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Protocol paper

Randomised trial of the clinical and cost effectiveness of a supraglottic airway device compared with tracheal intubation for in-hospital cardiac arrest (AIRWAYS-3): Protocol, design and implementation



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Abstract

Survival from in-hospital cardiac arrest is approximately 18%, but for patients who require advanced airway management survival is lower. Those who do survive are often left with significant disability. Traditionally, resuscitation of cardiac arrest patients has included tracheal intubation, however insertion of a supraglottic airway has gained popularity as an alternative approach to advanced airway management. Evidence from out-of-hospital cardiac arrest suggests no significant differences in mortality or morbidity between these two approaches, but there is no randomised evidence for airway management during in-hospital cardiac arrest.

The aim of the AIRWAYS-3 randomised trial, described in this protocol paper, is to determine the clinical and cost effectiveness of a supraglottic airway versus tracheal intubation during in-hospital cardiac arrest. Patients will be allocated randomly to receive either a supraglottic airway or tracheal intubation as the initial advanced airway management. We will also estimate the relative cost-effectiveness of these two approaches. The primary outcome is functional status, measured using the modified Rankin Scale at hospital discharge or 30 days post-randomisation, whichever occurs first.

AIRWAYS-3 presents ethical challenges regarding patient consent and data collection. These include the enrolment of unconscious patients without prior consent in a way that avoids methodological bias. Other complexities include the requirement to randomise patients efficiently during a time-critical cardiac arrest. Many of these challenges are encountered in other emergency care research; we discuss our approaches to addressing them.

Trial registration: ISRCTN17720457. Prospectively registered on 29/07/2022.

Keywords: In-hospital cardiac arrest, Cardiopulmonary resuscitation, Airway management, Endotracheal intubation, Laryngeal mask airway, Randomized clinical trial

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Introduction

Global rates of in-hospital cardiac arrest (IHCA) are not well described.^{1,2} The incidence of IHCA in the UK is 1.6 per 1000 hospital admissions,^{3,4} whereas in the US the incidence is 9–10 per 1000 admissions.^{5,6} Unadjusted survival following IHCA in both the UK and the US is around 18%,⁴ although this figure includes patients who are resuscitated quickly without advanced airway management and therefore more likely to have good outcomes. For those who require advanced airway management, the survival rate will be lower. The societal impact of cardiac arrest is substantial, evidenced by the years of productive life lost due to death and disability and the economic burden of caring for cardiac arrest patients resuscitated successfully but left with significant functional impairment.⁷

While tracheal intubation has long been considered the definitive technique for advanced airway management during IHCA,⁸ recent randomised controlled trials (RCTs) investigating out-of-hospital cardiac arrest (OHCA) suggest there may be advantages to using supraglottic airways (SGAs) such as faster and easier insertion,⁹ and less pauses in chest compressions.¹⁰ Two systematic reviews have compared airway interventions in OHCA and found no difference between supraglottic airways and tracheal intubation in long-term survival or neurologic outcome, while noting that intubation success rate is an important consideration.^{11,12} Recent resuscitation guidelines support the use of SGAs in settings where intubation success rates are lower.¹³ Changes have followed in OHCA systems where paramedics manage the airway but less so in IHCA where doctors are the airway provider.^{9,14} In the United States intubation rates during IHCA have significantly decreased since the 2010 American Heart Association guidelines¹⁵ that prioritised chest compressions over airway management.¹⁶

A recent systematic review identified a significant knowledge gap in the optimal airway management strategy for IHCA,¹² with substantial practice variation found in UK and international surveys.^{17,18}

Aims and objectives

The aim of this trial is to determine the relative clinical and cost effectiveness of an SGA versus tracheal intubation during IHCA.

The primary objective is to estimate the difference in functional outcome between IHCA patients receiving an SGA or tracheal intubation as the initial approach to advanced airway management by measuring the modified Rankin Scale (mRS) score at hospital discharge or 30 days post-OHCA,¹⁹ whichever occurs sooner. The study's secondary objectives are to conduct a 6-month pilot study to confirm the feasibility of a large-scale multi-centre trial and to estimate the cost-effectiveness of SGAs versus tracheal intubation through an integrated economic evaluation.

Methods and analysis

Design

AIRWAYS-3 is a multi-centre, open-label, pragmatic, individually randomised, parallel group, 1:1, superiority trial and economic evaluation to determine the clinical and cost effectiveness of an SGA versus tracheal intubation during IHCA. This protocol has been written in concordance with the SPIRIT guidelines and is summarised in Table 1.²⁰ The trial process is shown in Fig. 1.

Setting

Pilot

A 6-month internal pilot will confirm the feasibility of the large-scale multi-centre trial with 40 hospitals across England and Wales aiming to recruit 420 patients (10% of total sample). For the pilot trial, at least 25 hospitals (60%) must participate, and 252 patients (60% of target) must be recruited. The research team will continue to monitor the recruitment which will be overseen by both a data monitoring committee and trial steering committee.

Main trial

On reaching the pre-defined success criteria, the internal pilot will continue into the main trial and recruit a further 80 hospitals (120 in total) and an additional 3770 patients (4190 in total). If necessary, we will consider international recruitment.

Randomisation

Patients requiring advanced airway management will be randomly allocated 1:1 to receive an SGA or tracheal intubation using a bespoke mobile phone progressive web application (PWA) developed by Warwick Clinical Trials Unit (WCTU). When activated this displays the treatment arm the participant has been randomised to. Stratified randomisation will occur by hospital site and time of day (8am to 6 pm or outside these hours) to account for less favourable outcomes in out-of-hours cardiac arrests.²²

Patient enrolment

In participating hospitals, clinical staff will alert the cardiac arrest team via the hospital switchboard, following usual practice. A member of the team will assess eligibility (Table 2). If a participant is later found to be ineligible after randomisation, they will still be analysed according to the "intention to treat" principle. Randomised participants who do not receive the allocated intervention (e.g., achieving ROSC before advanced airway management) will be analysed in their assigned group.

Patient consent

Eligible patients in cardiac arrest are unconscious and unable to provide consent. Following ethics committee approval, patients will be randomised into the trial without prior consent in compliance with the Mental Capacity Act 2005.²³ We will also seek the approval of the Confidentiality Advisory Group (CAG) to collect primary outcome data from all patients without prior consent to prevent potential bias if survivors can withdraw their primary outcome data while non-survivors cannot.

Participants who survive and have not previously registered an NHS National Data Opt-Out (NDO) will be approached for consent in a dynamic process, tailored to their clinical condition and progress. If a participant lacks capacity an appropriate personal consultee will be approached. If no suitable personal consultee can be identified a professional consultee will be approached. Participants will be offered three consent options:

1. No further participation
2. Collection of routine data from the participant's health records, but no requests to complete follow-up questionnaires
3. Collection of routine data from the participant's health records and the completion of follow-up questionnaires

Table 1 – WHO trial registration data set.

Data category	Information
Primary registry and trial identifying number	International Standard Randomised Controlled Trial Number (ISRCTN) 17720457
Date of registration in primary registry	29/07/2022
Secondary identifying numbers	National Institute for Health and Care Research (NIHR) 131533
Source(s) of monetary or material support	National Institute for Health and Care Research
Primary sponsor	University Hospitals Bristol and Weston NHS Foundation Trust
Secondary sponsor(s)	Not applicable
Contact for public queries	airways3@warwick.ac.uk
Contact for scientific queries	Jonathan R. Bengler, Faculty of Health & Applied Sciences, University of the West of England, Bristol, UK.
Public title	Comparing advanced airway management for hospital patients in cardiac arrest
Scientific title	Randomised trial of the clinical and cost effectiveness of a supraglottic airway device compared with tracheal intubation for in-hospital cardiac arrest (AIRWAYS-3)
Countries of recruitment	United Kingdom
Health condition(s) or problem (s) studied	Cardiac arrest
Intervention(s)	Intervention: Supraglottic airway (SGA)Comparator: Tracheal intubation
Key inclusion and exclusion criteria	Adults of any sex who have suffered an in-hospital cardiac arrest (IHCA). See Table 2 for further details
Study type	Interventional Allocation: randomised; individual assignment Primary purpose: treatment
Date of first enrolment	December 2022
Target sample size	Pilot: 420 patients Main trial: 4216 patients
Recruitment status	Recruiting
Primary outcome(s)	Modified Rankin Scale (mRS) at hospital discharge or 30 days post-randomisation, whichever occurs first
Key secondary outcomes	Secondary outcomes reflect the recommendations of the Core Outcome Set for Cardiac Arrest (COSCA) in adults, ²¹ and are summarised in Table 3

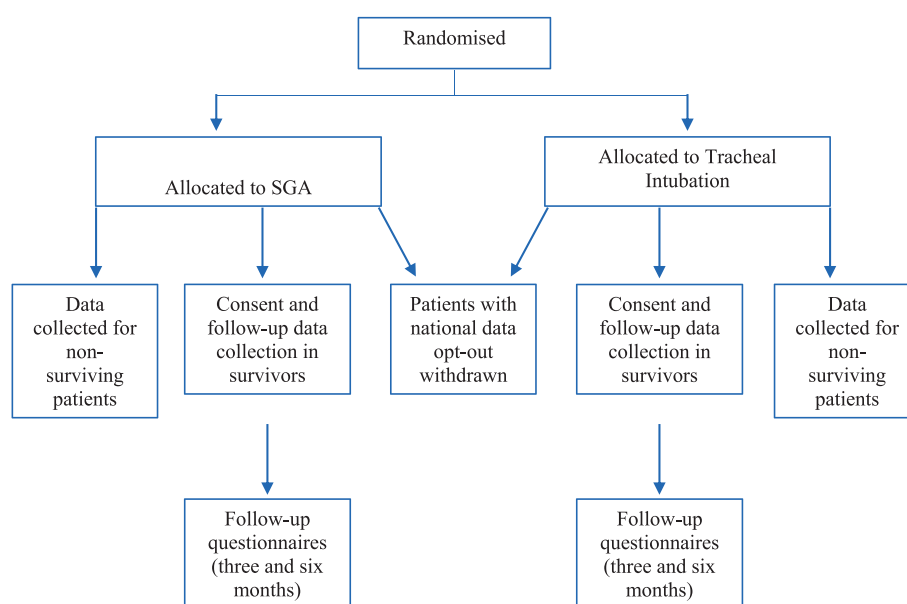
**Fig. 1 – Trial flow diagram.**

Table 2 – Patient inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
Adult (known or believed to be age ≥ 18)	Patients in the emergency department
In-hospital cardiac arrest, attended by the hospital cardiac arrest team in response to a cardiac arrest call (2222 or equivalent), and including a clinician who can undertake tracheal intubation or supraglottic airway placement within that hospital setting so either intervention can be delivered	People who are not a hospital inpatient (e.g., visitor, relative, staff or outpatient)
Undergoing resuscitation and requiring advanced airway management in the opinion of the clinician managing the patient's airway	Patients who are already have a tracheal tube in situ at the time of eligibility assessment
	Patients known to be pregnant
	Patients with a functioning tracheostomy

If at any point the participant (or their consultee) withdraws consent, no further data will be collected and the participant will not be contacted again. All non-identifiable data collected up to that point will be retained and included in the analysis.

England's NDO scheme allows individuals to opt out of using their healthcare data for future research. However, we cannot determine if a person has registered for NDO prior to their emergency treatment and randomization due to the urgent nature of IHCA. Hence, if a participant is found to have registered an NDO after randomization, they will be excluded from the trial before data collection and analysis.

Trial interventions

Tracheal intubation (comparator group)

Participants will be intubated as soon as possible after randomisation. The size and type of tracheal tube will be at the discretion of the clinician managing the airway. The clinician may choose to use video or direct laryngoscopy and may use adjuncts (bougie, stylet, etc.) at their discretion.

Supraglottic airway (SGA) (intervention group)

Participants will receive a supraglottic airway as soon as possible after randomisation. The treating clinician may choose any type and size of supraglottic airway at their discretion.

Procedure

Following an initial period of bag-mask ventilation as required, the allocated intervention will be provided. Strategies for confirming placement will be at the clinician's discretion but, in line with current UK guidance, it is anticipated that waveform capnography will be used to aid confirmation of the correct placement and functioning of any advanced airway management device. If successful, the allocated treatment should be used until resuscitation efforts cease or return of spontaneous circulation (ROSC) is achieved for 20 minutes, at which point further management will proceed as dictated by the treating clinician. If airway insertion is unsuccessful after two attempts, subsequent treatment will be determined by the treating clinician.

Outcome measures

Primary outcome

Functional outcome, measured using the Modified Rankin Scale (mRS) score at hospital discharge or 30 days post-randomisation, whichever occurs first.¹⁹ The mRS is a 7-point scale (0–6), with scores of 0–3 usually indicating a good functional outcome.²¹ A mRS score of 6 is allocated when a patient dies. Survivors are

assessed against the mRS scale by a research nurse using a standardised flow chart.¹⁹

Secondary outcomes

Secondary outcomes reflect the recommendations of Core Outcome Set for Cardiac Arrest (COSCA) in adults,²¹ and are summarised in Table 3. Regurgitation is defined as stomach contents being visible in the mouth or nose. Aspiration is defined as stomach contents being visible below the vocal cords or inside a correctly placed tracheal tube or airway channel of a supraglottic airway device.

Sample size

Results from UK audit data suggest survival to hospital discharge is 24% among all IHCA patients,³ but may be as low as 10% in those receiving tracheal intubation (Couper K, 2020 as cited in¹⁷). This is because cardiac arrests of a shorter duration are both less likely to require advanced airway management and less likely to have a poor outcome.^{12,24} The sample size calculation is based on mortality data. This is not identical to our primary outcome (for which data are not available), however the mRS is dominated by mortality (score 6) in this population. Observational evidence shows alternatives to tracheal intubation are associated with a 3.1% higher absolute difference in survival to discharge (19.4% vs. 16.3%).²⁵

The baseline survival rate of 10% is assumed to include an equal mix of patients who received either intervention. The 3% minimum clinically significant difference around this baseline of 10% has been set accordingly (8.5% vs. 11.5%). To demonstrate this effect size of 3% difference (8.5% to 11.5%) in patients with a 'good' functional outcome, a total of 4,190 patients is required with a power of 90% and a type I error of 5%. The sample size was not inflated to accommodate for the withdrawal of participants because we have approval from the Wales 1 Research Ethics Committee and the Confidentiality Advisory Group (CAG) to collect the primary outcome for everybody randomised in the trial.

Site staff training

Educational and training materials will be used to standardise the processes for training in study procedures, trial enrolment, treatment delivery, data recording and proportionate Good Clinical Practice (GCP) across all recruiting sites.

Data collection and patient follow-up

Data collection

The randomising clinician will input anonymised data about the cardiac arrest call and initial outcome using the PWA. A research nurse

Table 3 – Trial outcome measures and data collection points. WCTU: Warwick Clinical Trials Unit. ROSC: return of spontaneous circulation. EQ-5D-5L: EuroQol 5 Dimension, 5 Level measure. NCAA: National Cardiac Arrest Audi.

Data item	Immediately after the cardiac arrest. Collected by clinician through PWA app	In-hospital/ hospital discharge. Collected by a research nurse at the hospital site	3 months post IHCA (± 4 weeks). Collected by research team at WCTU	6 months post IHCA (± 4 weeks). Collected by research team at WCTU
Primary and secondary outcomes				
Outcome of resuscitation attempt (mRS)		√ ^a	√ ^a	√ ^a
Regurgitation/ aspiration	√ ^a			
ROSC > 20 minutes	√ ^a			
ICU and hospital length of stay		√ ^c		
Survival to hospital discharge	√ ^a	√ ^a	√ ^c	√ ^c
Health-related quality of life (EQ-5D-5L)		√ ^b	√ ^b	√ ^b
In-hospital stay utilization and costs		√ ^c	√ ^c	√ ^c
Additional unscheduled care and readmission			√ ^c	√ ^c
Adverse events/ serious adverse events	√ ^a	√ ^c	√ ^c	√ ^c

^a Collected for all participants (where participant survives to that point in the patient pathway).

^b Only collected for participants that consent to active follow-up.

^c Only collected for participants that consent to active or passive follow-up.

will then identify the patient using local processes, e.g., cardiac arrest call logs, and seek consent for follow-up data collection. The data collection schedule is summarised in Table 3. The research nurse will collect data from consenting patients and input this to a secure database. This will be combined with data that is routinely collected through the National Cardiac Arrest Audit (NCAA; a national clinical audit of in-hospital cardiac arrests in the UK) and the Case Mix Programme of the National Clinical Audit for Adult Intensive Care to assess our primary and secondary outcomes.

Patient follow-up

Follow-up data will be collected at 3 and 6 months (± 4 weeks) after IHCA. Patients who have provided consent will be invited to complete the mRS and a health-related quality of life EuroQol 5 Dimension, 5 Level (EQ-5D-5L) measure.^{26,27} Questionnaires can be completed by post, online or by telephone.

Serious adverse event management

All participants in this trial will be in an immediately life-threatening situation; many will not survive, and all of those who do will be hospitalised, with most survivors admitted to the Intensive Care Unit. Events that are related to cardiac arrest and would be expected in patients undergoing attempted resuscitation will not be reported. Events will only be reported to the Clinical Trials Unit if unexpected

and potentially related to the trial participation following a causality assessment.

Data analysis

The study will use intention to treat analysis to compare tracheal intubation versus an SGA for the primary outcome, mRS, which will be dichotomised into 'good' and 'poor' functional outcomes. Mixed-effect logistic regression will be used with and without adjustment for the covariates: age, sex, and stratification variables: hospital site (random effects) and time of day (fixed effect).

Subgroup analyses will be conducted for shockable vs. non-shockable initial rhythm and whether an SGA was already in situ at randomization.

The contamination effect due to participant crossover will be assessed using power curves and different degrees of crossover,²⁸ and the final analysis will use inverse probability weighted (IPW) analysis to account for crossovers. Further detail is included in the Statistical and Health Economics Analysis Plan (SHEAP), see [Supplementary material](#).

Economic analyses

The study will conduct a prospective economic analysis plan which will be publicly available (see [Supplementary material](#)) and follow the NICE Reference Case²⁹. The analysis will be conducted from

an NHS and societal perspective and will include intervention, hospital and community costs in the first 6 months. The EQ-5D-5L will be used to generate quality-adjusted life years (QALYs) using the then current value set recommended by NICE. Baseline EQ-5D-5L values, reflecting the unconscious health state, will be applied to all patients, minimising potential bias in the QALY AUC calculation.³⁰

Within-trial analysis using bivariate regression will be conducted to assess cost-effectiveness³¹ and multiple imputation methods used if missingness exceeds 5%.^{32,33} A decision-analytical model will be constructed to explore the long-term cost-effectiveness of SGA.

Dissemination

The trial results will be reported first to trial collaborators and then disseminated through publications in high-impact journals, conference presentations and engagement with the public, clinicians, academics, key policy makers and those involved in producing resuscitation guidelines.

Research approvals

Research ethics approval was granted by the Wales 1 Research Ethics Committee (ref: 22/WA/0156) in July 2022 and the Confidentiality Advisory Group subsequently gave approval for the trial under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002. These approvals were followed by full Health Research Authority (HRA) approval on 4th November 2022.

Trial management

The University Hospitals Bristol and Weston NHS Foundation Trust is the Sponsor organization, while the Warwick Clinical Trials Unit coordinates the trial. The trial is overseen by independent Trial Steering and Data Monitoring and Safety Committees.

Patient and public involvement

A Patient and Public Research Advisory Group made up of survivors, relatives and other interested individuals will meet every 3–4 months. Two of our patient and public involvement (PPI) contributors will join the Trial Steering Committee, and regular reports will be provided to all our PPI contributors throughout the study for their input and advice.

Discussion

Emergency care research presents a unique set of ethical challenges relating to patient consent and data collection. These complications are magnified in patients who have had a cardiac arrest, require immediate life-saving treatments and are unable to provide prior consent for research participation, as in AIRWAYS-3. It is also important to understand how these could lead to bias within the trial.

AIRWAYS-3 uses an established legal mechanism to collect primary outcome data for all patients, regardless of whether they survive. This is required because most patients do not survive to regain capacity, and if surviving patients were allowed to withdraw, they would preferentially be removed from the trial, creating bias that could substantially alter the results. The only exception to this is for patients who have registered a national data opt-out (NDO) prior to their cardiac arrest. This national mechanism allows patients to pre-specify that they do not wish their healthcare data to be used for purposes beyond direct care, including research. Patients with

a NDO may be inadvertently enrolled in the study since there is no opportunity to confirm their opt-out status prior to randomisation without delaying emergency care. Therefore, patients who are identified subsequently as having registered a NDO will be withdrawn from the study. Although it is typical to invite patients who have registered a NDO to participate in research prospectively, doing so would result in preferential inclusion and also carry the risk of bias. Therefore, all patients with an NDO will be removed from the study as soon as they are identified, regardless of their outcome.

We will not routinely inform relatives of non-survivors about their participation in the trial, based on consultation with our patient and public advisory group and approval from the Wales 1 Research Ethics Committee. This decision was made to avoid confusion and distress among the relatives, and because both tracheal intubation and SGAs are used routinely during in-hospital cardiac arrest (IHCA) with similar frequency and clinical equipoise.¹⁷ Measures are being taken to raise awareness of the trial nationally and at recruiting hospitals so patients, relatives and the public can seek further information if they wish.

A customized progressive web application (PWA) has been developed to prevent any delays in life-saving treatment and encourage clinician participation in the study.³⁴ The PWA is designed to work 'offline' (without a mobile or WiFi signal) thereby increasing reliability. To our knowledge, only one other published paper has described the use of a smartphone-based application tool for randomisation.³⁵ It has considerable advantages over the use of sealed opaque envelopes or telephone/computer-based randomisation systems in terms of availability, speed and vulnerability to tampering, and could be applied to future clinical trials requiring a reliable time-sensitive randomisation procedure.

Recruiting more than 4,000 eligible patients from 120 hospitals to ensure adequate statistical power is a challenge for the widespread uptake of AIRWAYS-3. However, previous studies have shown considerable interest from groups representing trainee doctors in anaesthesia and intensive care.¹⁷ To prioritize the invitation of potential sites, hospitals will be selected based on the number of cardiac arrests registered on the NCAA database. Online drop-in sessions will be provided to encourage participation in the trial. Training materials will also be available online for convenience.^{36,37}

The results from AIRWAYS-3, along with other ongoing research including the Hospital Airway Resuscitation Trial (HART) (clinicaltrials.gov NCT05520762); a similar clinical trial conducted in the United States,³⁸ will provide important insights into advanced airway management for IHCA. These findings should provide evidence that will reduce mortality and associated disability for IHCA patients, guiding clinicians in their choice of airway management. Tracheal intubation skills are limited to relatively few individuals, whereas the insertion of an SGA can be completed successfully by a wider range of healthcare staff. This has important implications for the composition and function of in-hospital cardiac arrest teams, with an opportunity for improved efficiency in the delivery of cardiac arrest care.

Trial status

The trial is currently in the pilot phase and the first patient was enrolled in December 2022.

The full protocol (17/11/2022 – version 2.0) is available at: <https://fundingawards.nihr.ac.uk/award/NIHR131533>.

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Author's contributions

AIRWAYS-3 is led by JRB. The funding application and initial protocol (version 1.0) was drafted by SW, FJC, CN, KS, GDP, RL, AH, HN, JPN, JS, DAH, DG, SJB, JM, KC, KS, SV, BS, LG, MT and JRB. All authors developed the final study protocol and procedures. SW, CT and JC drafted this manuscript and all authors contributed to its critical review and read and approved the final version.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GDP is Editor-in-Chief, and JPN, KC and JS are Editors of the journal Resuscitation Plus.

Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2023.100430>.

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REFERENCES

- Morrison LJ, Neumar RW, Zimmerman JL, et al. Strategies for Improving Survival After In-Hospital Cardiac Arrest in the United States: 2013 Consensus Recommendations. *Circulation* 2013;127:1538–63. <https://doi.org/10.1161/CIR.0B013E31828B2770>.
- Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA* 2019;321:1200. <https://doi.org/10.1001/JAMA.2019.1696>.
- National Cardiac Arrest Audit. Key statistics from the National Cardiac Arrest Audit 2019/20 2020.
- Nolan JP, Soar J, Smith GB, et al. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation* 2014;85:987–92. <https://doi.org/10.1016/J.RESUSCITATION.2014.04.002>.
- Holmberg MJ, Ross C, Chan PS, et al. Abstract 23: Incidence of Adult In-Hospital Cardiac Arrest in the United States. *Circulation* 2018;138. https://doi.org/10.1161/CIRC.138.SUPPL_2.23.
- Holmberg MJ, Ross CE, Fitzmaurice GM, et al. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. *Circ Cardiovasc Qual Outcomes* 2019;12. <https://doi.org/10.1161/CIRCOUTCOMES.119.005580>.
- Graham R, McCoy MA, Schultz AM, et al. Understanding the public health burden of cardiac arrest: The need for national surveillance; 2015.
- Soar J, Nolan JP. Airway management in cardiopulmonary resuscitation. *Curr Opin Crit Care* 2013;19:181–7. <https://doi.org/10.1097/MCC.0B013E328360AC5E>.
- Wang HE, Bengner JR. Endotracheal intubation during out-of-hospital cardiac arrest: new insights from recent clinical trials. *J Am Coll Emerg Physicians Open* 2019;1:24–9. <https://doi.org/10.1002/EMP2.12003>.
- Kurz MC, Prince DK, Christenson J, et al. Association of advanced airway device with chest compression fraction during out-of-hospital cardiopulmonary arrest. *Resuscitation* 2016;98:35–40. <https://doi.org/10.1016/J.RESUSCITATION.2015.10.011>.
- Wang CH, Lee AF, Chang WT, et al. Comparing effectiveness of initial airway interventions for out-of-hospital cardiac arrest: a systematic review and network meta-analysis of clinical controlled trials. *Ann Emerg Med* 2020;75:627–36. <https://doi.org/10.1016/J.ANNEMERGMED.2019.12.003>.
- Granfeldt A, Avis SR, Nicholson TC, et al. Advanced airway management during adult cardiac arrest: a systematic review. *Resuscitation* 2019;139:133–43. <https://doi.org/10.1016/J.RESUSCITATION.2019.04.003>.
- Soar J, MacOnochie I, Wyckoff MH, et al. 2019 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations: summary from the basic life support; advanced life support; pediatric life support; neonatal life support; education, implementation, and teams; and first aid task forces. *Circulation* 2019;140:E826–80. <https://doi.org/10.1161/CIR.0000000000000734>.
- Behrens NH, Fischer M, Krieger T, et al. Effect of airway management strategies during resuscitation from out-of-hospital cardiac arrest on clinical outcome: a registry-based analysis. *Resuscitation* 2020;152:157–64. <https://doi.org/10.1016/J.RESUSCITATION.2020.04.015>.
- Field JM, Hazinski MF, Sayre MR, et al. Part 1: executive summary. *Circulation* 2010;122. <https://doi.org/10.1161/CIRCULATIONAHA.110.970889>.
- Schwab K, Bühr RG, Grossetreuer Av, et al. Trends in endotracheal intubation during in-hospital cardiac arrests: 2001–2018. *Crit Care Med* 2022;50:72. <https://doi.org/10.1097/CCM.00000000000005120>.
- Goodwin L, Samuel K, Schofield B, et al. Airway management during in-hospital cardiac arrest in adults: UK national survey and interview study with anaesthetic and intensive care trainees. *J Intensive Care Soc* 2021;22:192–7. https://doi.org/10.1177/1751143720949458/ASSET/IMAGES/LARGE/10.1177_1751143720949458-FIG1.JPG.
- Penketh J, Nolan J, Skrifvars M, Resuscitation C-R. Airway management during in-hospital cardiac arrest: An international, multicentre, retrospective, observational cohort study. *Elsevier; 2020*.
- 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;82:1036–40. <https://doi.org/10.1016/J.RESUSCITATION.2011.03.034>.
- Chan AW, Tetzlaff JM, Gøtzsche PC, et al. explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;2013:346. <https://doi.org/10.1136/BMJ.E7586>.
- Haywood KL, Whitehead L, Perkins GD. An international, consensus-derived Core Outcome Set for Cardiac Arrest

- effectiveness trials: the COSCA initiative. *Curr Opin Crit Care* 2019;25:226–33. <https://doi.org/10.1097/MCC.0000000000000612>.
22. Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA* 2008;299:785–92. <https://doi.org/10.1001/JAMA.299.7.785>.
 23. Mental Capacity Act 2005 n.d. (Accessed 11 November 2022, at <https://www.legislation.gov.uk/ukpga/2005/9>).
 24. Andersen LW, Grossestreuer Av, Donnino MW. Resuscitation time bias—a unique challenge for observational cardiac arrest research. *Resuscitation* 2018;125:79. <https://doi.org/10.1016/J.RESUSCITATION.2018.02.006>.
 25. Buanes EA, Gramstad A, Søvig KK, et al. Cognitive function and health-related quality of life four years after cardiac arrest. *Resuscitation* 2015;89:13–8. <https://doi.org/10.1016/J.RESUSCITATION.2014.12.021>.
 26. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy (New York)* 1990;16. [https://doi.org/10.1016/0168-8510\(90\)90421-9](https://doi.org/10.1016/0168-8510(90)90421-9).
 27. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20. <https://doi.org/10.1007/s11136-011-9903-x>.
 28. Weinstein GS, Levin B. Effect of crossover on the statistical power of randomized studies. *Ann Thorac Surg* 1989;48:490–5. [https://doi.org/10.1016/S0003-4975\(10\)66846-4](https://doi.org/10.1016/S0003-4975(10)66846-4).
 29. Guide to the methods of technology appraisal 2013 Process and methods; 2013.
 30. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487–96. <https://doi.org/10.1002/HEC.944>.
 31. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004;13:461–75. <https://doi.org/10.1002/HEC.843>.
 32. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014;32:1157–70. <https://doi.org/10.1007/S40273-014-0193-3>.
 33. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Med Res Methodol* 2017;17:1–10. <https://doi.org/10.1186/S12874-017-0442-1/TABLES/2>.
 34. Brenner BE, Kauffmann J. Response to cardiac arrests in a hospital setting: delays in ventilation. *Resuscitation* 1996;31:17–23. [https://doi.org/10.1016/0300-9572\(95\)00905-1](https://doi.org/10.1016/0300-9572(95)00905-1).
 35. Bloom JE, Patrovi A, Bernard S, et al. Use of a novel smartphone-based application tool for enrolment and randomisation in pre-hospital clinical trials. *Resuscitation* 2023;109787. <https://doi.org/10.1016/J.RESUSCITATION.2023.109787>.
 36. Gurunathan U, Berry K, Way M. Intentions and barriers to research activities among Australian and New Zealand anaesthetists: a survey. *Anaesth Intensive Care* 2016;44:111–8. <https://doi.org/10.1177/0310057X1604400117>.
 37. Cavallo F, Mols P, Ramadan A, Taccone F, Claessens B. Comparison between in-hospital and out-of-hospital cardiac arrest: Epidemiology, etiology and outcome. *Resuscitation* 2015;96:115. <https://doi.org/10.1016/j.resuscitation.2015.09.272>.
 38. Hospital Airway Resuscitation Trial – Full Text View – ClinicalTrials.gov n.d. (Accessed 1 February 2023, at <https://clinicaltrials.gov/ct2/show/NCT05520762?term=airway&cond=cardiac+arrest&cntry=US&draw=2&rank=1>).