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# Regulatory challenges in conducting human subjects research in emergency settings: the National Trauma Research Action Plan (NTRAP) scoping review

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## SUMMARY

The complexity of the care environment, the emergent nature, and the severity of patient injury make conducting clinical trauma research challenging. These challenges hamper the ability to investigate potentially life-saving research that aims to deliver pharmacotherapeutics, test medical devices, and develop technologies that may improve patient survival and recovery. Regulations intended to protect research subjects impede scientific advancements needed to treat the critically ill and injured and balancing these regulatory priorities is challenging in the acute setting. This scoping review attempted to systematically identify what regulations are challenging in conducting trauma and emergency research. A systematic search of PubMed was performed to identify studies published between 2007 and 2020, from which 289 articles that address regulatory challenges in conducting research in emergency settings were included. Data were extracted and summarized using descriptive statistics and a narrative synthesis of the results. The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines. Most articles identified were editorial/commentary (31%) and published in the USA (49%). Regulatory factors addressed in the papers were categorized under 15 regulatory challenge areas: informed consent (78%), research ethics (65%), institutional review board (55%), human subjects protection (54%), enrollment (53%), exception from informed consent (51%), legally authorized representative (50%), patient safety (41%), community consultation (40%), waiver of informed consent (40%), recruitment challenges (39%), patient perception (30%), liability (15%), participant incentives (13%), and common rule (11%). We identified several regulatory barriers to conducting trauma and emergency research. This summary will support the development of best practices for investigators and funding agencies.

## BACKGROUND

The complexity of the care environment, the emergent nature, and the severity of patient injury make conducting clinical trauma research challenging.[1] These challenges hamper the ability to conduct potentially life-saving research that aims to deliver pharmacotherapeutics, test medical devices, and develop technologies that may improve patient survival and recovery.[2] Regulations intended to protect research subjects impede scientific advancements needed to treat the critically ill and injured and balancing these regulatory priorities is challenging in the acute setting. As a scoping review, this work attempted to systematically identify and summarize regulatory challenges in conducting trauma and emergency research.[3] Scoping reviews allow researchers to conduct a comprehensive search to gather information on a specific topic focused area. The information in this review synthesizes the evidence and assesses the size and scope of available research surrounding this topic.

In 2014, the National Trauma Institute, now known as the Coalition for National Trauma Research (CNTR), surveyed 16 federally funded investigators to identify facilitators and barriers to conducting trauma research.[4] Forty percent of the investigators reported challenges in obtaining regulatory approval. Several investigators encountered difficulties navigating the requirements for the Department of Defense (DoD) Human Research Protections Office (HRPO) approval processes. Multisite studies were delayed due to multiple institutional review board (IRB) reviews with conflicting revisions. The mean number of days from funding selection to IRB approval was 210 days, while the mean number of days from funding selection to the HRPO approval was 401 days. Other multisite studies have reported timelines of up to a year to obtain approval.[5–7] These data are evidence of the challenges investigators encounter while initiating trauma studies and the need for guidance.

In the 2016 National Academies of Sciences, Engineering and Medicine (NASEM) report that called for a national trauma care system, the authors concluded that 'a learning trauma care system cannot function optimally in the current federal regulatory environment'.[2] Identified barriers included ambiguity in the interpretation of federal regulations, regulatory silence on specific issues, a lack of flexibility in interpreting data that may lead to regulatory approval for new therapies, and the various applicable federal regulations. The NASEM report also recommended identifying regulatory barriers to trauma research and suggested that federal agencies work 'to revise research regulations

and reduce misinterpretation of the regulations through policy statements'.[2]

In 2018, the CNTR received DoD funding to develop the National Trauma Research Action Plan (NTRAP) (Contract No. W81XWH-18-C-0179). The NTRAP builds on the NASEM report with the understanding that reducing regulatory challenges requires a resourced, coordinated, and multidisciplinary approach. NTRAP's three aims were to: (1) perform a gap analysis of trauma research; (2) define optimal metrics to assess long-term outcomes in injured patients; and (3) identify trauma research regulatory barriers, develop regulatory best practices, and collaborate with federal entities to define optimal end points. On completion, the NTRAP will provide a road map for investigators and funding agencies to prioritize trauma research across the continuum of care. The objective of this study and analysis is to conduct a literature review to identify barriers and misinterpretations regarding the conduct of trauma research in emergency settings. Although researchers may be aware of research barriers, this scoping review details how often these barriers have appeared in the literature since 2007; therefore, providing a strong foundation of themes to prioritize and guide future direction on next steps.

## METHODS

### Protocol

Our scoping review protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines and revised by members of the NTRAP Publications Committee for scientific content and consistency of data interpretation with previous NTRAP publications.

### Eligibility criteria

Studies were included if they were in English and published from January 1, 2007 through November 4, 2020. Selecting 2007 as the beginning of the published date range aligned with the year that Congress passed the Food and Drug Administration Amendments Act of 2007, requiring more clinical trials registration, sharing additional trial information, and the submission of summary results, including adverse events.[8] Regulatory issues that were not applicable in the USA were excluded from the thematic analysis.

### Information sources

NTRAP investigators searched articles in PubMed using the search strategy detailed in online supplemental appendix A. Maintained by the National Center for Biotechnology Information, PubMed is the best source to capture the majority of the published work in this area.[9] The scoping review included human subjects protection issues in conducting trauma and emergency research using a combination of text words and Medical Subject Headings terms. The search strategy was developed in collaboration with an experienced librarian. Search results were downloaded and exported into EndNote (Thomson Reuters, New York, USA). The electronic database search was supplemented by checking the citation lists of included articles. Covidence, a Cochrane Review production tool, was used for article screening and data extraction due to its ability to manage and streamline the process.[10]

### Selection of sources of evidence

All citations were imported from Endnote into Covidence, and duplicate records were removed. The selection of sources of evidence was based on the inclusion/exclusion criteria and carried out manually by six reviewers in three stages:

1. Title and abstract screening (CLV, MAP)
2. Full-text review (CLV, MAP)
3. Extraction (ANM, AZ, CS, AT) with oversight and quality checking on all cases (CLV)

Disagreements on study selection were resolved by the consensus of two researchers (CLV, MAP).

### Data charting process

A data charting form was developed by two researchers (CLV and MAP) to determine variable extraction. Data specific to the review question and necessary for the narrative synthesis were extracted, including study characteristics, population characteristics, regulatory body discussed, and regulatory challenges addressed. The form was then reviewed by two additional researchers (EMB and JPH-E) for the inclusion of other critical variables (see online supplemental appendix B). These variables were used to create a data dictionary for the extraction phase. A training session was held with the review team, and ongoing training sessions were conducted to ensure that key points of clarification were examined. A team of four research associates (ANM, AZ, CS, AT) extracted the data, discussed the results, and updated the data charting form in an iterative process. One reviewer independently extracted the data from each included article, and a lead researcher (CLV) conducted quality assurance checks for all studies. Quality assurance checks were conducted using the data charting form to confirm that all the information was extracted and that each regulatory challenge discussed in the article was notated.

### Data items and synthesis of results

We abstracted data on article characteristics (eg, author, year of publication, country of origin, study type, keywords), population characteristics (eg, enrollment methods, number of participants, special populations, victims of violence, health disparities), regulatory issues mentioned and discussed (eg, regulatory body discussed, challenges addressed), along with conclusions and recommendations for researchers (table 1). Categories within this search included obtaining informed consent, working with legally authorized representatives (LARs), research ethics, research subject protection, understanding of applicable regulatory rules and processes, use of single IRBs for multisite studies, exception from informed consent (EFIC), patient participation, and recruitment. The characteristics of each article were summarized (52 elements) and a narrative synthesis of the results is presented following the PRISMA-ScR guidelines (figure 1).[11]

## RESULTS

### Search results

The search returned 2178 original articles for initial screening. Based on the inclusion and exclusion criteria, 289 studies were included in the final data extraction (figure 1). Most articles were from the US (49%), followed by the UK (11%), Canada (7%), Australia (4%), France (2%), Germany (2%), and 21% of articles did not reference a specific country (figure 2). Most articles (31%) were editorial/commentary in nature.

The research team worked with the NTRAP Investigators Group to identify regulatory-related keywords to be used as important categories. Table 2 shows the distribution of the regulatory challenges addressed. Regulatory challenges discussed in the articles were classified into 15 categories

**Table 1** Study characteristics

| Variable | Frequency | Percent (%) |
|---|---|---|
| Year of publication | | |
| 2007–2009 | 70 | 24 |
| 2010–2012 | 45 | 16 |
| 2013–2015 | 73 | 25 |
| 2016–2018 | 72 | 25 |
| 2019–2020 | 29 | 10 |
| Country | | |
| USA | 143 | 49 |
| UK | 33 | 11 |
| Canada | 19 | 7 |
| Australia | 12 | 4 |
| France | 6 | 2 |
| Germany | 5 | 2 |
| N/A | 62 | 21 |
| Study type | | |
| N/A | 130 | 45 |
| Qualitative | 68 | 24 |
| Quantitative | 68 | 24 |
| Mixed methods | 23 | 8 |
| Study design/Manuscript type | | |
| Editorial/Commentary | 89 | 31 |
| Other | 28 | 10 |
| Systematic review | 27 | 9 |
| Surveys | 24 | 8 |
| Other literature review | 20 | 7 |
| Observational | 19 | 7 |
| Randomized controlled trial | 19 | 7 |
| Other type of review/report | 15 | 5 |
| Interviews (structured or semi-structured) | 13 | 4 |
| Multiple designs | 10 | 3 |
| Case report | 8 | 3 |
| Case series | 7 | 2 |
| Policy statement | 6 | 2 |
| Non-randomized experimental study | 1 | 0 |
| Scoping review | 1 | 0 |
| Meta-analysis | 1 | 0 |
| Case-control study | 1 | 0 |
| Trauma/Emergency specific | 263 | 91 |
| Disparities in study enrollment addressed | 26 | 9 |
| Pediatric focused | 42 | 15 |
| Geriatric focused | 4 | 1 |
| Outbreak related | 26 | 9 |
| COVID-19 related | 3 | 1 |
| Regulatory body discussed | | |
| US Food and Drug Administration (FDA) | 119 | 41 |
| US Department of Health and Human Services (HHS) | 42 | 15 |
| EU/European Commission | 8 | 3 |
| Department of Defense (DoD) | 9 | 3 |
| National Institutes of Health (NIH) | 12 | 4 |
| Special populations included or addressed | | |
| Children | 52 | 18 |
| Prisoners | 3 | 1 |
| Pregnant women | 13 | 4 |
| Mentally disabled persons | 3 | 1 |
| Economically/Educationally disadvantaged | 9 | 3 |
| Students | 8 | 3 |
| Victims of violence | 19 | 7 |

Continued

**Table 1** Continued

| Variable | Frequency | Percent (%) |
|---|---|---|

DoD, Department of Defense; EU, European Union; FDA, Food and Drug Administration; N/A, not available; NIH, National Institutes of Health.

(figure 3): informed consent (225; 78%), research ethics (187; 65%), IRB (158; 55%), human subjects protection (156; 54%), enrollment (152; 53%), EFIC (147; 51%), engaging LARs (144; 50%), patient safety (118; 41%), community consultation (117; 40%), waiver of informed consent (WIC) (116; 40%), recruitment challenges (112; 39%), patient perception (88; 30%), liability (44; 15%), participant incentives (38; 13%), and the common rule (32; 11%). We also noted mentions within the articles about challenges specific to research engaging special populations and research during a pandemic or disease outbreak. Based on these results of the scoping review, 15 regulatory challenge topic areas were selected for inclusion in the thematic analysis (table 3). A complete list of challenge statements is mentioned in online supplemental appendix C. The regulatory topic areas below are listed from highest to lowest percentage; yet, researchers will have the ability to review the challenges identified to determine the areas to focus on. Furthermore, challenges that are associated with rules and policies can easily be identified and grouped together to address with the appropriate regulatory agencies.

## Informed consent

Informed consent was examined in 78% of the articles. Challenges identified included:

1. Improving readability of informed consent documents (eg, reducing redundancy, length of forms).
2. Communicating elements of informed consent in non-overwhelming and understandable ways.
3. Adequately considering cultural biases when addressing informed consent.

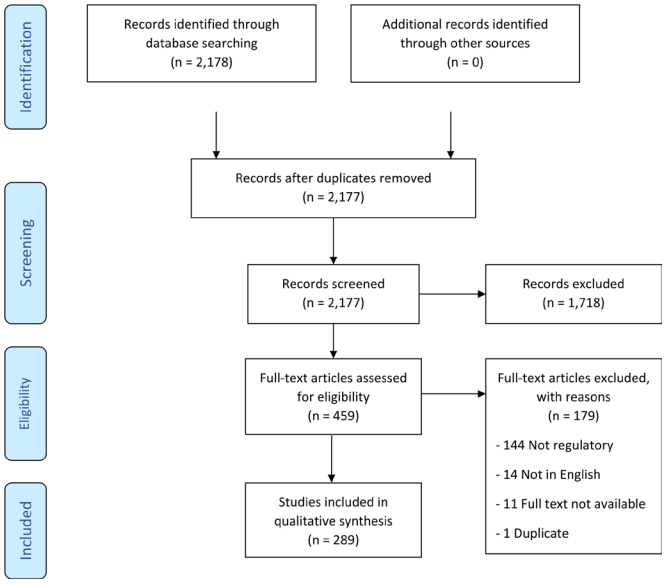
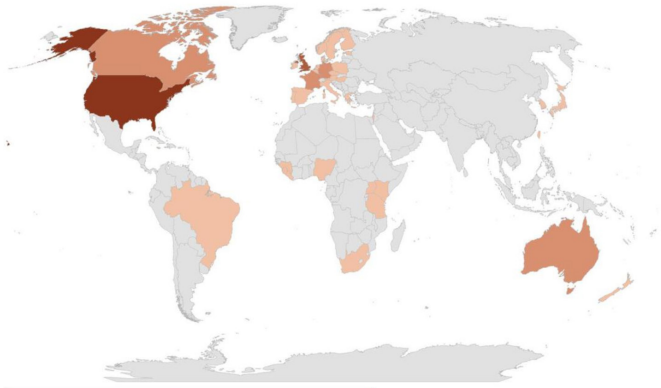



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of studies for inclusion in a scoping review of human subjects' protection and regulatory challenges in conducting emergency research.



| Top Countries | # of studies |
|---|---|
| US | 143 |
| UK | 33 |
| Canada | 19 |
| Australia | 12 |
| France | 6 |

**Figure 2** Heat map illustrating the countries in which the studies were conducted.

4. Developing trust and rapport with patients during the informed consent process.

## Research ethics

Researchers have a responsibility to protect their patients, provide risks and benefits, and disclose adverse events. Research ethics were discussed in 65% of the articles that cited challenges such as:

1. Ensuring study efficiencies to minimize patient exposure to potentially ineffective or unsafe therapies.
2. Ensuring adverse events disclosure to participants.
3. Ensuring that the patients who are the most likely to benefit from the research have the opportunity to participate.
4. Determining if regulations for emergency research may threaten public health by impeding advances in life-saving treatments.

**Table 2** Regulatory challenges addressed

| Variable | Frequency | Per cent (%) |
|---|---|---|
| Informed consent | 225 | 78 |
| Research ethics | 187 | 65 |
| Institutional review board | 158 | 55 |
| Human subjects protection | 156 | 54 |
| Enrollment | 152 | 53 |
| Exception from informed consent | 147 | 51 |
| Legally authorized representative | 144 | 50 |
| Patient safety | 118 | 41 |
| Community consultation | 117 | 40 |
| Waiver of informed consent | 116 | 40 |
| Recruitment challenges | 112 | 39 |
| Patient perception | 88 | 30 |
| Liability | 44 | 15 |
| Participant incentives | 38 | 13 |
| Common rule | 32 | 11 |

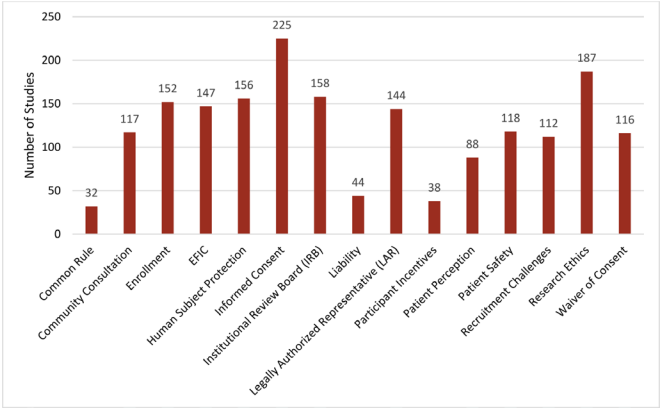



**Figure 3** Regulatory challenges addressed. EFIC, exception from informed consent.

## Institutional review board

IRBs are formally designated to review and monitor research involving human subjects. Over half of the articles (55%) detailed challenges that researchers face concerning the tasks that are required of their IRBs including:

1. Using multiple IRBs in a multicenter clinical trial, leading to inconsistent interpretation and consideration of the same protocol at different sites.
2. Varying implementation of community consultation and public disclosure activities across trial sites as determined by local IRBs.
3. Encouraging institutions involved in multi-institutional studies to use joint review or reliance on the review of another qualified IRB to avoid duplication of effort.
4. Working with local IRBs that have little to no experience with EFIC.

## Human subjects protection

Protecting patient information, their personal well-being, and interacting with patients are all important when protecting human subjects. Human subjects' protection was discussed in 54% of articles. Challenges discussed included:

1. Providing trial information that accommodates the lack of health literacy among large segments of the US population.
2. Ensuring participants' concerns and opinions are being heard prior to, during, and after enrollment.
3. Ensuring that IRBs are adequately overseeing patient safety throughout clinical trials.
4. Recognizing all potential conflicts of interest, disclosing them properly, and working with the IRB and research team to minimize them.

## Enrollment

The ability to determine eligible research participants and enroll them in a research study was discussed in 53% of articles. Specific challenges included:

1. Ensuring participant enrollment within the recruitment window.
2. Creating a network of institutions to produce larger patient populations.
3. Addressing possible impacts of enrollment in more than one trial (co-enrollment).
4. Developing trust and rapport with patients and families.

**Table 3** Definitions of regulatory challenges

| Regulatory challenge | Definition | Study |
|---|---|---|
| Common rule | The 'common rule' is the popular term for the Federal (US) Policy for the Protection of Human Subjects 45 CFR part 46, which outlines the criteria and mechanisms for IRB review of human subjects research. | Office for Human Research Protections[24] |
| Community consultation | The requirement for community consultation is one of the special protections provided whenever an EFIC is granted for emergency research. It serves as a 'vehicle to listen to the community's interests and concerns, to address ethical issues, and to communicate information about the research to the community'. | Ragin *et al*[25] |
| Enrollment | Determining eligible research participants for a research study. | Chamberlain *et al*[23] |
| Exception from informed consent (EFIC) | EFIC allows patients to be treated as part of research studies under special and rare circumstances. It can only be used in life-threatening emergencies, when there is a possibility for direct benefit to participants, and when consent is not possible. These studies are very public and transparent and have been discussed in the community. | Klein *et al*[26] |
| Human subjects protection | Human subjects protection refers to the federal, state, and institutional policies, procedures, and ethical considerations that protect the rights and welfare of people who participate in research as the subjects of that research. | Perlman[18]<br>University of Michigan[27] |
| Informed consent | The process in which a healthcare provider/researcher educates a patient about the risks, benefits, and alternatives of a given procedure or intervention. | Shah *et al*[28] |
| Institutional review board (IRB) | An administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. This group has been formally designated to review and monitor biomedical research involving human subjects. | Mansbach *et al*[29] |
| Legally authorized representative (LAR) | A person authorized under applicable law to consent on behalf of a prospective human subject to the subject's participation in a research study and to authorize the use or disclosure of protected health information. | Gillenwater[30]<br>Biros *et al*[31] |
| Liability | Legal risks associated with research involving human subjects. | Kapp[32] |
| Participant incentives | Something made to compensate individuals for participation in research studies. | Bernstein and Feldman[33] |
| Patient perception | Refers to the patients' view of research. | Ventolini *et al*[34] |
| Patient safety | Prioritizing patient/participant welfare. | Iserson[12] |
| Recruitment | Registering or entering eligible research participants into a research study. The dialogue that takes place between an investigator and a potential research participant. | Patel *et al*[35] |
| Research ethics | Norms of conduct that distinguish between acceptable and unacceptable behavior in research. A set of ethical guidelines that guide us on how scientific research should be conducted and disseminated. | Shah[36] |
| Waiver of informed consent (WIC) | A WIC requires a researcher to seek approval from an ethical review body to use a person's personal information or personal health information without actually obtaining consent directly from the individual in order to use that information in a research project. | Salzman *et al*[37]<br>Klein *et al*[26] |

Refer to bibliography for full citation.

## Exception from informed consent

EFIC allows patients to be treated as part of research studies without consent under special and rare circumstances. It can only be used in life-threatening emergencies, when there is a possibility for direct benefit to participants, and when consent is not possible. When using EFIC, researchers must ensure that the community is aware of the study and its benefits and opt-out procedures. EFIC was discussed in 51% of articles. Specific challenges included:

1. Recognizing that some participants will not recall any community consultation or public disclosure efforts before their enrollment.
2. Effectively communicating with community members regarding an EFIC study and opt-out procedures.
3. Understanding why community members opt out and providing adequate opt-out opportunities.
4. Employing adequate opportunities for community members to opt out of EFIC trials.

## Legally authorized representative

The use of LARs in which an authorized person may consent on behalf of a participant was discussed in 50% of the articles. Competency, capacity, and comprehension of the LAR were discussed as challenges, including:

1. Determining who is eligible to be a patient's LAR as dictated by-laws.
2. Locating a patient's LAR in a timely manner.
3. Ensuring that a LAR knows what the patient's wishes would be.
4. Evaluating whether a LAR is competent to provide consent.

## Patient safety

Patient safety was discussed in 41% of articles. Key challenges to consider include:

1. Ensuring that researchers place participants' welfare ahead of their own interests.
2. Validating that a researcher's assertion that the medication, technique, equipment, or system being tested is at least no worse than the current standard of care.
3. Estimating the amount of psychological and emotional distress that may emerge when asking participants questions about their past traumatic experiences.
4. Balancing the need for researcher objectivity with the need to decrease the emotional distance between researcher and participant in trauma settings.

## Community consultation

Community consultation is a special protection when EFIC is granted for emergency research. Forty percent of articles detailed challenges with the community consultation process including:

1. Gathering more information on community consultation to better understand the various levels of support, opposition, and uncertainty that are present in the community.
2. Using patient stakeholders in the development of content for materials and website that will be shared during the community consultation process.
3. Garnering interest and engaging the community in the consultation process.
4. Using public disclosure methods to ensure that the target population has a general understanding of the research study.

## Waiver of informed consent

Under a WIC, a researcher receives IRB approval to use a person's personal or health information without actually obtaining consent in order to use that information in a research project (eg, to determine if someone may be eligible for enrollment).

WIC was discussed in 40% of articles and the following challenges were cited:

1. Ensuring that enrollment under WIC only occurs in instances where it is reasonable to believe the patient would typically have consented and the study is not culturally or morally controversial.
2. Verifying that the magnitude of harm/discomfort anticipated in the research is not greater than encountered in routine medical examination and testing.
3. Encouraging consistent and rigorous reporting of regulatory prestudy requirements for publications and websites such as ClinicalTrials.gov.
4. Ensuring that enrollment under WIC only occurs in instances where it is reasonable to believe that the project is not culturally or morally controversial.

### Recruitment

The recruitment window often impacts the ability to identify eligible patients quickly and adequately. Recruitment was discussed in 39% of articles, and specific challenges included:

1. Reducing delays in identifying eligible patients.
2. Accurately representing the benefits of the study.
3. Burdening patients and families by trying to recruit during a vulnerable time.
4. Recruiting patients to more than one study (bombarding the patient).

### Patients' perception

Patients' perception was identified as a challenge in 30% of the articles, and some examples of challenges cited included:

1. Engaging community members to determine the acceptability of medical research and resuscitation research in particular.
2. Fostering patient engagement in the development and conduct of emergency and trauma research.
3. Minimizing the therapeutic misconception (ie, the tendency of prospective participant to assume that participation improves their chances for a favorable outcome).
4. Measuring the rate of approval or acceptance of an EFIC study among community members.

### Liability

Liability pertaining to the legal risks associated with human subjects' research was identified in 15% of the articles. Challenges included:

1. Identifying valid instruments to assess capacity to consent among intoxicated patients.
2. Obtaining written informed consent in the prehospital transport environment.
3. Managing liability associated with data repositories and data sharing.
4. Determining if the potential benefits of a study conducted under a waiver of consent justifies possible infringement on individual rights.

### Participant incentives

Another challenge that was addressed in 13% of articles was participant incentives or payments that are made to compensate individuals for participation in research studies. Challenges pertaining to incentives included:

1. Accurately disclosing the type and size of incentives.
2. Determining if incentives improve recruitment and retention.
3. Identifying an appropriate payment or incentive for specific populations.
4. Selecting incentives that are easy and convenient to use.

### Common rule

The common rule, which outlines the criteria and mechanisms for IRB review of human subjects research, was discussed in 11% of articles. Some examples of challenges were:

1. Ensuring that research complies with federal regulations.
2. Reducing the administrative burden of research.
3. Redefining criteria and terminology associated with vulnerable populations.

Furthermore, across all regulatory topic areas, we evaluated articles to determine the specific challenges presented by outbreak-related issues, special populations, and disparities.

### Outbreak/COVID-19-related issues

The challenges associated with conducting research during a pandemic or disease outbreak were discussed in 9% of articles. Flexibility is a critical component that emerged as the overall theme in the ever-changing climate characterized by an outbreak or pandemic. Some specific challenges cited were:

1. Expeditiously reviewing large clinical trial protocols.
2. Modifying the clinical trial protocol and design based on what is happening during an outbreak.
3. Maintaining the flexibility to adapt as an outbreak evolves.
4. Using alternative consent models to feasibly conduct research during a pandemic.

### Special population and disparities

Researchers recognize that protecting special participant populations such as pregnant women, prisoners, children, physically or mentally impaired persons, economically or educationally disadvantaged persons, and other vulnerable groups must be a research priority. Thirty-one percent of articles discussed special populations and cited challenges such as:

1. Communicating the unique risks and benefits that apply to children and special populations.
2. Ensuring that the enrollment of racial/ethnic minorities is proportionate to the prevalence of the condition being studied.
3. Addressing mistrust of research investigators by various racial and ethnic groups.
4. Avoiding the exploitation of vulnerable populations by researchers during emergency situations.

## DISCUSSION

### Regulatory barriers to trauma and emergency research

Regulations, intended to protect research subjects, impede scientific advancements needed to treat the critically ill and injured. A greater understanding of regulatory barriers will help to ensure that patient safety is maintained at all times.[12] Misinterpretation of regulatory requirements causes research teams to not have a full understanding of the intended goal of specific rules, regulations, and policies. Additionally, coordinating clinical studies across multiple sites and IRBs can be time-consuming and inefficient; however, multisite studies are necessary because a single trauma center usually do not have sufficient patient volume to conduct an adequately powered study. A recent report by the Defense Health Board noted, 'The IRB process is currently fragmented across the Services with different protocol templates, requirements, and methods of implementation'.[13] Investigators may be unaware of the unique DoD requirements for

the protection of human subjects (eg, second-level review by HRPO)[14] and of specific language in consent forms.[15] Additional barriers include fears of legal liability[16] and misunderstanding of the types and sizes of incentives provided to both participants and researchers engaged in clinical trials.[17]

## Challenges in obtaining consent and enrollment

Preserving the rights and welfare of patients is at the forefront of human subjects protections in trauma research.[18] Traditional informed consent indicates that adequate dialogue has occurred between a potential participant and a researcher.[19–21] However, previous trauma research demonstrates that severely injured trauma patients can seldom provide consent at the time of injury, and an LAR is often unavailable, in which case EFIC is necessary to recruit a representative sample.[22] Furthermore, as the trauma setting is emotionally complex, emergency researchers must be conscientious when approaching emotionally distraught LARs for trial enrollment.[23]

Implementation of EFIC trials requires a process of community consultation with those who could be potentially enrolled in the trial. Through engagement with community members, researchers are able to measure community members' perceptions of the proposed research activities. However, different IRBs have varied interpretations of the level of community engagement and support required to move forward with trial enrollment. The logistical challenges in implementing these requirements and the variable approaches have been seen as a barrier to the conduct of EFIC research. Further complicating the issue, there is a unique requirement for a high-level waiver from the Secretary of the Army prior to conducting DoD-funded research using EFIC.

## Limitations

Although publications originating from other countries were identified in the review, analysis of regulatory challenges was limited to those pertaining to the USA because the project's scope is to develop an action plan for the USA. Therefore, this review did not explore regulatory challenges related to conducting international or multinational research. This review also did not detail the limitations in conducting research on military service members. There are special and unique requirements for active-duty service members in participating in research.

## Next steps

In the next phase of NTRAP development, CNTR convened a multidisciplinary expert panel to complete an online Delphi survey regarding the importance or impact of the challenge statements identified in the scoping review. The panel reviewed survey results, made recommendations to address the most challenging topics, and outlined strategies to overcome these barriers. The results of the Delphi survey will be submitted for publication in 2023. Additionally, the results will be shared with regulatory bodies and the investigator team will request clarifications on guidance documents. The scoping review and stakeholder survey results will be included in the NTRAP. Including this critical information regarding regulatory challenges will serve to better direct the NTRAP, with the goal of refining the future direction of trauma research. The final step of these activities will be the creation of an investigators' toolkit for navigating regulatory requirements in trauma and emergency settings research.

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**Appendix A**. PubMed Search Strategy

(trauma research[tiab] OR emergency research[tiab] OR resuscitation research[tiab] OR (("Research"[mesh:noexp] OR "Biomedical Research"[mesh:noexp] OR "Research Design"[mesh:noexp] OR "Research Support as Topic"[mesh] OR "Clinical Trials as Topic"[mesh]) AND ("Emergencies"[mesh] OR "Emergency Medicine"[mesh] OR "Emergency Service, Hospital"[mesh] OR "Traumatology"[mesh])))

**Appendix B.** List of Extracted Variables

- Manuscript Title
- Authors of Manuscript
- Year of Publication
- Country of Origin
- Keywords
- Study Population
- Special Populations/Victims of Violence
- Trauma/Emergency Specific
- Pediatric or Geriatric Focused/age range to define each
- Outbreak Related/COVID-19 Related
- Study Type: quantitative, qualitative, or mixed
- Study Design: observational, RCT, systematic review, meta-analysis
- Number of patients included in the study/ Number of studies or papers in the review
- Years of Subject Enrollment
- Participant Recruitment Methods
- Regulatory Body Discussed (ex: FDA)
- Health Disparities Addressed
- Regulatory Challenge(s) Addressed
    - Informed Consent
    - Exception from Informed Consent (EFIC)
    - Waiver of Consent
    - Legally Authorized Representative (LAR)
    - Enrollment
    - Patient Safety
    - Recruitment Challenges
    - Patient Perception
    - Human Subjects Protection
    - Institutional Review Board (IRB)
    - Research Ethics
    - Common Rule
    - Liability
    - Participant Incentives
    - Community Consultation
    - Other Regulatory Challenges

- Regulatory Policies Addressed
- Finding/Recommendation Strategy
- Conclusion
- Study Funding Source

**Appendix C.** Challenge Statements

## Community Consultation

- Garnering interest and engaging the community in the consultation process
- Utilizing social media platforms as a viable option for facilitating community consultation
- Allowing trained university students to discuss research participation
- Understanding the geographic community (i.e., people in a geographic location/boundary area) versus the conditions community (i.e., the community of people where the medical condition is more likely to occur)
- Engaging with key community organizations
- Focusing on reducing costs and efficiency with traditional methods of community consultation (e.g., in-person meetings, newspaper, radio messages)
- Gathering more information on community consultation to better understand the various levels of support, opposition, and uncertainty that are present in the community
- Engaging Emergency Medicine Services (EMS) in community consultation efforts
- Utilizing patient stakeholders in the development of content for materials and websites that will be shared during community consultation process
- Maintaining sufficient focus on risks and benefits versus the specific features of the investigational agent
- Developing an assessment tool that helps researchers determine the adequacy of their community consultation process
- Determining what constitutes sufficient community consultation
- Utilizing public disclosure methods to ensure that the target population has a general understanding of the research study

## Common Rule

- Understanding the three levels of review for human research: exempt, expedited, and full (committee)
- Ensuring that research complies with federal regulations
- Determining when consent is ethically necessary
- Allowing research to be performed without informed consent in emergency situations
- Evaluating the risks versus benefits in research participation
- Maintaining regulatory flexibility
- Reducing the administrative burden of research
- Redefining criteria and terminology associated with vulnerable populations

## Enrollment and Recruitment

- Involving patients/participants who lack decision-making capacity due to the severity of their medical condition
- Reducing delays in identifying eligible patients
- Ensuring that the study team is able enroll patients within the recruitment window
- Prioritizing communication with patients and surrogates after initial enrollment (post-enrollment communication)
- Focusing greater attention to the post-enrollment debriefing process
- Reducing participants' perceptions of coercion into trial enrollment
- Addressing possible impacts of co-enrollment on clinical trials
- Ensuring that the enrollment of genders is proportionate to the prevalence of the condition being studied
- Using remote telemedicine to randomize and enroll patients
- Providing verbal communication and study materials in the patient's language
- Burdening parents and families by trying to recruit during a vulnerable time
- Addressing participants' concerns about time requirements during consent process
- Developing trust and rapport with patients and families
- Recruiting patients to more than one study (bombarding the patient)
- Creating a network of institutions to produce larger patient populations
- Accurately representing the benefits of the study during recruitment
- Relying solely on the presence of a research nurse to obtain consent
- Recruiting potential participants who lack a social support network
- Reducing fears of exploitation, therapeutic misconceptions, and myths about research
- Dispelling the myth that participating in clinical research will delay medical care
- Identifying potentially eligible patients before arrival to hospital
- Addressing fear and distrust of law enforcement and concerns that participation in research will have legal implications
- Utilizing machine learning algorithms to accurately predict patient enrollment numbers
- Discussing flexibility in scheduling research and follow up activities

## Exception From Informed Consent (EFIC)

- Recognizing that some participants may not recall their enrollment into an EFIC clinical study
- Recognizing that some participants will not recall any community consultation or public disclosure efforts prior to their enrollment in an EFIC trial
- Understanding that participants may not be aware of opt-out procedures
- Determining when to solicit and honor objections to EFIC trial enrollment from non-legally authorized representatives
- Ensuring that participants and their LARs recognize and understand the difference between clinical care and clinical research
- Employing adequate opportunities for community members to opt out of EFIC trials
- Recording and reporting the conditions and processes through which EFIC trials are conducted
- Including justifications for the use of EFIC in clinical trial publications
- Ensuring that trials considering EFIC involve patients with a "life-threatening condition"
- Evaluating acceptance of EFIC trials stratified by etiology of injury
- Improving strategies for communicating with patients and their surrogates regarding EFIC enrollment when clinical outcomes are poor
- Effectively communicating with community members regarding an EFIC study and opt out procedures
- Understanding why community members opt out of EFIC studies
- Understanding that personal experience with a traumatic condition plays a role in acceptance of EFIC trials
- Justifying access to critical survival data for EFIC trials regardless of consent status

## Human Subjects Protections

- Ensuring that data and safety monitoring boards (DSMBs) review interim and cumulative data to ensure proper study conduct, scientific validity and integrity, and overall patient safety while trials are in progress
- Protecting participants and others by ensuring that research publication is not unreasonably delayed and that all information (including negative results, safety issues, unfavorable data, etc.) is disclosed
- Ensuring that IRBs are adequately overseeing patient safety throughout clinical trials
- Determining how much information needs to be disclosed to patients to ensure transparency
- Ensuring that all research involving either interactions or interventions with living individuals in which their identifiable personal information is obtained is prospectively reviewed by an IRB
- Quantifying the difference between various levels of risk (e.g., more than minimal risk/less than minimal risk)
- Recognizing all potential conflicts of interest, disclosing them properly, and working with the IRB and research team to minimize them
- Providing trial information that accommodates the lack of health literacy among large segments of the U.S. population
- Determining how the terms "unproven or unsatisfactory" should be interpreted when evaluating existing treatments and a request for a study to be deemed appropriate for EFIC

## Patient Safety

- Ensuring that researchers place participants' welfare ahead of their own interests
- Validating that a researcher's assertion that the medication, technique, equipment, or system being tested is at least no worse than the current standard of care
- Estimating the amount of psychological and emotional distress that can emerge when asking participants questions about their past trauma experiences
- Interacting with participants to ensure their concerns and opinions are being heard prior to, during, and after enrollment into a trial

## Informed Consent

- Improving readability of informed consent documents (e.g., reducing redundancy, length of forms)
- Providing high quality explanations of all elements of consent
- Addressing fear of new treatment with patients
- Addressing language barriers so that the individual who signs the consent form does so with full understanding of what is stated on the form
- Disclosing too much information on potential side effects may scare the patient from a potentially life-saving surgery or procedure
- Obtaining informed consent from vulnerable groups who are relatively incapable of protecting their interests
- Developing trust and rapport with patients during the informed consent process
- Overwhelming the patient with sequential visits by different study teams who want to explain their study and gain informed consent
- Considering cultural biases when addressing informed consent
- Tracking consent expiration dates
- Communicating how a research study may impact end of life preferences
- Demonstrating that a patient comprehends the information that is provided
- Communicating elements of informed consent in non-overwhelming and understandable ways
- Identifying potential dual or competing interests that an investigator may have or appear to have in relation to their research
- Determining the health literacy of a patient
- Ensuring that informed consent documents are at an appropriate reading level
- Evaluating whether the potential benefits of proposed research is substantial enough to justify waiver or exception from informed consent

## Institutional Review Board (IRB)

- Working with local IRBs that have little to no experience with Exception from Informed Consent (EFIC)
- Using multiple IRBs in a multicenter clinical trial, leading to inconsistent interpretation and consideration of the same protocol at different sites
- Ensuring that IRBs can sufficiently protect human subjects throughout the duration of a clinical trial
- Mandating the use of a single IRB for applications involving more than one site (mandated by the funding source)
- Encouraging institutions involved in multi-institutional studies to use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoiding duplication of effort
- Developing a plan for how IRBs will review proposed research during epidemic or disaster conditions that protects participants while remaining quick and efficient
- Determining when public health practice becomes research and IRBs should become involved to help implement research regulations
- Varying implementation of community consultation and public disclosure activities across different clinical trial sites as determined by local IRBs

## Legally Authorized Representative (LAR)

- Determining who is eligible to be a patient's LAR as dictated by laws
- Locating a patient's LAR in a timely manner
- Evaluating whether an LAR is competent to provide consent in emergency situations
- Ensuring a patient's LAR is able to comprehend the trial information
- Determining when non-LAR surrogates (friends, significant others, etc.) should have an opportunity to object to trial enrollment
- Ensuring that a LAR knows what the patient's wishes would be
- Determining if a LAR can abdicate or reassign the legal authority and responsibility of being the LAR
- Employing a high threshold for determining LAR incapacity, but low threshold for honoring LAR refusals/objections

## Liability

- Mitigating nursing staff concerns about liability in recruiting research participants and balancing clinical responsibilities
- Identifying valid instruments to assess capacity to consent intoxicated patients (under enrollment time constraints)
- Determining if the potential benefits of a study conducted under a waiver of consent justifies possible infringement on individual rights
- Obtaining written informed consent in the pre-hospital transport environment
- Managing liability potentially associated with data repositories and data sharing

## Outbreak/COVID-19 Related

- Expeditiously reviewing large clinical trial protocols
- Modifying the clinical trial protocol and design based on what is happening during an outbreak
- Maintaining flexibility to adapt as an outbreak evolves
- Utilizing alternative consent models to feasibly conduct research during a pandemic

## Participant Incentives

- Accurately disclosing the type and size of incentives
- Minimizing the potential for financial incentives to exploit participants
- Adjusting financial incentives to reflect the socioeconomic status of participants
- Disclosing incentives provided to physicians/practitioners involved in recruitment/retention
- Determining if incentives improve recruitment and retention in trials
- Avoiding large, potentially coercive incentives
- Ensuring incentives do not compromise one's voluntary participation
- Selecting incentives that are easy and convenient to use (gift cards)
- Ensuring that recruiting incentives are not considered "research benefits" or "humanitarian aid"
- Identifying what is an appropriate payment or incentive for specific populations

## Patients' Perception

- Engaging community members to determine the acceptability of medical research in general, and resuscitation research in particular
- Fostering patient engagement in the development and conduct of emergency and trauma research
- Measuring the rate of approval or acceptance of an EFIC study among community members
- Minimizing the therapeutic misconception (i.e., the tendency of prospective research subjects to assume that an anticipated result of participation is improving their own chances for a favorable outcome) among potential participants

## Research Ethics

- Extending responsibility for patient safety to include those who have indirect (but significant) control over decisions that affect patient welfare (e.g., hospital administrators)
- Following through on the professional obligation to disclose adverse events to patients
- Anticipating and addressing 'everyday ethical issues' that arise during the course of research adequately
- Ensuring that the patients who are the most likely to benefit from the research trial have the opportunity to participate
- Verifying that all aspects of a clinical research trial are scientifically sound
- Determining if regulations for emergency research may threaten public health by impeding advances in life-saving treatments
- Ensuring that studies are as efficient as possible to minimize patient exposure to potentially ineffective or unsafe therapies
- Ensuring that all systematic investigations designed/intended to contribute to generalizable knowledge follow all ethical and regulatory requirements for research
- Meeting public disclosure requirements regarding financial interests in any public presentation of data (e.g., conferences, lectures, speaking events, journals, articles, letters to the editor, etc.)

## Special Populations and Disparities

- Ensuring that the enrollment of racial/ethnic minorities is proportionate to the prevalence of the condition being studied
- Avoiding the exploitation of vulnerable populations by researchers during emergencies
- Determining if attitudes toward EFIC trials vary by race/ethnicity
- Protecting vulnerable populations may lead to their frequent exclusion from research
- Addressing mistrust of research investigators by various racial and ethnic groups
- Evaluating cross-cultural differences in research participation
- Communicating the unique risks and benefits that apply to children and special populations
- Understanding parents' attitudes toward research without prior consent for non-interventional studies
- Effectively communicating (including the timing of discussion) with parents about their child participating in an emergency study with deferred consent
- Understanding factors associated with parents consenting to their child's participation in emergency research (e.g., invasiveness of study, compensation, and time requirement)
- Understanding why aging adults decline to participate in fall prevention studies
- Conducting follow-up visits with older adults who are more comfortable with their existing physicians than a research team
- Recruiting geriatric patients with altered mental status (assessing capacity to consent)
- Managing the potential liability and IRB concerns regarding asking participants about previous trauma experiences
- Explaining study participation to individuals without causing additional stress and/or heightening their risk

## Waiver of Informed Consent (WIC)

- Verifying that the only foreseeable risk in a WIC trial is discomfort
- Verifying that the magnitude of harm/discomfort anticipated in the research is not greater than encountered in routine medical examination and testing
- Encouraging consistent and rigorous reporting of regulatory pre-study requirements for WIC trials in clinical trial publications and/or on websites such as ClinicalTrials.gov
- Encouraging published reports of WIC studies to routinely provide explanations/justifications of why WIC was necessary to answer the question under study
- Ensuring that enrollment under WIC only occurs in instances where it is reasonable to believe the patient would normally have consented
- Ensuring that enrollment under WIC only occurs in instances where it is reasonable to think that the project is not culturally or morally controversial