Background: Recently the NIH released released a Request for Information around Optimizing the Design and Implementation of Emergency Medical Care Research Conducted Under Exception from Informed Consent Requirements for Emergency Research (EFIC) Requirements and Guidelines (https://grants.nih.gov/grants/guide/notice-files/NOT-HL-18-654.html)

The ACEP/SAEM Research Committees each have subcommittees in place designed to rapidly respond to such requests. An *ad hoc* task force composed of committee members from both organizations, clinical investigators with established experience in emergency care research with an emphasis on EFIC experience, and national emergency medicine thought leaders in Exception From Informed Consent trials were recruited and contributed their recommendations to this response, and had the opportunity to review and contribute to the summary recommendations below. The specific questions posed by the NIH are provided in bold, followed by point-by-point responses.

"The most challenging aspects of implementing emergency medical care research conducted under EFIC across a range of local settings (e.g., urban, suburban, rural), including suggestions for tools and training that might be useful for addressing these challenges"

Enabling research across a range of local settings

- Large tertiary care centers typically have a research infrastructure in place including paid research coordinators and paid on-call research staff. These sites have largely been successful in enrolling patients into trials utilizing EFIC. Maintaining a full research infrastructure at each enrollment site can be financially and logistically burdensome and limits scalability. *Existing hub-and-spoke models should be expanded, with specific assessment criteria that emphasizes the inclusion of centers that expand diversity in all forms:* this should include not only racial and ethnic diversity, but also diversity of rural and suburban patient populations, as well as diversity of clinical practice environments to maximize generalizability.
- When possible, *automate patient enrollment within existing clinical practice paradigms.* Examples would include leveraging electronic medical records to automatically alert both clinical providers and regional coordinators when potentially eligible patients arrive to expidite rapid screening and randomization, development of outreach programs by regional clinical coordinating centers, and development of local nursing and physician champions.
- *Streamline data collection techniques* to prevent or lessen interference with clinical duties, minimize real-time data collection to only the most critical data points, and preferentially design studies to leverage routinely collected clinical data. Ensuring sites routinely capture essential data points within routine clinical care should be considered in evaluation of suitibility for particularly trials.
- *Develop methods to acknowledge and reward providers and spoke site institutions* for their contributions to trials. This is critical to ensure that spoke sites are represented in terms of enrollments and not in name only and is critical for network success.

Central EFIC board

- Given a lack of working knowledge and experience at local IRBs with EFIC regulations, *create a central EFIC advisory board* to review the need and justification for each proposed EFIC study and that each proposed EFIC plan follows all applicable federal regulations. This board should be responsive and timely. The proposed studies can then be funneled to central or institutional IRBs to incorporate local context and community consultation plans appropriate to their practice setting.

"Ways to enhance training to better equip prehospital providers/emergency medical services personnel to participate in emergency medical care research conducted under EFIC guidelines (e.g., research protocol implementation, including patient enrollment, family notification and data collection), and strategies for evaluating such approaches across a range of local settings (e.g., urban, suburban, rural)"

- *Asynchronous learning should be leveraged to maximize efficiency of clinical trial training.* Brief modular (web-based) methods for educating prehospital providers and emergency medical services personnel on emergency medical research should be created to assist in the rapid and comprehensive dissemination of trial information.
- Because of complexities of the prehospital phase can raise challenges for both clinical care and research, a meaningful discussion of a patient's involvement in a research study is not possible. Rather, *for each study, a central system for communicating research information to family members and proxies should be developed* to aid in research transparency, consent for continued involvement in the investigation following the initial enrollment and randomization period, and for follow-up data collection. This could be deployed at the hub level or housed within a federal government website. Examples could include *readily available brief patient information sheets* provided to family with *web-based publically available videos*, and/or *a centralized study-based email* address to respond to questions and/or complaints, and central websites. These resources should include information regarding the ethical vetting and approval of the study, the community consultations performed, and the study question and importance. Pending success, these approaches could also apply to ED- and ICU-based research.

"Practices for effectively communicating with the participant's legally authorized representative (LAR) regarding research being conducted under EFIC, including strategies for informing the LAR of impending enrollment of the patient into EFIC research when the LAR is immediately/readily available so that consent can be obtained"

- *The approach to obtaining a family member's or legally authorized representative's (LAR) permission or consent should vary by the urgency of required clinical care and the therapeutic window of the study intervention.*
  - It is nearly impossible to have any meaningful discussion of a research protocol with a patient or their family member in the midst of an emergency medical event. These conversations are rarely comprehended and can be misleading. *Therefore, in trials with either no therapeutic or a very brief therapeutic window*, defined as a therapeutic window too short to allow a full informed consent discussion*, the patient should be enrolled in the trial without a <u>prospective</u> discussion of the research protocol if all criteria and ethical approvals for EFIC apply.*
  - *Notification should be delayed until later, when the patient and family are in a better emotional state to understand the information.* There should be no attempt and no expectation of an attempt, to communicate the trial details to patients/family in the midst of its execution.
  - *Consideration should be given to expand EFIC-eligible studies to include patients who are not completely obtunded but who are unlikely to fully comprehend the risks, benefits, and alternatives to research participation.* Example illnesses include ST-elevation myocardial infarction, stroke, and sepsis, where many interventions would require rapid enrollment that precludes a meaningful discussion of the research protocol.

- *In trials with a reduced therapeutic window long enough to allow an informed consent discussion, informed consent with legally authorized representatives should be attempted prior to enrollment.*
    - *Methods of e-consent and verbal phone consent should be developed and considered acceptable in narrow time window trials (*e.g. several hours).
    - *Considerarion should be given to the development of new consent methodology* in which legally authorized representatives are approached if available in person or by phone, but if none exist or cannot be contacted during the therapeutic window despite faith good efforts, the patient should be enrolled in the trial.
    - In all cases, good faith efforts to obtain consent should be documented. Examples could include approaching and discussing the trial with any family present or expected to be present based on prehospital reports, and/or calling any contact numbers in the medical record.

- *Trials with a sufficiently long therapeutic window should require full, written informed consent.*

- *An independent body should review and assess the research protocol and provide independent verification of the evidence to support the existance of a narrow therapeutic window that would require the use of EFIC and preclude the use of standard full informed consent.* Most local IRBs lack sufficient familiarity with EFIC and have insufficient clinical representation of experts in emergency care with importannt expertise surrounding the practice of medicine in the most promixal hours of treatment. *Therefore, we recommend independent assessment of proposed approaches to consent by an EFIC advisory board.*

Approaches to obtaining family member permission for the patient's participation in emergency medical care research conducted under EFIC, and strategies for evaluating such approaches

<u>Referring to post-enrollment permission for continued study activities after the initial intervention (as pre-enrollment permission was discussed above):</u>

- *A toolkit should be developed for EFIC post-enrollment notification*, including:
    - A *uniform brochure or handout common* to all EFIC research to enable family members and LARs to more easily understand emergency research without consent.

    - *Standardized scripts* to approach grieving or distraught family members to notify them of enrollment and seek consent for continued participation should be made available but not mandated.

- Current guidelines (21 CFR 50.24) state: "The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject…" *The "earliest feasible opportunity" should be interpreted in the context of the clinical trial.* For example, In trials with no further intervention after enrollment (eg, randomized trials of emergency airway management) it may be appropriate to defer informing the subject until after an appropriate grieving or recovery period. In trials with further interventions after enrollment (eg, repeated doses of an investigational medication), efforts to inform the patient or LAR and obtain consent for continued participation should persist and may need to occur during the grieving or recovery period. *The appropriate timeframe should be determined by*

the local environment, and subject to local context review to acknowledge regional and cultural differences in medical care.

Approaches to family presence during emergency medical care research conducted under EFIC and strategies for evaluating such approaches, including the impact of family presence and needs/experiences of family members in this setting

- *The conduct of emergency care research should not change whether the family is allowed to be present during resuscitation.* Family presence during resuscitation has been shown to lower post-traumatic stress disorder without interfering with clinical care. Communication of research procedures when the family is present could be difficult, but transparency in all research is paramount, particularly when utilizing EFIC. If clinical care permits, the medical team should be clear which interventions are standard of care and which are research.
- *Targeted funding through an RFA should be considered to determine public attitudes towards participation in EFIC research following enrollments, and should include both enrolled patients and family members who were and were not present at the time of enrollment.* Mixed methods approaches that consider both smaller, focused qualitative approaches to determine specific themes and then larger quantitative approaches to assess differences across geographic and racial/ethnic groups would be critical in understanding patient attitudes.

Practices for community consultation and public disclosure regarding emergency care research conducted under EFIC across a range of local settings (e.g., urban, suburban, rural) and strategies for assessing the effectiveness of such approaches

<u>Community consultation and engagement</u>

- *"Town hall" meetings reach only a small segment of a community and may not necessarily represent the views of the community as a whole*, particularly if turnout is poor. At a minimum, documentation of how many and which members of the community attend should be reported.
- *Explore the use of social media platforms as a method to engage underrepresented groups.* The rise of social media may provide an opportunity to better engage the community and solicit important feedback on proposed trials. Choice of platform and advertising algorithms will necessarily impact and potentially bias the sample of engaged citizens. Use of several different community engagement methods, therefore, is critical. Collection and reporting of deidentified data regarding who participated in these various engagement platforms, with common reporting requirements might be a process worth exploring.
- *Novel strategies to engage the populations most likely to be enrolled should be considered in developing the methods for community consultation and public disclosure.* For example, in a cardiac arrest trial, dissemination of information booklets in a cardiology clinic might be a reasonable approach.
- *Common toolkits with a series of best practices, where sites can choose the most efficacious and approproiate methods of engaging their local community should be considered.* Local oversight of the appropriateness of the engagement plan should be ceded to local settings.
- *Consider the development of regional community representative boards independent of the institutional review board.* These would allow broader representation of community views.

<u>Public disclosure</u>

- *The effectiveness of public disclosure should be systematically assessed to determine efficacy.* For example: community knowledge and penetration that an EFIC study is planned

to be performed could be assessed by random sampling methodology. Alternatively, assessment for dissemination penetration could be assessed among patients and family members of study participants after enrollment, regarding their knowledge of a community EFIC study on the topic. Reporting requirements of the percentage of patients and/or families aware of a study (including regional variation) could be considered as a reportable metric to be included in CONSORT study flow diagrams of EFIC trials. However, this is a high bar given relatively low medical literacy in general and difficulty in communicating the most basic public health information. It is highly likely, therefore, that current methodologies would seem to fall far short of the penetration needed.

- Methods of public disclosure should be a considered peer review criterion. Budgetary line items dedicated to targeted social media advertising should be considered to identify high risk or underrepresented communities. Many social media platforms have highly complex algorithms and predictive analytics that might be effectively leveraged for this purpose.
- *For EFIC trials, consideration should be given to the development of requirements to publically disclose study results beyond peer-reviewed medical publications* (including press releases to local media, social media, and other outlets) in order to increase transparency, public engagement, and decrease stigmatization of EFIC related medical research.

Brian Driver, MD
Henry Wang, MD
Jill Baren, MD
Michelle Biros, MD
Daren Beam, MD
Zachary Meisel, MD *SAEM* R*esearch Committee Chair*
Manish Shah, MD *ACEP Research Committee Chair*
Michael Puskarich, MD *Subcommittee Chair*