Ethical and regulatory challenges in advancing prehospital research: focus on sepsis

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There are a variety of barriers to conducting prehospital, emergency research. Practical challenges range from ambulances functioning as mobile ‘laboratories’ that are always in flux, to short encounter times, to local variation in Emergency Medical Services (EMS) protocols and practices that make it challenging to measure and detect a treatment effect. The most obvious ethical barrier to prehospital research, however, relates to informed consent. It is difficult to involve patients in enrollment decisions due to several key factors including acuity of illness, the need for rapid participant enrollment, limited personnel available to conduct informed consent, and lack of investigator presence. Consent-related challenges are ubiquitous and well-known in prehospital research, but they have received the most attention in the context of trials for conditions such as status epilepticus, traumatic brain injury, and cardiac arrest. In these situations, patients are typically unconscious and unable to participate in enrollment decisions. In contrast, patients with conditions like sepsis exhibit varied levels of consciousness and a wide range of capacity for participating in enrollment decisions. Some patients may be fully capacitated to provide consent for enrollment while other patients are profoundly impaired. We describe and clarify the controversy related to these ethical and regulatory barriers and pose potential solutions. We focus on sepsis to illustrate the controversy, explore these issues in greater detail, and provide a model for a variety other life-threatening, time-sensitive diseases and conditions.

Sepsis is a major public health concern due to high incidence, high mortality, and high associated healthcare costs. Because early recognition of sepsis is of paramount importance in facilitating life-saving treatment, providing targeted sepsis care in the EMS setting has the potential to be highly beneficial to patients. Prehospital sepsis care is thus ripe for further study, but several barriers limit the ability of researchers to perform clinical
investigation in this context. Prehospital sepsis trials encompass a wide range of study designs and interventions that may involve substantially different trial-related risks. For example, a prehospital trial of biomarker analysis poses different potential risks than a placebo-controlled trial investigating a novel therapeutic agent delivered in the prehospital setting. In order to continue scientific advancement in this unique and challenging field of study, clarifying the regulatory road map for various types of clinical investigation will be important.

Current regulatory structure

Both patients’ ability to participate in enrollment decisions and trial-related risks exist on a spectrum (Figure 1), and both considerations affect the need for and potential role of informed consent. In this respect, sepsis is like many other acute conditions for which prehospital care is critical. For example, prehospital studies of myocardial infarction and respiratory failure face similar challenges. Unfortunately, the current regulatory structure may not appropriately recognize the range of studies or facilitate enrollment procedures that are appropriately context-specific.

Current FDA and HHS regulations explicitly acknowledge the connection between trial-related risk and the need for patient involvement in enrollment decisions. IRBs are, for example, allowed to waive or permit alterations to some or all of the required elements of consent if a trial poses no more than minimal risks, research could not practicably be carried out without the waiver, enrollment will not negatively affect patients’ rights or welfare, and subjects will, when appropriate, be provided with additional information at a later time. Rather than recognizing a spectrum of risk, however, the regulations dichotomize risk into “minimal” or “more than minimal”. As has been illustrated in recent debates about trials comparing standards of care, the proper interpretation of minimal risk and assessment of foreseeable trial-related risk in the acute setting has been highly controversial. IRBs can find flexibility in how “practicably” is interpreted. Factors such as introducing selection bias and affecting the validity of the research design can in specific studies be considered by the IRB in making the waiver of informed consent determination.

The other mechanism by which an IRB can permit prehospital clinical trials in the context of consent-related barriers is to use the exception from the requirement for informed consent for research in emergency settings (EFIC). The EFIC regulations do not require that trials be considered minimal risk. Rather, these regulations require that the condition under study must be life-threatening, that there must be a reasonable prospect of direct benefit from the intervention under study, that existing treatment must be unsatisfactory or unproven, and that the risks of the intervention must be reasonable as compared to the background risk of the condition itself and existing therapy. Additionally, investigators must conduct community consultation (CC) prior to study approval and public disclosure (PD) of the intent to perform the study and of study results after completion. Both forms of public engagement can take a variety of different forms but involve significant expense and effort. The Food and Drug Administration (FDA) has issued guidance on EFIC regulations, but importantly this advice is not legally binding on IRBs.
Mapping studies to the regulations and clarifying the gap

Some prehospital sepsis studies fit cleanly into this regulatory structure. For example, observational studies in the prehospital setting often easily meet criteria for waiver or alteration of consent under the minimal risk designation. Such examples might include analysis generated from large, observational data sets, or process improvement measures aimed at refining prehospital assessment strategies of first responders.

Similarly, prehospital trials of novel, potentially riskier interventions in patients with profound septic shock—most of whom have altered sensorium—fall appropriately under the EFIC mechanism. Examples of such efforts might include a randomized trial of a novel drug that appears promising in early-phase trials but is associated with a defined increase in risk of bleeding. Well-described challenges exist regarding how best to conduct public engagement activities for EFIC studies and how, particularly, to use community consultation feedback. However, the EFIC mechanism is an established route for conducting important studies like this in the prehospital setting.

The EFIC mechanism has rarely been used in trials in which most patients have some ability to play a role in enrollment decisions. The IMMEDIATE trial, for example, which compared glucose-insulin-potassium (GIK) solution versus placebo in prehospital STEMI was conducted under EFIC. However, because most patients were conscious, a brief description of the trial was given by participating EMS providers to patients, and patients were given the option to opt out of enrollment. If patients did not have the capacity to be told about the study using this tool, or if they declined to participate in the ambulance, they were not enrolled. For those who agreed to enrollment prehospital, informed consent for continuation was obtained in the hospital. This case illustrates, importantly, that the EFIC regulations can apply to conscious patients and that EFIC trials can include involvement of patients even when full consent is not possible, as may be the case of patients with sepsis.

The IMMEDIATE trial took a novel approach to the application of EFIC regulations by using an opt out mechanism. It is important to highlight this consent model as an example for other prehospital conditions including sepsis. For example, one could consider an opt out process for alert subjects and enrollment via EFIC for sicker participants.

The greatest challenges lie at the margins of these categories and in the gap between them. The hypothetical example described earlier of a trial of point of care lactate assessment to guide early antibiotic administration exemplifies the low-risk end of this spectrum. Clearly the lab test itself poses few risks to patients, as does an early dose of antibiotic. However, the goal of the study would be to alter management based on the test results in order to reduce significant morbidity or mortality. And presumably such a study would only be undertaken if there were preliminary data to suggest that such a different in major outcome may be present. Whether a study like this should be properly considered minimal risk is a contentious issue given the magnitude of what is “at stake” for the patient.

Trials comparing qualitatively similar treatments that are part of standard care—such as many comparative effectiveness studies—may also be considered by some to present no more than minimal risks on the view that they do not expose patients to any risks that the patients...
would not otherwise face. For example, a trial of two common volume resuscitation strategies (e.g. normal saline versus lactated Ringer’s) might fit this description. On the one hand, trials such as these involve essentially no risks because the patient will receive one of the two interventions anyway, and providers have no strong basis for choosing one over the other. Randomization alone, after all, does not pose risks. On the other hand, the trial is being conducted in a high stakes situation precisely in order to ascertain whether differences exist in major outcomes that are important to patients. Even if the trial technically “introduces” few risks, it may not follow that patients do not want to play a role in enrollment decisions. This issue has become a topic of vigorous debate in recent years (especially in the wake of the prenatal SUPPORT trial) and is of real importance given the emergence and expansion of comparative effectiveness trials and novel designs including pragmatic and large, simple trials \( \text{19} \). Ascertaining what risks are risks of standard care and what risks are “foreseeable risks” attributable to a randomized research study is the focus of draft guidance recently issued by ORHP that is currently undergoing public comment \( \text{20} \).

If some of these lower risk trials are not considered minimal risk, the only regulatory route that may facilitate their conduct is implementation of the EFIC regulations. There are, however, two potential problems with use of the EFIC regulations in this context. First, the regulations do contain the requirement that existing therapies be considered “unproven or unsatisfactory.” Although this requirement is defined as treatment that has limited evidence to support its use or suboptimally improves outcomes, its application is unclear in the context of trials comparing the relative effectiveness of interventions which have been demonstrated to be effective treatments \( \text{21} \). Second, the EFIC regulations’ requirement to conduct community engagement activities is often viewed as a significant barrier to conducting trials under this mechanism. The proper role of community engagement, as well as what needs to be done to satisfy the requirement, is not well-established. It is particularly unclear what is needed in lower risk trials, though some groups have explicitly argued that a study’s risk level should dictate the extensiveness of community engagement efforts\( \text{12} \).

Using the spectrum of risk and participation to advance prehospital sepsis research

The need for regulatory frameworks to address and adapt to the evolving nature of clinical research is important in order to continue to improve health outcomes and protect participants. Prehospital sepsis trials, and prehospital research generally, often fall in an area of ethical and regulatory uncertainty within the current structure.

Analyzing the range of prehospital sepsis research across the spectra of trial-related risk and potential patient involvement clarifies several key questions. First, there is a need to define what trials should be considered to represent minimal risk in the context of acute illness. This is a contentious topic that is at the heart of efforts to expand clinical trials necessary to address important clinical and policy challenges. Second, what level of combined trial-related risk and patient impairment should trigger utilization of the EFIC mechanism? Third, what is the value to patients of alternative involvement processes such as opt-out, informed refusal, or assent as was done in the IMMEDIATE trial? These processes clearly do not meet
expectations of informed consent but may have value to patients. Finally, what approach is most appropriate for clinically relevant and relatively low risk studies that fall in the problematic middle ground of risk and consent-related barriers?

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References


Figure 1. Spectrum of patient involvement and trial-related risk
Definitions: CER – comparative effectiveness research

- **Patient involvement**
  - None (Ex: waiver of consent)
  - Limited (Ex: patient assent)
  - Full (Ex: informed consent)

- **Trial-related risk**
  - Minimal (Ex: observational study)
  - Low (Ex: CER)
  - Higher (Ex: novel therapeutics)