

Public Access Defibrillation by activated volunteer citizen first responders - the HeartRunner Trial

General Information

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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 2019 and run for up to 4 years.

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Abbreviations:

AED	Automated External Defibrillator
CPC	Cerebral Performance Category
CPR	Cardio Pulmonary Resuscitation
EMD	Emergency Medical Dispatch
EMS	Emergency Medical Service
ERC	European Resuscitation Council
OHCA	Out-of-hospital cardiac arrest
ROSC	Return of Spontaneous Circulation
PAD	Public Access Defibrillation
VF/pVT	Ventricular fibrillation/pulseless ventricular tachycardia

1. Scientific summary

A large proportion of out-of-hospital cardiac arrest (OHCA) patients have an initial cardiac rhythm that can be treated by means of defibrillation. As the chance of survival decreases by 10% per minute from collapse to first defibrillation,^{1,2} efforts to decrease the time to first shock are crucial. Whereas the overall survival rate following OHCA is 12% in Denmark, 7 out of 10 may survive if defibrillated by an automated external defibrillator (AED) within the first minutes after collapse.³ In 2007, an AED registry was implemented in Denmark to make AEDs easier to locate (www.hjertestarter.dk/english). In 2010, the AED registry became nationwide and linked to the emergency dispatch centres in Denmark allowing the dispatchers to direct OHCA bystanders to the nearest available AED. In May 2017, the registry held approximately 16,000 publicly available AEDs but despite these initiatives, AEDs are only used in 3-4% of all OHCA in Denmark.^{4,5} Therefore, new strategies aimed to increase public AED use are warranted. The aim of the “Heart-Runner Trial” is to evaluate a unique logistical model for instantly identifying and recruiting nearby volunteer citizen responders (called ‘heart runners’) through a smartphone app to retrieve an AED in case of nearby OHCA with the purpose of increasing OHCA survival.

At any time, a mobile phone can be geographically positioned with an accuracy of 0-100 m in urban areas. Using this information, volunteer citizens that are located within 1800 m distance of the OHCA can be alerted from the emergency dispatch center to retrieve the nearest AED and bring it to the cardiac arrest location. The volunteer citizen responder receives a digital map on the smartphone and a description of where the AED is located as well as the closest way to the site. Such a smartphone application has already been developed and tested in Sweden.^{6,7} For all OHCA, the dispatcher will always “activate” the Heart-runner mobile positioning system, and then randomization (1:1) will be carried out within the computer system at the dispatch center. Accordingly, only in 50% of the cases there will be an actual dispatch of volunteer citizen responders by means of smartphone activation. Data on all OHCA (both those where citizen responders were activated or not by their smartphones) are collected at the EMS in Copenhagen to compare the effect of volunteer citizen activation.

In addition, it is unclear whether it is physically and mentally safe for the activated citizen responders to quickly find and bring an AED to the cardiac arrest location and begin cardiopulmonary resuscitation (CPR) before ambulance arrival. No studies have investigated the

risk of physical damage when alerted citizen responders are activated to move as quickly as possible through the traffic to the cardiac arrest victim. Similarly, there are very few studies investigating the mental burden and stress that lay-persons might experience when attending in a resuscitation attempt. Studies on a lay-responders experience in resuscitation attempts reports that up to 40% experienced mild/tolerable psychological effect whereas 10% had severe psychological effect.⁸⁻¹⁰ Accordingly, the Heart-runner Trial will examine whether it is safe both physically and psychologically to activate citizen responders to find an AED, bring it to the OHCA patient, and initiate CPR and defibrillation before EMS arrival. All citizen responders who receive an alarm and either accept or decline the alarm will receive a short questionnaire on their smartphones 90 minutes after the alarm. The questionnaire will include questions about the resuscitation attempt as well as psychological distress and physical harm for the citizen responder.

The HeartRunner Trial will be implemented and tested in the Capital Region of Denmark comprising 1.8 million inhabitants with approximately 1,400 OHCAs per year. It is expected to run for approximately 4 years and include approximately 1700 cases of suspected out-of-hospital cardiac arrests.

The primary aims of the HeartRunner Trial are:

- 1). To test whether activating volunteer citizen responders (heart runners) can improve 30-day survival after out-of-hospital cardiac arrest.
- 2). To examine the potential physical or psychological risk involved for the activated heart runners when alerted to a suspected cardiac arrest to start resuscitation before EMS arrival.

As the chance of successful resuscitation is very dependent on the time from collapse to first defibrillation, the HeartRunner trial (including randomization) will be conducted in 3 predefined strata according to expected time from call to arrival of a heart-runner: <3 minutes (group 1), 3-9 minutes (group 2), and >9 minutes (group 3). The study is powered to test difference in survival in groups 1 and 2.

The study is designed to randomize activation of heart runners (activation of heart runners vs no activation of heart runners) for incoming calls to the emergency dispatch center which are 'suspected cardiac arrest' (all cases of suspected cardiac arrest). Standard treatment including dispatch assisted CPR, guidance to a nearby AED if any and dispatch of ambulance and a physician

manned ambulance is carried out in all cases of suspected cardiac arrest regardless of heart runner randomization. The study design has been approved by the Ethical Committee in the Capitol Region of Denmark which did not find it necessary to obtain informed consent from cardiac arrest patients.

2. Rationale

This study is a comparison of activation of volunteer citizen responders (heart runners) and usual care for patients with out-of-hospital cardiac arrest.

Scientific Background

Out-of-hospital cardiac arrest (OHCA) is a major health problem, accounting for approximately 3,500 OHCA in Denmark,⁴ and more than 700,000 annual arrests in the United States and Europe.¹¹ CPR and early defibrillation have been shown to be the most significant factors for improving OHCA survival.¹² Though CPR is unlikely to eliminate ventricular fibrillation and restore a perfusing rhythm,¹³⁻¹⁵ CPR can prolong the time until the brain cells are damaged and can increase the probability for a successful defibrillation and survival.^{1,2} Early CPR has been shown to triple the chances of survival,^{12, 14, 16, 17} as well as the quality of CPR performed is relevant for the chance of survival. Efforts to decrease the time to first shock are crucial as the chance of survival decreases by 10% per minute from collapse to first defibrillation.^{1,2} In cases where defibrillation is performed within five minutes, more than 50% of all patients can be saved.^{3, 18, 19} 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 above mentioned criteria are met like airports,¹⁸ on aeroplanes,^{20, 21} and in casinos,³ with reported survival rates as high as 49% to 75%.^{3, 18, 20, 21} These findings have led to a more widespread AED deployment in public locations with positive effect on OHCA survival.^{19, 22-24}

Since 2010, a national AED registry has been set up as an initiative from the Danish foundation TrygFonden to collect the geographic location of all AEDs in Denmark (www.hjertestarter.dk/english). The rationale behind this is that a national registry enables lay people to find the closest AED and increase awareness among the public of AED placement in the

community. A great effort has been made with regards to quality control and every AED in the registry is checked every 12th month for functionality, location, and confirmed opening hours. By the end of 2018 the registry holds more than 19,000 AEDs throughout the entire country. In 2010, the AED registry was linked to the emergency dispatch centres in Denmark allowing the dispatchers to direct OHCA bystanders to the nearest available AED. Despite increased AED dissemination and public awareness, AEDs are only used in 3-4% of all OHCA in Denmark.^{4,5}

There are several reasons for low AED use: a) AEDs are not dispatched by conventional alarm systems, b) AEDs must be transported to the cardiac arrest site within few minutes, c) AEDs might not be accessible at the time of OHCA, and d) only few cases of cardiac arrests occur in high-incidence places where an on-site AED is located. Furthermore, the vast majority of all cardiac arrests (65-80%) occur in residential areas,²⁵⁻²⁷ where stationary on-site AEDs are rarely available,^{25,28} and the chance of bystander defibrillation is very low (1-2%).^{4,5,28,29}

To benefit optimally from AEDs, both public and residential areas are in need of early first-responder activation. 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 by the dispatch center. One solution implemented by several regional dispatch centers in Europe is a text message, or smartphone alert system.^{6,30,31} Such systems alert local citizen responders to perform CPR and directs them to a nearby AED before EMS arrival. In case of a suspected OHCA, the dispatcher manually activates the alert process and a software program then automatically identifies nearby available volunteer citizen responders as well as nearest accessible AEDs and sends text/push messages to citizen responders in proximity of the OHCA location. Such systems have been tested and implemented in several regional dispatch centers in Europe.^{6,30,31} Experiences from Holland and Sweden showed that not only did activated citizen responders shorten the time from collapse to first defibrillation,³⁰ and increased bystander CPR rate,⁶ but these responders also reached OHCA victims in residential areas normally not reachable with public access defibrillation (PAD) programs.

Using new smartphone technology, this renders a possibility of activating citizen responders to help improving efficacy of public AED use as a compliment to the existing EMS system.^{6,32} Thus, engaging the society at large using volunteer citizens that can be dispatched to nearby OHCA to recruit the closest defibrillator hold the potential to increase AED use, bystander CPR, and ultimately OHCA survival.

3. Study aims

Patient Outcomes

The overall aim of the HeartRunner Trial is to test whether activating citizen responders (heart runners) can improve survival after out-of-hospital cardiac arrest and to assess whether it is safe, psychologically and physically, to dispatch citizen responders to resuscitation attempt. As the chance of successful resuscitation is very dependent on the time from collapse to first defibrillation, the HeartRunner trial will be conducted in 2 predefined strata according to expected time from call to arrival of a heart runner: <3 minutes (group 1) and 3-9 minutes (group 2). Data from our study pilot shows only 4% of all cases would be classified as group 3 (> 9 minutes) and for this reason, the study was not designed to test outcomes in this group. Nevertheless, data and outcomes will be reported for this group as well.

Feasibility

The trial will also examine a unique logistical model for instantly identifying and recruiting nearby volunteer citizen responders to retrieve an AED in case of nearby OHCA using new smartphone technology with the purpose of increasing OHCA survival.

Heart runner Outcomes

For safety outcomes, the trial aims to examine the risk of physical injuries as well as psychological stress or anxiety among activated citizen responders after (4 weeks).

3.1 Outcome Measures

Primary outcome:

1. 30-day survival in OHCA patients included in the HeartRunner trial.

Secondary outcome measures:

1. Rates of bystander defibrillation prior to EMS arrival
2. Rates of bystander cardiopulmonary resuscitation
3. Rates of return of spontaneous circulation at hospital arrival
4. 30-day neurological intact survival (cerebral performance category score of 1-2)³³
5. 1-year survival

The study is powered to independently address primary and secondary outcomes in two strata according to expected time from 1-1-2 call to arrival of a heart runner who can assist with resuscitation: <3 minutes (group 1) and 3-9 minutes (group 2).

For safety outcomes the secondary outcomes are:

1. Physical injuries or accidents among activated heart runners
2. Psychological stress or anxiety among activated heart runners after 4 weeks using the revised impact of event scale (IES-R).^{8,34}

4. Study methods

4.1 Study design

The study is an investigator initiated, investigator-blinded, prospective, randomized controlled trial, comparing the number of OHCA patients who survived 30 days between patients served by EMS-activated volunteer citizen responders prior to EMS arrival with patients who received usual care. The estimated project period will run over 4 years in the Capital Region of Copenhagen, beginning February 2019. As indicated below the study is planned to include 1466 patients.

4.2 Study settings

The study will take place in the Capital Region of Denmark (covering approximately 2 559.4 km² and with a resident population of \approx 1,8 million). There are approximately 1400 cardiac arrests annually in the Capital Region of Denmark. The Danish AED network is a nationwide registry of publicly accessible AEDs, linked to all emergency medical dispatch centers. Approximately 5700 AEDs are currently registered in the Capital Region of Denmark, 37.8% of which are accessible 24/7. The registry has previously been described in detail.^{35,36} The emergency medical dispatch center in the Capital Region of Denmark covers the entire study area with one single activation number (1-1-2) and will be the only dispatch center involved in the HeartRunner study. The system is public, and users are free of any charge. Emergency Medical Dispatchers are trained in a standardized manner, including training in recognition of cardiac arrest. All dispatchers use a medical index computer system to aid dispatchers in emergency call handling. This system includes standardized questions to determine whether there is a suspicion of cardiac arrest. The EMS in the Capital Region of Denmark is a two-tiered system comprising advanced life support provided by

physician-manned ambulances and basic life support provided by ambulances equipped with defibrillators. In all cases of suspected cardiac arrest, both tiers of response are dispatched simultaneously. In case of a suspected cardiac arrest, the medical index system recommends the dispatcher to choose a pre-specified response plan for cardiac arrest: 1) Activation of the EMS system (dispatching an ambulance and a physician-manned ambulance), 2) Guiding bystanders to perform CPR (dispatch-assisted CPR), 3) when feasible, guiding bystanders to retrieve the nearest accessible AED.

The HeartRunner system has been running as a pilot study since September 1, 2017. The system has been successfully implemented in the Capital Region of Denmark and modified as necessary. Integration of the software with the emergency medical dispatch center has been completed and the app is fully functional. Until randomization begins, emergency medical dispatchers activate the system for all consecutive cases of suspected cardiac arrests, following the inclusion and exclusion criteria described below.

4.3 Patient Population

A cardiac arrest will be defined as the absence of consciousness and no normal breathing, identified by dispatcher at the Emergency Dispatch Center. The emergency medical dispatch center does not activate the HeartRunner system in case of an OHCA of traumatic origin, in children under eight years of age, when the caller is not in direct contact with the victim, or when an AED is not indicated, e.g. in nursing homes where trained personal is already present (as described in exclusion criteria).

4.4 Volunteer Responder Population – Heart runners

Heart runners are citizens who have volunteered and registered through the HeartRunner app. The only requirement for registration is age ≥ 18 years. Prior training in CPR skills and AED use compliant with contemporary European Resuscitation Council (ERC) guidelines is recommended but not mandatory. Heart runners are recruited through advertisements in newspapers, TV, radio, social medias, CPR instructors, etc. Contact information (name, age, county, e-mail, cell-phone number) as well as information about completed CPR training is registered online in a database. At registration, heart runners are asked whether they are professional healthcare workers (e.g. as part of being healthcare personnel, police or firefighters, or CPR instructors).

4.5 Inclusion criteria

All EMS-treated OHCAs within the Capital Region of Denmark in whom the HeartRunner-system was activated through the emergency dispatch center.

4.6 Exclusion criteria

Emergency medical dispatchers are instructed not to activate heart runners in case any of the exclusion criteria below. However, since it can be challenging for emergency medical dispatchers to gather sufficient information about the patient within the first few minutes, heart runners will admittedly be activated even though they should not have been. Since randomization will occur for all cases in which a heart runner is activated, cases with any of the exclusion criteria below will be secondarily excluded.³⁷

OHCA-related

- Not true cardiac arrest (suspected, but not verified)
- EMS-witnessed OHCAs
- OHCAs due to trauma, intoxication, or suicide
- OHCAs not treated by the EMS due to ethical reasons or obvious signs of death
- OHCAs under the age of 8
- OHCAs in nursing homes or health care facilities
- OHCAs with no heart runners within 1800 meters
- OHCAs where the 1-1-2 caller cannot see the cardiac arrest victim (to secure safe environment for heart runners)

These cases will be accounted for but not included in analyses of outcome. Our pilot study showed approximately 60% of suspected cardiac arrests were true cardiac arrests. Therefore, we expect 40% of cases for which heart runners were dispatched not to be true cardiac arrests.

4.7 Study procedure

When the Emergency Medical Dispatcher receives a call, the geographical location of the incoming call is already determined. As explained above, in case of a suspected cardiac arrest the medical index system recommends the dispatcher to choose a specific response plan for cardiac arrest. During the HeartRunner Trial, the cardiac arrest response plan will always include the usual OHCA care including dispatch of an ambulance and a physician manned ambulance, CPR instructions to the caller and if feasible, instruct bystanders to retrieve a nearby AED. In addition to activating

usual care, activating heart runners are done through the mobile phone positioning system for heart runners. The location of the incoming emergency call will be compared to the geographical mapping of mobile phones connected to the HeartRunner app. The app sends out new locations whenever heart runners changes their positions according to the “significant change of location service”³⁸ and the latest updated position is stored as coordinates and used to identify heart runners 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 heart runners (mobile phones) within a radius of 1800 meters (configurable) from the suspected cardiac arrest and up to 20 heart runners (configurable) closest to the site of cardiac arrest will receive an alarm on their smartphone requesting whether they are able to respond. When the heart runners 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 go fetch a publicly accessible AED. An algorithm will be used to instruct heart runners who accept an alarm (Figure). Starting from the first heart runner accepting the alarm, the first four heart runners will be instructed to fetch the nearest accessible AEDs and then go to the cardiac arrest location. The fifth heart runner is instructed to go directly to the cardiac arrest location and perform CPR. This algorithm is performed up to 4 times dependent on how many heart runners that are close to the cardiac arrest. If a heart runner aborts the alarm, the assignment (AED or CPR) is relocated to the next heart runner accepting the alarm. If there are no publicly available AEDs close to the cardiac arrest, all heart runners who accept the alarm will be directed to start CPR. The software includes the total distance from heart runner to AED and then to cardiac arrest to select the 20 nearest heart runners. The location of cardiac arrest is displayed on a map through the HeartRunner app including the address of the cardiac arrest. A map showing the route from heart runner to location of cardiac arrest is also provided. The HeartRunner app is linked to the Danish AED-Network and only takes accessible AEDs into account, at time of alarm.

4.8 Randomization method

During the study period, in all cases of suspected cardiac arrest, the dispatcher will follow the same dispatch procedure and activate the advanced medical response system for OHCA described previously, as well as activating the HeartRunner system in every OHCA incident. However, the

HeartRunner system will be randomized to operate in 50% of the cases (the intervention arm). Therefore, randomization is blinded to both dispatchers and researchers. All cases of suspected cardiac arrest will routinely be assigned a unique incident-ID at the dispatch center. This number will then be the intervention key, and allocation is blinded to dispatchers and to investigators until randomization code is broken at final analysis.

The HeartRunner randomization will be run in the 3 independent strata. The mission server will identify heart runners who will likely be able to arrive <3 minutes (0-359 meters), 3-9 minutes (360-1080 meters), and ≥ 10 minutes (> 1080 meters) after being alerted based on calculated distance from the heart-runner to the nearest accessible AED and from there to the location of the OHCA. Distance is calculated as straight line and default speed is set to 2 m/s (4.47 mph). This probability estimation will be performed automatically at the mission server (supplemental material) for every suspected cardiac arrest alarm providing 1:1 randomization to HeartRunner or no HeartRunner activation. The alarm activation is assigned to one of the 3 predefined time groups accordingly.

Randomization will take place independently in the 3 pre-specified strata. For each stratum, randomization ensures that allocation is random, maintains balance between the treatment arms, and ensures that the randomization procedure is unpredictable. Randomization will occur prior to any interaction with heart runners. To reduce the chance randomizing cases for which no heart runners accepted the alarm, randomization will only be activated when at least 4 potential heart runners have been identified in a given strata (< 3min, 3-9 min, > 9 min). Thus, to activate randomization in strata 1 (<3 min), at least 4 heart runners have to be identified in strata 1. This limit was set based on data from our pilot study showing that only 25% of all heart runners who were alerted actually accepted the alarm. Thus, to increase the chance that at least 1 heart runner accepts the alarm in a given stratum when randomized to be activated, at least 4 heart runners need to be identified within the given stratum prior to randomization. When an alarm is sent to the HeartRunner server from the emergency dispatch center, this alarm will then undergo randomization at the server based on a simple algorithm based on the estimated straight-line distance between cardiac arrest location, nearest accessible AEDs and the individual heart runners:

1). Strata 1: Are there at least 4 (≥ 4) heart runners within 3 min (0-359 meters straight-line distance from the suspected OHCA)?

- If ‘yes’, this alarm is then categorized as a ‘Group 1’ response and randomization occurs (either ‘control’=no activation or ‘active’ alarm=sending a mission to all potential heart runners within the maximum distance of the OHCA)
- If ‘no’, then the algorithm continues to question 2):

2). *Strata 2: Are there at least 4 (≥ 4) heart runners not included in Strata 1 and within 9 minutes (<1080 meters) straight-line distance from the suspected OHCA?*

- If ‘yes’, this alarm is then categorized as a ‘Strata 2’ response and randomization occurs (either ‘control’=no activation or ‘active’ alarm=sending a mission to all potential heart runners within the maximum distance of the OHCA)
- If ‘no’, then the algorithm continues to question 3):

3). *Strata 3: Are there at least 4 (≥ 4) heart runners not included in Strata 1 or 2 and within 15 minutes (<1800 meters) straight-line distance from the suspected OHCA?*

- If ‘yes’, this alarm is then categorized as a ‘Strata 3’ response and randomization occurs (either ‘control’=no activation or ‘active’ alarm=sending a mission to all potential heart runners within the maximum distance of the OHCA)
- If ‘no’, then this alarm is categorized as a ‘Group 3’ response if there is at least *one* heart-runner within 1800 meters and randomization occurs (either ‘control’=no activation or ‘active’ alarm=sending a mission the potential heart-runner within the maximum distance of the OHCA).
- If no (zero) heart runners are within 1800 meters, then no randomization will occur, and the case should be marked in data to make it possible to trace how many of these cases we have.

The categories are mutually exclusive.

OHCAs for which there are no potential heart runners within 1800 meters will be excluded. During the pilot phase of the trial, only 11 out of 433 cardiac arrests had no heart runners within 1800 meters, so this number is expected to be low. Further, approximately half of heart runners were in stratum 1 and half in stratum 2 and only few in stratum 3.

All activated heart runners are therefore assigned to either strata 1, 2, or 3 with corresponding suspected arrival time from received alarm to location on the cardiac arrest location.

Calculations of distance according to walking pace:

We have used the assumption that the walking pace for a heart runner is 2.0 meters/second. This may be slower than most people’s walking pace but takes probable delays, such as time from receipt of alarm to acceptance of alarm and beginning to move towards the cardiac arrest, time to retrieve an AED, find the cardiac arrest location and so on. We have also assumed heart runners

only need to walk a one-way distance. Finally, the estimated time from potential heart runners to the location of the cardiac arrest calculated by the mission-server (based on an average speed of 2 m/s) is based on a straight-line distance, not taking the local infrastructure into account. Based on previous experiences looking at the correlation between straight-line and real walking-route distances, real walking-route distances are approximately 1.5 times longer than straight-line distances.

4.9 Randomization process at the mission-server.

Using a simple random allocation scheme each participant has equal likelihood of being assigned to treatment versus reference groups. However, by chance an unequal number of individuals may be assigned to each arm of the study and thus decrease the power to detect statistically significant differences between groups. Additionally, an imbalance of treatment groups within confounding factors may occur. This is especially true for small sample sizes. We therefore intend to use block randomization, a commonly used technique in clinical trial design to reduce bias and achieve balance in the allocation of participants to treatment arms, especially useful when the sample size is small.

Random permuted block randomization will take place independently in the 3 strata planned. Blocking ensures the treatment groups are balanced at the end of every block. By using blocking within strata, important prognostic characteristics (the stratification factors) are balanced between the treatment groups and ensure that allocation is random.

The randomization process is described in detail in Appendix 1.

4.10 Implementation period

The first 17 months (From September 2017 through January 2019) were used to test whether the HeartRunner system was operational, to ensure technical stability, and to recruit approximately 25,000 voluntary heart runners in the capital region of Copenhagen. Also, this period was used to set up the mission server to estimate the heart runner transportation time from location of smartphone alert to arrival at the OHCA location.

4.11 Trial period

The HeartRunner trial period is scheduled to start in February, 2019. The 3 time groups will run in parallel and groups 1 and 2 will be evaluated separately (group 3 will not be evaluated during the

trial period). The HeartRunner trial is planned to run for 4 consecutive years, but each stratum can be terminated by the independent safety committee if significant improvement in survival is obtained or if serious adverse events are experienced.

4.12 Data collection

All incoming 1-1-2 calls are registered at the EMD center. The process of OHCA identification is supported by the criteria-based, nationwide Emergency Medical Dispatch System (Danish Index for Emergency Care).³⁹ Four data sources will be used.

1. HeartRunner App – Mission server: the mission server registers all cases where the HeartRunner system is activated. Every time a dispatcher activates the system, the mission server produces a unique mission ID. For each mission ID, a unique HeartRunner ID for each heart runner identified within a radius of 1800m of cardiac arrest is recorded. For each HeartRunner ID detailed information is collected (see table).
- 2.

Mission ID x	HeartRunner ID	Notified time (1/0), including time, date and HeartRunner position	Alarm confirmed by HeartRunner app (1/0), including time and date	Alarm accepted or declined by HeartRunner (1/0), time and date. Updated position if heart runner accepted the alarm.	Alarm cancelled by HeartRunner (1/0), time, date and HeartRunner position	AED position and ID (if HeartRunner was guided to retrieve AED)

The Emergency Medical Services, electronic dispatch system (CAD): each 1-1-2 call generates a unique incident ID. From the Incident ID the following data is collected: time of incoming call, patient unique social security number, exact incident address (GIS location), type of EMS response, time of ambulance dispatch, time of EMS arrival (vehicle stop at scene).

3. Danish Cardiac Arrest Registry

Data from all cardiac arrests are routinely and systematically collected and entered into the Danish Cardiac Arrest Registry immediately after handling the patient. The Danish Cardiac Arrest Registry has existed since 2001 and has previously been described in detail.⁴ The National Cardiac Arrest Registry follows the Utstein template for reporting cardiac arrest.⁴⁰ 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).

4. Questionnaire:

All heart runners who have accepted or declined an alarm will receive a text message with a link to a short questionnaire within 90 minutes after the alarm. The questionnaire will obtain information about 1) The cardiac arrest: whether the heart runner reached the scene of arrest, whether they arrived prior to EMS, performed CPR and/or defibrillation and 2) Psychological impact and physical injury. Physical injuries will be classified as ‘serious’ defined as requiring hospital admission, ‘minor’ injuries defined as not requiring hospital admission, or risk of been injured or close to get injured on the way to the cardiac arrest or during the resuscitation attempt.

Heart runners who report significant psychological distress will be contacted and offered debriefing by phone by healthcare personnel. The full questionnaire is displayed in appendix 2. A text message reminder will be sent to heart runners that have not completed the questionnaire within 24 hours. If the questionnaire is not completed within 1 week of cardiac arrest, the heart runner will be contacted by phone.

5. Danish Civil Registry:

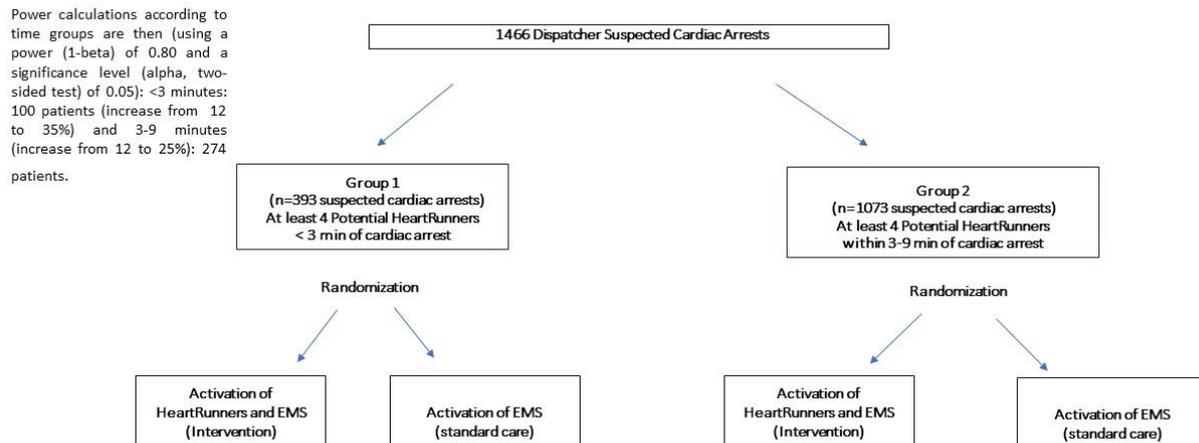
Information on whether the patient is alive or dead after 30 days will be retrieved from the Danish Civil Registry.

5. Statistics and power calculations

5.1 Statistical analyses

Eligibility, allocation, inclusion and exclusion are displayed in a Consort diagram (Figure 1). Differences in baseline characteristics will be tested by Pearson’s chi-square for dichotomous variables. Continuous variables will be tested by either Student’s t-test or Mann Whitney U-test depending on distribution. Outcome variables will be tested with Pearson’s chi-square test and displayed in a Kaplan Meier survival curve to 30 days. The estimated between group differences will be presented as proportions and 95% confidence intervals (CI), which will be calculated by means of the asymptotic method without continuity correction. P-values below 0,05 will be considered statistically significant. Main results will be reported as proportions. Binary logistic

regression will be used to study associations between intervention and primary outcome adjusted for confounding factors and be presented as odds ratios and corresponding 95% CI intervals.



Data from the pilot study showed approximately 64% of suspected OHCA were real OHCA and in approximately 40% of cases for which a heart runner was activated, at least 1 heart runner arrived prior to EMS. Thus, for group 1: 100 cases of true OHCA would be identified among 157 cases of suspected cardiac arrests. To achieve at least 157 suspected cardiac arrests where at least one activated heart runner arrived prior to EMS, it would require 393 suspected cardiac arrests. For group 2, following the same calculations lead to 1073 cardiac arrests. Thus, in total, 1466 suspected cardiac arrests would be necessary to complete the study.

Figure 1. Consort Diagram

5.2 Power calculations

There was an overall survival in the study region of approximately 12% in 2015. Based on prior studies from Stockholm and Holland time to arrival of bystanders decreased by 2.5 minutes with introduction of activated lay persons (heart-runners). Experiences from Sweden have shown that volunteer citizen responders can be recruited and arrive before all dispatched units in 25% of the cases.^{6, 30}

Power calculations for increased 30-day OHCA survival:

Sample size and power calculations are based on an assumed effect size using a binary outcome (30-day survival). Data from Danish OHCA cases without introduction of a HeartRunner program showed a decreased chance of survival with increasing EMS response times (30-day survival for all OHCA cases were 12%, 8%, and 4% for EMS response times of <5 minutes, 5-10 minutes, and >10 minutes, respectively).¹² Similarly, the chance of having a shockable heart rhythm (ventricular fibrillation/pulseless ventricular tachycardia) decreased from 50% within 5 minutes, 30% within 5-10 minutes, and below 20% for EMS response times above 10 minutes.¹²

Estimated 30-day survival chances according to heart runner response times are: 35% within 3 minutes, 25% within 3-9 minutes, and 4% after 9 minutes.

Power calculations according to time groups are then (using a power (1-beta) of 0.80 and a significance level (alpha, two-sided test) of 0.05): <3 minutes: 100 patients (increase from 12 to 35%) and 3-9 minutes (increase from 12 to 25%): 274 patients.

Data from the pilot study showed approximately 64% of suspected OHCA were real OHCA. Further, in approximately 40% of cases for which a heart runner was activated, at least 1 heart runner arrived prior to EMS. It is thus necessary to account for these conditions when calculating power for this study. Thus, for group 1: 100 cases of true OHCA would be identified among 157 cases of suspected cardiac arrests. To achieve at least 157 suspected cardiac arrests where at least one activated heart runner arrived prior to EMS, it would require 393 suspected cardiac arrests. For group 2, following the same calculations leads to 1073 cardiac arrests. Thus, in total, 1466 suspected cardiac arrests would be necessary to complete the study.

Subgroup Analysis

1. Usual care vs. HeartRunner intervention: only including cases randomized to heart runner dispatch in which at least one heart runner arrived prior to EMS.
2. Usual care vs. HeartRunner intervention: only patients with witnessed arrest
3. Usual care vs. HeartRunner intervention: ambulance response time < 5 minutes, 5-10 minutes, 10 minutes

6. Study Quality

The study will be conducted according to principles of Good Clinical Practice, apply to ethical principles and regulatory requirements.

The study will be monitored according to a monitoring plan, according to principles of Good Clinical Practice for clinical studies.

The study will be subject to audit as required by authorities.

7. Ethical Aspects

Scientific aspect

Overall survival following OHCA is 12% in Denmark but 7 out of 10 may survive if defibrillated by an AED within the first minutes after collapse.³ The AED registry in the Capital Region of Denmark currently holds nearly 6000 AEDs, but AEDs are only used in 3-4% of all OHCA.^{4, 5, 41} Bystander defibrillation is not only crucial for survival, but also survival with favourable neurologic outcome and chance of returning to work.^{42, 43} Activating citizen responders may increase rates of bystander CPR and defibrillation, and consequently, survival. If citizen responder activation indeed increases survival, it is necessary to understand how many persons need to be activated to save a life and consider the extent of physical injury or psychological stress for the citizen responders. Given this background we find that the risks involved with the study are justified by a good chance of improving outcomes.

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.: 17018804). This decision was based on the design of the study which randomizes each 1-1-2 call with suspicion of cardiac arrest to heart runner activation vs. no heart runner activation (standard care).

The study is registered by the 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 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).

Patient information and informed consent

The study is designed to randomize activation of heart runners (activation of heart runners vs no activation of heart runners) for incoming calls to the emergency dispatch center which are 'suspected cardiac arrest' (all cases of suspected cardiac arrest). Standard treatment including dispatch assisted CPR, guidance to a nearby AED if any and dispatch of ambulance and a physician manned ambulance is carried out in all cases of suspected cardiac arrest regardless of heart runner randomization. The Ethical Committee in the Capitol Region of Denmark which did not find it necessary to obtain informed consent from cardiac arrest patients.

Heart runners: 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 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 to Danish data legislation.

8. Safety Management

A Data Safety and Monitoring Board with statistical, cardiological and prehospital expertise will follow the study. Formal interim analyses are not planned. This committee is composed of members otherwise independent of the study. They can recommend the steering committee to discontinue the study, but it is the only body which during the course of the study received unblinded results grouped by treatment. The Safety Committee and Monitoring Board will form its own guidelines. The major events to be considered by the safety committee are survival rates (effect) and serious physical injuries or psychological stress among heart runners (safety).

The primary tracking of safety uses a research computer linked directly to the HeartRunner mission server. Using this system, responses can be tracked continuously, and reports can be prepared for the study Data Safety and Monitoring Board.

Further, events that come to the attention of study staff and which are not covered by tracking of heart runner responses and which are either fatal, life threatening, causes hospitalization or lengthening of hospitalization, results in significant or lasting disability or leads to a congenital defect will be reported as well.

Practical reporting of safety

For the purpose of this trial all heart runner hospitalizations and deaths in relation to responding as heart runners are considered serious adverse events. These events will be tabulated on a quarterly basis for the whole trial based on heart runner survey responses.

Protocol version 1. February 5, November 2019.

Further, events that are serious according to the above definition and not on the listings from surveys will be reported as well.

Risks and side effects of trial procedures

Activating Volunteer Citizens to Respond to OHCA

Prior studies have activated volunteer citizens to respond to OHCA and have only reported mild psychological stress. Physical injuries have not been reported.^{6, 8} During our pilot study, 1% of heart runners reported moderate or severe psychological stress and one case of serious physical injury was reported (a foot fracture).

9. Data management

Data for this study are derived from the Danish Cardiac Arrest Registry, the HeartRunner Mission Survey and heart runner survey as previously described. Further source data are those collected in register via the research environment in Statistics Denmark.

A single statistician has access to the study code during the course of the trial and can provide listings and calculations for the Data Safety and 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 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 few people in the research group have access with data logging and a code to access data. Data will be stored for 10 years after closing of the study.

10. Patient, Caregiver and HeartRunner Engagement Team

Since this trial will be conducted in the community including patients, caregivers and heart runners, an engagement team consisting of a cardiac arrest patient, a caregiver and heart runners with different backgrounds will be formed to participate in planning, conducting, and disseminating the results of our study. The team will provide feedback on the study protocol and the follow up

questionnaire to heart runners. The team will also oversee the implementation and conduct of the trial, with special focus on ethical issues.

11. Dissemination of results

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.

12. Financing and Insurance

The study is financed by an unrestricted research grant from TrygFonden. Provision of this support is provided with a contract signed by TrygFonden, 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 a treatment.

13. Relation between TrygFonden and Investigators

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. A representative from TrygFonden is a member of the Steering Committee of the trial.

14. Trial organization

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

The steering committee is responsible for study conduct and all decisions regarding management of the study needs to be taken by the steering committee.

During the study the steering committee remains blinded to study outcome, but the committee will be continuously informed on study progress and blinded information on outcome. 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.

These updates are restricted to being either a recommendation to continue the study or to stop the study. No further information can be given by the Safety Committee during the course of the study.

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Appendix 1:

Randomization

Functionality

Randomization is configurable in the HeartRunner MissionServer. For the HeartRunner trial, randomization is activated and divides each incident into two groups by random: Intervention group and control group. The ratio in which the incidents are divided is configured to 1:1 randomization during the whole study period.

Intervention group:

1. Perform standard missions

Control group:

1. Abort mission, i.e do nothing meaning that the incident is invisible to all candidates.

Random allocation

The process of deciding if an incident is an intervention incident or a control incident need to follow certain statistical rules in order to satisfy scientific requirements.

Block randomization

Block randomization is used to ensure that the same number of incidents fall into each group even with small sample size. Simply speaking, block randomization means that for certain block size, for example 6, every 6th subsequent incidents will have 3 incidents in control group and 3 incidents in intervention group. Then the next 6 incidents will also have 3 of each. Within each block the pattern is random. Instead of the simple approach of using fixed block size, MissionServer will use a variable block sizes of 4, 6 and 8, meaning that for each new block the next block is randomly selected to have size 4, 6 or 8.

Note that the intervention/control ratio must match every block size used.

Example of variable block size with 24 incidents using 1:1 ratio. Here, these 24 incidents make up 4 entire blocks:

Incident #	Block size	Group
1	8	Control
2	8	Control
3	8	Intervention
4	8	Control
5	8	Intervention
6	8	Intervention
7	8	Control

8	8	Intervention
9	4	Control
10	4	Intervention
11	4	Intervention
12	4	Control
13	6	Intervention
14	6	Control
15	6	Intervention
16	6	Control
17	6	Control
18	6	Intervention
19	6	Intervention
20	6	Intervention
21	6	Control
22	6	Control
23	6	Intervention
24	6	Control

Stratified randomization

MissionServer will support stratified randomization based on candidate-proximity. The idea behind stratified randomization is to ensure that important baseline variables (like candidate proximity in this case) thought to be associated with the outcome, are evenly distributed between groups. Each incident is grouped into one proximity group depending on how far the four nearest candidates (citizen responders) are located. Then separate block randomization lists are applied to each group.

Proximity group	Criteria	Stratum list
1	At least 4 candidates with TVP < 180 sec	List 1
2	At least 4 candidates with TVP < 540 sec	List 2
3	At least 4 candidates with TVP < 900 sec	List 3
4	At least 1 candidate with TVP < 900 sec	List 3
Rest	No candidate with TVP < 900 sec	No alert (no randomization)

Note these criteria are evaluated in the specified order.

Note that if the incident does not match any of the proximity groups there will be no alarm.

Appendix 2:

Survey

Survey sent to all citizen responders whose app has confirmed the alarm. The original survey is in Danish and here translated to English.

Start question

- Q0 Did you accept the alarm?
Yes (Go to Q1)
No (Go to Q50)

Accept questions:

- Q1 Did you try to retrieve a defibrillator?
Yes (Go to Q2)
No (Go to Q3)
- Q2 Did you succeed in retrieving a defibrillator?
Yes (Go to Q4)
No (Go to Q3)
- Q3 Why did you not succeed in retrieving a defibrillator?
The alarm did not include enough information
The defibrillator was not accessible
The defibrillator I was directed to was already taken
There were technical problems with the app
I was not directed to a defibrillator
Other reason
- 1 (Go to Q4)
2 (Go to Q4)
3 (Go to Q4)
4 (Go to Q4)
5 (Go to Q4)
6 (Go to Q4)
- Q4 Did you try to reach the cardiac arrest location?
Yes (Go to Q6)
No (Go to Q5)

- Q5 Why did you not try to reach the cardiac arrest location?
I was unavailable to help
I noticed the alarm too late
It was too far away
There were technical problems with the app
Other reason
- 1 (Go to Q17)
2 (Go to Q17)
3 (Go to Q17)
4 (Go to Q17)
5 (Go to Q17)
- Q6 Did you succeed in reaching the victim?
- Yes, by foot (Go to Q8)
Yes, by bike (Go to Q8)
Yes, by car (Go to Q8)
Yes, with other transportation (Go to Q8)
No (Go to Q7)
- Q7 Why did you not succeed in reaching the victim?
The alarm did not contain sufficient information
I aborted the alarm when I saw the emergency personnel
There were technical problems with the app
Other reason
- 1 (Go to Q17)
2 (Go to Q17)
3 (Go to Q17)
4 (Go to Q17)
- Q8 Did you reach the victim before the emergency personnel?
Yes (Go to Q9)
No, I arrived after the emergency personnel (Go to Q9)
- Q9 Was cardiopulmonary resuscitation initiated when you arrived?
Yes (Go to Q11)
No (Go to Q10)
- Q10 Did you initiate cardiopulmonary resuscitation?
Yes (Go to Q12)
No (Go to Q12)

- Q11 Who performed cardiopulmonary resuscitation?
Emergency personnel
Other bystander
- 1 (Go to Q12)
2 (Go to Q12)
- Q12 Did you or any other citizen responder attach a defibrillator to the patient?
Yes (Go to Q13)
No (Go to Q14)
- Q13 Did the defibrillator deliver a shock to the patient?
Yes (Go to Q14)
No (Go to Q14)
- Q14 Did you perform cardiopulmonary resuscitation?
Yes (Go to Q15)
No (Go to Q16)
- Q15 What kind of cardiopulmonary resuscitation did you perform?
Only chest compressions
Only ventilations
Both chest compressions and ventilations
- 1 (Go to Q17)
2 (Go to Q17)
3 (Go to Q17)
- Q16 Why did you not perform cardiopulmonary resuscitation?
The patient was not in cardiac arrest
The patient was awake
Someone else performed cardiopulmonary resuscitation
Other reason
- 1 (Go to Q17)
2 (Go to Q17)
3 (Go to Q17)
4 (Go to Q17)

- Q17 Did you suffer any physical injuries or were you at risk of physical injuries on your way to the cardiac arrest location?
Yes
No
- 1 (Go to Q20)
2 (Go to Q18)
- Q20: On your way to the cardiac arrest location:
Were you at risk of physical injuries or close to getting injured?
Did you suffer minor injuries without need for treatment/hospitalization?
Did you suffer severe injuries with need for treatment/hospitalization?
Other?
- 1 (Go to Q18)
2 (Go to Q18)
3 (Go to Q18)
4 (Go to Q18)
- Q18: It can be stressful to participate in cardiac arrest resuscitation.
What impact did the experience have on you?
1. I was not affected
 2. Only minor distress
 3. Moderately distress
 4. Severe distress, but no need for follow-up by healthcare personnel
 5. Severe distress, with need for follow-up by healthcare personnel
- 1 (Go to Q19)
2 (Go to Q19)
3 (Go to Q19)
4 (Go to Q19)
5 (Go to Q19)
- Q19: Do you want to continue as a citizen responder?
1. Yes
 2. No
 3. In doubt
- 1 (Go to END)
2 (Go to END)
3 (Go to END)
- END If you need debriefing or follow-up by healthcare personnel, please send an e-mail to hjerteloeber.den-praehospitale-virksomhed@regionh.dk
Please be aware that we cannot reveal any information or outcome about the cardiac arrest patient.
Thank you for your participation.

Decline questions:

Q50: We ask you to answer two short questions to help us improve the citizen responder system.

What was the reason you did not accept the alarm?

1. I was unavailable to accept the alarm
2. I did not feel comfortable to help
3. I expected the emergency personnel to get there before me
4. Technical problems

1 (Go to Q51)

2 (Go to Q51)

3 (Go to Q51)

4 (Go to Q51)

Q51: Do you want to continue as a citizen responder?

1. Yes
2. No
3. In doubt

1 (Go to END2)

2 (Go to END2)

3 (Go to END2)

END2 If you want to contact us, please send an e-mail to hjerteloerber.den-praehospitale-virksomhed@regionh.dk