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Characteristics, reporting, risk of bias and pragmatism in prehospital emergency care randomised trials from 2010 to 2024: a protocol for a meta-epidemiological study

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ABSTRACT

Introduction Prehospital emergency care (PEC) requires rapid evidence-based decisions to maximise the effectiveness of care and to improve clinical outcomes. There are multiple challenges related to clinical research performed in the PEC setting. The aim of our study is to systematically review and assess the characteristics, quality of reporting, risk of bias and pragmatism in recent PEC trials, thereby identifying potential gaps and strengths that can guide the design of future prehospital studies.

Methods and analysis We will systematically search databases MEDLINE, Embase and Cochrane CENTRAL to identify all randomised controlled trials conducted in the field of PEC and published in English language between 2010 and 2024. No restrictions will be made to the participants, interventions and outcomes. Risk of bias will be evaluated using the Cochrane Risk of Bias 2 tool. The level of pragmatism will be assessed using the Pragmatic-Explanatory Continuum Indicator Summary-2 score. Exploratory data analysis will be used to investigate and summarise main patterns. Differences in characteristics between PEC fields, study designs, publication year and associations between pragmatism levels, risk of bias and quality of reporting will be the primary focus.

Ethics and dissemination There are no ethical concerns directly relevant to this review. This study has been previously registered with the Open Science Framework (osf.io/rzn9j). The manuscript will be submitted for publication to a relevant, peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A key strength of our study is the development of a rigorous search strategy and screening methodology, aligned with the standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions.
⇒ We will employ established assessment tools, and two independent reviewers will evaluate reporting quality, risk of bias and the level of pragmatism in the included studies, thereby enhancing the robustness and reliability of the findings.
⇒ A potential limitation of our study is the restriction to studies published between 2010 and 2024, which may limit the generalisability of the findings to earlier trials.
⇒ We will not search for grey literature and in specialist databases; consequently, despite a systematic search, there may be studies that we will not be able to identify.

INTRODUCTION

Prehospital emergency care (PEC) is a rapidly evolving field of medicine; however, its features and conditions differ markedly from hospital clinical practice. Care and interventions provided in the first minutes of acute emergencies have a significant impact on subsequent outcomes; therefore, evidence-based decisions and guidelines are required. Conducting clinical research in the prehospital setting can be challenging. Unpredictability, time constraints, the diversity of patients and care providers, limited diagnostic and therapeutic resources, limited access to patient data, the intricacy of obtaining consent, performing rapid randomisation and organising follow-up are all considerable difficulties.[1–3] Hence, the number of clinical trials in this area is limited.[4]

Well-designed randomised controlled trials (RCTs) serve as the foundation for evaluating the effects of interventions, as they minimise confounding and other potential biases. Explanatory trials aim to understand the mechanism of interventions and tend to be characterised by highly controlled settings, not accurately reflecting real-world conditions.[5] In contrast, pragmatic RCTs (pRCTs) are designed to assess the effectiveness of decisions to use interventions in routine practice.[6–8] To meet their purpose, pRCTs often have broader eligibility criteria, are more

often conducted in usual care settings, do not use artificial restrictions in the delivery of interventions and may also often use routinely collected data, focusing on practical outcomes relevant to everyday clinical decisions.[9–11]

Internal validity of RCTs refers to the extent to which the observed results of a study accurately reflect the true causal relationship between the randomised decision and outcomes, with low risk of bias, confounding factors or random errors. In contrast, external validity refers to the generalisability of the results of the study to other populations, settings or conditions. The controlled environment in explanatory trials generally emphasise internal validity, while real-world settings of pragmatic trials may promote external validity.[5] However, it should be noted that these two approaches are not contradictory, and trials are most useful when containing pragmatic and explanatory elements simultaneously, maximising both internal and external validity.[8]

Given the circumstances, PEC is not the optimal setting to investigate the mechanisms of novel interventions. Rather, it may be a more feasible approach to assess which treatment strategies provide better outcomes and would be better choices in real-world PEC practice, despite the diversity of patients and providers.[7] In addition, implementing explanatory design features in PEC settings may be unfeasible (eg, using placebo in emergent cases or ensuring close follow-up monitoring), this presumably shifts the focus of PEC trials in the pragmatic direction.

The primary objective of our meta-epidemiological study is to systematically identify and evaluate the characteristics of RCTs between 2010 and 2024 in the field of PEC, focusing on methodological features, participants included, types of interventions, outcomes, funding sources and publication details. Co-primary objectives are to assess the quality of reporting, risk of bias and level of pragmatism. We aim to evaluate the differences in characteristics and reporting quality between PEC fields, study designs and publication year, and also to assess associations between risk of bias, pragmatism and quality of reporting.

METHODS AND ANALYSIS

Eligibility criteria

We will consider RCTs that include participants (either patients or care providers) who were randomised and received interventions during PEC or during the transportation from the PEC scene to the hospital (primary transportation). Interventions that are initiated during PEC but continued beyond hospital admission (eg, mechanical ventilation) will also be eligible. Due to the expected substantial number of trials employing a quasi-randomised design (q-RCTs), these will also be deemed eligible.[3] Study populations can include participants of any age, sex or health condition from any country and healthcare system. Any type of intervention will be considered, including pharmaceutical, device-based therapies and non-pharmaceutical interventions. Interventions should be compared against an active comparator, standard or usual care, placebo or sham therapy, or no intervention. Outcomes of interest are not restricted and may include clinical (eg, mortality, events, hospitalisation), patient-reported (eg, symptoms, quality of life), surrogate (eg, biological or psychological biomarkers), health service-level operational (eg, response time metrics, quality of care indicators), economic (eg, cost and resource use) and composite outcomes. Only completed studies, published in peer-reviewed journals (Introduction, Methods, Results and Discussion structure) between 1 January 2010 and 31 December 2024 in English language will be included.

Non-randomised, observational studies and trials conducted exclusively in settings other than prehospital care (emergency department, in-hospital care, allied healthcare facilities, primary care, first aid provision, focusing on training or based in educational facilities, and during inter-facility (secondary referral) transportation) will be excluded. Studies with interventions administered by laypersons and interventions on healthy subjects will not be eligible. Our work primarily focuses on civilian prehospital care, and given the substantial contextual and ethical differences of military emergency care, we do not consider studies conducted in military settings.[12] Extension studies, post-hoc, secondary or sub-analyses of previous RCTs, abstract-only publications and articles other than original (ie, opinion-based such as letter, commentary or editorial) will be excluded.

Information sources and search strategy

The following databases will be searched: MEDLINE (via Ovid), Embase (via embase.com) and Cochrane CENTRAL. The search strategy was developed by a medical librarian (LC) and a PEC field expert (GT), based on Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions[13] and the Search Filters for Prehospital Care, Paramedicine and Emergency Medical Dispatch developed by the Library & Knowledge Service for NHS Ambulance Services in England (see online supplemental material).[14] The search strategy was verified by one reviewer (SL) according to the Peer Review of Electronic Search Strategies guideline.[15] The Cochrane Highly Sensitive Search Strategy for identifying randomised trials was applied in MEDLINE and Embase.[13] In addition, backward and forward citation searching, based on all eligible and identified trials, will be performed using Citationchaser to identify further eligible studies.[16]

Selection process

In the first round, pairs of review authors will independently screen the title and abstract of retrieved records to determine which trials should be assessed further. We will obtain the full texts of all potentially relevant records and screen them for eligibility in a second round, also using pairs independently. We will perform the screening using Covidence software (Veritas Health

Innovation, Melbourne, Australia). Any disagreements will be resolved through consensus or by discussion to a third review author. We will present a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram to describe the process of trial selection.[17] Inter-rater agreement will be assessed using the Cohen's kappa statistic. In the case of multiple reports from the same trial, the report of the primary analysis will be selected.

Data collection process, data items and assessment of reporting quality

Full-text report of all identified RCTs will be evaluated using the CONsolidated Standards Of Reporting Trials 2010 (CONSORT 2010) checklist, a validated tool comprising a checklist of 37 items, to evaluate the quality of reporting.[18] Regarding the subgroup of feasibility and pilot trials, the related extension of the CONSORT 2010 statement will be applied.[19]

A list of data items to be extracted related to trial characteristics has been established following the CONSORT checklist structure and is presented in online supplemental material table 1. Variables were formulated in accordance with the PragMeta database, which is a non-commercial, open-data platform of pragmatic trials.[20 21] In case the sought information is not available in the primary report, we will first attempt to extract it from the referenced study protocol and subsequently check the trial registration. If the information remains unavailable, we will contact the corresponding author for clarification via e-mail.

We will use a dedicated, Microsoft Excel-based data collection form to extract data. The collected data will be double-checked to ensure accuracy. In case of uncertainty, the decision will be based on discussion with a second reviewer. Overall quality of reporting will be presented as the percentage of reported items to total items of the CONSORT 2010 checklist after removing items rated as 'Not applicable'. We will also calculate the rate of reporting for individual domains.

Evaluation of bias and pragmatism

Risk of bias for the primary outcome will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, the most widely recognised and recommended instrument to assess RoB.[22] When the primary outcome is not clearly defined, we will presume it is the outcome either (1) described under aims/objectives of the study, (2) the outcome used to determine the sample size or (3) the first outcome reported in the publication. In the case of multiple primary outcomes, each will be assessed separately. Regarding composite outcomes, the frequency or contribution of each component will be taken into account and the risk of bias due to the most influential components will be assessed.

Two review authors will independently assess RoB 2 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 the selection of the reported result. Each domain will be rated as 'low risk of bias', 'some concerns' or 'high risk of bias' using the official Excel tool to implement RoB 2.[23] Any disagreements will be resolved through consensus or by discussion to a third review author. We will reach an overall RoB judgement for a specific outcome according to Chapter 8 of the Cochrane Handbook.[22] In the case of multiple, outcome-level RoB assessments (multiple primary outcomes or composite outcomes), a primary outcome-level RoB judgement will be achieved applying the same principle, using the individual outcome level overall judgements as domains. Of note, in case of pragmatic trials, we will not assess 'bias due to deviations from intended interventions' as such deviations are part of the effectiveness of a decision to use an intervention and are not applicable.

The pragmatism level of included trials will be evaluated using the Pragmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) tool, which is focusing on key trial design domains (eligibility criteria, recruitment, setting, organisation, flexibility in intervention delivery and adherence, follow-up, primary outcome and primary analysis). Each domain can be rated on a five-point Likert scale (1, very explanatory; 2, rather explanatory; 3, equally pragmatic and explanatory; 4, rather pragmatic; 5, very pragmatic) using the official PRECIS-2 toolkit,[8 24] in accordance with the PragMeta protocol.[21] Each domain will be independently evaluated by two reviewers, and any disagreements will be resolved through consensus or by discussion to a third review author.

An overall PRECIS-2 score will be calculated using the mean score over the nine domains. We will also consider various determinants of pragmatism: we will separately record for each trial the type of comparator, to specifically analyse situations where the comparator would be incompatible with a pragmatic approach (eg, a placebo or sham control). We will also specifically record if those involved or affected by care (eg, physicians, patients) have been blinded, as this also compromises pragmatism.

Other considerations related to the analysis plan

Feasibility and pilot trials will be classified as a distinct subgroup. Within this subgroup, only study characteristics and reporting quality will be analysed, while risk of bias and pragmatism will not be assessed, as these studies do not primarily evaluate effectiveness of interventions; therefore, the risk of bias or pragmatism assessment might be biased and inappropriate.

As our study is not focusing on a pre-defined patient population, intervention and outcomes, rather on the overview of trial characteristics and reporting practices, we do not plan to quantitatively synthesise study results and derive clinical recommendations. Therefore, publication bias assessment, sensitivity analyses and Grading of Recommendations Assessment, Development and Evaluation evaluation are not planned.

Data analysis

We plan to perform exploratory data analyses to evaluate and summarise main characteristics of the dataset, employing summary statistics, data visualisation methods and regression modelling. Our primary focus will be on differences across PEC fields, publication years and study designs. Primary outcomes will be the proportion of reported CONSORT 2010 items, mean level of pragmatism assessed using the PRECIS-2 tool and overall RoB 2 judgement. Data on methodological features, participants included, types of interventions, outcomes assessed, funding sources and publication details will be considered as secondary outcomes.

Categorical variables will be presented as count (percentage), continuous variables will be presented as mean (median) +/− standard deviation (IQR, minimum–maximum). These will be given overall for the whole sample and stratified according to PEC fields, study designs and publication year. Data will be visualised with bar plots for categorical variables and with one-dimensional scatterplots (dot plots) for continuous variables. Kernel density estimates will be used in the latter case, sample size permitting. Plots will also be stratified according to PEC fields, study designs and publication year.

Univariate, nominal categorical variables will be compared across PEC fields, study designs and publication years using X^2,[25] ordinal categorical variables and continuous variables will be compared with Kruskal-Wallis test. Association between overall RoB category and mean PRECIS-2 score will be described by Pearson correlation coefficient (Spearman's rank correlation coefficient). Association between risk of bias and pragmatism will be visualised with a scatterplot (with jittering if there is a substantial number of entities).

For multivariate modelling, logistic and proportional odds logistic models will be used for nominal and ordinal categorical outcomes, and linear regression will be used for continuous outcomes.[26] In the case of publication year, regressions will be run both with the year included as categorical variable and as continuous variable; in the latter case, spline expansion will also be used to account for potential non-linearity. All explanatory variables will be entered without variable selection. Point estimates will be presented together with their 95% CIs. P values less than 0.05 will be considered statistically significant. Analyses will be carried out under the R statistical software (version 4.4.2 or higher, R Foundation for Statistical Computing, Vienna, Austria).

ETHICS AND DISSEMINATION

We will use data from publicly available sources for our analyses; therefore, ethical approval is not required. Preliminary findings will be presented at relevant scientific conference(s). The final manuscript will be written according to the guidelines for reporting meta-epidemiological methodology research[27] and submitted for publication to an international, peer-reviewed journal. Data on characteristics and pragmatism of eligible pRCTs will be shared via the PragMeta database.[20 21]

This study has been previously registered with the Open Science Framework (osf.io/rzn9j).

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Patient and public involvement Patients or the public were not involved in the design of this work. However, we plan to provide a plain language summary of our findings and to disseminate and make it openly sharable on social media platforms.

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