Public Access Defibrillation by Activated Volunteer Citizen Responders - the HeartRunner Trial

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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 8 years.

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Abbreviations:

AED	Automated External Defibrillator
CPC	Cerebral Performance Category
CPR	Cardiopulmonary 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.[4] 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.[5, 6] [7]Therefore, new strategies aimed to increase public AED use are warranted. The aim of the "HeartRunner 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 and 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.[8, 9] For all OHCAs meeting the activation criteria explained in the Method section, the dispatcher will always "activate" the HeartRunner mobile positioning system, and then randomization (1:1) will be carried out within the computer system thus blinded for the emergency dispatchers. Accordingly, only in 50% of the cases will there be an actual dispatch of citizen responders by means of smartphone activation. Data on all OHCAs (both those where citizen responders were activated or not by their smartphones) are collected at the EMS in Copenhagen to compare the effect of citizen responder 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 citizen responders are activated to move as quickly as possible through 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.[10-12] Accordingly, the HeartRunner 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 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 1400 OHCAs per year. It is expected to run for approximately 8 years and include approximately 4200 cases of suspected out-of-hospital cardiac arrests.

The primary aims of the HeartRunner Trial are:
1) To test whether activating volunteer citizen responders can improve 30-day survival after out-of-hospital cardiac arrest.
2) To examine the potential physical or psychological risk involved for the activated citizen responders 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 activation to arrival of a citizen responder: <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 citizen responders vs no activation of citizen responders for incoming calls to the emergency dispatch center which are ‘suspected cardiac arrest’. Standard treatment including dispatch assisted CPR, guidance to a nearby AED, if feasible, and

dispatch of ambulance and a physician manned ambulance will be carried out in all cases of suspected cardiac arrest regardless of citizen responder randomization.
The Ethics Committee's responsibility is to assess medical research projects. The Ethics Committee has evaluated the study protocol and deemed the study is not a medical research project as defined in the Ethics Committee's § 2. The study is therefore deemed not notifiable and can be initiated without further approval from the Ethics Committee (Journal nr.: 17018804).
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) and data will be stored in accordance to Danish data legislation. The study has also been registered with the Danish Patient Safety Authority (3-3013-2721/1, 31-1522-14, and R-20051145) and will adhere to Danish law regarding handling og personal data for patients.

2. Rationale

This study is a comparison of activation of volunteer citizen responders 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 4000 OHCAs in Denmark,[13] and more than 700,000 annual OHCAs in the United States and Europe.[14] CPR and early defibrillation have been shown to be the most significant factors for improving OHCA survival.[15] Though CPR is unlikely to eliminate ventricular fibrillation and restore a perfusing rhythm,[16-18] 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,[15, 17, 19, 20] 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, 21, 22] 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,[21] on aeroplanes,[23, 24] and in casinos,[3] with reported survival rates as high as 49%

to 75%.[3, 21, 23, 24] These findings have led to a more widespread AED deployment in public locations with positive effect on OHCA survival.[22, 25-27]

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 held 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.[5, 13]

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,[28-30] where stationary on-site AEDs are rarely available,[28, 31] and the chance of bystander defibrillation is very low (1-2%). [5, 13, 31, 32]

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.[8, 33, 34] 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.[8, 33, 34] Experiences from Holland and Sweden showed that not only did activated citizen responders shorten the time from collapse to first defibrillation,[33] and increased bystander CPR rate,[8] but these responders also reached OHCA

victims in residential areas normally not reachable with public access defibrillation (PAD) programs.

Using new smartphone technology renders a possibility of activating citizen responders to help improving efficacy of public AED use as a compliment to the existing EMS system.[8, 35] Thus, engaging the society at large using volunteer citizens that can be dispatched to nearby OHCAs 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 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 attempts. 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 citizen responders: <3 minutes (group 1) and 3-9 minutes (group 2). Data from our pilot study 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.

Citizen Responder 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.

3.1 Outcome Measures

Primary outcome:

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

Secondary outcome measures:

1. Bystander defibrillation prior to EMS arrival
2. Bystander cardiopulmonary resuscitation prior to EMS arrival
3. Return of spontaneous circulation at hospital arrival
4. Neurological intact survival at hospital discharge (cerebral performance category score of 1-2)[36]
5. 1-year survival

The study is powered to independently address primary outcomes in 2 time strata according to expected time from activation to arrival of a citizen responder who can assist with resuscitation: <3 minutes (stratum 1) and 3-9 minutes (stratum 2).

For safety outcomes the secondary outcomes are:

1. Physical injuries or accidents among activated citizen responders
2. Psychological stress or anxiety among activated citizen responders

Physical injuries and psychological stress will be assessed through an electronic survey sent out 90 minutes after activation. Non-responders will be followed up by phone call, text message or e-mail.

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 with activation of citizen responders vs. no activation of citizen responders (usual care). The estimated project period will run over 8 years in the Capital Region of Copenhagen, beginning May 2019. As indicated below the study is planned to include 4200 patients.

4.2 Study settings

The study will take place in the Capital Region of Denmark (covering approximately 2 559.4 km^2 and with a resident population of ≈ 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.[4, 37] 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). Accordingly, the patient population for this study only includes patient where the HeartRunner system has been activated.

4.4 Volunteer Responder Population – Citizen responders

Citizen responders are individuals 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. Citizen responders 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, citizen responders are asked whether they are professional healthcare workers, police/firefighter/ambulance personnel, student, or "other".

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 citizen responders 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, citizen responders will admittedly be activated even though they should not have been. Since randomization will occur for all cases in which the HeartRunner system is activated, cases with any of the exclusion criteria below will be secondarily excluded.[38]

OHCA-related

- Not true cardiac arrest (suspected, but not verified by the Danish Cardiac Arrest Registry)
- 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 citizen responders within 1800 meters

These cases will be accounted for but not included in analyses of outcome. Our pilot study showed approximately 64% of suspected cardiac arrests were true cardiac arrests. Therefore, we expect 36% of cases for which citizen responders 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, activation of citizen responders will be carried out through a mobile phone positioning system for citizen responders. 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 citizen responders changes their positions according to the "significant change of location service"[39] and 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 citizen responder 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 and up to 20 citizen responders (configurable) closest to the site of cardiac arrest will receive an alarm as a notification on their smartphone requesting whether they are able to 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 1800 meters. If the citizen responder is >1800m of the cardiac arrest, the citizen responder will be informed they are now too far from the cardiac arrest and their help will therefore not be required. The system will not find a new replacement for this citizen responder. The system will recruit the remaining citizen responders to either go directly to the site of arrest and begin CPR or go fetch a publicly accessible AED. An algorithm will be used for allocation of the citizen responders who accept an alarm. Starting from the first citizen responder who accepts the alarm, the first four citizen responders will be instructed to fetch the nearest accessible AEDs and then go to the cardiac arrest location. Based on the updated position, the citizen responders are directed to the closest accessible AED at the time of alarm. 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 dependent on how many citizen responders are located close to the OHCA location. If a citizen responder aborts the alarm, the assignment (AED or CPR) is reassigned to the next citizen responder accepting the alarm. If there are no publicly available AEDs close to the OHCA, all citizen responders who accept the alarm will be directed to start CPR. The software includes the total distance from citizen responder to AED and then to cardiac arrest to select the 20 nearest citizen responders. The OHCA location is displayed on a map through the HeartRunner app including OHCA address. If the citizen responder is directed to an AED, that location and address is also shown on the map, including additional accessibility information. A map showing the route from citizen responder 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 that meets the activation criteria described above. 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 investigators. 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 HeartRunner server will identify citizen responders who will likely be able to arrive <3 minutes (0-359 meters), 3-9 minutes (360-1080 meters), and ≥9 minutes (> 1080 meters) after being alerted based on calculated distance from the citizen responder 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 HeartRunner server (Appendix 1) for every suspected cardiac arrest alarm providing 1:1 randomization to citizen responder activation or no citizen responder activation. The alarm is assigned to one of the 3 predefined time strata accordingly.

Randomization will take place independently in the 3 predefined 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 citizen responders and thus before the citizen responders accept the alarm and update their position. Therefore, the allocation to stratum is based on assumed location (latest updated position). To reduce the chance randomizing cases for which no citizen responders accepted the alarm, randomization will only be activated when at least 4 potential citizen responders have been identified in a given strata (< 3min, 3-9 min, > 9 min). Thus, to activate randomization in stratum 1 (<3 min), at least 4 citizen responders must be identified in stratum 1. This limit was set based on data from our pilot study showing that only 25% of all citizen responders who were alerted actually accepted the alarm. Thus, to increase the chance that at least 1 citizen responder accepts the alarm in a given stratum when randomized to be activated, at least 4 citizen responders 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 citizen responders:

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

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

2). Stratum 2: Are there at least 4 (≥4) citizen responders 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 'Stratum 2' response and randomization occurs (either 'control'=no activation or 'active' alarm=sending a mission to all potential citizen responders within the maximum distance of the OHCA)
- If 'no', then the algorithm continues to question 3:

3). Stratum 3: Are there at least 4 (≥4) citizen responders 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 'Stratum 3' response and randomization occurs (either 'control'=no activation or 'active' alarm=sending a mission to all potential citizen responders within the maximum distance of the OHCA)

- If 'no', then this alarm is categorized as a 'Stratum 3' response if there is at least *one* citizen responder within 1800 meters and randomization occurs (either 'control'=no activation or 'active' alarm=sending a mission the potential citizen responder within the maximum distance of the OHCA).
- If no (zero) citizen responders 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 strata are mutually exclusive.

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

All activated citizen responders are therefore assigned to either strata 1, 2, or 3 with corresponding assumed arrival time from received alarm to location of the cardiac arrest.

Calculations of distance according to walking pace:
We have used the assumption that the walking pace for a citizen responder is 2.0 meters/second, which was recently found in a Swedish citizen responder population[40]. 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 citizen responders only need to walk a one-way distance. Finally, the estimated time from potential citizen responders to the location of the cardiac arrest calculated by the HeartRunner 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 HeartRunner 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 20 months (From September 2017 through April 2019) were used to test whether the HeartRunner system was operational, to ensure technical stability, and to recruit approximately 30,000 voluntary citizen responders in the Capital Region of Denmark. Also, this period was used to set up the HeartRunner server to estimate the citizen responder 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 May 15, 2019. The 3 time strata will run in parallel and stratum 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 8 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).[41] Six data sources will be used.

1. HeartRunner App – HeartRunner (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 citizen responder identified within a radius of 1800m of cardiac arrest is recorded. For each HeartRunner ID detailed information is collected (see table).

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, and date	AED position and ID (if HeartRunner was guided to retrieve AED)

2. 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 citizen responder 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. The Danish Cardiac Arrest Registry has existed since 2001 and has previously been described in detail.[13] 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 alive).

4. Patient Charts

   For neurologic outcome data will be obtained from patient charts from in-hospital treatment and patient's performance at discharge. Neurological outcome will be categorized using the Cerebral Performance Category (CPC) score. The CPC score ranges from 1 to 5 where 1 equals good cerebral performance, 2 equals moderate

cerebral disability, 3 equals severe cerebral disability, 4 equals coma or vegetative state, and 5 equals brain death. We will classify good neurological outcome as 1-2.

5. Questionnaire:
All citizen responders 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 citizen responder 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.
Citizen responders 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 citizen responders that have not completed the questionnaire within 24 hours. A second text message reminder will be sent to citizen responders who have accepted an alarm and not completed the questionnaire within 1 week. In case of no reply after the second reminder, citizen responders will be contacted by phone, text message or email.

6. 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 trial diagram (Figure 1). Analysis will be performed following an intention-to-treat principle (patients for whom the HeartRunner system was activated vs. not activated). Baseline characteristics will be summarized as means and standard deviations, medians and interquartile ranges, or percentages.

The primary outcome will be reported as proportion of patients surviving 30 days with and without the intervention. The comparison will be by Fischer's exact test. Survival during the first 30 days will be presented using Kaplan-Meier estimates.

Analysis of bystander defibrillation, bystander cardiopulmonary resuscitation, return of spontaneous circulation on hospital arrival, and neurological intact survival at hospital discharge (cerebral performance category score of 1-2) will be reported as proportions and compared within intervention groups using Fischer's exact test. Survival during the first year will be presented using Kaplan-Meier estimates and compared with the log-rank test.

All tests will be performed independently in the 2 time strata of the study. As a secondary analysis, data from stratum 1 and 2 will be combined.

Additional Statistical Analysis

In addition to the standard frequentist analysis, to aid interpretation of the results, we will also perform a Bayesian analysis. If the assumptions underlying the design of the trial are found to be substantially incorrect (for example, the proportion of survivors may be lower than was anticipated), the precision of the trial's results may be reduced, which would reduce the chance of any treatment difference reaching the conventional threshold for statistical significance. In this situation, interpretation of the results by clinicians and decisionmakers will be helped by producing a quantitative summary of the probability that activation of HeartRunners is beneficial, taking into account existing evidence and the trial's results.

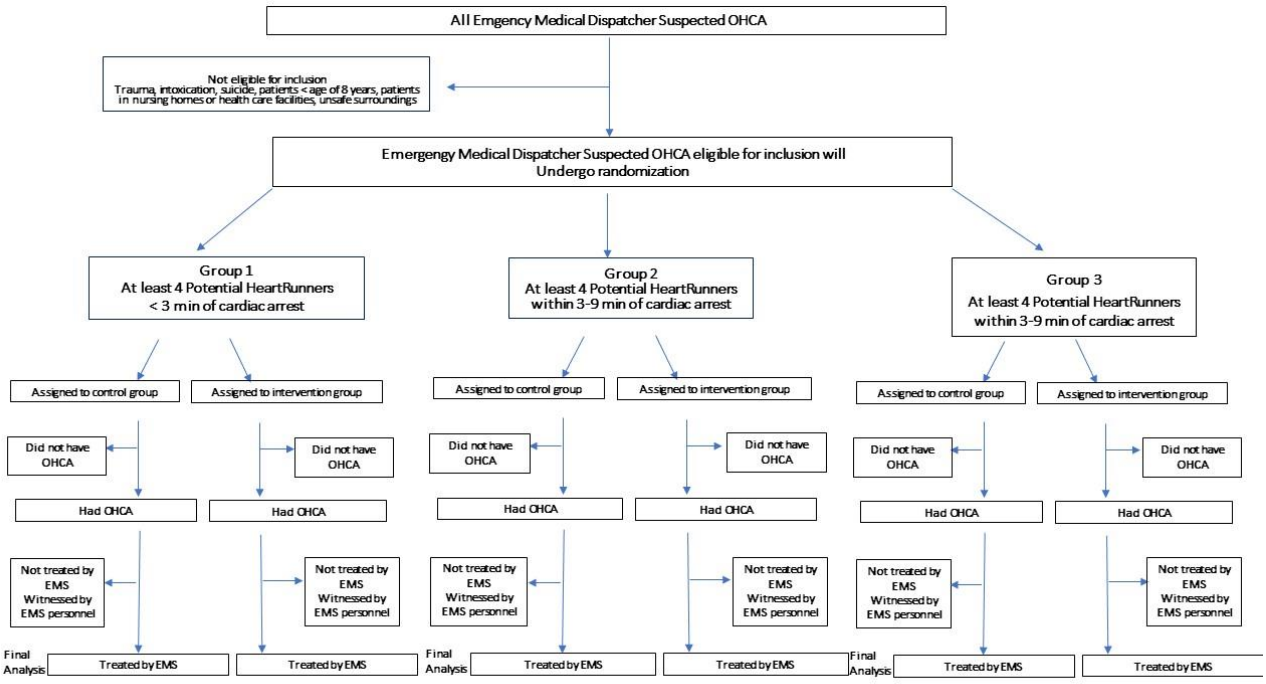

Figure 1. Trial Diagram

5.2 Power calculations

There was an overall survival of approximately 15% in 2018 in Denmark. Based on prior studies from Stockholm and Holland time to arrival of bystanders decreased by 2.5 minutes with introduction of activated lay persons. Experiences from Sweden have shown that volunteer citizen responders can be recruited and arrive before all dispatched units in 25% of the cases. [8, 33]

This is a superiority trial and 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).[15] 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.[15]

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

Power calculations estimated by Fisher's exact test 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: 536 patients (increase from 15 to 25%) and 3-9 minutes (increase from 15 to 25%): 536 patients.

Data from the pilot study showed approximately 64% of suspected OHCA were real OHCA. Further, in approximately 40% of cases for which the HeartRunner system was activated, at least 1 citizen responder arrived prior to EMS. It is thus necessary to account for these conditions when calculating power for this study. Thus, for group 1 and 2, 536 cases of true OHCA would be identified among 838 cases of suspected OHCAs. To achieve at least 838 suspected OHCAs where at least one activated citizen responder arrived prior to EMS, it would require 2094 suspected OHCAs. Thus, in total, 2094 suspected cardiac arrests in stratum 1 and in stratum 2 are estimated to be included in the study. Power calculations were performed using the procedure Power (with the twosamplefreq statement based on Fisher's exact test) in SAS version 9.4 (SAS Institute, Cary, NC, USA).

5.3 Subgroup Analysis

Since time from cardiac arrest to defibrillation is the most powerful determinant of survival, there may be heterogeneity of the intervention effect between subgroups that inherently differ in time from cardiac arrest to citizen responder intervention due to practical circumstances.[43] Differences in the primary outcome are therefore anticipated in the following groups:

1. Witnessed OHCA defined as someone (not EMS) sees or hears the person collapse with a cardiac arrest.
2. According to ambulance response time (< 5 minutes, 5-10 minutes, >10 minutes) defined as time from emergency call to arrival of EMS at the OHCA location, not at the patient's side.
4. Cardiac arrests occurring in public settings. Public OHCA will be defined as a cardiac arrest occurring in public buildings, sport facilities, airports, work/office buildings, outdoor locations, and in public transport.
5. Cardiac arrest in residential setting. Residential OHCA will be defined as a cardiac arrest occurring in private homes or in nursing homes.
6. Distance from OHCA to nearest AED (0-250m, 251-500m, 501-1000m, >1000m). Distances will be calculated as straight-line.

A test for interaction in subgroups in relation to the intervention effect (citizen responder activation) will be performed for the primary outcome for the above-mentioned groups. This study is not powered to detect differences in primary outcome between intervention and control arm in the subgroups.

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

7.1 Scientific aspect

Overall survival following OHCA was 15% in Denmark in 2018 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.[5, 13, 44] Bystander defibrillation is not only crucial for survival, but also survival with favourable neurologic outcome and chance of returning to work.[45, 46] 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.

7.2 Legal aspects

The Ethics Committee's responsibility is to assess medical research projects. The Ethics Committee has evaluated the study protocol and deemed the study is not a medical research project as defined in the Ethics Committee's § 2. The study is therefore deemed not notifiable and can be initiated without further approval from the Ethics Committee (Journal nr.: 17018804).

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) and data will be stored in accordance to Danish data legislation. The study has also been registered with the Danish Patient Safety Authority (3-3013-2721/1, 31-1522-14, and R-20051145) and will adhere to Danish law regarding handling og personal data for patients.

7.3 Patient information and informed consent

Patients: The study is designed to randomize activation of citizen responders (activation of citizen responders vs no activation of citizen responders) for incoming calls to the emergency dispatch center which are '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 citizen responder randomization.

Citizen 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 identification of individual patients. Citizen responders also sign a confidentiality agreement ensuring personal information about the patient or resuscitation attempt is not to be disclosed. Citizen responders agree to be geographically located when they are logged on to the app, including before receiving alarms and to be contacted by the research team. Citizen responders can delete their app end withdraw from the HeartRunner program at any given time.

8. Safety Management

8.1 The Safety Committee and Monitoring Board

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 citizen responders (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 citizen responder 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.

8.2 Practical reporting of safety

For the purpose of this trial all citizen responder hospitalizations and deaths in relation to responding as citizen responders are considered serious adverse events. These events will be tabulated on a biannual basis for the whole trial based on citizen responder survey responses. In order to monitor adverse events, we will follow-up on non-responders by email, text-messages and phone call. Further, events that are serious according to the above definition and not in the listings from surveys will be reported as well.

8.3 Risks and side effects of trial procedures

Prior studies have activated volunteer citizens to respond to OHCA and have only reported mild psychological stress. Physical injuries have not been reported.[8, 10] During our pilot study, 1% of citizen responders reported moderate or severe psychological stress and one case of serious physical injury was reported (a foot fracture).

9. Data management

9.1 Data access

Data for this study are derived from the Danish Cardiac Arrest Registry, the HeartRunner Mission Server, the citizen responder survey, the Danish Civil Registry, and the emergency dispatch center as previously described.

Data managers at the Copenhagen EMS has access to the study data 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.

9.2 Data storage and security

Data is stored in accordance to Danish data legislation.

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 citizen responders, an engagement team consisting of a cardiac arrest patient, a caregiver and citizen responders 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 citizen responders. The team will also oversee the implementation and conduct of the trial, with special focus on ethical issues.

11. Dissemination of results

The study will be presented as a manuscript following CONSORT guidelines.[47] 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.

14. Trial organization

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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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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 configurated 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
hjerteloeber.den-praehospitale-virksomhed@regionh.dk