Canadian Journal of Emergency Medicine
https://doi.org/10.1007/s43678-025-00874-w

CAEP ACADEMIC SYMPOSIUM PAPER

CAEP 2024 Academic Symposium: adaptive platform trials in emergency medicine in Canada

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Received: 14 January 2025 / Accepted: 24 January 2025

Abstract

Objective The Canadian Association of Emergency Physicians 2024 Academic Symposium Panel on adaptive platform trials explored whether adaptive platform trials could be implemented in Canadian emergency departments (EDs). This panel aimed to propose and refine recommendations formulated by the results of a rapid review and responses from a panel of experts about conducting adaptive platform trials in EDs.

Methods From November 2023 to May 2024, a rapid review was conducted on the existing logistical and ethical barriers and facilitators to structuring adaptive platform trials in emergency medicine. The emerging themes and ideas were collected and used to conduct individual semi-structured interviews with key stakeholders, including leaders in emergency medicine research, methodologists and biostatisticians specializing in these designs, patient partners, research personnel, and investigators involved in platform trials across Canada and abroad.

Results From 23 articles and 17 expert interviews, we identified facilitators and barriers to adaptive platform trials in Canadian emergency medicine spread across five domains: evidence strength and quality, relative advantage, adaptability, complexity, and implementation climate and readiness. The most salient needs according to investigators were purposeful and clinically relevant trial design, methodological expertise, and harmonious collaboration with ethics authorities. We provide 14 recommendations across 4 levels: policy, trialist, site, and patient to address barriers to adaptive platform trials in emergency medicine. For each recommendation, we provided corresponding implementation strategies from the Expert Recommendations for Implementing Change (ERIC).

Conclusions Adaptive trial designs are well suited for emergency settings provided the interventions are both easy for clinicians to administer and relevant enough to ameliorate the practice of emergency medicine. These designs are particularly tailored to tackle confirmatory trials, emerging diseases, and trauma care, but barriers like a chaotic ED, complex statistical and methodological requirements, and regulatory considerations persist and require thoughtful implementation strategies.

Keywords Emergency medicine · Adaptive platform designs · Adaptive clinical trials · Rapid review · Patient-centered clinical trial design

Résumé

Objectif Le Symposium académique 2024 de l'Association canadienne des médecins d'urgence sur les essais cliniques de plateforme adaptatifs a examiné la possibilité de mettre en œuvre des essais cliniques de plateforme adaptatifs dans les services d'urgence (SU) canadiens. Ce panel avait pour but de proposer et d'affiner les recommandations formulées à partir d'une revue rapide de la littérature et des réponses d'un panel d'experts sur la conduite d'essais cliniques de plateforme adaptatifs dans les SU.

Méthodes De novembre 2023 à mai 2024, une revue rapide de la littérature a été menée sur les obstacles et les facilitateurs logistiques et éthiques existants pour structurer des essais cliniques de plateforme adaptatifs en médecine d'urgence. Les

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Published online: 29 April 2025

thèmes et idées émergents ont été recueillis et utilisés pour mener des entrevues semi-structurées individuelles avec des intervenants clés, y compris des leaders en recherche en médecine d'urgence, des méthodologistes et des biostatisticiens spécialisés dans ces devis d'étude, des patients partenaires, du personnel de recherche, et des chercheurs participant à des essais cliniques de plateforme adaptatifs au Canada et à l'étranger.

Résultats À partir de 23 articles et de 17 entrevues d'experts, nous avons identifié les facilitateurs et les obstacles aux essais cliniques de plateforme adaptatifs en médecine d'urgence au Canada dans cinq domaines: robustesse et qualité des données probantes, adaptabilité, avantages relatifs, complexité, et climat et niveau de préparation pour la mise en œuvre. Selon les chercheurs, les besoins les plus importants étaient une conception des essais ciblée et cliniquement pertinente, une expertise méthodologique et une collaboration harmonieuse avec les autorités en matière d'éthique. Nous formulons 14 recommandations réparties sur quatre niveaux : politique, chercheurs, site d'étude et patient afin de surmonter les obstacles aux essais cliniques de plateforme adaptatifs en médecine d'urgence. Pour chaque recommandation, nous avons fourni les stratégies de mise en œuvre correspondantes tirées des Recommandations d'Experts pour la Mise en œuvre du Changement (ERIC).

Conclusions Les essais cliniques de plateforme adaptatifs sont des devis d'étude bien adaptés aux situations d'urgence, à condition que les interventions soient à la fois faciles à administrer pour les cliniciens et suffisamment pertinentes pour améliorer la pratique de la médecine d'urgence. Ces devis d'étude sont particulièrement adaptés pour adresser les essais de confirmation, les maladies émergentes et la traumatologie, mais des obstacles comme l'environnement chaotique qui règne aux services d'urgence, des exigences statistiques et méthodologiques complexes et des considérations réglementaires persistent et nécessitent des stratégies de mise en œuvre réfléchies.

Mots-clés médecine d'urgence · essais cliniques de plateforme adaptatifs · essais cliniques adaptatifs · revue rapide · conception d'essais cliniques centrés sur le patient

Introduction

Adaptive platform trials are randomized trials that allow for the evaluation of multiple treatments for specific conditions and the implementation of pre-registered modifications during the trial [1]. Modifications occur as data accumulate in hopes of achieving better outcomes for participants and to maximize statistical efficiency [2]. These approaches involve an iterative preplanned revision of prior statistical assumptions as evidence accumulates [3].

Adaptive platform trials combine three different concepts that we define here to better understand our recommendations. Adaptive platform trials are clinical trials that prospectively compare different alternative care strategies and platforms because they use a master protocol, upon which multiple questions can be addressed about the effectiveness of interventions for a particular disease or condition. They are adaptive because they use information to adjust the design or make early stopping decisions. Characteristics of adaptive platform trials can be found in Appendix A (Supplementary File 1) . At interim analysis, some of the study groups can be stopped, and other new experimental groups can be added in accordance with predefined decision rules [4, 5].

Readers may be familiar with existing and emerging adaptive platform trials in critical care in the wake of COVID-19, notably the international trials REMAP-CAP, PRACTICAL, PANTHER, TRAITS, and INCEPT [6]. Each of these platform trials studied different interventions for community-acquired pneumonia, acute hypoxemic respiratory failure and critical illness [6]. Adaptive designs hold promise for emergency medicine because they are designed to be durable and flexible learning health systems that can pivot urgently in response to emerging epidemics or natural disasters [7]. They may also potentially answer research questions more efficiently than traditional comparative effectiveness trials [2]. However, they are difficult to conceptualize because of their integration of multiple treatments for a common control group or groups, and because investigators do not know a priori whether or which adaptations may occur over the course of the trial [8]. Furthermore, not all adaptations in adaptive platform trials may be appropriate: some may complicate the interpretation of results or introduce bias to the estimated effect. As such, these designs require considerable planning and expertise [3].

We sought to identify the current state of adaptive platform trials within the field of emergency medicine with the goal of understanding: (1) is the Canadian emergency medicine community prepared to conduct adaptive platform trials? (2) Which interventions would be appropriate to investigate with an adaptive platform trial in emergency medicine? (3) What recommendations can be drawn with a rapid review of the existing literature about adaptive platform trials in emergency medicine and from experts within the field to scaffold adaptive platform trials design within emergency medicine in Canada?

Methods

Rapid review

We conducted a rapid review of the literature to provide an overview of the barriers and facilitators to implementing adaptive platform trials in emergency medicine. We used Covidence with two reviewers, following interim guidance for the reporting of rapid reviews [9]. We applied search criteria (Appendix B (Supplementary File 1)) to Medline, Ovid, PsycINFO, Embase, and PubMED from their dates of inception until March 6, 2024. We also searched the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov databases. We included trials with both pediatric and adult patients. We excluded studies where patients were not recruited within the emergency department (ED). Populations only seen in the intensive care unit (ICU), on the ward, in the community, and public health investigations were excluded.

Expert interviews

We conducted semi-structured interviews of experts from Canada and the United Kingdom in methodology, emergency medicine, and clinical trial management relevant to the undertaking of adaptive platform trials. Interview questions (Appendix C (Supplementary File 1)) were developed iteratively with panel members using three conceptual frameworks (see next section). Expert interviewees were recruited with snowball sampling. Interviews were conducted between April 8, 2024, and May 14, 2024, by a single interviewer. Interviews were audio recorded and transcribed verbatim. Transcript content was coded with Taguette (https://www.taguette.org/), an open-source qualitative data analysis tool by a single researcher.

Triangulation

We applied three consecutive conceptual frameworks from implementation science, adapted to analyze opportunities for the improvement of the conduct of clinical trials [10]. We used Proctor's Implementation Outcomes Framework [11] for advantages and disadvantages of adaptive platform trials in emergency medicine, the Consolidated Framework for Implementation Research [12] for facilitators and barriers, and the Expert Recommendations for Implementing Change [13] to report implementation strategies. For each framework, we identified and triangulated themes emerging in the results of the rapid review and from expert interviews to present a set of integrated recommendations to the conduct of adaptive platform trials in emergency medicine. We presented them at the Canadian Association of Emergency Physicians (CAEP) Academic Symposium on June 8, 2024, in Saskatoon, Saskatchewan. We refined our recommendations after considering the comments and suggestions of attendees present at the Academic Symposium.

Patient engagement

Following best practices in engaging patient partners in emergency medicine research [14], we involved a patient partner to interpret our study findings, present our results at the Academic Symposium and review and edit the final manuscript.

Results

Rapid review

Among 534 retrieved references, 23 articles were included in the analysis (Fig. 1). Two articles were protocols [15, 16], 8 were reviews [17–24], 6 were clinical trials with results [25–30], 2 were simulation studies [31, 32], and 5 presented qualitative [33, 34], survey [35], or mixed-methods results [36, 37]. COVID-19 was the most studied condition in an emergency context [16, 25–29], followed by trauma and hemorrhage [17–20], stroke and neurological emergencies [30, 31, 35, 37], pediatric airway management [15] and Ebola [22]. Characteristics of individual articles can be found in Appendix D (Supplementary File 1).

Among the review articles, the ADAPT-IT [24, 33, 34, 37] project sought to identify and characterize the most promising adaptive clinical trial (ACT) methods for use in confirmatory phase clinical trials in emergency medicine. The ADAPT-IT investigators described three main advantages to adaptive platform trials amenable to emergency medicine. Concerning efficiency, adaptive designs reduce patient numbers and trial duration. For ethical benefits, the patient's exposure to ineffective treatments can be minimized under some designs (e.g., a response-adaptive randomization design). Within survey research on adaptive platform trials, a response-adaptive randomization design was found to attract more participation interest in a survey of adult ED patients compared to standard randomization [35]. For decision-making, interim analyses can guide adjustments to the trial, making them more pragmatic and reflective of real-world changes. Adaptive platform trials need outcomes that can be rapidly assessed to allow for the implementation of response-adaptive randomization, where patients are preferentially assigned to better performing arms based upon accruing data at regular interim

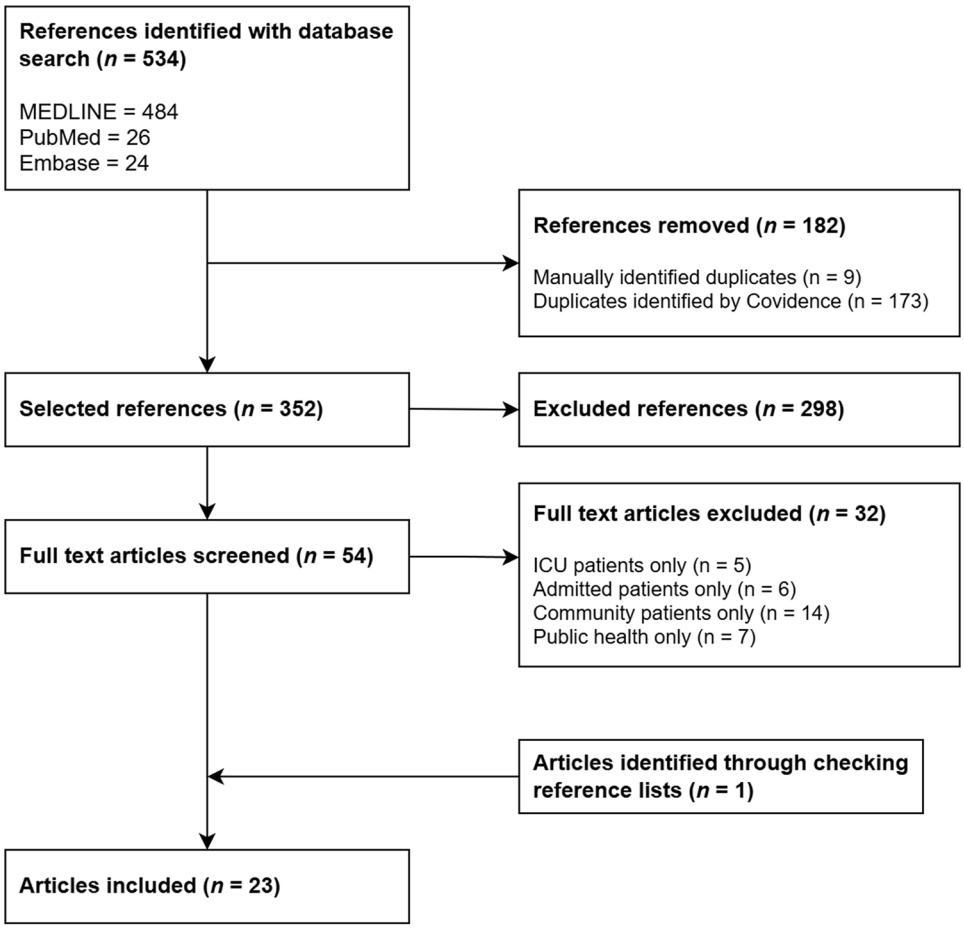

Fig. 1 Selection flowchart for screened and included articles

analyses [16]. This makes them particularly well suited for emergency medicine because many clinical questions in emergency medicine have a short time to primary outcome occurrence and assessment relative to the time it takes to recruit patients [21].

Concerning disadvantages, adaptive platform trials require complex operational consideration and planning, which may be challenging in a chaotic ED. They also require robust statistical methodologies: some of which are costly or proprietary [31]. Methodologies in adaptive platform trials tend to privilege a Bayesian approach in lieu of a frequentist approach, which is what most researchers, clinicians, and reviewers are accustomed to appraising [38, 39]. Lastly, regulatory considerations are a challenge posed to the uptake of adaptive platform trials in emergency medicine [19]. Adaptive designs can align with contemporary regulatory expectations (e.g., the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, the Food and Drug Administration (FDA) in the USA), but the ADAPT-IT investigators emphasized the necessity of clear communication with regulators throughout to ensure that modifications to the trial design are acceptable [24, 33].

Expert interviews

Seventeen expert respondents were interviewed, including 6 clinician scientists, 1 epidemiologist, 1 biostatistician, and 2 clinical trial coordinators. We also captured expertise from 1 patient partner and 6 medical students who performed screening assessments for an adaptive platform trial in the ED. Among university-affiliated researchers, one was based in the UK and the rest were based in Canada. Half of researchers considered themselves mid-career, one early-career, and 3 late-career.

Integrated results

We triangulated results from both the rapid review and expert interviews using three implementation science frameworks (see "Methods"). We classified the advantages and disadvantages of adaptive platform trials in emergency medicine using Proctor's implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation costs, penetration, and sustainability (Table 1). We classified facilitators and barriers to adaptive platform trials in emergency medicine into 39 constructs across 5

Table 1 Advantages and disadvantages of adaptive platform trials for emergency medicine research in Canada classified using the Proctor's Implementation Outcomes Framework

Implementation outcome	Advantages	Disadvantages
Acceptability	Fewer patients exposed to ineffective therapies Less apparent risk and potential for better outcome Population enrichment designs can hone in on what would be beneficial for each patient	Complexity of the methodology Difficult to implement in under-resourced areas Administrative burden Time-sensitive conditions limit recruitment Perception that trial decisions can be made ad hoc, and therefore, complex methods can be manipulated
Adoption	New study arms can be added more efficiently as new treatments are approved Results can be integrated faster into clinical practice	Requires more time to set up Requires added collaborations across multiple investigators, institutions, and settings Frequent updates might confuse busy clinicians Urgent care needs outweigh complex randomization process
Appropriateness	Improved ethical balance Time efficient Study arm may stop when equipoise is no longer met Well suited to identify therapies in high fatality conditions	Potential exposure to treatments that may remain unproven at the end Equipoise harder to define and explain when comparing more than two treatments Thresholds chosen for benefit may be determined opaquely
Feasibility	Smaller average or expected sample size May yield sufficient quantity and quality data in less time	Requires more effort and time to plan Requires highly trained statisticians Identification of eligible patients, and obtaining consent in the context of urgent clinical interventions complicates real-time randomization Complex administrative structure Training of multidisciplinary data and safety monitoring board Logistics of storage of many drugs for the same trial may not be feasible in an ED
Fidelity	Master protocol ensures core design	Early stopping of a treatment may jeopardize validity Smaller sample size or early stop of trials might result in reduced power for secondary outcomes
Implementation cost	Reduced average or expected sample size and overall costs Avoids costs of each individual trial start-up for each individual treatment	Increased costs for planning and design Increased coordination costs Need for highly trained personnel
Penetration	Simultaneous evaluation of multiple therapeutic options within each domain perceived as gain of time	Difficult to understand and explain to patients Lack of intuitive common language may set back trialists Resource-poor settings might not be represented
Sustainability	May be planned ahead and triggered in times of crisis	Requires more effort and time to nurture communications with all stakeholders Requires recurrent funding

domains from the Consolidated Framework for Implementation Research: intervention characteristics, the outer setting, the inner setting, characteristics of individuals, and process (Table 2). We simplified and distilled 14 recommendations for the conduct of adaptive platform trials in emergency medicine, at 4 different levels: policy level, trialist level, site level, and patient level (Table 3). For each recommendation, we provided corresponding implementation strategies from the Expert Recommendations for Implementing Change framework. We also provide wishlist items from experts who were asked to describe what their needs would be to conduct an adaptive platform trial in the ED (Table 4). Only items mentioned by at least two experts were collated, with items mentioned more frequently at the top of the list. Appendix E (Supplementary File 1) presents the conditions that participants at the Academic Symposium believed to be the most relevant to investigate using an adaptive platform trial.

Discussion

Is emergency medicine in Canada ready for adaptive designs?

Despite the appropriateness of adaptive designs for the ED, uptake has been woefully slow worldwide [21]. In

Table 2 Barriers and facilitators of adaptive platform trials for emergency medicine research in Canada classified using the Consolidated Framework for Implementation Research Domains

Domain	Construct	Facilitators	Barriers
Intervention characteristics	Evidence strength and quality	• Platform trials produced timely high-quality evidence during pandemic	• Few adaptive platform studies conducted in the field of emergency medicine
	Relative advantage	• Facilitate the study of repurposed drugs • Individual treatment groups may be removed from trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s) • Ensure types of adaptations are well understood	• Difficulty demonstrating clinical equipoise when multiple treatments are studied • Potential for low event rate • Outcomes must be rapidly known relative to time to complete accrual
	Adaptability	• Integration of usual practice • Clinicians can choose from multiple different domains • New experimental interventions can be more rapidly activated • Evaluation of the efficacy of multiple agents in a heterogeneous population • Multiple treatment groups that may change over time	• Dynamic disease changes (e.g., variants of concern, vaccine effectiveness) may create doubts in validity • Longer, more difficult consent process
	Trialability	• Simulations	• Higher up-front preparation costs
	Complexity	• Use of a master protocol	• Complex design planning • Statistical complexity inherent to the methodology • Involvement of many specialists and subspecialists • Extensive scientific deliberations to select candidate therapies
	Costs	• Financial simulations can inform costs by not using a typical trial design	• Need for highly trained staff and specialists • Long-term platform trials are costly to maintain
Outer Setting	Patient needs and resources	• Community engagement • Use of an open forum in the development	• Lack of representativeness resulting from reliance on busier, urban sites • Can prolong patient stay in the ED
	Cosmopolitanism*	• Collaborations with other adaptive platform trials • Recognition of the utility of the design and in learning new methodologies	None identified
	External policy and incentives	• Cultivate awareness on adaptive designs • Funding agencies overcoming budget uncertainties and regulatory concerns • Engagement of public health systems	• Time needed to justify study design to regulators • Reviewers not ready for adaptive platform trials • Heterogeneity in regulatory processes
Inner Setting	Structural characteristics	• Experienced staff • A clear workflow and hierarchy • Adequate secure storage and access to drugs • Using waiting time or information collected at triage to begin the recruitment or consent process	• Heterogeneity in site capabilities • Logistical complexity difficult to evaluate at local scale • Adequate research space • Insufficient equipment and technology

Table 2 (continued)

	Networks and communications	• Involvement of medical students, residents, nurses and physicians in knowledge transfer activities • Some research assistant activities can reduce clinical workflow (history-taking)	• Added burden to clinical and research workflows
	Culture	• Developed, collaborative research culture	• Distance in rapport between patients and their physicians, paternalism • Research assistants or staff feeling "in the way" of clinical staff
	Implementation climate and readiness	• Involvement of statisticians and research pharmacists • Capacity to extract data from multiple systems • Facilitated informed consent process • Support from institution • Incentives to continuing education • Dedicated recruitment or research space within the ED	• Chaotic ED environment • Explaining trial to potential participants in a chaotic ED • Clinical task at hand more important than consent and real time randomization • Cumbersome research ethics boards process • Low risk tolerance of research ethics boards and institutions • Local needs are not aligned with local resources
Characteristics of individuals	Knowledge and beliefs about intervention	• Communication • Overreliance on frequentist statistics • Willingness to trust the design and adhere to regulations (respecting blinding and avoiding data-peeking)	• Lack of knowledge and expertise • Lack of common vocabulary about APT methodology
	Individual state of change	None identified	• Investment of time
Process	Planning	• Thorough consultations with stakeholders • Use of simulations to clarify concepts • Use of simulations to plan implementation and sample size • Involvement of all stakeholders • Use of open forums	• Complex planning process • Lack of funding for study planning • Challenge for public and patient engagement and consultation for complex study design • Shortage of Bayesian experts • Time for training
	Engaging	• Frequent updates and communications as trial progresses • In-person meetings	• Extensive time for communication • Lack of funding to promote communications with research staff
	Executing	• Highly trained staff • Efficient coordinating center	• Data cleaning and harmonization variations
	Reflecting and evaluating	• Effective communication of interim results	• Keeping momentum with perpetual nature of adaptive platform trials

The CFIR has five domains: intervention characteristics, the outer setting, the inner setting, characteristics of individuals, and process; *Cosmopolitanism: The degree to which an organization is networked with other external organizations

a 2017 review of emergency medicine trials around the world, 93% of retrieved emergency medicine trials could have used adaptive methods [21]. In our rapid review, we found only one published adaptive platform trial conducted in part in Canadian EDs [25]. However, some trials are still ongoing [40, 41]. Certain design characteristics within adaptive trials are especially amenable to emergency medicine [42]. For emerging infections, population enrichment designs allow for the adjustment of inclusion criteria in order to hone in upon patients and sub-groups of the population most likely to benefit from a treatment [43]. Response-adaptive randomization designs use information gained as the trial progresses and as data come in to alter the allocation probability for all treatments, including the control treatment [23]. Importantly, response-adaptive randomization requires that outcomes are rapidly known

Table 3 Recommendations for adaptive platform trials in Canada from the literature and from interviews with experts

Number	Level	Recommendation	Corresponding ERIC* strategies
1	Policy	Federal and provincial governments and funding agencies should adopt a national strategy to support a novel integrated clinical research ecosystem like the United Kingdom in academic, community, and rural settings	Alter incentive/allowance structures; involve executive boards; mandate change
2	Policy	Federal and provincial governments should fund trial infrastructure to follow a Learning Health System that integrates trial processes and allows for the collection and analysis of data resulting from routine clinical care	Alter incentive/allowance structures; mandate change; obtain and use patients/consumers and family feedback
3	Policy	Funding agencies should support a national research network to plan, conduct, and maintain adaptive platform trials in emergency medicine	Alter incentive/allowance structures; build a coalition
4	Policy	Funding agencies should work with the research community to structure a framework for the evaluation of grant proposals to help reviewers overcome adaptive platform trial uncertainties	Create or change credentialing standards; conduct educational meetings; create a learning collaborative
5	Trialist	Trialists should develop educational tools to promote awareness on adaptive platform trials about methods, biostatistics, logistics and ethical considerations in emergency medicine	Conduct educational meetings; create a learning collaborative; conduct ongoing training
6	Trialist	Trialists should engage early with biostatisticians who have expertise with adaptive platform trial designs	Identify and prepare champions; conduct local needs assessment
7	Trialist	Trialists should engage early and actively with local ED clinicians to ensure the acceptability, relevance and feasibility of adaptive platform trials	Conduct cyclical small tests of change; model and simulate change
8	Trialist	The emergency medicine research community should identify priorities for future adaptive platform trials based on patients', clinicians', and policymakers' priorities	Identify and prepare champions; involve patients/consumers and family members; obtain and use patients/consumers and family feedback; conduct local consensus discussions
9	Site	Site investigators should use a readiness assessment tool upstream of implementation to assess feasibility of the study domains	Conduct local needs assessment
10	Site	Local research ethics committees should coordinate with a central ethics committee to streamline ethics approval	Assess for readiness and identify barriers and facilitators; build a coalition; use train-the-trainer strategies
11	Site	Site investigators should ensure regular communications about the adaptations impacting the trial conduct and standard of care	Promote adaptability; develop educational materials; organize clinician implementation team meetings; provide ongoing consultation; distribute educational materials
12	Patient	Trialists should engage patients at all levels of the planning, conduct, interpretation and knowledge translation of adaptive platform trials in emergency medicine	Involve patients/consumers and family members; prepare patients/consumers to be active participants
13	Patient	Policymakers should build and support a Canadian steering group that includes patients to formulate ethical guidelines for acceptable consent procedures for adaptive platform trials in emergency settings	Involve patients/consumers and family members; create or change credentialing standards
14	Patient	EDs should provide safe and quiet spaces to discuss research projects, answer questions and obtain informed consent	Change physical structure and equipment; mandate change; involve patients/consumers and family members

**ERIC*: Expert Recommendations for Implementing Change (13)

Table 4 Responses from experts when asked "If you had to implement an adaptive platform trial in the ED, what would your needs be?"

Importance	Need
★★★	A trial design that is both easy to administer and has clinical relevance, having the potential to meaningfully affect emergency medicine practice after completion of the trial
★★★	Methodological and biostatistical expertise, especially in Bayesian designs
★★★	Close collaboration with ethics boards and regulators across the provinces to determine the best ways to explain the assignment of patients to study arms and to solicit informed consent
★★	Timely and robust data collection processes and storage, ideally with linkage to electronic health records
★★	Deferred consent or waivers of consent to participate in a trial in emergency situations
★★	Funding for a platform over a lengthier horizon, ideally at the national level
★	Substantial clinical staffing with more hours of coverage at the ED who are both aware of ongoing trials and who collaborate with research staff
★	Buy-in across the research and clinical teams
★	Language services to recruit patients who do not speak English as a first language
★	Clear, timely communication and appropriate training at all levels of the platform

Items mentioned between 2 and 3 times by different experts were given ★ in terms of importance, between 4 and 5 given ★★, and 6 mentions and up, ★★★

relative to the time it takes to complete subject accrual, which makes this characteristic of adaptive platform trials especially well suited to emergency medicine research [20, 21]. This way, emergency medicine researchers can intervene with preplanned adaptations to the trial, while patients are still being enrolled in the study [44].

Statistical complexity, data infrastructure, access, monitoring, extensive simulations, and the involvement of many specialist stakeholders are all barriers that increase operational difficulty [17–24, 33–37]. These up-front costs to time and highly qualified resources can be insurmountable without adequate funding support and methodological expertise. There are now open-source adaptive platform trials resources [8] (e.g., Highly Efficient Clinical Trials Simulator (HECT), and PANDA: A Practical Adaptive & Novel Designs and Analysis toolkit; https://panda.shef.ac.uk/), and a growing body of emergency medicine methodologists trained in both frequentist and Bayesian designs who will no doubt be able to address this need for methodological expertise.

A critical barrier to implementing adaptive platform trials in emergency medicine is the chaotic ED environment, which limits recruitment and complicates trial explanations to ED staff and patients. The priority in emergency care will always be to address the emergency, and not to determine study eligibility—especially at a time where EDs are overburdened and under-resourced. The greatest facilitator to adaptive platform trials within EDs according to both clinicians and researchers is strong engagement and buy-in from the clinical team. Experts interviewed who performed screening for adaptive platform trials in the ED frequently mentioned that having a quiet, designated space to explain the trial and the consent process would improve recruitment and retention, and their involvement may also reduce clinician workload and lower a parallel barrier to adopting adaptive platform trials in the ED.

Which interventions are appropriate for adaptive platform trials in emergency medicine?

Concerning appropriate points of clinical inquiry, adaptive platform trials in emergency medicine would be especially effective for confirmatory phase (Phase III) clinical trials, which are large confirmatory studies meant to establish an acceptable profile of benefit or safety [24]. Sometimes outside of the ED but within the scope of emergency medicine, remote damage control resuscitation is another area well suited to adaptive designs [20], along with trauma [19]. Emerging and re-emerging infections present another point of inquiry relevant to both emergency medicine and public health. The implementation of such a trial that can theoretically run in perpetuity, pivot to respond to real-world changes, improve patient care in the ED may progress emergency medicine in a way that is both more equitable and efficient. In March 2020, shortly after the novel coronavirus was declared a global pandemic by the World Health Organization, the RECOVERY trial, an adaptive platform trial, was initiated by the National Institute for Health and Care Research in the United Kingdom and set a precedent for how adaptive platform trials can be effectively used in crisis situations to quickly identify life-saving treatments [45]. RECOVERY and the multitude of ongoing adaptive platform trials it inspired not only generate evidence for treating conditions, but more importantly, they emphasize the urgent need to make adaptive trials an integral part of contemporary ED care.

What can be recommended to improve the uptake of adaptive platform trials in Canadian EDs?

The limiting factors to the uptake of adaptive platform trials in emergency medicine appear to be both ethical and logistical, and it is from these angles that we have provided our 14 recommendations. Adaptive randomization is, on its face, more ethical than a standard fixed clinical trial design [34] and is considered more attractive by solicited ED patients [35]. The main ethical challenge of adaptive platform trials is to demonstrate equipoise—the ethical balance between treatment options—because there are often multiple treatment arms under study, and continuously updating results can sow doubts upon the likelihood of success across treatments and create confusion among participating clinicians. This necessitates clear and frequent statistical evidence to justify ongoing modifications. We recommend an iterative ethics process to navigate the complex ethical considerations with methodologists, emergency medicine clinicians, regulators and patient partners, in which there are feedback mechanisms to adjust over time. A concern for the potential manipulation of adaptive designs inappropriately used to data dredge or to ignore findings not in line with the desired outcome was raised during our panel presentation discussion. Adaptive designs, although flexible, do not allow decisions to be made on an ad hoc basis. All possible adaptations for a design must be described before the trial begins, and the data safety and monitoring board does not devise or make adaptations unless the revisions respond to a concern for the safety of research participants [46].

There is ongoing work in emergency medicine research to expand patient-oriented research and enable patient-centered adaptive platform trials in anticipation of future health crises. At the policy level, uncertainty as to the conduct of these trials could be mitigated with clear guidelines and expectations put forth by funding agencies for adaptive trials in collaboration with patient partners. At the trialist level, there is a need for more training, capacity building and a better understanding of patient, clinician and policy maker priorities for adaptive platform trials. Downstream at the site level, local research ethics committees should coordinate with a central ethics committee to streamline ethics approval and to navigate both provincial and local ethical considerations.

Conclusion

While adaptive platform trials demonstrate promise for emergency medicine, their adoption has been slow due to ethical, logistical, and operational challenges. Adaptive designs are well suited for emergency settings, particularly in confirmatory trials, emerging diseases, and trauma care, but barriers like a chaotic ED environment, complex statistical and methodological requirements, and regulatory considerations hinder their adoption. We provide 14 recommendations across 4 levels: policy, trialist, site and patient with the hope of overcoming these obstacles for the improvement of patient care within emergency medicine.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43678-025-00874-w.

Acknowledgements We gratefully thank Steve Goodacre, Jahnavi Chenrayan, Matthew Palmer, and Vi Ho for participating in our interviews. We also thank all the attendees of the 2024 CAEP Academic Symposium who contributed their feedback during the Symposium and those who helped plan the 2024 CAEP Conference.

Author contributions MA, LG, SM, SLM, AM, CH, IC, JCM, and PMA obtained funding for the study. NG, MA, SLM, AM, CH, IC, and PMA designed the study. NG, MA, and GOC collected and interpreted the data. NG, MA and PMA wrote the paper with input from all the authors. The study findings and final manuscript were critically revised and approved by all the authors. The study findings and final manuscript were critically revised and approved by all the authors.

Funding This research was funded through a SPOR Innovative Clinical Trials Catalyst Grant awarded by the Canadian Institutes of Health Research (#505652). Nathalie Germain has received a Canadian Institutes of Health Research Master's Award. Patrick M. Archambault has received a Fonds de recherche du Québec—Santé (FRQS) Senior Clinical Scholar Award (#283211).

Declarations

Conflict of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

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