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