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[Intervention Protocol]

Different methods of providing automatic external defibrillators to out-of-hospital cardiac arrests to prevent sudden cardiac death

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To establish the effectiveness of different methods of early AED application (non-dispatched layperson, dispatched layperson, dispatched professional, drone delivery - all interventions) versus standard care (comparator) in adults who suffer a witnessed out-of-hospital cardiac arrest in a public setting (population) upon outcomes of survival and neurological function.

BACKGROUND

Description of the condition

A cardiac arrest occurs when the heart stops pumping in an effective manner to support blood flow around the body. It is the common endpoint of any life-threatening condition. There are four heart rhythms that occur in cardiac arrest. Two are the “shockable” rhythms of ventricular fibrillation (VF) and ventricular tachycardia (VT). The other two are the “non-shockable” rhythms of asystole and pulseless electrical activity (PEA). "Out of hospital cardiac arrest" (OOHCA) describes any cardiac arrest occurring outside of the hospital setting.

OOHCA remains a major public health problem worldwide with significant mortality. Worldwide, the incidence of cardiac arrest is 55 per 100,000 person-years, which extrapolates to more than 4 million events annually (Berdowski 2019). In the United States alone, up to 460,000 people suffer a cardiac arrest annually, either out-of-hospital or in the emergency department. Around 70% of these arrests are related to coronary artery disease and are, therefore, likely due to shockable rhythms (Centers for Disease Control and Prevention 2002) that may respond to prompt defibrillation.

Furthermore, it has been observed that early defibrillation with automatic external defibrillators (AEDs) is associated with improved rates of survival to hospital discharge, and that every minute delayed increases the mortality risk by 10% (Valenzuela 1997). The mechanism by which this effect may be generated is described in the section below.

Despite increasing availability of defibrillators and public health campaigns in many developed countries emphasising the importance of cardio-pulmonary resuscitation (CPR), the survival of all OOHCA remains poor, with only 8% of patients surviving to hospital discharge. Within this population, patients presenting with a shockable rhythm fare considerably better with around 25% surviving to hospital discharge (Chan 2014).

Description of the intervention

Defibrillation (changing an abnormal rhythm to normal rhythm using electricity) of a shockable rhythm with an AED can cardiovert shockable rhythms (VT and VF) and restore sinus rhythm (which is the normal natural rhythm of the heart). Sinus rhythm is named as such because it starts from the sino-atrial node (a part of the heart which gives off electrical rhythms). AEDs are machines that can automatically detect abnormal rhythms if their pads are placed onto a patient without a pulse and prompt the resuscitator to give a shock that is delivered with the press of a single button. The machine automatically decides whether the shock is needed by analysing the electrical rhythm and sets the energy to be delivered automatically. The simplicity of the process (applying adhesive pads to the patient, turning the machine on, pressing the shock button if prompted) means that they can be used by lay people without the training required for more complex manual defibrillation. In contrast, manual defibrillation requires the resuscitator to identify the cardiac rhythm, decide on the shock energy to be delivered, charge the device and then deliver the shock.

However, an AED is used only as a part of cardio-pulmonary resuscitation which also involves chest compressions and artificial ventilation. This is labelled by the Resuscitation Council UK as the "chain of survival". An AED is an important part of CPR but should not stop chest compressions and artificial ventilation continuing throughout the period of pulseless cardiac arrest because these interventions preserve circulation to vital body organs when there is minimal cardiac output (Sekhon 2017).

How the intervention might work

The mechanistic role of AEDs in restoring cardiac output

When a patient suffers a cardiac arrest in a "shockable rhythm", the most efficient way to restore cardiac output is to stop the life-threatening arrhythmia (VT or VF) and allow the resumption of normal electrical function of the heart, known as sinus rhythm. Whilst the pathophysiology of these rhythm disturbances are different, the fastest method to restore sinus rhythm in both cases is to apply a synchronised direct current stimulus of up to 360 Joules. This causes depolarisation of all the cardiac myocytes (the heart muscle cells) simultaneously, allowing the heart's intrinsic pacemaker, the sino-atrial node, to take over stimulation again. The restoration of coordinated contraction will, in the right circumstances, re-establish cardiac output. A defibrillator is any machine that can give the controlled direct current electric shock.

Until the invention of the automatic external defibrillator (AED), defibrillation required an appropriately trained professional to operate the machine. The possible problems from manual defibrillation include giving an ineffective shock by not using the correct current or giving inappropriate shocks. At best, giving a direct current shock to the heart inappropriately, for example, in a non-shockable cardiac rhythm, will have no direct negative effect on the heart aside from wasting unnecessary time between chest compressions whilst the shock is delivered. At worst, an inappropriate shock can convert pulseless electrical activity (a non-shockable rhythm) into VF, requiring further cardioversion and delaying treatment of the cardiac arrest. An AED has the technology and the interface to guide a layperson through the process of giving an appropriate electric shock and the correct timing of shocks between chest compressions (Kitamura 2016).

Prompt defibrillation leads to higher survival rates

The natural history of shockable rhythms is to degenerate into non-shockable rhythms with associated poorer outcomes and, therefore, earlier defibrillation has been shown to improve outcomes of cardiac arrest. Patients arresting in a shockable rhythm have a limited time window in which to be defibrillated. The longer a patient is left without cardiac output, with or without chest compressions, the longer the patient remains hypoxic. Hypoxia and hypercapnia lead to a combined metabolic and respiratory acidosis with electrolyte disturbances. Under these circumstances, defibrillation of VT or VF to sinus rhythm does not necessarily lead to a restoration of cardiac output due to reduced contractility of the cardiac myocytes. Therefore, early defibrillation of shockable rhythms can restore sinus rhythm before the patient enters this spiral of hypoxia, acidosis and electrolyte imbalance which are often not recoverable (Sekhon 2017).

This pathophysiological argument has been supported by observational data. An observation study in casinos (Valenzuela 1997) was instrumental in showing that time to external defibrillation was inversely proportional to survival because the timings of the cardiac arrest and the subsequent defibrillation were

accurately recorded by security cameras. This suggested that for every minute defibrillation is delayed, mortality risk increased by 10%. If defibrillation for a shockable rhythm was delivered within three minutes, the survival rate was shown to be around 74%. This tallied with data looking at implantable cardioverter defibrillators (ICDs) which generally shock within 20 seconds, and are almost completely successful in cardioverting shockable rhythms to sinus rhythm (Bardy 1993). A recent observational study of over 4000 witnessed and public OOHCAs showed that a bystander-delivered shock before the arrival of the emergency services was associated with a greater than two-fold increase in the odds of favourable functional survival (Pollack 2018). Therefore, it is well proven that early defibrillation of shockable arrhythmias leads to better survival.

Chest compressions are also important

As detailed above, chest compressions are a vital part of the response to any cardiac arrest. Good quality chest compressions are integral to maintaining cerebrovascular perfusion and therefore increasing the time window in which a shock will lead to successful resuscitation in terms of favourable cardiac and neurological outcomes. Without chest compressions, the time window for successful defibrillation in a public place is very narrow. This is supported by Sasson and colleague's 2010 review of almost 142,000 cardiac arrests which showed that bystander CPR improves survival from 3.9% to 16.1% (Sasson 2010).

Methods of achieving "early" defibrillation

As laid out above, early defibrillation improves survival of shockable rhythms. In the developed world, most emergency medical service (EMS) crews carry defibrillators on board and, therefore, the limiting factor to defibrillation is the response time of emergency service crews. Therefore, the interventions being examined here are those that aim to bring and attach AEDs to the patient before the EMS arrives.

There are four methods that have been used to accomplish this:

1. AEDs are strategically placed in locations likely to have a cardiac arrest (e.g. sports centres, shopping centres, airports, railway stations, restaurants) and, in the event of a cardiac arrest, any bystander can access and use the AED. In this case, a non-assigned bystander uses the AED.
2. An "assigned volunteer" bystander near to the arrest is alerted in some way (usually telephone, text message or smartphone application) by the EMS operator or dispatcher. This volunteer can access an AED and attend the cardiac arrest before the traditional EMS.
3. A professional trained in CPR, but not a health professional (for example, a firefighter, police officer or security guard) is dispatched with an AED, and again can arrive earlier than the EMS.
4. An AED is brought to the arrest site by a dispatched drone.

The common aim of these methods is to reduce the time taken to attach an AED to an arrested patient and therefore to increase the likelihood of successful resuscitation. Whilst the first three are fairly well-established methods of early AED provision, the final method of drone delivery is novel and promising, and therefore requires a brief description of the method and its potential advantages.

When an emergency call is made, an EMS crew is dispatched as normal, but a drone with an AED pre-attached is also dispatched to the arrest scene. These drones can potentially travel at up to 70 km/hour (Claesson 2016). There are several positive points to drone delivery aside from the obvious speed of delivery advantage of travelling in a straight line without road traffic considerations. Firstly, a lay responder may be able to interact with and receive instructions from dispatchers (Sanfridsson 2019). Secondly, drone delivery could be effective in rural areas where it may not be feasible to have fixed AEDs distributed in the same way as in cities (Cheskes 2020). Thirdly, in rural areas where ambulance crews take longer to arrive at cardiac arrests due to increased distances of travel, drones can be located more strategically than ambulance bases and reduce the time to providing an AED. In a feasibility study, Claesson and colleagues showed that drone-delivered AEDs arrived up to 19 minutes before the EMS in rural areas as opposed to 1.5 minutes in urban areas (Claesson 2016). Modelling of optimal drone base locations has shown exciting potential theoretical improvements in median defibrillator arrival times to 2.7 minutes, which clearly would have a huge potential impact on survival (Bogle 2019; Boutilier 2017). Finally, another potential advantage to drone delivery is that the rescuer carrying out CPR does not have to interrupt chest compressions to locate and retrieve an AED (Zègre-Hemsey 2020), which could have survival implications beyond just reduced time to defibrillation.

Why it is important to do this review

It is now accepted that Automatic External Defibrillators (AEDs), if used promptly, can prevent sudden cardiac death. Therefore, these devices have become commonplace in public and private spaces in developed countries (Fredman 2018, Griffis 2016). This practice is supported by resuscitation guidelines worldwide. This expansion has come at not inconsiderable financial outlay because each defibrillator costs in the region of £1000 (Andersen 2019). As the American Heart Association guidelines state (Kronick 2015), AEDs should be placed "in public locations where there is a relatively high likelihood of witnessed cardiac arrest (e.g. airports, casinos, sports facilities)". The Resuscitation Council UK guidelines contain a similar message promoting public access AEDs so that "someone nearby [can] use an AED to deliver the shock that may save a life" (Perkins 2015).

However, it is not clear what the most efficient method is of delivering an AED to an arrested patient. There have been three randomised controlled trials looking at public AED use and they are very heterogeneous:

1. *The Public Access Defibrillation (PAD) Trial* (Hallstrom 2004): In this trial, AEDs were placed in 993 public installations. In the control arm, lay volunteers in the installations were trained in CPR. In the treatment arm, lay volunteers were trained in CPR and AEDs were supplied. The primary outcome measure was survival of OOHCA to hospital discharge. The trial included both witnessed and unwitnessed cardiac arrests. The trial did show an increase in survival to hospital discharge in the control group, although the result was very fragile: if one survivor had died in the treatment arm, the result would have lost statistical significance.

2. *Home Use of Automated External Defibrillators for Sudden Cardiac Arrest* (Bardy 2008): This trial enrolled 7001 patients who were at high risk for sudden cardiac death but did not have implantable ICDs in situ. In the control arm, cohabiters or carers were trained in

CPR. In the treatment arm, carers or cohabiters were trained in CPR and in the use of an AED, which was then supplied to the residence. There were 117 deaths of which only 58 were witnessed, and only 14 shocks given. The trial showed no significant benefit to residential AED supply in this group.

3. *Use of Automated External Defibrillator by First Responders in Witnessed Out of Hospital Cardiac Arrest: Prospective Controlled Trial* (Van Alem 2003): This trial compared areas randomly assigned to trained but non-medical first responders (fire brigade or police depending upon the district) equipped with AEDs to areas with trained first responders without AEDs. The control and treatment areas switched every four months. The trial showed no significant difference in survival to hospital discharge between the arms.

There are two other ongoing trials that may also be of interest. The first is assessing the use of a smartphone application to direct dispatched lay volunteers to the nearest AED - *The Scandinavian AED and Mobile Bystander Activation Trial* (NCT02992873). The second is assessing the benefit of AED delivery by drone (NCT04723368).

These trials all have issues that demonstrate the pitfalls of assessing single randomised trials in this subject area. In the Bardy trial, for instance, there were 117 cardiac arrests but only 58 were witnessed, and only 14 were shocked. This is commensurate with other evidence about OOHCA - namely that arrests at home are more likely to be non-shockable because they are often unwitnessed and therefore shockable rhythms degenerate into non-shockable rhythms. Furthermore, patients who arrest at home are more likely to have multiple comorbidities that lead to non-shockable rhythms. In contrast, arrests in public places are more likely to be shockable rhythms due to the nature of the conditions that cause them: the patients are well enough to leave the house before suffering, for example, an acute coronary syndrome. The data supports this: 60% of witnessed, public OOHCAs are shockable, whereas only 25% of residential cardiac arrests occur with VF or VT as the initial recorded rhythm (Weisfeldt 2017). Therefore, as a synthesis of these points, in order to test the effectiveness of an AED intervention, it is most rigorous to examine their effectiveness only in situations of witnessed cardiac arrest.

Similarly, the statistically insignificant result in the Van Alem trial can largely be explained by the slow response time between the two arms - the non-EMS responders (i.e. treatment group) arrived on average just over 11 minutes after the witnessed arrest, and the control group at almost 13 minutes. Even patients with shockable rhythms who are not defibrillated for 12 minutes have only a 2% to 5% chance of survival (AHA 2000) and, therefore, the number of survivors was low and the intervention was not overly effective, and certainly not enough for the sample size.

Therefore, the burden of proof for public access AEDs mainly falls on large, non-randomised studies. These have been instrumental in showing that AEDs, when applied by the public, can be used safely, effectively, and with survival benefit. This has been shown in numerous observational studies and, perhaps most convincingly, in a recent meta-analysis (Holmberg 2017). Other Cochrane reviews have focussed upon time to bystander CPR rather than time to defibrillation (Barry 2019) or the method of chest compression provision (Wang 2018). However, there is no consensus yet as to the best way in which to supply AEDS to would-be resuscitators to make use of their life-saving capabilities.

Furthermore, there has been theoretical discussion around different phases of cardiac arrest, and the relative importance of CPR and AED use during these phases. As Weisfeldt and Becker laid out, the first few minutes of a cardiac arrest can be described as the "electrical" phase, where defibrillation is all-important (Weisfeldt 2002). In Valuenzela's 1997 study, those who were defibrillated without prior CPR still had a 90% survival rate (Valenzuela 1997). Once an arrest moves beyond four minutes, the arrest enters a "circulatory" phase where CPR is necessary to maintain perfusion and remove toxic metabolites and inflammatory compounds that result from prolonged ischaemia. Subgroup analysis of the collected data could be very illuminating in assessing this theory by determining at what time point defibrillation becomes dependent upon prior CPR. This will have indirect theoretical implications in describing different phases of cardiac arrest in addition to providing evidence with practical applications for how best to apply CPR and defibrillation at different time points in cardiac arrest.

Therefore, this meta-analysis will assess the survival rates to hospital discharge, functional survivor status, and cost-effectiveness of the different strategies of early AED provision to witnessed cardiac arrests. It will synthesise the findings from randomised controlled trials, and will compare the four main methods of early AED provision with standard care, where the first AED is brought by the EMS. An important subgroup analysis will be between defibrillation success rate by time, with and without prior CPR. The hope is that these conclusions will help public health decision-makers to utilise AED resources in the most efficient way.

OBJECTIVES

To establish the effectiveness of different methods of early AED application (non-dispatched layperson, dispatched layperson, dispatched professional, drone delivery - all interventions) versus standard care (comparator) in adults who suffer a witnessed out-of-hospital cardiac arrest in a public setting (population) upon outcomes of survival and neurological function.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and cluster-RCTs for the main statistical analysis.

Studies included will be those reported as full text, published as abstract only, and unpublished data.

Cross-over trials will be included because the intervention does not have a washout period or effect after cross-over. Period effects are unlikely in these trials due to the stable frequency of cardiac arrests.

We will not include non-randomised trials due to potential confounding.

Types of participants

This review will include patients in randomised studies assessing the effectiveness of early AED provision in an out-of-hospital arrest setting.

Inclusion criteria:

1. Patients who suffer a witnessed public OOHCA
2. Patients aged 18 years and above

Exclusion criteria:

1. Patients with implanted ICDs (Implanted Cardioverter Defibrillators)
2. Cardiac arrest in a non-public location including private residences
3. Arrest witnessed by EMS

We will only include trials with participants under the age of 18 yearsor with ICDs if they include a subset of eligible participants and then only if separate data for the eligible participants are available or if more than 80% of the patients are eligible.

Types of interventions

We will include studies comparing different methods of early AED provision for treatment of witnessed out of hospital cardiac arrests (intervention) versus standard care (control).

Comparisons (method of AED application):

1. AED applied by non-dispatched lay responders (e.g. people who witness an arrest and use a nearby AED) versus standard care (control)
2. AED applied by dispatched lay responders (e.g. lay volunteers who are summoned via telephone, text message and know the location of an AED) versus standard care (control)
3. AED applied by dispatched professional but non-medical first responders (e.g. security guards, police officers, firefighters) versus standard care (control)
4. Drone-delivered AED used by non-dispatched lay responders (e.g. people who witness an arrest and use the delivered AED) versus standard care (control)

Definition of control (standard care)

Standard care is defined as any case where the first access to a defibrillator occurs when it is brought by a trained healthcare professional (usually emergency medical services).

The primary outcome will measure these methods individually and pooled versus the standard care comparator.

Types of outcome measures

Reporting one or more of the outcomes listed here in the trial is not an inclusion criterion for the review. Where a published report does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. Relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, will be included in the review as part of the narrative. For all outcomes, we will use the trial results at longest follow-up.

Specifically, with regards to neurological outcome, there is significant heterogeneity of outcomes scores reported in the various studies. The primary outcome measure for neurological recovery will be “discharge with favourable neurological outcome” as measured by a Cerebral Performance Category (CPC) score of less than or equal to 2, or a modified Rankin score (mRS) of less than or equal to 3 (Safar 1981; Saver 2010). It has previously been shown that there is fair correlation between these scores (Rittenberger 2011).

If another scoring system is used in a study, then two authors will map the scores into this system based upon available data. For example, in the PAD trial. those with “mild” disability are defined as having “sufficient cerebral function for part-time work in a sheltered environment or independent activities of daily life” which approximates to a CPC score of 2 (“sufficient cerebral function for independent activities of daily life [and] able to work in sheltered environment”). Therefore, those with a score of “mild” disability in this trial would be classed as “discharged with good neurological outcome” because the “mild” score can be mapped to a CPC score of 2. If there is not enough information to convert the trial neurological outcome data to either the CPC or the mRS score, then data will be described narratively in the neurological outcome section.

If both the mRS and CPC are reported, and do not place the patient in the same category of "discharge with favourable neurological outcome", then the mRS will take precedence in the hierarchy of outcomes.

Primary outcomes

1. Survival to hospital discharge
2. Favourable neurological function at longest available follow-up. Please see above for a description of how this is defined.

Secondary outcomes

1. Cost-effectiveness of each method of early AED provision
2. Median time from arrest to first shock or rhythm assessment
3. Proportion of patients with return of spontaneous circulation (ROSC) after cardiac arrest

The cost-effectiveness of each intervention will be described as a brief economic commentary rather than an integrated full systematic review of economic evidence. We will focus on the incremental benefit of each method of early AED provision, divided by the incremental cost above standard care. Using this, we will calculate the cost per additional life saved (if applicable) and quality-adjusted life years (QALYs) examining neurological data.

In the largest single trial (PAD), the average age of cardiac arrest was 69.8 years. This means that there is a potential for, on average, a decade of further life in resuscitated survivors, or a decade of high care costs if a survivor has a poor neurological outcome that could have been ameliorated by earlier AED provision. However, early AED provision is a costly exercise as it involves training large numbers of volunteers or professionals, and/or providing a high density of publicly accessible AEDs. Therefore, we believe that an economic evaluation of the different methods of AED provision is important and could affect policy decisions in future.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE (Ovid, from 1946 onwards)
- Embase (Ovid, from 1980 onwards)
- CPCI-S (Conference Proceedings Citation Index-Science) Web of Science (Clarivate Analytics, from 1990 onwards)

The preliminary search strategy for MEDLINE (Ovid) (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximising RCT filter (Lefebvre 2019) will be applied to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the ISRCTN registry (International Standard Randomised Controlled Trial Number) (www.isrctn.com/) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) for ongoing or unpublished trials. We will contact authors of unpublished trials.

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status.

Searching other resources

We will check reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We will also examine any relevant retraction statements and errata for included studies.

We will be contacting authors for missing data and will contact authors of ongoing trials by email.

Data collection and analysis

All the identified abstracts and articles from the databases will be imported to Covidence software for referencing and screening.

Selection of studies

Two review authors (HB, CB) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search. If there are any disagreements, a third author will be asked to arbitrate (HV). We will retrieve the full-text study reports/publication and two review authors (MA, AT) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (HV). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (HB, MW) will extract study characteristics from the included studies. We will extract the following study characteristics.

1. Methods: author, year of publication, country of publication, the study design, the number of centres taking part
2. Participants: If randomised: N randomised, how they were randomised (allocation random, allocation sequence concealed), baseline differences between intervention groups, were participants aware of intervention, were carers aware of intervention, deviations from outcome due to trial context, were these deviations in both groups, what analysis done to estimate the effect of assignment to intervention
3. N lost to follow-up/withdrawn, N analysed, mean age, age range, gender, inclusion criteria, and exclusion criteria
4. Interventions: intervention, comparison
5. Baseline characteristics of participants including age, number of males and females, smoking status, hypertension, diabetes mellitus, high cholesterol, history of Cardiovascular Disease (CVD), history of previous reduced LV function, previous stroke, previous coronary artery bypass graft surgery, previous history of Atrial Fibrillation (AF), baseline lung function, previous Percutaneous Intervention (PCI), body mass index, New York Heart Association (NYHA) class, CPR pre-arrest (Y/N) and on scene AED (Y/N), and time from arrest to shock. For the public CPR performers, we will collect data on age, sex, employment status, relationship to patient, dispatched lay responders, non-dispatched lay responders and dispatched professional but non-medical first responders.
6. Outcomes: primary and secondary outcomes specified and collection, time points, measurement methods and thresholds reported. We will also specifically look at the amount of missing data.
7. Notes: funding for trial, and notable conflicts of interest of trial authors

Two review authors (CB, GA) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (MA). One review author (MA) will transfer data into the Review Manager (Revman Web 2020) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (AT) will spot-check study characteristics for accuracy against the trial report. We will contact the authors of the trials by email to ask for the data, if they have not been reported sufficiently in the publication.

Assessment of risk of bias in included studies

Two review authors (HB/CB) will independently assess risk of bias for each study using version two of the Cochrane risk of bias tool (RoB2), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019c). We will resolve any disagreements by discussion or by involving another author (AT).

Our effect of interest is the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended. The rationale for using intention-to-treat analysis is that this review is examining health system level policy regarding the effectiveness of different methods of AED delivery. Therefore, the conclusions of this review should be applicable in recommending policy for a health system rather than individual patient treatment decisions and intention-to-treat analysis fits more closely with this aim.

The risk of bias of specific results of a trial will be assessed according to the following domains:

1. bias arising from the randomisation process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome; and
5. bias in selection of the reported result.

We will assess the risk of bias for the following outcomes of the included studies that will be included in our Summary of Findings table by utilising:

1. a series of 'signalling questions' (answers can be Yes, Probably Yes, Probably No, No and No information) regarding the above risk of bias domains
2. a judgement regarding risk of bias for the domain, using the ROB 2 algorithm which will map responses to the signalling questions to proposed judgements
3. free text boxes to justify responses to the signalling questions and the risk of bias judgements
4. the prediction option to give a predicted risk of bias

We will use this to give an overall risk of bias for the outcome which can be categorised as low risk of bias, some concerns and high risk of bias. The outcomes we will be looking at will be:

1. Survival to hospital discharge
2. Favourable functional neurological status at longest available follow-up
3. Median time from arrest to first shock or rhythm assessment
4. Proportion of patients with return of spontaneous circulation (ROSC) after cardiac arrest

We will be using the ROB Excel tool to carry out our assessments [ROB Excel Tool]. Due to the large amount of data generated by the ROB 2 tool, we will be unable to list all of this in the full review apart from a ROB 2 table reporting an overall risk of bias. We will, however, list all the consensus decisions for the signalling questions in supplemental data files.

We will use the RoB 2 variant for cluster-RCTs (https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials?authuser=0) and use the guidance in the *Cochrane Handbook* (version 6) chapter 23, section 23.1.2 (Higgins 2021) and Table 23.1.a.

We will use the RoB 2 variant for cross-over RCTs (https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/rob-2-for-crossover-trials) and use guidance in the *Cochrane Handbook* (version 6) chapter 23 (Higgins 2021) to help answer the signalling questions.

Measures of treatment effect

Dichotomous data will be analysed as risk ratios with 95% confidence intervals and continuous data as mean difference or standardised mean difference with 95% confidence intervals. We will analyse continuous data as mean difference (MD) with 95% CIs, provided the studies have all used the same tool to measure the outcome. If studies have used different tools to measure an outcome (such as neurological outcome), we will use the standardised mean difference (SMD) with 95% CIs instead. For SMD, we will use Hedges' (adjusted) g which uses a pooled SD in the denominator of its calculation (Higgins 2020a). This pooled SD is an estimate of the SD using outcome data from the intervention groups, based on the assumption that the SDs in the two groups are similar. An SMD less than 0.2 will be interpreted as trivial, between 0.2 and 0.5 as small, between 0.5 and 0.8 as medium, and greater than 0.8 as large (Cohen 1988).

Data presented as a scale will be presented with a consistent direction of effect. The one-half standard deviation will be the benchmark of an outcome measure and a patient whose outcomes improve more than one-half of the outcome score's standard deviation will be classed as having achieved a minimal clinically important difference (Norman 2004).

In the case of continuous data provided as a mean difference or change from baseline, data will be extracted on both change from baseline and post-intervention outcomes if the required means and SDs are available, but mean difference will be preferred. The advantage of using an MD is that it allows the possibility of combining end of follow-up data with change from baseline data, if reported by different studies. This contrasts with the SMD, where this cannot be done.

Skewed data will be narratively reported as medians and interquartile ranges (Higgins 2019a).

Unit of analysis issues

Multi-arm, cluster and cross-over RCTs will be included. Unit of analysis errors in cluster-randomised trials will be overcome by conducting the analysis at the same level as the allocation. The data will be analysed considering each cluster as a unit of analysis. However, for cluster-RCTs in which the unit of analysis is not reported, we will calculate the effective sample size using an ICC (Higgins 2020b). Cluster-randomised trials will be combined with individually randomised trials in the same meta-analysis.

If trials are included that could contribute multiple, correlated comparisons with multiple treatment arms, the groups will be combined to create a single pairwise comparison for analysis.

For a hierarchy of outcomes, please see the Types of outcome measures section above.

With regard to multiple observations on patients, the longest follow-up from each study will be included. However, this could cause a lack of consistency across studies, giving rise to heterogeneity.

For cross-over trials, data will be analysed from all study periods as there is unlikely to be a cross-over effect from this intervention.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where possible, the Revman Excel tool will be used (https://training.cochrane.org/resource/revman-calculator) to calculate missing standard deviations using other data from the trial, such as confidence intervals, based on methods outlined in the *Cochrane Handbook* (Higgins 2019b). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore

the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

Forest plots will be inspected visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of I^2 when there are only a small number of studies; we will also consider the P value from the Chi^2 test ($P < 0.05$). If we identify substantial or considerable heterogeneity (indicated by an I^2 value greater than 50%), it will be reported and the authors will explore possible causes by prespecified subgroup analysis. The following boundaries will be used for I^2:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If more than 10 trials are pooled, a funnel plot will be created to explore possible small study biases for the primary outcomes (Egger 1997). It should be noted that if fewer than ten trials are included, the power of the tests is too low to distinguish chance variation from real asymmetry (Higgins 2019a).

Data synthesis

Meta-analyses will only be undertaken when it could be meaningful, for example, if the treatments, participants and the underlying clinical question are similar enough for pooling be appropriate. All studies will be included in the primary analysis and to assess the potential effects of studies at high risk or high risk/some concerns, sensitivity analyses will be performed.

Cross-over RCTs, parallel-group RCTs and cluster-RCTs will be included. An analysis would be precluded in cross-over trials if we managed to find significant period effects such as a significant difference in frequency of cardiac arrests before and after cross-over. In that case, we would use only the first period before cross-over. We will identify cluster-randomised trials and explicitly state how we have dealt with the data.

A random-effects model will be used due to the high probability of heterogeneity in the RCTs that will be included in this review.

If a meta-analysis is not possible, then data will be presented narratively using the nine-point checklist in the new SWIM guidance. Using this, studies will be grouped by intervention and vote-counting will be used based on the direction of effect. In addition, characteristics such as study design, sample sizes and risk of bias will be presented. Synthesis findings will be reported describing the contribution and limitations of each synthesis (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. Primary outcome measures by presenting rhythm: shockable (VF/VT) versus non-shockable (PEA/asystole) as first rhythm. This will assess to what extent the effectiveness of AEDs is driven by the presenting rhythm and hence by the population that the studies are based within.
2. Primary outcome measures by time (0-4 minutes, 4-10 minutes, > 10 minutes) to first shock (further broken down by CPR versus no CPR for each time category). The rationale for this is to examine whether there is any evidence to support the three-phase model for effective defibrillation, and whether CPR before defibrillation has different levels of efficacy during the different phases (Weisfeldt 2002).
3. CPR versus no CPR before defibrillation - linked to above.

We will use the formal test for subgroup differences in Review Manager (Review Manager 2014), and base our interpretation on this. The I^2 statistic will also be computed for subgroup differences. We will undertake a standard test for heterogeneity across subgroup results instead of individual study results. We will consider the P value from the test to look for a statistically significant subgroup difference. This test assesses the difference between the pooled effect estimates for each subgroup. A P value for this test of less than 0.1 would indicate a statistically significant subgroup effect.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result:

1. Assessment of the effect of studies with low risk of bias compared to pooling all studies. This will help to contribute to the decision to include studies with some risk of bias or high risk of bias in the overall model.
2. We will examine a fixed-effect model in addition to our prespecified random-effects model.
3. We plan to explore the impact of missing data. If we identify studies with missing data that were unobtainable, we will repeat the analyses excluding them to find their impact on the primary analyses.
4. Excluding cluster-randomised trials from our analysis

Summary of findings and assessment of the certainty of the evidence

Summary of findings tables will be created using the following outcomes:

1. Survival to hospital discharge
2. Favourable functional neurological status at longest available follow-up
3. Median time from arrest to first shock or rhythm assessment
4. Proportion of patients with return of spontaneous circulation (ROSC) after cardiac arrest

The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) will be used to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use the overall ROB 2 judgement to feed into GRADE. A GRADE table will be created by GRADEpro software (GRADEpro GDT 2015). We will justify all decisions to downgrade the certainty of studies using footnotes and we will

make comments to aid readers' understanding of the review, where necessary (Schünemann 2019).

Judgements about evidence certainty will be made by two review authors (GA, MW) working independently, with disagreements resolved by discussion or involving a third author (MA). Judgements will be justified, documented and incorporated into reporting of results for each outcome.

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REFERENCES

Additional references

AHA 2000

American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 4: The automated external defibrillator: key link in the chain of survival. *Circulation* 2000;**102**:I-60–I-76.

Andersen 2019

Andersen LW, Holmberg MJ, Granfeldt A, James LP, Caulley L. Cost-effectiveness of public automated external defibrillators. *Resuscitation* 2019;**138**:250-8. [DOI: 10.1016/j.resuscitation.2019.03.029]

Bardy 1993

Bardy GH, Hofer B, Johnson G, Kudenchuk PJ, Poole JE, Dolack GL, et al. Implantable transvenous cardioverter-defibrillators. *Circulation* 1993;**87**(4):1152-68. [PMID: 8462144]

Bardy 2008

Bardy GH, Lee KL, Mark DB, Poole JE, Toff WD, Tonkin AM, et al. Home use of automated external defibrillators for sudden cardiac arrest. *New England Journal of Medicine* 2008;**358**(17):1793–804. [PMID: 18381485]

Barry 2019

Barry T, Doheny MC, Masterson S, Conroy N, Klimas J, Segurado R, et al. Community first responders for out-of-hospital cardiac arrest in adults and children. *Cochrane Database of Systematic Reviews* 2019, Issue 7. Art. No: CD012764. [DOI: 10.1002/14651858.CD012764.pub2]

Berdowski 2019

Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation* 2010;**81**(11):1479-87. [DOI: 10.1016/j.resuscitation.2010.08.006]

Bogle 2019

Bogle BM, Rosamond WD, Snyder KT, Zègre-Hemsey JK. The case for drone-assisted emergency response to cardiac arrest: an optimized statewide deployment approach. *North Carolina Medical Journal* 2019;**80**(4):204–12.

Boutilier 2017

Boutilier JJ, Brooks SC, Janmohamed A, Byers A, Buick JE, Zhan C, et al. Optimizing a drone network to deliver automated external defibrillators . *Circulation* 2017;**135**(25): 2454–65.

Campbell 2020

Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline . *British Medical Journal* 2020;**368**:6890.

Centers for Disease Control and Prevention 2002

Centers for Disease Control and Prevention (CDC). State-specific mortality from sudden cardiac death - United States, 1999. *MMWR Morbidity and Mortality Weekly Report* 2002;**51**(6):123-6. [PMID: 11898927]

Chan 2014

Chan PS, McNally B, Tang F, Kellermann A, CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. *Circulation* 2014;**130**(21):1876-82. [PMID: 25399396]

Cheskes 2020

Cheskes S, McLeod SL, Nolan M, Snobelen P, Vaillancourt C, Brooks SC, et al . Improving access to automated external defibrillators in rural and remote settings: a drone delivery feasibility study. *Journal of the American Heart Association* 2020; **9**(14): e016687.

Claesson 2016

Claesson A, Fredman D, Svensson L, Ringh M, Hollenberg J, Nordberg P, et al . Unmanned aerial vehicles (drones) in out-of-hospital-cardiac-arrest. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2016;**24**(1):124 .

Cohen 1988

Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edition. Hillsdale, NJ, USA: Erlbaum, 1988.

Egger 1997

Egger M, Smith GD, Schneider M, Christoph M. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629.

Fredman 2018

Fredman D, Ringh M, Svensson L, Hollenberg J, Nordberg P, Djarv T, et al. Experiences and outcome from the implementation of a national Swedish automated external defibrillator registry. *Resuscitation* 2018;**130**:73-80. [DOI: 10.1016/j.resuscitation.2018.06.036]

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Griffis 2016

Griffis HM, Band RA, Ruther M, Harhay M, Asch DA, Hershey JC, et al. Employment and residential characteristics in relation to automated external defibrillator locations. *American Heart Journal* 2016;**172**:185-91. [DOI: 10.1016/j.ahj.2015.09.022]

Hallstrom 2004

Hallstrom AP, Ornato JP, Weisfeldt M, Travers A, Christenson J, McBurnie MA, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *New England Journal of Medicine* 2004;**351**(7):637-46. [PMID: 15306665]

Higgins 2019a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook/archive/v6.

Higgins 2019b

Higgins JP, Li T, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpson M, Li T, Page MJ, et al, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated October 2019). The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook/v6.

Higgins 2019c

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, et al, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated October 2019). The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook/v6.

Higgins 2020a

Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors(s). Cochrane Handbook for Systematic Reviews of Interventions . 2nd edition. Chichester (UK): John Wiley & Sons, 2020.

Higgins 2020b

Higgins JP, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors(s). Cochrane Handbook for Systematic Reviews of Interventions . 2nd edition. Chichester (UK): John Wiley & Sons, 2020.

Higgins 2021

Higgins JP, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions, Version 6.2 (updated February 2021). Cochrane 2021. Available from training.cochrane.org/handbook.

Holmberg 2017

Holmberg MJ, Vognsen M, Andersen MS, Donnino MW, Andersen LW. Bystander automated external defibrillator use and clinical outcomes after out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation* 2017;**120**:77-87. [PMID: 28888810]

Kitamura 2016

Kitamura T, Kiyohara K, Sakai T, Matsuyama T, Hatakeyama T, Shimamoto T, et al. Public-access defibrillation and out-of-hospital cardiac arrest in Japan. *New England Journal of Medicine* 2016;**375**(17):1649-59. [DOI: 10.1056/NEJMsa1600011]

Kronick 2015

Kronick SL, Kurz MC, Lin S, Edelson DP, Berg RA, Billi JE, et al. Part 4: Systems of care and continuous quality improvement: 2015 American Heart Association Guidelines Update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;**132**:S397–S413. [PMID: 26472992]

Lefebvre 2019

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s), Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0 (updated October 2019). The Cochrane Collaboration, 2019. Available from training.cochrane.org/handbook/archive/v6.0.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLOS Medicine* 2009;**6**(7):e1000100.

NCT02992873

NCT02992873. The Scandinavian AED and Mobile Bystander Activation trial (SAMBA). clinicaltrials.gov/ct2/show/NCT02992873 (first posted 14 December 2016).

NCT04723368

NCT04723368. AED-delivery using drones in suspected OHCA. clinicaltrials.gov/ct2/show/NCT04723368 (first posted 25 January 2021).

Norman 2004

Norman G, Sloan J, Wyrwich K. The truly remarkable universality of half a standard deviation: confirmation through another look. *Expert Review of Pharmacoeconomics & Outcomes Research* 2004;**4**:581-5.

Perkins 2015

Perkins, G, Colquhoun M, Deakin C, Handley A, Smith C, Smyth M. UK Resus Council Guidelines 2015: adult basic life support and automated external defibrillators. www.resus.org.uk/resuscitation-guidelines/adult-basic-life-support-and-automated-external-defibrillation (accessed prior to 21 September 2021).

Pollack 2018

Pollack RA, Brown SP, Rea T, Aufderheide T, Barbic D, Buick JE, et al. Impact of bystander automated external defibrillator use on survival and functional outcomes in shockable observed public cardiac arrests. *Circulation* 2018;**137**(20):2104-13. [PMID: 29483086]

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, the Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

Revman Web 2020 [Computer program]

The Cochrane Collaboration Revman Manager Web. Version 1.22.0. The Cochrane Collaboration, 2020.

Rittenberger 2011

Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. *Resuscitation* 2011;**82**(8):1036-40. [PMID: 21524837]

Safar 1981

Safar P. Resuscitation after brain ischemia. In: Grenvik A, Safar P, editors(s). Brain Failure and Resuscitation. New York: Churchill Livingstone, 1981:155-84.

Sanfridsson 2019

Sanfridsson J, Sparrevik J, Hollenberg J, Nordberg P, Djärv T, Ringh M, et al. Drone delivery of an automated external defibrillator - a mixed method simulation study of bystander experience. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2019; **27**(1):40. [DOI: 10.1186/s13049-019-0622-6]

Sasson 2010

Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circulation: Cardiovascular Quality and Outcomes* 2010;**3**(1):63-81. [DOI: 10.1161/CIRCOUTCOMES.109.889576]

Saver 2010

Saver JL, Filip B, Hamilton S, Yanes A, Craig S, Cho M, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). *Stroke* 2010;**41**(5):992-5.

Schünemann 2019

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, et al, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated October 2019). The Cochrane Collaboration, 2019. Available from www.training.cochrane.org/handbook/archive/v6.

Sekhon 2017

Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. *Critical Care* 2017;**90**:21. [DOI: 10.1186/s13054-017-1670-9]

Valenzuela 1997

Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. *Circulation* 1997;**96**(10):3308-13. [PMID: 9396421]

Van Alem 2003

Van Alem AP, Vrenken RH, De Vos R, Tijssen JG, Koster RW. Use of automated external defibrillator by first responders in out of hospital cardiac arrest: prospective controlled trial. *British Medical Journal* 2003;**327**(7427):1312. [PMID: 14656837]

Wang 2018

Wang PL, Brooks SC. Mechanical versus manual chest compressions for cardiac arrest. *Cochrane Database of Systematic Reviews* 2018, Issue 8. Art. No: CD007260. [DOI: 10.1002/14651858.CD007260.pub4]

Weisfeldt 2002

Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA* 2002;**288**(23):3035-8. [PMID: 12479769]

Weisfeldt 2017

Weisfeldt ML, Pollack RA. Public access defibrillation: is this making any difference? Controversial issues in resuscitation from cardiac arrest. *Cardiac Electrophysiology Clinics* 2017;**9**(4):551-7. [PMID: 29173401]

Zègre-Hemsey 2020

Zègre-Hemsey JK, Grewe ME, Johnson AM, Arnold E, Cunningham CJ, Bogle BM, et al . Delivery of automated external defibrillators via drones in simulated cardiac arrest: users' experiences and the human-drone interaction. *Resuscitation* 2020; **157**:83–8. [DOI: 10.1016/j.resuscitation.2020.10.006]

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 Defibrillators/ (1828)
2 ((Automatic or automated or external) adj3 defibrillator*).tw. (3347)
3 (AED or AEDs).tw. (9238)
4 (early adj3 defibrillat*).tw. (561)
5 1 or 2 or 3 or 4 (12912)
6 heart arrest/ or out-of-hospital cardiac arrest/ (33272)
7 (OOHCA or OHCA).tw. (2631)
8 Cardiac arrest*.tw. (34287)
9 cardiopulmonary arrest*.tw. (2387)
10 Heart arrest*.tw. (640)
11 Heart attack*.tw. (5524)
12 6 or 7 or 8 or 9 or 10 or 11 (55915)

13 5 and 12 (2222)
14 randomized controlled trial.pt. (510864)
15 controlled clinical trial.pt. (93789)
16 randomized.ab. (488116)
17 placebo.ab. (209911)
18 drug therapy.fs. (2225413)
19 randomly.ab. (338309)
20 trial.ab. (514955)
21 groups.ab. (2076966)
22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (4763732)
23 exp animals/ not humans.sh. (4723792)
24 22 not 23 (4134340)
25 13 and 24 (371)

CONTRIBUTIONS OF AUTHORS

AT and MA have written the protocol.

HV, HB, CJB, GA, WM, AB, RP, SH all edited the protocol.

DECLARATIONS OF INTEREST

AT: none known

HV: none known

HB: none known

CJB: none known

GA: none known

MW: none known

MA: none known

AB: declares receipt of fees for advisory board memberships with Pfizer, Astra Zeneca and Novo-Nordisk on topics unrelated to this systematic review. AB also declares grants paid to their institution by Astra Zeneca. None of these companies market any of the interventions/controls which are the topic of this review. AB is a trustee of the South Asian Health Foundation.

RP: none known

SH: declares an Education Grant for a study from Abbott and honoraria from PCHF London course - both outside of this study.

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  Place of employment of first author

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