Statistical Analysis Plan

1. Outcome Measures

Primary outcome:

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

Secondary outcomes:

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)[1]
5. 1-year survival

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.

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. [2, 3]

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).[4] 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.[4]

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 strata 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).

The study is powered to independently address primary outcomes in the 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).

3. Statistical Analysis

Eligibility, allocation, inclusion and exclusion are displayed in a trial diagram (Figure 1) and described in section 4 Study Methods in the study protocol version 3. Analysis well be performed following an intention-to-treat principle (patients for whom the HeartRunner system was activated vs. not activated), except for cases excluded as described in subsection 4.6. Baseline characteristics will be summarized as means and standard deviations, medians and interquartile ranges, or frequencies (number, percentages). The following baseline characteristics will be reported for both groups (intervention vs. control): median age, proportion of male patients, proportion with an initial shockable heart rhythm, proportion of witnessed OHCAs, proportion of OHCAs at home, time of day (8 a.m.-4 p.m., 4 p.m. -12 a.m., 12 a.m.- 8 a.m.), median EMS response time (defined as time from call to vehicle stop at scene), time difference between dispatch of EMS and dispatch of citizen responders, defibrillation performed by EMS, and median distance to nearest AED from the OHCA location.

The primary outcome (30-day survival) will be reported as proportion of patients surviving 30 days for the intervention and control group. Fischer's exact test will be used to test whether activating the citizen responder system can improve 30-day survival. Results will be presented as a relative risk (RR) with a corresponding 95% confidence interval (95% CI) and a risk difference (RD) with a corresponding 95%

confidence interval (95% CI), Table 1. Survival during the first 30 days will be presented using cumulative survival.[2]

Analysis of the secondary outcomes (bystander defibrillation, bystander cardiopulmonary resuscitation, return of spontaneous circulation on hospital arrival, and neurological intact survival (cerebral performance category score of 1-2 at hospital discharge), and 1-year survival) will be reported as proportions and compared within intervention groups using Fischer's exact test as described above for the primary outcome.

All tests will be performed independently in the 2 time stratum of the study. As a secondary analysis, data from stratum 1 and 2 will be combined. The combined analysis will be performed using a logistic regression with intervention (yes, no) and time (<3 and 3-9) as fixed effects. An exact test of the effect of the intervention will be performed. Stratum 3 will be described but not statistically analysed since this group is expected to be very small.

The safety outcomes physical injuries and psychological distress and anxiety among the activated citizen responders will be presented by frequency distributions (number, percentages).

Outcome	Intervention $N_{OHCA}/N_{survival}$ (%)	Control $N_{OHCA}/N_{survival}$ (%)	RR (95% CI)	RD (95% CI)	p-value
Primary outcome: 30-day survival					
<3 min					
3-9 min					
>9 min					
Secondary outcome: Bystander defibrillation prior to EMS arrival					
<3 min					
3-9 min					
>9 min					

Table 1. Primary and secondary outcome. RR, relative risk; RD, risk difference; CI, confidence interval; OHCA, out-of-hospital cardiac arrest; EMS, emergency medical services

4. 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.

Bayesian analyses will be performed to estimate the posterior distribution of the OR and the corresponding 95% credible intervals for each outcome stratified by time stratum.

The Bayesian analysis will model each outcome (primary and secondary) using betabinomial distributions (as the outcomes are binary). The posterior distribution of the odds ratio for each outcome will be estimated. Analyses will use separate priors for the intervention and comparison groups. For the comparison group, a weakly informative prior will be used. For the intervention group, an informative prior based on data from previous studies will be used. Sensitivity analyses will examine the effect of changing the prior distributions.

5. 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.[5] 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.
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.

To test whether the effect of the intervention (citizen responder activation) differ significantly between the subgroups for the primary outcome (30-day survival), the interaction between the intervention and subgroup (subgroup-intervention interaction) will be tested. A logistic regression with intervention (yes, no), subgroup and the interaction between intervention and subgroup will be used. The analysis will include stratum 1 (<3min) and stratum 2 (3-9 min) and stratum will therefore be included as fixed effects. An exact test of the subgroup-intervention interaction effect will be performed. Results will be presented as proportion of patients surviving 30 days in the intervention and comparison groups, relative risk (RR) with a corresponding 95% confidence interval (95% CI) and a risk difference (RD) with a corresponding 95% confidence interval (95% CI), Table 1.

6. Statistical stopping criteria

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.

7. References

1. Jennett B and Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480-4.
2. Ringh M, Rosenqvist M, Hollenberg J, Jonsson M, Fredman D, Nordberg P, Jarnbert-Pettersson H, Hasselqvist-Ax I, Riva G and Svensson L. Mobile-phone dispatch of laypersons for CPR in out-of-hospital cardiac arrest. *N Engl J Med*. 2015;372:2316-25.
3. Zijlstra JA, Stieglis R, Riedijk F, Smeekes M, van der Worp WE and Koster RW. Local lay rescuers with AEDs, alerted by text messages, contribute to early defibrillation in a Dutch out-of-hospital cardiac arrest dispatch system. *Resuscitation*. 2014.
4. Rajan S, Wissenberg M, Folke F, Hansen SM, Gerds TA, Kragholm K, Hansen CM, Karlsson L, Lippert FK, Kober L, Gislason GH and Torp-Pedersen C. Association of Bystander Cardiopulmonary Resuscitation and Survival According to Ambulance Response Times After Out-of-Hospital Cardiac Arrest. *Circulation*. 2016;134:2095-2104.