5–7 min after the recognition of OOH-CA. In Rochester, Minnesota, the median time to

first shock is 5.9 min [9]. In 19 urban and suburban communities participating in the Ontario Pre-hospital Advanced Life Support (OPALS) study, improving the proportion of OOH-CA patients who were reached by a defibrillation-equipped ambulance within 8 min from 77 to 93% increased survival to hospital discharge from 3.9 to 5.2% ( $P < 0.03$ ) [13]. To the best of our knowledge, no city has been able to provide defibrillation for the majority of OOH-CA victims within 5 min of the recognition of the event.

Automated external defibrillators (AEDs), devices capable of automatically detecting and treating VF, have made it possible for public safety personnel to defibrillate safely. Community trials of AEDs used by emergency medical technicians (EMTs) have demonstrated that this technology saves lives. These devices defibrillate the heart with a high degree of sensitivity and specificity. However, about 5% of EMS systems in the United States still lack access to 911, early defibrillation capability, or advanced life support [14].

Several published studies have reported the results of defibrillation by targeted responders, i.e. persons with a duty to respond to medical emergencies—police, firefighters, or 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 casinos). These targeted responders can defibrillate safely and effectively in the field [9,15–17]. These studies demonstrated that a 39–71% survival to hospital discharge was associated with a short time to defibrillation [9]. A meta-analysis of ten studies demonstrated a 9.2% absolute increase in survival when basic EMTs used AEDs in the field [6]. 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 1 min decrease in time to defibrillation was associated with a 0.7–2.1% absolute increase in survival [18]. If survival were increased nationwide from 5 to 10% of events, the premature death of approximately 30 000 persons could be prevented in the United States annually [19].

Alternate models for providing early defibrillation need to be considered because arrival of a trained defibrillation-capable person with a duty to respond to the side of the OOH-CA victim is often delayed. One potential avenue for decreasing time to defibrillation is implementation of a community-based response program composed of non-medical volunteer responders. These volunteers, who typically are not expected to respond to medical emergencies, would be trained to use, and have access to, AEDs. Such strategies have been referred to as Public Access Defibrillation (PAD) [20–22].

Improvement in survival rates has not been as good when true (i.e. non-public safety) lay persons have been

trained to use AEDs. However, existing studies are over a decade old and were conducted at a time when the technology was less mature and devices were more difficult to use [23–25]. Studies that have evaluated defibrillation by spouses or family members of at-risk patients suggest that not all laypersons can use AEDs effectively, despite extensive training [25]. Presumably, strong community support will be needed to maximize survival when trained lay persons assume responsibility for defibrillation.

The need to improve public defibrillation capability is not universally acknowledged. Two major arguments against this approach revolve around issues of health-related quality of life (HRQL) and costs associated with such a strategy. However, previous studies suggest that the HRQL of survivors is acceptable [11–13,26–29] and that successful implementation of PAD is likely to be economically attractive [19].

Therefore, the PAD Trial was designed to determine the effectiveness, HRQL, and costs of this approach compared with standard care. The PAD Trial differs from trials conducted previously by focusing on volunteer non-medical responders (e.g. merchants, bank tellers, building superintendents, and co-workers). The rationale, methods, and unique aspects of the effectiveness evaluation are described in this paper.

## 2. Methods

### 2.1. Study aims

The overall aim of the PAD Trial is to assess the effectiveness of broad implementation of PAD in large, urban community units. It will compare survival to hospital discharge of patients with OOH-CA served by trained, non-medical responders using AEDs, compared with units receiving traditional optimum training in CPR. Secondary comparisons include neurological status, HRQL, cost, and cost-effectiveness between the two groups. Collectively these assessments will develop informed public policy regarding the use of AEDs by volunteer non-medical persons.

### 2.2. Study design

The study design is a prospective, randomized community-based trial, comparing the number of OOH-CA victims who survive to hospital discharge between sites that have trained responders who can recognize the event, call 911, and perform CPR versus sites that can, in addition, provide early defibrillation by having the trained responders apply and use an on-site AED (Fig. 1).

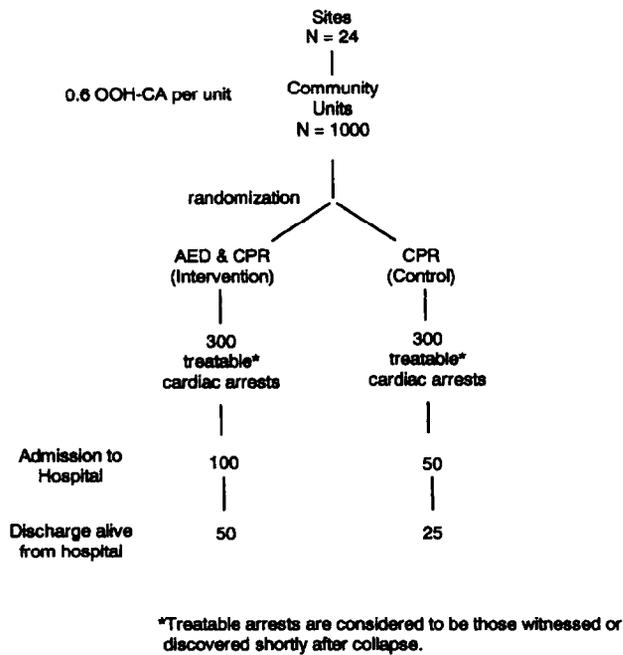


Fig. 1. PAD trial design.

### 2.3. Study site selection

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

Potential centers were disqualified from participation if any of the following applied: (1) current existence of a community-wide, targeted responder defibrillation program; (2) inability to obtain Institutional Review Board (IRB) approval or waiver of informed consent; (3) legal issues that could not be resolved, such as the absence of local Good Samaritan laws; (4) problems associated with implementation of a volunteer responder defibrillation program, or (5) lack of support from the local EMS director.

Each field center agreed to: (1) carry out community consultation and public disclosure regarding the study; (2) identify approximately 40 distinct community units; (3) identify and train volunteers in each unit, and (4) collect data associated with episodes of presumed cardiac arrest. The Field Center locations are listed in Table 1, along with the numbers of community units enrolled and the numbers of EMS systems serving the units.

Table 1  
PAD field centers

Field center	EMS systems (N)	Community units (N)
Birmingham, AL	10	41
Calgary, AB, Canada	1	28
Chicago, IL	1	56
Cincinnati, OH	18	46
Detroit, MI	54	60
Edmonton, AB, Canada	1	42
Indianapolis, IN	23	41
Milwaukee, WI	1	19
Minneapolis, MN	1	25
Mission Viejo, CA	1	44
New York, NY	1	36
Newark, NJ	1	46
Phoenix, AZ	5	40
Pittsburgh, PA	16	60
Portland, OR	5	60
Richmond, VA	3	22
Seattle/King County, WA	2	22
Riverside/Palm Springs, CA	3	41
Salt Lake City, UT	8	70
Stony Brook, NY	1	49
Syracuse, NY	4	28
Virginia Beach, VA	1	70
Vancouver, BC, Canada	1	54
Washington, DC	1	42

### 2.4. Patient population

The patient population was defined as individuals (age  $\geq 8$ ) with OOH-CA (asystole, ventricular tachycardia [VT], VF, or pulseless electrical activity [PEA]). The choice of age cutoff is consistent with AHA Emergency Cardiovascular Care Guidelines, using standard-sized adult defibrillation pads and paddles [30]. However, the incidence of OOH-CA in persons under 21 is low. The 'at-risk' population consists primarily of individuals above 50 years of age with coronary artery disease and/or cardiomyopathy [31]. Patients with arrest and unconsciousness due to trauma or obvious drug overdose are excluded.

### 2.5. Volunteer rescuer population

The volunteer population of interest consists of laypersons (without a responsibility to provide medical assistance in emergencies as their primary job description) who are willing to be trained to respond to episodes of OOH-CA in their respective units. Volunteers with first aid and/or CPR training are acceptable only if they do not have previous AED training. Examples of acceptable volunteers include office workers, lifeguards, and workers trained in industrial first aid who expect to respond to emergencies but have no previous AED training. Specifically excluded from participation are law enforcement officers, firefighters,

nurses, and physicians because they have a traditional duty to respond to medical emergencies.

### 2.6. Study unit (unit of randomization)

The study randomized approximately 1000 identifiable community units at 24 Field Centers in the United States and Canada. Randomized units consist of apartment buildings, office complexes, gated communities, sports venues, senior centers, shopping malls, etc. The intervention will last approximately 15 months. Community unit inclusion criteria for participation in the PAD trial consisted of the following:

- The unit must have a clearly defined geographic boundary (note, however, that the unit could consist of several distinct areas, e.g. two or more apartment buildings might form a unit).
- The estimated EMS response time to defibrillation must be within 15 min at least 90% of the time so that the study results can be generalized to the vast majority of existing EMS systems.
- The volunteers must be able theoretically to deliver an AED to the victim within 3 min of notification of an event, if that unit is randomized to the AED intervention arm.
- Eligible units must have approximately a 50% risk of experiencing one OOH-CA over 1.25 years. This condition was met by documenting either a minimum number of exposure hours of persons > 50 years of age or an ongoing history of treatable OOH-CA (witnessed or discovered shortly after collapse). Acceptable evidence of adequate risk included: (1) EMS or other data documenting an average, over several years, of at least one on-site cardiac arrest per 2 years, or (2) documentation of an 'at risk' population, with exposure time equivalent to that of at least 250 people > 50 years of age on site during waking hours (i.e. 16 h/day). This approach maximizes power by approximating randomization by episodes and is pragmatic for training purposes. Participating centers' initial estimates were that such units would require 4–6 AEDs and 8–12 volunteers.
- There must be an existing identifiable group(s) of eligible potential volunteer responders.
- The AED and/or CPR ancillary supplies (e.g. pocket masks or face shields) must be easily accessible within the community unit.
- 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 were:

- A previous non-traditional (i.e. non-EMS-based) defibrillation program is in place.

- On-site medical or nursing personnel are able to respond to the victim's side within 3 min of notification more than 10% of the time.
- The EMS system is able to respond with a defibrillator to a victim's site within 3 min of notification more than 10% of the time.

The latter two exclusion criteria were intended to eliminate units with such excellent current response capabilities as to make any measurable impact of PAD difficult to achieve.

### 2.7. Training

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

- 3–4 h in length,
- student to instructor ratio of 4:1, not to exceed 6:1,
- no more than 12 students per class,
- scenario-based training using case studies or real-life examples,
- skills practice per trainee—30 min optimal with a minimum of at least 20 min,
- not more than 45 min total for instructor lecture/demonstration,
- dispatcher assistance encouraged where available,
- minimum instructor requirement of BLS certificate for initial training, and
- video recommended for CPR/AED training.

PAD training skills guidelines followed the AHA guidelines outlined in the HeartSaver ABC program for units randomized to CPR training, and the HeartSaver AED program for units randomized to CPR+AED [32]. PAD guidelines differ somewhat from the AHA guidelines in that they do not require a pulse check or a written test, and they allow some flexibility in the instructor certification requirement. Since the purpose of the study is to assess the feasibility of broad implementation of PAD, the use of AHA training materials was not required, in order to accommodate different preferences among the sites. Any training course could be used, providing that it met the PAD guidelines and any criteria required by specific state legislation and by the relevant device manufacturer. At the end of training, volunteer competence is assessed and documented.

### 2.7.1. 'Do not attempt resuscitation (DNAR)' orders

PAD field centers are responsible for identifying their local method of identification for patients who have been legally designated as 'Do Not Attempt Resuscitation'. The method of identification varies from state to state, e.g. a bracelet, a necklace, or a legal document placed conspicuously in the patient's residence. Volunteers are instructed to recognize DNAR designations and must not attempt resuscitation on these patients.

### 2.8. 'Mock' cardiac arrest training episodes

As part of the training for both for the volunteers and the Site Coordinators, 'mock episodes' or 'episode dry runs' are performed at each site. These episodes are designed to be as realistic as possible, within reason. The simulated episode is followed by full data collection, including debriefing of the volunteer(s). The mock cardiac arrest is used to ensure that systems are in place for volunteer and EMS contacts and that the AED, if available at that site, can be accessed within 3 min. A successful mock cardiac arrest was used as an indication that a site is ready for the trial phase of the study to begin.

### 2.9. Retraining

Retention of skills is an important, but inadequately studied, determinant 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 are tested and retrained to proficiency between 3 and 6 months after initial training. By random assignment of units, one-quarter of the volunteers are tested and retrained to proficiency at each of 3, 6, 9 and 12 months after their first retraining. All volunteers are tested at the end of the study (approximately 17–18 months after initial training). The retraining schedule will be intensified if the results of the early testing indicate insufficient skill retention.

### 2.10. AED devices

AEDs from three manufacturers are used in the study. The devices currently on the market are assumed to be comparable with respect to ease of use, application technique, operating steps, safety, and efficacy. No attempt was made to alter device appearance, arrhythmia detection algorithms, or instructions to make them more comparable. All devices have voice recording capability to facilitate interpretation of the sequence of events occurring during the resuscitation. With the exception of New York City (where all three AED devices are used), each field center uses a single manufacturer's AED model (models were randomly assigned to field centers). Device installation and main-

tenance are monitored at least monthly, according to manufacturers' guidelines.

### 2.11. Integration with the EMS system

The EMS system is an integral part of the study. A close-working relationship between EMS and volunteer responders is critical for the following reasons: (1) EMS responds to 911 calls and will treat cardiac arrest victims not already defibrillated by the responders; (2) EMS transports all surviving cardiac arrest patients to the hospital; (3) EMS provides other definitive care such as endotracheal intubation, medications, etc. and (4) most systems keep logs of all EMS runs, and many systems record CA data on a special form.

### 2.12. Randomization

Randomization to either CPR-only or CPR+AED was stratified by site and within site by type of unit, i.e. residential or public. Sites were not required to match units as pairs, but characteristics such as demographics were monitored by the PAD Clinical Trial Center (CTC) at the request of the Data and Safety Monitoring Board (DSMB). Large units with more than four expected treatable cardiac arrests formed a stratum across sites and required a suitable match to achieve balance between the treatment arms.

### 2.13. Primary and secondary outcome measures

The primary outcome measure for the study is the number of successfully resuscitated cardiac arrest victims (i.e. survival through hospital discharge). Initially, survival rates were considered as a potential primary outcome measure. However, while the number of survivors forms the numerator of the rate, the logical denominator—all episodes of OOH-CA—is subject to differential ascertainment across arms because strips from an ECG are the best means of determining whether a cardiac arrest has occurred. This ascertainment bias will make it appear that there are more cardiac arrests in the AED arm, since strips will be available more often, but it should not affect the number of survivors because it is very rare for a person to survive a cardiac arrest without being defibrillated at some point. Another conceivable denominator is the sum of all successes and all deaths that occur in the community unit, irrespective of cause. 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. However, such populations are highly variable, particularly in public units, due to fluctuations related to time

of day, day of the week, month, season, etc. Thus, to the extent that differential identification of cases occurs, an analysis that considers the proportion of survivors would likely be more biased across arms than the number of successes. Hence, the primary outcome measure for the PAD Trial is the count of successes within each arm. If any individual patient experiences more than one cardiac arrest during the study, only the first episode will be counted, since successful resuscitation may be as much a function of the patient's characteristics (e.g. a fast VT vs. a VF rhythm) as the system's characteristics.

Secondary outcome measures for the PAD Trial consist of:

- 1) CPR/AED skills retention;
- 2) cerebral function at discharge: the Cerebral Performance Category (CPC) is a five-point scale that measures global health from grade 1 (normal function) to 5 (brain dead) [33,34];
- 3) neurological status at 3 months post discharge: Neurological status is collected on each survivor using the Adult Lifestyle and Function (ALFI) version of the Mini-Mental Status Exam (MMSE) [35,36];
- 4) generic quality of life: the Health Utilities Index (HUI) Mark 2 and 3 systems [36,37] will be used at 3 months post-discharge;
- 5) morbidity: Long-Term Survival and Morbidity status are ascertained monthly to 3 months and then every 3 months after discharge, using the 'SF-1' (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?') and the 'SOS'—(Simple Outcome Screen) that consists of two simple questions used previously to assess outcome from stroke [38];
- 6) costs and incremental cost-effectiveness: design and methods of the economic evaluation of PAD will be detailed in a future manuscript.

#### 2.14. Identification of events

Events that will trigger data collection are defined as those for which:

- 1) the EMS was dispatched for presumed OOH-CA (includes non-cardiac arrest situations involving unconsciousness, seizure, syncope, choking, etc), 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—even if the EMS was not notified.

The final definition of OOH-CA is crucial because the primary endpoint of the PAD Trial is OOH-CA survival to hospital discharge. Thus, an adjudication committee, blinded to the intervention arm, will 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 cases that could conceivably be cardiac arrests are adjudicated. The committee reviews a (blinded) narrative including rhythm strips and notation as appropriate. There are some 'sham blindings' 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.

#### 2.15. Statistics

##### 2.15.1. Sample size estimates for 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. The latter analysis will, of necessity, exclude units with no OOH-CA. A priori subgroup analyses were specified for residential versus public community units.

Participating sites for which data were available historically had an average survival rate of  $6.6 \pm 4.8\%$ . Units were chosen such that, on average, they were expected to have 0.6 treatable cardiac arrests over 15 months. The recruitment goal of approximately 1000 community units was based on detecting roughly a doubling of survival to hospital discharge for the CPR + AED units, compared with the CPR units (from 7 to 14%), using a two-sided test with a significance level of  $\alpha = 0.05$  at 80% power. This seemingly optimistic assumption is based on reported increases due to AED deployment at Chicago O'Hare Airport and in Las Vegas Casinos [15]. Details for the power calculations are provided in the Appendix A.

In addition, stratified randomization should yield a reduced variance (small within-stratum variability, compared with between-stratum variability) and, hence, improved power. Table 2 presents power to detect various increases in survival with  $N = 1000$  units. Power is presented for the case where no improvement results from stratification and for the case where a 10%

Table 2

Power to detect increases in the probability of successfully resuscitated cardiac arrest victims for AED units relative to CPR units, with  $N = 1000$ 

Percent increase in survival in AED units relative to CPR units (%)	75	100	125	150	200
Power assuming no effect of stratification on variance (%)	53	73	87	95	99
Power assuming stratification results in 10% decrease in variance (%)	57	78	90	97	99

reduction in variance results due to stratification. Table 2 indicates that, for  $N = 1000$ , power is between 73 and 78% for detecting a 100% increase in survival, depending on the impact of stratification. For an increase of 150% or more, power is between 95 and 99%. For increases < 100%, power is marginal to poor.

### 2.15.2. Plan for dealing with 'contamination'

Contamination is defined as use of an AED at a unit assigned to standard treatment (i.e. a CPR unit). Identified study units were required to be sufficiently separated physically so as to eliminate the possibility of contamination of a control unit by rescuers bringing an AED from a nearby intervention unit. However, the major source for contamination is more likely to be due to aggressive marketing of AEDs or community AED implementations, such as local Operation Heartbeat AHA activities. Both the AHA and the AED manufacturers have pledged to refrain from marketing AEDs or AED-related programs in the study units for the duration of the study. In addition, when Site Coordinators complete the monthly contact logs, they will seek to identify any installation of non-study AEDs in control units.

## 2.16. Protection of human subjects

### 2.16.1. Institutional review board

The Code of Federal Regulations (21 CFR 50.24) requires certain procedures for exception of informed consent for emergency research, including:

- 1) assurance that a broad-spectrum of the community is represented in community consultations to include, but not be limited to, local leaders of community ethnic groups, local government, and other members of the community;
- 2) suggestions for community involvement, including public meetings to discuss the protocol;
- 3) other methods for disclosure of study goals and methods to inform the community and its representatives, including use of newspaper media, radio and television, and
- 4) making the results available to each community or unit after the study is completed.

The PAD CTC developed templates for obtaining informed consent from patients and study volunteer responders, and for community consultation and public

disclosure. However, each site is responsible for developing and implementing their local plan, which was reviewed and approved by their local IRB.

All patients are informed about the study as soon as they are conscious and able to understand the discussion. In the event of a patient's death or persistent impairment, the legal next-of-kin are notified of the study as soon as they can be identified and located. In addition to notification, patients who survive to hospital admission and discharge are asked to give informed consent for participation in the follow-up studies.

All volunteers are required to give informed consent for participation in the study.

### 2.16.2. Investigational device exemption

The United States Food and Drug Administration (FDA) determined that an Investigational Device Exemption (IDE) and a waiver of informed consent were both required for the PAD Trial. The IDE application and waiver of consent were reviewed, and the IDE was issued in 1998.

### 2.16.3. Data and safety monitoring board

The National Heart, Lung, and Blood Institute (NHLBI) convened a DSMB to provide independent review and monitoring of CTC and site performance, safety issues, adverse events, and endpoints in the trial. The Board consists 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 DSMB reviewed and recommended approval of the protocol, and meets at least annually to monitor the study.

## 2.17. Timeline

Fig. 2 outlines the timeline for PAD Trial completion.

## 3. Discussion

### 3.1. Major challenges

Organizing such a large trial involving many cities, EMS systems, and a network of lay responders poses a number of major challenges.

First, is the difficulty of minimizing contamination. Private organizations and community facilities are generally unaware of the need to maintain a particular

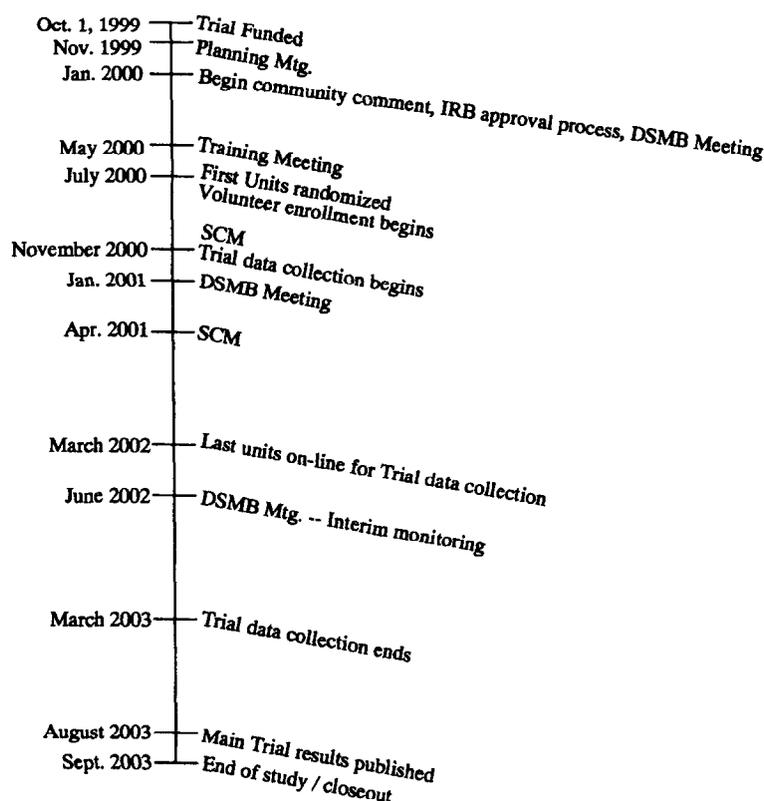


Fig. 2. Timeline for the PAD trial.

group assignment in a research project. Extensive discussions were held with local researchers to convey the ‘intent-to-treat’ concept and explain that crossovers would negatively impact study power. In addition, a letter of understanding was given to units prior to randomization, and agreements were obtained with the AED manufacturers to forego marketing in these facilities. To date, the vast majority of units have maintained the original assignment, and these study strategies should, therefore, be considered successful.

Second, because this type of study has not previously been undertaken, the manpower (and hence, funding requirements) was difficult to determine a priori. Major uncertainty was associated with the effort required to recruit eligible units with acceptable demographics and willing executives, risk managers, and lay volunteers. This process was particularly difficult in some cities due to existing AED programs. The inability to transfer significant startup funds prior to documentation of unit recruitment (payment for deliverables concept) presented challenges in hiring research staff necessary to recruit units, train volunteers, and gather baseline data. Despite generous contributions from the NHLBI, the AHA and AED manufacturers, most sites required additional local funding, donated time (e.g. for training), or other innovative approaches to successfully cover infrastructure costs.

Third, there are many training and retraining hypotheses of interest that could be tested in the PAD Trial. Little is known about the retention of lay person skills or the ability to act in a real-life cardiac arrest response. The Steering Committee believed that comparing retention of skills by different schedules would provide the most valuable support rather than comparing different methods of training.

Fourth, community consultation, public disclosure, and waiver of informed consent were untested processes in most sites. The procedures were expected to be laborious, costly, and quite variable from site to site. This experience will be extremely valuable as the first broad-based feedback to the FDA on its regulations outlining acceptable processes for cardiac arrest research.

### 3.2. Limitations

Comparing the numbers of survivors in each group is a unique approach to an outcome measure in a community-based trial, but is different from other randomized trials of cardiac arrest which enroll a particular patient only if individual randomization is possible. Historically, these other trials compare proportions of survivors, using a clear denominator. It will

not be possible to compare the results of the PAD Trial directly to other randomized, controlled trials.

The results will pertain only to the implementation of lay-person defibrillation in public or homogenous private settings with some type of organized emergency response. They cannot be generalized to the majority of cardiac arrests, since most arrests occur in the home, rather than a public place. Likewise, the results will only apply to units with a defined window of EMS response times (i.e. between 3 and 15 min). Also, the value of layperson, on-site AED response, particularly in rural centers or on isolated facilities such as ferry boats with delayed EMS response, will not be answered by this study.

Finally, the site teams provide an extensive training program and have significant expertise in AED and CPR training. Training programs will likely vary across sites, and it is difficult to assess the extent of standardization.

#### 4. Conclusions

The PAD trial is poised to answer an important, fundamental public health question—whether well-trained lay AED responders in large, urban settings can increase the number of cardiac arrest survivors in a community. This collaboration of centers has demonstrated that large, clinically relevant trials of OOH-CA are possible using the waiver of informed consent procedures. Using the primary question asked in the PAD Trial as a focus, an effective network and organizational structure of pre-hospital cardiac arrest researchers has been created to efficiently answer this and further relevant questions.

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#### Appendix A: Details for power calculations

Assumptions:

- 1) A two-tailed test at  $\alpha = 0.05$ .

- 2) The number of cardiac arrests over the 15 months 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) PAD improves the success probability by a factor of  $\lambda$  (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  $0.6\lambda c$ , where  $c$  is the success probability that unit would have had without PAD. Thus, the mean difference,  $\delta$ , between PAD and control is:

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

where  $\mu$  is the average success probability of control units.

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:

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

respectively, where  $\sigma^2$  is the variance of the control success rates of the units.

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

$$v = \frac{0.6\mu + 0.36\sigma^2 + 0.6\lambda^2\sigma^2}{n}.$$

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  $\Phi(\delta/v^{1/2} - 1.96)$ .

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