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Protocol paper

Route of drug administration in out-of-hospital cardiac arrest: A protocol for a randomised controlled trial (PARAMEDIC-3)

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Abstract

Aims: The PARAMEDIC-3 trial evaluates the clinical and cost-effectiveness of an intraosseous first strategy, compared with an intravenous first strategy, for drug administration in adults who have sustained an out-of-hospital cardiac arrest.

Methods: PARAMEDIC-3 is a pragmatic, allocation concealed, open-label, multi-centre, superiority randomised controlled trial. It will recruit 15,000 patients across English and Welsh ambulance services. Adults who have sustained an out-of-hospital cardiac arrest are individually randomised to an intraosseous access first strategy or intravenous access first strategy in a 1:1 ratio through an opaque, sealed envelope system. The randomised allocation determines the route used for the first two attempts at vascular access. Participants are initially enrolled under a deferred consent model. The primary clinical-effectiveness outcome is survival at 30-days. Secondary outcomes include return of spontaneous circulation, neurological functional outcome, and health-related quality of life. Participants are followed-up to six-months following cardiac arrest. The primary health economic outcome is incremental cost per quality-adjusted life year gained.

Conclusion: The PARAMEDIC-3 trial will provide key information on the clinical and cost-effectiveness of drug route in out-of-hospital cardiac arrest.

Trial registration: ISRCTN14223494, registered 16/08/2021, prospectively registered.

Keywords: Cardiac arrest, Epinephrine, Intraosseous, Intravenous, Clinical trial protocol

Introduction

Each year over 30,000 people in the UK receive treatment from National Health Service (NHS) Ambulance Services for an out-of-hospital cardiac arrest.[1] Following arrival of the ambulance service, treatment transitions from bystander-delivered basic life support (where delivered) to paramedic-led advanced life support, including airway management, ventilation, and drug therapy.

The PARAMEDIC-2 trial showed that parenteral adrenaline, compared with placebo, in adult out-of-hospital cardiac arrest is highly effective at achieving return of spontaneous circulation (adjusted OR 3.83 (95% confidence internal (CI) 3.30–4.43), but had a much smaller effect on long-term survival (OR 1.39 (95% CI 1.06–1.82)

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and favourable neurological function (OR 1.18 (95% CI 0.86–1.61).[2] In PARAMEDIC-2, drug treatments were administered on average 21 minutes after cardiac arrest. In a secondary analysis of data from the PARAMEDIC-2 trial, the clinical-effectiveness of adrenaline was found to be highly time-dependent, such that each one-minute reduction in time to drug administration was associated with an absolute increase in 30-day survival of 0.7%.[3]

Data from randomised controlled trials and observational studies shows that the intraosseous (IO) drug route may be quicker to successfully establish, potentially facilitating more rapid drug administration.[4,5] However, there is important uncertainty as to how quickly drugs administered via the IO route reach the central circulation, potentially obviating any potential benefit of securing vascular access more quickly.[6] To date, studies comparing the clinical-effectiveness of the IO and intravenous (IV) drug routes are limited to observational research.[6–8] These studies consistently show that the IO route, is associated with similar or worse outcomes. However, the findings of these observational studies are challenging to interpret in the context of important residual confounding and resuscitation time bias.[9]

Current clinical guidelines recommend that cardiac arrest drugs are administered through the intravenous (IV) route, with the intraosseous (IO) route used only where IV access cannot be rapidly established.[10,11] These recommendation are driven principally by the lack of clinical evidence supporting the use of the IO route in adult cardiac arrest. Despite this, there is evidence of changes in clinical practice with use of the IO route during adult cardiac arrest in England increasing from 23% in 2015 to 43% in 2020.[12]

Driven by ongoing uncertainty regarding the optimum route for drug administration in cardiac arrest, the International Liaison Committee on Resuscitation has highlighted the need for a randomised controlled trial to evaluate the clinical effectiveness of the IO and IV routes in out-of-hospital cardiac arrest.[10] In response to an investigator-led funding application, the National Institute of Health and Care Research commissioned the PARAMEDIC-3 trial. The trial complements other ongoing trials in this clinical area, namely an ongoing Chinese trial (NCT04130984), the Taiwanese VICTOR trial (NCT04135547), and the Danish IVIO trial (NCT05205031).[6,13]

Methods

PARAMEDIC-3 is a pragmatic, allocation concealed, open-label, multi-centre, superiority randomised controlled trial. The trial was prospectively registered as ISRCTN14223494 (https://www.isrctn.com/ISRCTN14223494). The first trial participant was recruited on 13th November 2021. The planned trial end date is 31st March 2025.

The trial is currently recruiting across nine English NHS ambulance services, the Welsh NHS ambulance service, and one air ambulance service. The trial registration page contains a list of organisations currently recruiting participants to the trial.

The protocol was developed by the trial investigators in accordance with national legislation, Good Clinical Practice, the declaration of Helsinki,[14] and the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) checklist.[15] The trial is sponsored by the University of Warwick and co-ordinated by the University of Warwick Clinical Trials Unit. This protocol manuscript was written in concordance with the SPIRIT guidelines.[15]

The trial was approved by the South Central- Oxford C Research Ethics Committee (reference 21/SC/0178) and Health Research Authority Confidentiality Advisory Group (20/CAG/0092).

The current trial protocol (V4.0, date 10th August 2023) is available in the supplementary materials. The statistical and health economic analysis plans will be made available on the trial website once finalised: https://www.warwick.ac.uk/paramedic3. Any updates to the protocol and analysis plans will be made available on the trial website. The trial will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) reporting recommendations for parallel group randomised trials.[16] An example trial CONSORT flow diagram is included as Fig. 1.

Trial objectives

The primary trial objective is to evaluate the clinical effectiveness of intraosseous-first strategy in the treatment of OHCA, measured by our primary outcome of 30-day survival.

Our secondary trial objectives are:

1) To evaluate the effect of an IO first strategy on neurological function, quality of life and survival at other time-points, and

2) To determine the cost-effectiveness of an IO first strategy.

Eligibility criteria

The trial includes individuals who sustain an out-of-hospital cardiac arrest and receive cardiopulmonary resuscitation by a participating ambulance service with a requirement for vascular access to administer cardiac arrest drugs. Individuals are excluded if they are a child (known or appear to be <18 years), are known or appear to be pregnant, or already have vascular access.

Study interventions

Eligible participants are randomised to either an IO-first or IV-first strategy.

For participants randomised to an IO-first strategy, the first attempt at vascular access is made via the IO route. If the attempt is unsuccessful, then a further attempt at IO vascular access is made.

For participants randomised to an IV-first strategy, the first attempt at vascular access is made via the IV route. If the attempt is unsuccessful, then a further attempt at IV vascular access is made.

Once vascular access is obtained, then cardiac arrest drugs are administered via that route. If after two vascular attempts, the treating clinician has been unable to successfully secure vascular access, then further attempts at vascular access may be made by any route at the discretion of the treating clinician. The anatomical site for all vascular access attempts is at the discretion of the treating clinician.

Decisions about what drugs to administer and the time-point for administration will be made by the treating clinicians, based on Resuscitation Council UK and national ambulance clinical guidelines.[17,18]

Trial outcomes

Trial outcomes include long-term survival, favourable neurological function and health related quality of life. These outcomes were identified as core outcomes for cardiac arrest trials by the Core Outcome Set for Cardiac Arrest (COSCA) initiative.[19] Our list of outcomes was developed in collaboration with our patient and public collaborators.

The primary clinical trial outcome is survival at 30-days.

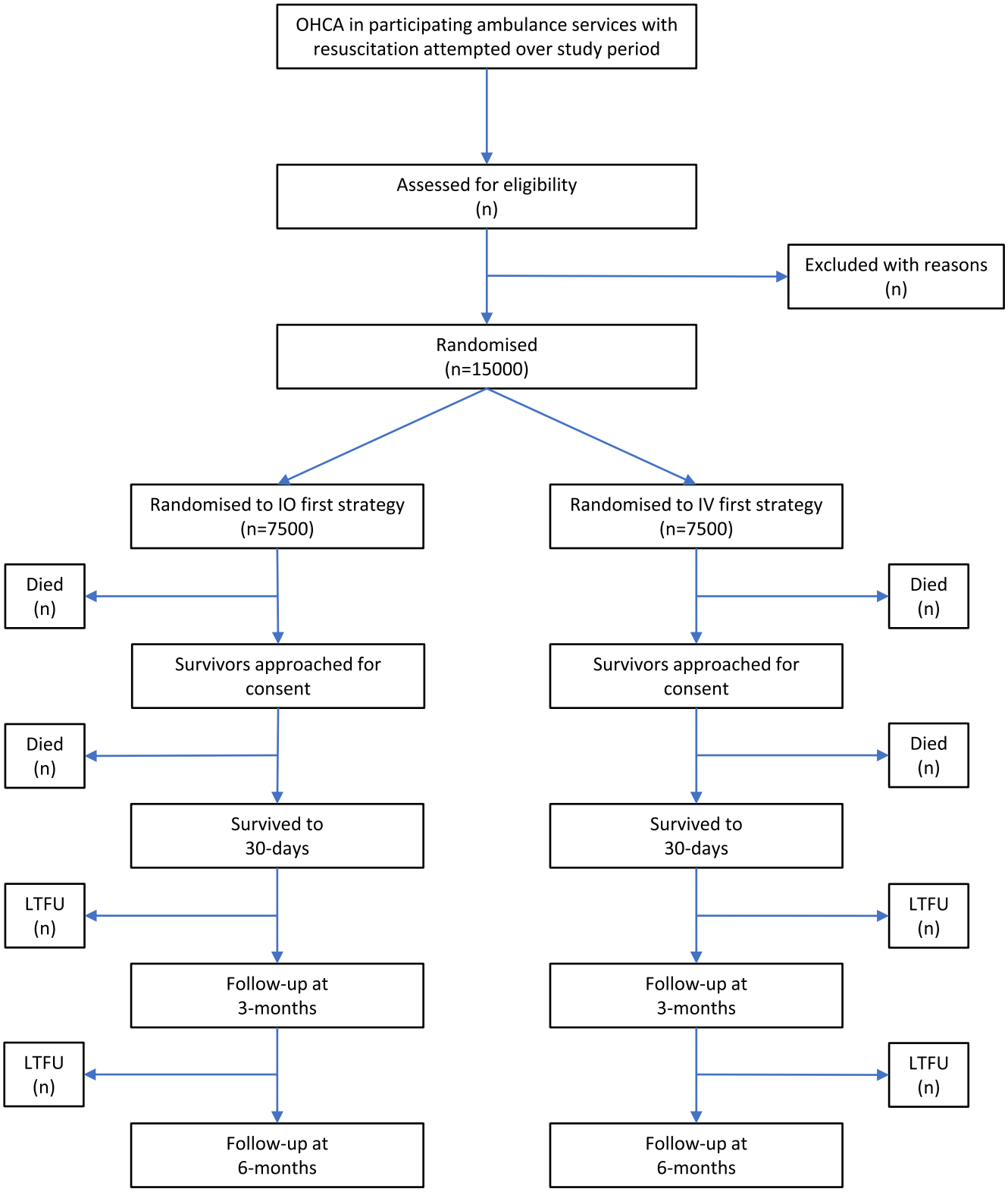

Fig. 1 – PARAMEDIC-3 trial CONOSRT diagram. Figure footer: OHCA- out-of-hospital cardiac arrest; IO- Intraosseous; IV- Intravenous.

Secondary clinical trial outcomes are:

- Any return of spontaneous circulation (ROSC)
- Time to ROSC
- Survived event (sustained ROSC at hospital handover)
- Survival to hospital discharge, 3 and 6 months
- Neurological function (measured by modified Rankin Scale (mRS) at discharge, 3, and 6 months)

- Health related quality of life (measured by EQ-5D-5L at 3 and 6 months)
- Hospital length of stay
- Critical care length of stay

We will also report relevant safety outcomes.

The primary health economic Incremental cost per quality-adjusted life year gained from the perspective of the National Health Service and personal social services.

Participant recruitment and randomisation

Trial-trained attending ambulance clinicians enrol patients into the trial. The ambulance clinician determines whether there is a requirement for vascular access to administer cardiac arrest drugs, assesses the patient's eligibility for trial participation and, where appropriate, then proceeds to randomisation.

Eligible patients are randomised in a 1:1 ratio to either an IO first strategy (intervention) or IV first strategy (control) through use of opaque, sequentially numbered sealed envelopes (or an equivalent system, such as peelable stickers, scratch cards or sealed treatment packs).

At the point that the envelope (or equivalent) is opened, the patient is categorised as being randomised for the intention-to-treat analysis.

The allocation sequence is generated by the study statistician. The sequence uses variable block sizes and is stratified by ambulance service. Envelopes are packed centrally by the Warwick Clinical Trials Unit trial team.

Blinding

The nature of the trial interventions precludes blinding of ambulance clinicians to treatment allocation. Hospital staff will be aware which vascular access routes are in place upon hospital arrival but they will not be specifically briefed on the randomised allocation. Participants will be initially unaware of treatment allocation by virtue of being unconscious during the resuscitation attempt.

Consent, data collection and follow-up

PARAMEDIC-3 recruits individuals who are unconscious following a cardiac arrest and whose treatment is time-critical. In this context, it would not be practical to consult a carer or independent registered medical practitioner without placing the potential participant at risk of harm from delaying treatment. On this basis, the research ethics committee has supported trial enrolment under a deferred consent model, in accordance with national legislation. The trial protocol outlines in detail the key trial ethical considerations, including a detailed justification for use of a deferred consent model based on the framework developed by Davies and colleagues.[20]

Participants who survive are approached following their cardiac arrest for consent to collect patient reported outcome measures and health resource use data. Where a participant lacks capacity to make decisions about ongoing trial participation, agreement is sought from either a personal consultee or a professional consultee if a personal consultee is not available.

Trial participants are followed up for 6-months following cardiac arrest. Table 1 summarises the data that is collected at key time-points. Key data definitions align with the Utstein style for out-of-hospital cardiac arrest.[21] Most data are collected from ambulance service records or hospital clinical records. Follow-up questionnaires incorporating the EQ-5D-5L and health resource use questionnaire are sent to surviving participants at 3-months and 6-months, along with a gift voucher to thank them for their time in completing the questionnaire. Where possible, data are linked with national UK datasets, such as the Intensive Care National Audit and Research Centre case-mix programme, Patient Episode Database for Wales and Hospital Episode Statistics.

Sample size and statistical analysis

The planned sample size is 15,000 participants.

Our sample size is based on evidence from the PARAMEDIC-2 trial which showed that each 1-minute reduction in time to drug administration was associated with an increase in 30-day survival rate of 0.7%.[3] The reduction in time to drug administration reported in the literature when using the IO route ranges from 1 to 6.2 minutes.[4,5]

Table 1 – Summary of data collection across study time-points.

	Cardiac arrest	Hospital stay	Hospital discharge	30-days	3-months (±1-month)	6-months (±1-month)
Inclusion/exclusion criteria	✓	x	x	x	x	x
Randomisation	✓	x	x	x	x	x
Intervention	✓	x	x	x	x	x
Cardiac arrest data	✓	x	x	x	x	x
Patient identifiers	✓	✓	x	x	x	x
Safety reporting	✓	✓	✓	x	x	x
Hospital stay data	x	✓	x	x	x	x
Survival status	✓	✓	✓	✓	✓	✓
Neurological function	x	x	✓	x	✓	✓
Notification of enrolment and invitation to participate in follow-up	x	✓	✓	✓	x	x
Informed consent	x	✓	✓	x	x	x
Quality of life (EQ-5D-5L) and health resource use questionnaire	x	x	x	x	✓	✓
Check for national data opt-out	✓			x	x	x

Key: mRS – modified Rankin score.

A sample size of 14,972 participants will enable us to detect a conservative but worthwhile difference in 30-day survival of 1% (3.2% to 4.2%, proportionally 31%) with a two-sided significance level of 5% and power of 90%. Based on high levels of data completeness for the primary outcome (99.9%) in the PARAMEDIC and PARAMEDIC-2, we have only slightly increased the sample size to 15,000 participants to account for loss to follow-up.[2,22]

We will undertake formal interim analyses to assess early stopping either for efficacy or harm during the main trial, whilst maintaining the type I error rate of 5%. The results of these analyses are confidential to trial statisticians and the data monitoring committee. We have undertaken our first interim analysis (early monitoring after recruitment of 10% participants) and plan one further interim analysis (mid-way monitoring after recruitment of 50% participants).

The primary statistical analysis will be by intention-to-treat amongst those randomised to the IO first strategy versus the IV first strategy. The primary outcome of 30 days survival rate will be assessed using logistic regression model with adjustment for important covariates.

Categorical secondary outcomes will be analysed in a similar way to the primary outcome. Continuous secondary outcomes will be assessed using linear regression models. Results will be reported using odds ratio or mean difference with 95% confidence interval.

We plan several sub-group analyses, as described in the full protocol and statistical analysis plan, to explore whether any observed treatment varies across sub-groups. These exploratory sub-group analyses will be analysed using interaction term (treatment x sub-g roup) in the statistical models and reported using 95% confidence intervals.

Health economic analysis

We will undertake a prospectively planned economic evaluation from an NHS and personal social services perspective, according to the recommendations of the National Institute for Health and Care Excellence (NICE) reference case.[23]

Our within-trial analysis (to 6 months) will use bivariate regression of costs and quality-adjusted life-years to inform a probabilistic assessment of incremental treatment cost-effectiveness.[24] Mechanisms of missingness of data will be explored and multiple imputation methods will be applied if required to impute missing data.[25–27] Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis.

These within-trial findings will inform a lifetime decision-analytic model. Modelling will draw upon best available information from the literature to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Sensitivity analyses will be undertaken to explore uncertainty and to consider issues of generalisability of the study.

Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[28]

Safety monitoring

PARAMEDIC-3 is evaluating the clinical and cost-effectiveness of two interventions that are routinely used in NHS practice, and which will be used in line with their current market authorisation.[12] Given the nature of cardiac arrest, events such as death and hospitalisation are expected and are collected as trial outcomes. On this basis, the trial will only collect information on adverse events and serious adverse events that occur between randomisation and hospital discharge, which are possibly related, probably related, or definitely related to the trial interventions, and which are not already collected as a clinical outcome.

Trial oversight

The PARAMEDIC-3 trial is co-ordinated by the Warwick Clinical Trials Unit. Trial management is overseen by the Trial Management Group which meets monthly and is comprised of trial co-investigators and project staff. The Trial Steering Committee meets at least annually to review trial progress, including protocol adherence and participant safety. The Data Monitoring Committee meets at least annually to review confidential reports summarising recruitment, protocol compliance, safety data and interim assessments of outcomes.

Patient and public involvement

PARAMEDIC-3 is supported by a public and patient representative who is a member of the Trial Management Group. Two public and patient representatives sit as members of the Trial Steering Committee.

The trial is also supported by a diverse six-member patient advisory panel that meets six-monthly and provides a public perspective on key issues, such as co-enrolment and data processing. Members include cardiac arrest survivors. A summary of patient and public involvement throughout the trial will be developed using the GRIPP2 framework and included in the final study report.[29]

Data sharing

The trial team will consider requests to share an anonymised patient-level dataset from six-months after the publication of the primary results paper. Data access requests should be addressed to the corresponding author of the primary results paper. All requests for data should specify the planned use of the data and will be reviewed by the trial co-investigator team.

Dissemination

Our dissemination strategy targets clinicians, policy makers, and patients and members of the public.

Key dissemination strategies include open access publication in peer-reviewed journals, conference presentations, podcasts, lay summaries, press releases, infographics, and targeted communications to key national and international organisations (e.g. College of Paramedics, Resuscitation Council UK, European Resuscitation Council, International Liaison Committee on Resuscitation).

We will draw on co-applicant and collaborator links with guideline organisations (Resuscitation Council UK, European Resuscitation Council, International Liaison Committee on Resuscitation, Joint Royal College Ambulance Liaison Committee) to support the implementation of research findings in clinical practice.

Conclusion

There is ongoing clinical uncertainty about the optimum route for drug administration in cardiac arrest. The PARAMEDIC-3 trial is a pragmatic, allocation concealed, open-label, multi-centre, superiority randomised controlled trial that will determine the clinical- and cost-effectiveness of an IO-first strategy in adult out-of-hospital cardiac arrest.

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CRediT authorship contribution statement

Keith Couper: Conceptualization, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. **Chen Ji:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Ranjit Lall:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Charles D Deakin:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Rachael Fothergill:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **John Long:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **James Mason:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Felix Michelet:** Investigation, Methodology, Writing – review & editing. **Jerry P Nolan:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Henry Nwankwo:** Investigation, Methodology, Writing – review & editing. **Tom Quinn:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Anne-Marie Slowther:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Michael A Smyth:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Alison Walker:** Investigation, Writing – review & editing. **Loraine Chowdhury:** Investigation, Project administration, Writing – review & editing. **Chloe Norman:** Investigation, Project administration, Writing – review & editing. **Laurille Sprauve:** Investigation, Project administration, Writing – review & editing. **Kath Starr:** Investigation, Project administration, Writing – review & editing. **Sara Wood:** Investigation, Project administration, Writing – review & editing. **Steve Bell:** Investigation, Writing – review & editing. **Gemma Bradley:** Investigation, Writing – review & editing. **Martina Brown:** Investigation, Writing – review & editing. **Shona Brown:** Investigation, Writing – review & editing. **Karl Charlton:** Investigation, Writing – review & editing. **Alison Coppola:** Investigation, Writing – review & editing. **Charlotte Evans:** Investigation, Writing – review & editing. **Christine Evans:** Investigation, Writing – review & editing. **Theresa Foster:** Investigation, Writing – review & editing. **Michelle Jackson:** Investigation, Writing – review & editing. **Justin Kearney:** Investigation, Writing – review & editing. **Nigel Lang:** Investigation, Writing – review & editing. **Adam Mellett-Smith:** Investigation, Writing – review & editing. **Ria Osborne:** Investigation, Writing – review & editing. **Helen Pocock:** Investigation, Writing – review & editing. **Nigel Rees:** Investigation, Writing – review & editing. **Robert Spaight:** Investigation, Writing – review & editing. **Belinda Tibbetts:** Investigation, Writing – review & editing. **Gregory A. Whitley:** Investigation, Writing – review & editing. **Jason Wiles:** Investigation, Writing – review & editing. **Julia Williams:** Investigation, Writing – review & editing. **Adam Wright:** Investigation, Writing – review & editing. **Gavin D Perkins:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GDP is co-chair of the International Liaison Committee on Resuscitation (ILCOR). CD and JPN are emeritus members of the ILCOR Advanced Life Support task force. KC and HP are current members of the ILCOR Advanced Life Support task force. GDP is editor-in-chief and JPN is founding editor of Resuscitation Plus. KC is associate editor of Resuscitation Plus and guest editor for the research methodology special edition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2023.100544.

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