A cluster-randomized clinical trial of strategic AED deployment in high-risk residential areas combined with activation of residents:

The CARAMBA Trial

Cardiac Arrest in Residential Areas with Mobile First-responder Activation

General Information

Primary Investigator and sponsor: Fredrik Folke, MD, PhD, Associate Professor, Head of Research, Emergency Medical Services Copenhagen, and Herlev Gentofte Hospital, Department of Cardiology.

Co-Principal Investigator: Carolina Malta Hansen, MD, PhD [1, 2]

Responsible Investigator: Fredrik Folke, MD, Ph.D., Associate Professor

NCT ID: Not yet assigned

Steering Committee

Freddy K. Lippert, MD[2]

Christian Hassager, MD, DMSc[4]

Christian Torp-Pedersen, MD, DMSc[3]

Jesper Kjærgaard, MD, DMSc[4]

Annette Kjær Ersbøll, Professor of Statistics[5]

Anne Juul Jørgensen, MD, PhD-student[2]

Gunnar Gislason, MD, PhD[1]

[1]*Department of Cardiology, Copenhagen University Hospital Gentofte, Denmark*

[2]*The Emergency Medical Services, Copenhagen, Copenhagen University, Denmark*

[3]*Department of Clinical Investigation and Cardiology, North Zealand Hospital, Denmark*

[4]*The Heart Centre, Copenhagen University Hospital Rigshospitalet, Denmark*

[5]*Department of Population Health and Morbidity, National Institute of Public Health, Denmark*

This is an investigator-initiated study.

This study will be conducted in accordance with this protocol. The study will comply with regulatory and ethical requirements.
The study will initiate in 2020 and run for up to 5 years

This protocol has been developed based on the SPIRIT checklist[1].

Index

Abbreviations

AED	Automatic External Defibrillator
CPR	Cardio Pulmonary Resuscitation
EMD	Emergency Medical Dispatch
EMS	Emergency Medical Services
OHCA	Out-of-hospital Cardiac Arrest
CARMABA	Cardiac Arrest in Residential Areas with Mobile First Responder Activation
ICC	Intra Class Coefficient
CV	Coefficient of Variability

1 Introduction

1.1. Background

Out-of-hospital cardiac arrest (OHCA) is a major health problem. In Europe and the United States, 700,000 OHCAs happen annually[2], and in Denmark alone, there are 5,000 events every year[3]. OHCA is an acute health emergency and needs to be treated within minutes to ensure survival, and early defibrillation is the core of the treatment[4, 5]. In Denmark, different initiatives have been undertaken to increase bystander defibrillation (from here on referred to as defibrillation), but despite these initiatives, defibrillation rates remain low in residential areas. Specifically, it has been challenging to increase defibrillation in residential areas, which is where 85% of all OHCAs occur[6]. This study aims to increase defibrillation rates and survival after OHCA in residential areas.

Early defibrillation may be the most critical determinant for survival of out-of-hospital cardiac arrest. The chance of survival decreases with 10% per minute from collapse to first defibrillation[4, 5]. Hence, efforts to decrease time to first defibrillation are crucial. In many cases, the time from recognition of cardiac arrest to arrival of Emergency Medical Services (EMS) is long [7], leaving bystanders in a critical position to increase survival by bystander cardiopulmonary resuscitation (CPR) and rapid defibrillation by a nearby Automated External Defibrillator (AED). AEDs have shown to increase survival markedly after OHCA and are safe and effective to use by laypersons. Strategies of placing publicly available AEDs in high-risk areas in the community have evolved, providing the opportunity of defibrillation before the arrival of the EMS [8-12]. For optimal survival benefit AEDs need to be used within minutes of the event and, thus, be close to the victim, easily locatable, and accessible to bystanders. Several studies have shown a significant increase in OHCA survival when AEDs are placed in public locations where the criteria mentioned above are met like airports[8], on aeroplanes[9, 10], and in casinos[11], with reported survival rates as high as 49% to 75%[8-11]. These findings have led to a more widespread AED deployment in public locations with a positive effect on OHCA survival[12-15]. In accordance, several countries have implemented national public-access defibrillation programs with AED deployment in public high-risk areas of OHCA[13, 15-17], in agreement with current international guidelines recommendations[18, 19].

1.2. Initiatives within Denmark

In Denmark, various initiatives have been undertaken to increase survival after OHCA. In 2007, the Danish AED network was established, and in 2010 it was integrated with the EMS system so dispatchers can guide bystanders to the nearest AED. Since 2011, emergency medical dispatchers have followed a standardized protocol guiding bystanders to perform CPR and retrieve the nearest AED when cardiac arrest is suspected. Since 2012 the AED network has been made available through a mobile application (app) showing the nearest accessible AED. Resuscitation training has been mandatory in elementary schools since 2005 and when acquiring drivers licenses since 2006. From 2001-2012 defibrillation rates for OHCA in public increased from 1.2 to 15.3%. Disappointingly defibrillation rates for residential areas remained unchanged at 1.3% in the same period.[6] Since 2017 EMS dispatchers have been able to alert citizen first responders through a mobile application (app) based alert system called HeartRunner when they suspect an OHCA. Citizens can voluntarily sign up as citizen first responders. There are no requirements for prior training in CPR or AED use; nevertheless, the majority of citizen responders have undergone training. Citizen first responders are either guided to collect an AED and bring it to the scene of the OHCA or to go straight to the scene and perform CPR. The effect on survival and defibrillation rate from this intervention is currently under investigation, and no results have yet been published. Dispatcher also have the option of connecting to the scene of the OHCA through one of the bystanders smart phones. This way, the dispatcher can reassess the diagnosis and guide CPR.

1.3. Residential areas

The vast majority of all cardiac arrests (65-80%) occur in residential areas[20-22], where on-site AEDs are rarely available[20, 23], and where the chance of successful resuscitation is only achieved in 2-4% of cases[3, 23, 24]. Patients in non-public places are therefore primarily assisted by dispatched first-responders (police or firefighters bringing an AED) or the EMS system. Furthermore, only a few attempts have been made with public access defibrillation in residential areas, and the results have been disappointing [14, 25, 26]. The most extensive study to date is the Home use of AED trial with 7,001 patients with previous anterior wall myocardial infarctions who were not candidates for an implantable cardioverter-defibrillator. The patients were randomly assigned to receive either standard care or standard care plus a home AED [25]. Disappointingly, access to a home AED did not significantly improve overall survival, mainly because the rate of OHCA was less than 1% per year (corresponding to the chance of AED use not exceeding 1% per year even if an AED was used in every event).

Whereas the home AED strategy only provides the opportunity to treat those in the immediate household, placing AEDs outside people's homes in selected high-risk residential areas provides the opportunity to use an AED in treating any one of many persons at risk. Residential areas need early first-responder activation to benefit optimally from AEDs. Such a responder needs to be closer to the cardiac arrest patient than traditional first responders (police or firefighters) and/or EMS and must be alerted to act.

One solution implemented in several regional dispatch centres in Europe including Denmark, is an app-based alert system[27]. In the case of a suspected OHCA, the dispatcher manually activates the alert process, and a software program then automatically identifies nearby available citizen responders and AEDs. The app alerts citizen first responders and directs them to the OHCA or to retrieve an AED and bring it to the OHCA. The aim is for the citizen responders to perform CPR and defibrillate before EMS arrival. Such systems, based in either apps or text messages, have been tested and implemented in several regional dispatch centres in Europe [28, 29]. Experiences from Holland showed that by activating citizen first responders, it was possible to shorten the time from OHCA to first defibrillation significantly and importantly, that among citizen responders activated by a text message alert 87.5% were used in residential areas.[27]

1.4. Research Hypothesis

Strategic deployment of public access AEDs and training of residents to be citizen responders is superior to standard care after OHCA regarding the proportion of OHCA patients defibrillated by bystanders.

1.5. Study Objectives

To determine if strategic deployment of public access AEDs, training residents in CPR and AED use and recruiting them as citizen responders in high-risk residential areas is superior to "standard care" with the primary endpoint being bystander defibrillation.

1.6. Trial Design

The Cardiac Arrest in Residential Areas with Mobile First Responder Activation (CARAMBA) trial is a prospective cluster-randomized superiority trial that will compare the proportion of bystander defibrillation between geographically defined intervention and control areas. Twenty-six residential areas will be pair-matched and allocated 1:1 to intervention or control. In the interventional areas, AEDs will be strategically deployed, and residents will undergo training in CPR and AED use. Further, in the case of suspected OHCA, registered citizens will be activated to respond through the HeartRunner app system. The intervention will serve as a supplement to standard care, and the control area will receive existing standard care from emergency medical services in the case of suspected OHCA.

2 Methods: Participants, Interventions, and Outcomes

2.1 Study Setting

The study will take place in residential areas within the metropolitan area of Copenhagen, covering approximately 355.7 km^2 and with a resident population of ≈ 1,2 million. A total of twenty-six areas have been selected for the trial. Each area has between 600-5000 inhabitants, ranging from 0.04-0.77 km^2 and each area had between 2-7 cardiac arrests per year. The mean OHCA incidence rate in the twenty-six selected residential areas is 194 OHCA/100,000 inhabitants, CI(184;285). In comparison, the incidence rate for the Capital Region of Copenhagen is 83 OHCA/100,000 inhabitants. The areas are characterized by high rise buildings, high living density, low socio-economic status, and high incidence of cardiac arrest. The areas primarily consist of public housing and housing cooperatives.

2.1.1 Identifying research areas

The clusters have been selected based on criteria of:

- High living density of people above 60 years of age[24].
- The presence of shared social infrastructures such as volunteer organizations, resident cafés, or sports associations. This criterion was prioritized in order to facilitate the implementation of the intervention taking advantage of existing social structures.
- At least one historic cardiac arrest per area per year.

Procedure for identification of clusters:

1. To identify the relevant study areas which fulfilled the criteria of high density of persons > 60 years of age, we used data on age and living density in 100x100 meter grid cells covering all of Denmark. Using the Geographic Information Systems program, QGIS, and maps of Denmark from the Agency of Data Supply and Efficiency, the number of persons above 60 years of age was mapped as a gradient.

2. To identify residential areas with a high risk of OHCA, we mapped all historic cardiac arrests from the Capital Region of Copenhagen from 2016-2018 as well as cardiac arrest from the Copenhagen Municipality from 1994-2015.

To identify housing units of an appropriate size with shared social infrastructures and to exclude nursing homes, every area with a high density of persons above 60 and a high incidence of OHCAs was evaluated using google search and google maps. When a nursing home was identified inside the relevant areas, the

nursing home coordinates were fenced off through the GIS program, thus excluding the appropriate geographical location from the study.

2.2 Eligibility Criteria

2.2.1Inclusion criteria

All EMS-treated OHCAs, except those describe in the exclusion criteria, within the twenty-six clusters will be included in the trial. The cases are included, no matter how many citizen responders are within 1800 meters or their response to the alarm.

2.2.2 Exclusion criteria

The following OHCAs will not be included in the analysis:

- Not true OHCA (suspected, but not verified)
- EMS-witnessed
- Not witnessed by a bystander
- Due to trauma, intoxication, or suicide
- Not treated by the EMS due to ethical reasons or apparent signs of death
- Under the age of 8
- In nursing homes or health care facilities

These cases will be accounted for but not included in the analysis of the outcome.

2.3 Interventions

The intervention will consist of three parts; strategically deployed AEDs, training residents in CPR and AED use, and recruiting residents as citizen first responders.

2.3.1 Strategically placed AEDs

AEDs will be deployed visibly and with 24/7 accessibility so that all residents will have a maximum of 1.5-minute walking distance to and AED. A total of 70 AEDs will be deployed in cabinets, and appropriate signage will be installed. All AEDs will be registered with the national AED network and thus linked to the emergency dispatch center.

2. CPR and AED training

Residents in the intervention areas will be recruited to be in the beginning of the study period. Training will consist of 30-minute hands-on training courses in groups of 5-10 participants each, following recommendations from de the Danish Resuscitation Council. During the first year, approx. 120 residents in each intervention area (1,560 residents in total). Later, it will be evaluated whether it is necessary to organize more training for new residents depending on how many are still active or has moved to another area.

As standard practice in intervention studies, a board of residents from the study areas will conduct meetings to discuss the intervention, recruitment, and unforeseen challenges as they appear, in order to ensure successful implementation of the intervention[30]. The discussion will follow the theory of change, which is currently under development for the project. The theory of change describes every step necessary for the intervention to succeed and every assumption made. It serves as a means to identify challenges and explain the findings of the study. It is a dynamic tool that will be developed on an ongoing basis during the implementation, recruitment, and trial phase[31].

2.4 Study procedure

For control areas, the following standard procedure will take place:

- For all 1-1-2 calls with suspected OHCA to the emergency dispatch center will activate a two-tiered response consisting of dispatch of an ambulance with an emergency medical technician, a physician-staffed mobile emergency care unit, and citizen first responders through the Heart Runner app.
- The medical dispatcher offers telephone assisted CPR to bystanders. Furthermore, if more than two bystanders are present and an AED is accessible within 1½ minute travel distance (depending on the type of terrain), then one bystander is guided to localize and retrieve the AED.

For intervention areas, the following procedure will take place:

- Standard care, as described above for control areas.
- Strategical deployment of AEDs with 24:7 availability and 1½ minute walking distance to every residence within the area. The AEDs will be registered with the AED network and thus linked to the emergency dispatch center.
- The emergency dispatch center will retrieve data from used AEDs.
- For each interventional area, approximately 120 residents will receive a course in CPR and AED use and subsequently be recruited as citizen responders, so they can be activated through the HeartRunner app in case of a nearby OHCA.

2.4.1 Procedure for activation of citizen responders

For the CARAMBA Trial, the Heart Runner system will be activated in every case of suspected OHCA in both intervention and control areas. The location of the incoming emergency call will be compared to the geographical mapping of mobile phones connected to the Heart Runner app. The app sends out new locations whenever a citizen responder changes positions according to the "significant change of location service"[32]. The latest updated position is stored as coordinates and used to identify citizen responders nearby a cardiac

arrest. If a position is over 72 hours old, the heart runner is considered inactive and not included. The HeartRunner software will identify all citizen responders (mobile phones) within a radius of 1800 meters (configurable) from the suspected cardiac arrest. Up to 20 heart runners (configurable) closest to the site of cardiac arrest will receive an alarm on their smartphone requesting whether they can respond. When the citizen responders accept the alarm, they will send out a new, updated, position and the software will confirm that the updated position is within 1,800 meters. If the heart runner is >1,800m of the cardiac arrest, the heart runner will be informed they are now too far from the cardiac arrest and their help will therefore not be required. The system will then recruit the remaining heart runners to either go directly to the site of arrest and begin CPR or to fetch a publicly accessible AED. An algorithm will be used to instruct citizen responders who accept an alarm. Starting from the first citizen responder accepting the alarm, the first four citizen responders will be instructed to fetch the nearest accessible AEDs and then go to the cardiac arrest location. The fifth citizen responder is instructed to go directly to the cardiac arrest location and perform CPR. This algorithm is performed up to 4 times, depending on how many first citizen responders that are close to the cardiac arrest. If a citizen responder aborts the alarm, the assignment (AED or CPR) is relocated to the next citizen responder accepting the alarm. If there are no publicly available AEDs close to the cardiac arrest, all citizen responders who accept the alarm will be directed to start CPR. The software includes the total distance from the citizen responder to the AED and then to the cardiac arrest to select the 20 nearest heart runners. The location of cardiac arrest is displayed on a map through the Heart Runner app including the address of the cardiac arrest. A map showing the route from the citizen responder's location to the location of the cardiac arrest is also provided. The Heart Runner app is linked to the Danish AED-Network and only takes accessible AEDs into account, at the time of alarm.

2.5. Outcomes

The primary outcome is bystander defibrillation, and the secondary outcome is 30-day survival. Both outcomes are based on OHCA witnessed by a bystander.

Exploratory outcomes are

- Time from OHCA collapse to first defibrillation (either AED or manual defibrillator)
- Proportion of OHCA patients achieving return of spontaneous circulation (ROSC) at hospital admission
- Whether surviving patients after admission return to their home or a nursing home.
- Whether surviving patients who were in work prior to the OHCA return to their occupation or not.
- Diagnosed with cerebral injurie

2.6. Participant Timeline

The trial will have a phase of implementation of the intervention of an estimated 12 months and will start in June 2020. The data collection in each pair of clusters will start as soon as the intervention cluster has completed CPR training and AEDs have been deployed and registered with the AED network. Given that the implementation phase will occur sequentially among clusters, data collection will start for some clusters during the implementation phase. The trial is planned to run for 5 years.

Participant timeline	2020		2021		2022		2023		2024		2025	
	Jan - Jun	Jul-Dec	Jan - Jun	Jul-Dec	Jan - Jun	Jul-Dec	Jan - Jun	Jul-Dec	Jan - Jun	Jul-Dec	Jan - Jun	Jul-Dec
Pair-matching and randomization												
Recruitment of residential areas												
Deployment of AEDs		*Implementation*										
CPR and AED training												
Data collection												
Analysis and results submission												

2.7. Sample Size

From 2016-2018, 1 out of 186 OHCAs within the study areas received bystander defibrillation. This mounds to a defibrillation rate of 0.5 (0.01;3.0) %. Based on data from the Danish Cardiac Arrest Registry, the total number of historic OHCAs per year in the selected areas is 79. For this study, we will strive to improve the proportion of patients receiving bystander defibrillation from 1 to 12%, based on prior evidence and assessed clinical relevance[33].

2.7.1. Clustering effect

In contrast to individual randomized trials, OHCAs within residential areas are not independent in cluster-randomized trials. OHCAs within each residential area (i.e. cluster) are more alike as compared to OHCAs in different clusters. In order to conduct the power calculation, the Intra Cluster Coefficient (ICC) was taken into account[34, 35]. Since there have been no prior trials of this kind, existing literature does not provide possible examples of ICCs. It is also not feasible to conduct a pilot study due to the rarity of the disease. When ICC is unknown, it is customary to assume the value of 0.05-0.10.

It is possible to calculate ICC based on data of historic cardiac arrests within the research areas. For this trial, ICC has been calculated for age using cardiac arrest data 1994-2018 and for rates of bystander defibrillation and OHCA witnessed by a bystander using data from 2016-2018. The ICC for age is 0.026 (0.0001;0.086). The ICC for defibrillation rates is <0 and for witnessed status is 0.001. A negative ICC can be interpreted as close to zero, meaning that members within a cluster are not more alike than members between clusters. The data suggest that the ICC for this trial might be low, but with the wide confidence interval, it is important to remain conservative when estimating the sample size. ICC has been calculated in R using the ICC-package for continuous data and the ICCbin-package for binary data[36, 37].

Power calculations were done to estimate the trial duration since the number of clusters (i.e. residential areas) was known. With the desired power of 80% and a significance level of 5%, power calculations were conducted with varying ICCs and effect sizes to determine a conservative estimation of the sample size.

Obs	Number of clusters	intraclass correlation	Number of individuals in a cluster	Effect size (standardiseret difference)	power
1	13	0.05	5	1% til 15%	0.84
2	13	0.05	10	1% til 10%	0.81
3	13	0.05	10	1% til 12%	0.90
4	13	0.05	10	1% til 15%	0.97
5	13	0.10	5	1% til 15%	0.79
6	13	0.10	10	1% til 12%	0.81

Tabel 1: Powercalculation using varying ICC, cluster sizes, and effect size.

To make a conservative estimation of the ICC, option no. 6 was chosen. That corresponds with a sample size of 130 witnessed OHCAs in each arm, which would result in a study duration of 5 years. This calculation does not take into account that an OHCA must have occurred in each cluster. For the statistical analysis, a strategy has been chosen that can account for cluster with no events. A study duration of 5 years is anticipated to achieve the desired number of cases.

2.7.2. Varying cluster sizes

It is recommended to take variable cluster sizes into account when the coefficient of variability (CV) being the variance of mean cluster size is greater than 0.23.[35, 38]

$$CV = \text{standard deviation}_{\text{cluster size}}/\text{mean}_{\text{cluster size}},$$

In this study, the CV of the expected cluster sizes is 0.5. Pair matching can account for varying cluster sizes. After pair-matching, CV is replaced with variances of cluster means within the pairs. CV_{pairs} range from 0.00 to 0.24, allowing us not to take varying cluster sizes into account when conducting power calculations.[34, 38]

2.8. Recruitment

For this trial to succeed, it will be important to ensure it is anchored in the intervention areas. We plan to use the existing structures of social, sports, or cultural activities already present in the areas. Through this method, the goal is to reach members of the communities that are socially well connected and resourceful. Each of the selected residential areas has a website or a Facebook group and by searching the sites, one key informant for each intervention area will be identified. This informant will help get an overview of the community and the subgroups and ensure contact. The different subgroups within the areas must be included in the CPR training in order to ensure broad support and engagement within the community.

For each AED, a supporter within the community will be recruited. The task of the supporter will be to look after the AED and contact AED services when problems occur, such as malfunction, vandalism, etcetera. The supporter will further recruit twelve people for a CPR/AED use course.

3. Methods: Assignment of Interventions

3.1. Pair-matching

Pair-matching of research areas has been conducted to balance baseline characteristics. Optimal pair-matching increases power in CRTs and makes covariate adjustment during data analysis more effective[34, 39]. Variables for the pair-matching are chosen based on their association with the outcomes and availability data. The variables included are age, number of inhabitants, and AED/km^2. To conduct the pairing, distances matrixes were created for every included variable. The distance matrixes create the distances of the chosen variables for every possible pair. The age variable has been weighed in order to gain balanced pairings. Some of the areas are located close to each other. In order to prevent contamination between the areas, they will be linked during randomization and will both be either intervention or control. For that reason, they cannot become a pair, which has been defined in the matrix. Using the pre-selected twenty-six areas, the trial has 276 possible pairs. The distance matrixes are used to create 12 pairs with the minimum absolute sum of distances creating the best possible matches. The R-package “designmatch” has been used to conduct the above described pair-matching.[40] The function nmatch does nonbipartite matching by several variables. Afterward, the quality of the matching has been checked by reviewing the pairs manually.

3.2. Allocation

Within each pair, the areas are randomized to either intervention or control. To limit contamination between areas, areas with less than 1000 meters apart have been linked, meaning that they both become either control or intervention areas. In total six areas have been linked two and two. Each pair have been randomized using an R-program that accounts for the linked areas. Since all areas will receive the same standard emergency medical care, the dispatcher continues, as usual, not knowing whether the OHCA is in an interventional area, observational area, or outside the study sites.

3.3. Blinding

Due to the nature of the study, treatment allocation is not blinded to rescuers or patients. The steering committee will, during the study, receive information on total numbers of arrests and overall success of providing defibrillation. The steering committee will not receive information on whether defibrillation took place in areas allocated to intervention or no intervention. Only the safety committee will have access to all information.

4. Methods: Data Collection, Management, and Analysis

4.1. The study sites and data collection area

The study sites consist of one major housing association and have a varying size from 0.05 to 0.77 km^2. Since we expect that the residents will act not only within their own housing association but also in the surrounding area, the inclusion of cases will occur from the data collection area. The data collection area consists of the study site and a buffer zone surrounding the study site (map 1). The buffer zone does vary from area to area. It can consist of one family houses or high-rise buildings but most often it is a combination of the two. Non-residential areas such as shopping centers and train stations has been excluded from the buffer zone. This design has the benefit of supporting the study with a higher amount of cases, which is needed to produce significant results within a reasonable time frame. The buffer should be big enough to achieve enough cases but small enough so that all cases can be expected to benefit from the intervention. A buffer distance of 250 meters achieves enough cases and results in an average distance from the center of the study site to the outer edge of the buffer zone of approx. 500 meters, which is an appropriate distance for a citizen responder. Within the study site and buffer zone, elderly homes have been excluded (map 1). Further, parts of the buffer zone that are cut off by impassible structures such as train railway tracks or highways are excluded (map 1).

Map 1: data collection area consists of both the study sites and the buffer zone. Railway tracks become the boundary on the east side of the buffer zone. The hole in the middle of the study site represents an elderly home that has been excluded from the data collection area.

4.2 Data Collection and Management

During the trial, data on cardiac arrest within the areas will be collected through the existing data collection system, the Danish Cardiac Arrest Registry, which records all OHCAs in Denmark[3, 41]. The Danish Cardiac Arrest Registry has existed since 2001 and has previously been described in detail. The National Cardiac Arrest Registry follows the Utstein template for reporting cardiac arrest.[42] The following information is collected through the Danish Cardiac Arrest Registry: witnessed status, location of arrest, first recorded rhythm, whether bystander performed CPR and/or defibrillation, EMS CPR and/or defibrillation, whether the arrest was EMS treated, time of EMS first shock, return of spontaneous circulation, time to return of spontaneous circulation, patient status at hospital admission (terminated at the scene, ongoing CPR, return of

spontaneous circulation but comatose or Glasgow Coma Scale >8, alive). Each case is validated through patient charts to validate the cardiac arrests and exclude misclassified cases.

Data on 30-day survival will be retrieved through Statistics Denmark. Data on neurological status will be retrieved from patient journals. Data on socioeconomic factors will retrieved through Statistics Denmark. Through the exact location of arrest, it will be possible to identify OHCAs in the study area.

Personal data will be treated with the usual secrecy in compliance with current regulations and legislation in the Capital Region of Copenhagen, Denmark. Personal Identifier numbers such as social security numbers and all other data that may lead to the identification of subjects included in the study will be coded and keys for decoding will only be accessible to key persons in the project.

Data will be stored on a dedicated and secure server at the Emergency Medical Services Copenhagen, Capital Region of Denmark. Only a few people in the research group have access to data logging and a code to access data. Data will be stored for ten years after the closing of the study.

4.2. Statistical Methods

Eligibility, allocation, inclusion, and exclusion are displayed in a trial diagram (Figure 1).

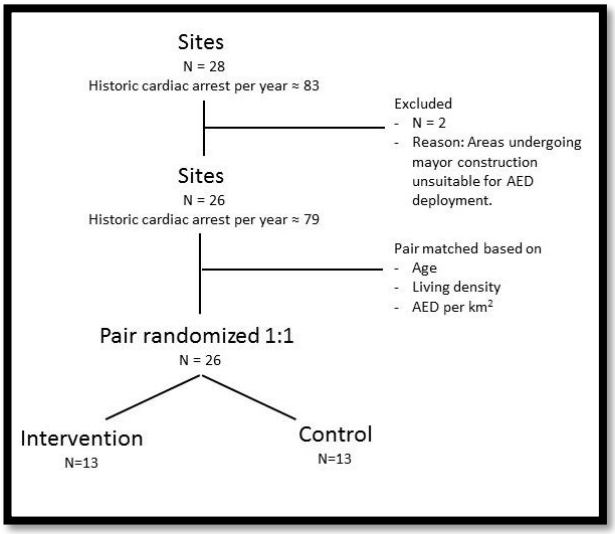


Figure 1 Trial diagram

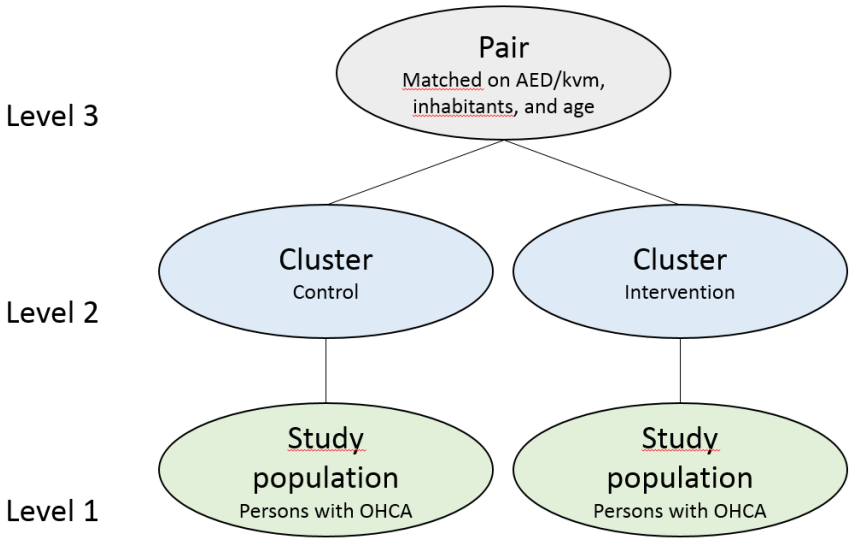
The primary outcome is bystander defibrillation, and the secondary outcome is 30-day survival.

The statistical analysis for this trial will be conducted as a stratified (matched) logistic regression with an exact score test of intervention will be used. The data structure is multilevel with 3 levels being pairs, areas (clusters) nested within pairs and intervention group, and finally, cardiac arrests (figure 2). Data will be aggregated at area level, as number of OHCA and number of outcome events. In the stratified logistic regression, number of outcome events out of number of OHCA within area is an event/trial outcome. Pair of areas is the strata variable. Intervention is a fixed. An exact score test of the effect of intervention on the outcome will be used.

For the primary outcome, we will conduct the above described stratified logistic regression with an exact score test of intervention. The event/trial outcome is number of primary events out of number of OHCA.

The secondary outcome will be analyzed using the same statistical procedure as described for the primary outcome. The event/trial outcome is number of secondary events out of number of OHCA.

An assumption for the analysis is independent observations. It is assumed that the observations are independent as we expect no relation between OHCA cases. Aggregation of data at area level and using a stratified analysis account for the hierarchical data structure.



5. Safety Monitoring board

For the course of the study, a safety committee with statistical and clinical insight will be appointed. This committee functions independent of the steering committee and will be the only body receiving all information during the conduct of the study. Thus, the steering committee will follow the overall development of the study and be provided overall numbers of cardiac arrests and defibrillations. The Safety Monitoring Board will receive all information available including the areas randomized to intervention.

During the course of the study, the steering committee will oversee the general conduct of the trial and provide the safety committee will information. The safety committee will restrict information to the steering committee only to recommend the continuation of the study or discontinuation.

6. Financing and Insurance

The study is financed by an unrestricted research grant from TrygFonden. Further, Zoll provided 100 AEDs and funding for AED cabinets purchase and deployment. Provision of this support is provided with contracts signed by TrygFonden and Zoll respectively, the principal investigator and the head of the Emergency Medical Services in Copenhagen. This is an investigator-initiated trial and Danish patients are in general covered by rules that ensure coverage of patients when exposed to adverse events during the course of treatment.

7. Ethics and Dissemination

7.1. Ethical considerations

7.1.2. Scientific aspects

In Denmark, survival following OHCA at home is 6.5% and the rate of defibrillation is 1,7%[41] but 7 out of 10 may survive if defibrillated by an AED within the first minutes after collapse.[11] The AED registry in the Capital Region of Denmark currently holds nearly 6000 AEDs[3, 6, 43]. Bystander defibrillation is not only crucial for survival but also survival with a favourable neurologic outcome and the chance of returning to work.[44, 45] By deploying AEDs strategically within the areas and ensuring the presence of well-trained citizen first responders the proportion of patients who receive bystander of defibrillation and survival may increase. Given this background, we find that the risks involved with the study are justified by a good chance of improving outcomes.

7.1.3. Legal aspects

The ethical committee in the Capital Region of Denmark has evaluated the project and found that it is not notifiable to the ethical committee in the Capital Region of Denmark and that the project can be initiated without approval from the ethical committee (Journal nr.: 19037170). This decision was based on the design of the study which randomizes residential areas to intervention with AED deployment and training in CPR and AED use vs. control with standard care.

The study is registered by the Danish Data Protection Agency via The Capital Region of Denmark (journal nr.: 2012-58-0004, VD-2018-28, I-Suite nr.: 6222). The study is also registered by the Danish law regarding the handling of personal data for patients will be adhered to. The study has also been registered with the Danish Patient Safety Authority (3-3013-2721/1).

7.1.4. Information regarding the intervention during the study

This study performs intervention in selected areas and no intervention in other areas. The intervention is provided on top of all currently provided treatment and no area is therefore deprived of treatment that could

have been expected. In the areas of intervention efforts are performed to disseminate knowledge of the intervention and to train local people. No information is provided in areas without intervention. The intervention adds a greater likelihood of bystander defibrillation which is part of standard treatment. Therefore, patients subjected to treatment in intervention areas are not provided further information and not requested to consent.

Citizen first responders: To complete the registration through the HeartRunner app, all volunteer citizens must sign the terms of agreement. These include not to disclose any details about suspected cardiac arrests that could lead to the identification of individual patients. Heart runners also sign a confidentiality agreement ensuring personal information about the patient or resuscitation attempt or patient is not to be disclosed. Heart runners also agree to being geographically located when they are logged on to the app, including before receiving alarms and to be contacted by the research team. Heart runners can erase their user information in the app at any given time. Data is stored in accordance with Danish data legislation.

7.2. Declarations of interests

The principal investigators have previously received grants from TrygFonden to perform epidemiological studies of out-of-hospital cardiac arrest. The investigators are otherwise independent of TrygFonden.

Zoll Medical Corporation has donated AEDs and funding for cabinets and deployment. Zoll Medical Corporation does not influence the study design, data collection, data analysis, or article writing in any way.

7.3. Access to data

Data for this study are derived from the Danish Cardiac Arrest Registry and the HeartRunner Mission Survey. Further sources of data are those collected in register via the research environment in Statistics Denmark.

A single statistician has access to the study code during the trial and can provide listings and calculations for the Safety Monitoring Board. When the study closes as scheduled, or prematurely, the code is made available to further study staff.

Personal data will be treated with the usual secrecy in compliance with current regulations and legislation in the Capital Region of Copenhagen, Denmark. Personal Identifier numbers such as social security numbers and all other data that may lead to the identification of subjects included in the study will be coded, and keys for decoding will only be accessible to key persons in the project.

Data will be stored on a dedicated and secure server at the Emergency Medical Services Copenhagen, Capital Region of Denmark. Only a few people in the research group have access to data logging and a code to access data. Data will be stored for 10 years after the closing of the study.

7.4. Dissemination policy

Regardless of the result of the study the main result will be published in an international peer-reviewed journal and presented at relevant congresses. The protocol will be made publicly available as the study starts and will be registered as required for proper publication.

8. Trial organization

8.1. Principal investigator

Fredrik Folke, MD, PhD, Associate Professor

Herlev and Gentofte Hospital, Department of Cardiology,

Copenhagen University Hospital,

Kildegårdsvej 28, 2900 Hellerup and

Head of Research, Emergency Medical Services Copenhagen,

Telegrafvej 5, opgang 2, 3.sal
2750 Ballerup

Fredrik.Folke@Regionh.dk

0045-28182978

8.3. Co-principal Investigator

Carolina Malta Hansen, MD, PhD

Postdoctoral Researcher, Emergency Medical Services Copenhagen

Carolina.malta.hansen.01@regionh.dk

8.2. Executive scientific steering committee:

Professor Christian Torp-Pedersen, Department of Clinical Investigation and Cardiology, North Zealand Hospital, Denmark

Professor Annette Kjær Ersbøll, Department of Population Health and Morbidity, National Institute of Public Health, Denmark

Dr. Jesper Kjærgaard, Department of Cardiology, Rigshospitalet, Denmark

Professor Christian Hassager, Department of Cardiology, Rigshospitalet, Denmark

Professor Gunnar Gislason, Herlev and Gentofte Hospital, Hellerup, Denmark and the Danish Heart Foundation, Denmark

Dr. Freddy Lippert, Emergency Medical Services Copenhagen, Ballerup, Denmark

Dr**.** Carolina Malta Hansen, Emergency Medical Services Copenhagen, Ballerup, and Herlev and Gentofte Hospital, Division of Cardiology, Capital Region of Denmark, Denmark.

Dr. Anne Juul Jørgensen**,** Emergency Medical Services Copenhagen, Ballerup, Denmark

Assistant Professor Fredrik Folke, Emergency Medical Services Copenhagen and Herlev and Gentofte Hospital, Hellerup, Denmark (chair)

The steering committee is responsible for study conduct. All decisions regarding management of the study will be made by the steering committee. During the study the steering committee will remain blinded to study outcome, but the committee will be continuously informed of study progress. This ensures that the steering committee has sufficient information to handle any problems with study progress. The steering committee will regularly be provided with updates by the Safety Committee and Monitoring Board. These updates are restricted to a recommendation to either continue or discontinue the study. No further information can be given by the Safety Committee and Monitoring Board during the course of the study.

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