Trauma Surgery & Acute Care Open

Leveraging existing infrastructure to answer clinically important questions in trauma: registry-based randomized clinical trials

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Received 20 January 2025
Accepted 12 March 2025

To cite:
Ghneim M, Zarzaur BL, Murphy PB. *Trauma Surg Acute Care Open* 2025;**10**:e001769.

BACKGROUND

Research-driven clinical changes have collectively contributed to a substantial reduction in trauma-related morbidity and mortality. As the field has evolved, conducting high-quality clinical trials faces challenges of insufficient funding opportunities, regulatory hurdles, data quality and consistency, and complex logistical coordination.[1–3] Therefore, continued investment in trauma research requires innovative and effective research methodologies. The National Trauma Research Action Plan (NTRAP) has emerged as a pivotal initiative, identifying key gaps and priorities in trauma research.[4] Concurrently, the American College of Surgeons Committee on Trauma (ACS-COT) Trauma Quality Improvement Program (TQIP) has established itself as a robust data infrastructure, capturing crucial information on trauma care across numerous institutions.[5] This article proposes that by leveraging the gaps outlined in NTRAP and using the existing data infrastructure of TQIP, researchers can design and implement powerful registry-based cluster randomized controlled trials (cRCTs) that overcome some of the current limitations and have the potential to significantly advance trauma care and improve patient outcomes.

NTRAP AND TQIP

NTRAP is a collaborative effort initiated by the National Trauma Institute, the Coalition for National Trauma Research, and the ACS-COT.[4] NTRAP's primary goal is to establish a coordinated, sustainable, and diverse national trauma research agenda. Through a rigorous consensus-building process involving diverse stakeholders, including clinicians, researchers, policymakers, and patient advocates, NTRAP has identified critical research priorities and gaps in 11 trauma topic areas.[4]

Similarly, TQIP, developed by the ACS-COT, is a national quality improvement initiative.[5] TQIP collects standardized data from trauma centers across the USA, providing a repository of information on trauma care processes and outcomes. TQIP data encompass a wide range of variables, including demographics, injury characteristics, treatments, complications and outcomes. While TQIP has proven successful as a quality improvement program, its reliance on retrospective data collection presents inherent limitations, including confounding and potential Hawthorne effects when hospitals focus on specific outcome measures.[6] While TQIP captures short-term, in-hospital outcomes, significant gaps exist in long-term outcome measures, including quality of life and functional and financial outcomes. These limitations preclude addressing some of the gaps in knowledge outlined by NTRAP. However, the potential for TQIP to be used to collect data and evaluate interventions in a prospective fashion should not be underestimated, particularly when augmented by the addition of research-specific variables.

REGISTRY-BASED CLINICAL TRIALS

A registry-based clinical trial (RBCT) offers an innovative alternative to financial and logistic-related challenges related to large multicenter trials.[7 8] Unlike traditional trials, RBCTs leverage pre-existing, well-supported clinical registries for data collection, which eliminates the need for a separate data management system. This method reduces the logistical burden and lowers costs since participating centers already have established data collection infrastructure and trained personnel.[7] Consequently, RBCTs are inherently more efficient, requiring less time, labor, and training to implement compared with conventional clinical trials.[7 8] The feasibility of RBCTs has been validated through studies such as TASTE,[9] SAFE-PCI,[10] and most recently the NSQIP-based RCT evaluating the prophylactic use of antibiotics for pancreaticoduodenectomy.[7 8]

Designing a cluster randomized clinical trial

Designing cRCTs requires careful consideration of several key factors.[11 12] Unlike individual randomization, cRCTs randomize groups or 'clusters' of participants, such as hospitals, clinics, or geographical areas, to intervention or control conditions. This approach is particularly useful when interventions are naturally implemented at a group level or when there is a risk of contamination between intervention and control participants within the same cluster. Trauma offers a unique opportunity to design and run cRCTs, as many hospitals implement guidelines differently and have unique local protocols. Key considerations in designing cRCTs include: (1) cluster selection and definition; (2) stratification or matching of clusters prior to randomization; (3) timing of randomization and recruitment; (4) blinding; and (5) ethical considerations (table 1).

Sample size calculations for cRCTs are more complex than for individually randomized trials due to the need to account for intracluster correlation

Table 1 Considerations for cluster RCTs

Consideration	Approach
Cluster selection and definition	Ensure clusters are well defined. Clusters should be representative of the target population.
Stratification or matching	Stratify clusters prior to randomization to improve balance across study arms.
Timing of randomization and recruitment	Decide whether to randomize clusters before or after participant recruitment depending on the study question.
Blinding	Can help reduce bias, but for most trauma questions, it is impossible.
Ethical considerations	The need for consent should be considered at both the individual and institutional levels.
Statistical analysis	Account for the clustered nature of the data and use appropriate statistical methods (eg, mixed-effects models, generalized estimating equations)

RCTs, randomized controlled trials.

(ICC).[13] The ICC quantifies the degree to which individuals within a cluster are more similar to each other than to individuals in other clusters. A higher ICC leads to a larger required sample size. To calculate the required sample size, researchers need to estimate the following: the expected effect size of the intervention; the ICC; the average cluster size; and the desired power and significance level. TQIP offers numerous advantages where the cluster size is known and the ICC is more easily calculated based on existing data. It is also crucial to consider potential cluster-level attrition and to plan for an adequate number of clusters, as the effective sample size in a cRCT is more closely related to the number of clusters than the total number of individuals. Given the complexity, a statistician experienced in cluster randomized designs should be consulted in the planning stages.

DEVELOPING AN ACS-COT TQIP CRCT TO ADDRESS GAPS IN KNOWLEDGE IDENTIFIED BY NTRAP

A successful multicenter prospective study typically demands significant financial investment and complex logistical planning, including the creation or acquisition of a secure data-sharing platform to manage patient data. Building on the demonstrated success of RRCTs, designing a registry-based cRCT using TQIP represents an innovative and efficient approach to advancing trauma research. This model can strategically incorporate key knowledge gaps identified by NTRAP to guide the assessment of outcomes and interventions, ensuring that the study addresses the most critical and impactful areas in trauma care. National trauma organizations, such as the Western Trauma Association, the Eastern Association for the Surgery of Trauma, and the American Association for the Surgery of Trauma, can support the design, implementation, and funding of the registry-based cRCTs. Their involvement lends validity to the study, provides essential expertise, and offers access to a robust research infrastructure necessary for executing a high-quality, multi-institutional trial. A single institutional review board can be used across all participating centers. To overcome TQIP's inherent limitations[6] such as data points not currently collected within TQIP, supplemental, but limited data collection strategies can be employed. These strategies may include follow-up assessments and specialized data abstraction to ensure a holistic and accurate evaluation of the intervention's impact and expand the achievable NTRAP questions. Examples of NTRAP aims relevant to RRCT are outlined in table 2.

There are a number of limitations related that must be considered and overcome for a successful registry-based cRCT. First, variability in data entry timelines across registries may impede planned interim and final analyses. This must be planned for prior to study initiation. Second, as described above, researchers must ensure all relevant data are captured by existing registries. The addition of variables increases local logistical demand and resource utilization. Relatedly, data quality is generally high; investigators must ensure, a priori, that the collected data accurately reflect the clinical outcome of interest. Finally, researchers must consider serious adverse event (SAE) reports and consent. Registries do not have a mechanism for reporting SAEs. Investigators must follow regulatory guidelines for SAE reporting to study investigators and the institutional review board. The 'Ottawa Statement' outlines a framework for consent in cRCT and should be used to guide investigators regarding exceptions.[14]

Overall, this approach holds significant implications for trauma research. By using an efficient, registry-based cRCT design, the methodology has the potential to produce

Table 2 Examples of NTRAP-identified gaps in knowledge amenable to TQIP-based cluster randomized design

Topic	Gaps in knowledge
Acute resuscitation	Does early whole blood improve outcomes in hemorrhagic shock? Prehospital or early hospital?
Geriatric trauma	Does a standardized delirium prevention practice in high-risk patients reduce the incidence of delirium in the geriatric trauma population? Do regional anesthetic techniques for lower limb orthopedic injuries improve outcomes in geriatric trauma patients? For older trauma patients on blood thinners (eg, warfarin, DOAC, antiplatelets), does a reversal protocol vs. no reversal protocol lead to lower rates of bleeding complications and improved survival/long-term functional outcomes?
Long-term functional outcomes and rehabilitation	In geriatric trauma populations, does consultation by a geriatric specialist reduce length of stay or readmissions compared with no geriatric specialist consultation?
Post-admission critical care	Does the use of whole blood in trauma resuscitation improve critical care outcomes compared with use of component therapy?
Trauma systems and informatics	In severely injured trauma patients in hemorrhagic shock, does the use of prehospital blood products decrease mortality compared with saline or no infusate? Does routine use of prehospital transfusion (pRBC vs. liquid plasma vs. whole blood) in trauma patients (including non-compressible torso (and/or junctional) hemorrhage) improve outcomes in patients who do not have rapid access to a trauma center (within the golden hour) compared with those who do not undergo prehospital transfusion?

DOAC, Direct Oral Anticoagulants; NTRAP, National Trauma Research Action Plan; pRBC, Packed Red Blood Cells; TQIP, Trauma Quality Improvement Program.

high-quality, generalizable evidence that can directly inform clinical practice and policy. Moreover, the collaborative effort with national trauma societies enhances the study's reach and impact, ensuring that findings are widely disseminated and translated into meaningful improvements in trauma care. These methods maximize the existing TQIP infrastructure and set a precedent for future research in the field, demonstrating the feasibility of cost-effective, large-scale clinical trials in trauma.

CONCLUSION

The field of trauma care stands at a critical juncture, where the need for high-quality evidence to guide practice meets significant challenges in conducting traditional clinical trials. The approach outlined in this article—leveraging the gaps identified by NTRAP and the data infrastructure of TQIP to conduct cRCTs—offers a promising path forward.

This innovative methodology addresses many of the limitations currently faced in trauma research, including sample size requirements, data quality and consistency, and logistical challenges. By using existing networks and data collection systems, it allows for the efficient conduct of large-scale, multicenter studies that can generate robust evidence to inform clinical practice.

Further, this approach aligns with the evolving landscape of healthcare research, which increasingly emphasizes pragmatic trials and learning healthcare systems. The ability to integrate research into existing quality improvement frameworks enhances the efficiency of research and facilitates the rapid translation of findings into practice. By bridging the gap between identified research priorities and existing quality improvement infrastructure, we have the potential to usher in a new era of trauma research—one that is efficient and impactful.

Acknowledgements EAST Multicenter Trials Committee

Collaborators EAST Multicenter Trial Committee: Navpreet Dhillon, Ryan P Dumas, Paul Albini, John Tierney, Jordan Lilienstein, Patricia Martinez Quinones, Carrie Laituri.

Contributors Drafting of the article: PBM, MG, BLZ. Critical revision: PBM, MG, BLZ. Guaranteed by PBM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests PBM provides educational consultation for Boston Scientific through the Medical College of Wisconsin.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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