Ethics and Regulatory Barriers to Research in Emergency Settings

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Patients, clinicians, payers, and policymakers need meaningful evidence on which to base treatment decisions, but designing and conducting research to generate such evidence raises unique challenges in emergency settings. As reported in this issue of Annals, Klein et al1 sought to discover which among 4 commonly used intramuscular sedatives is most effective in treating patients with acute agitation. Because these patients have altered mental status, the investigators proposed a randomized, controlled, comparative effectiveness trial under the exception from informed consent requirements for research in emergency settings.2 After their initial application to the Food and Drug Administration (FDA) was denied, the investigators conducted an “observational” study in which the emergency department systematically rotated which of the 4 drugs was used in 3-week blocks. Because collection of outcome data was considered to pose no more than minimal risk, the institutional review board approved this approach under a waiver of informed consent.3 Although this study advances understanding in regard to the management of acute agitation, it raises important ethical and regulatory concerns about research in emergency settings.

Although these investigators’ approach was creative, it has limitations. At minimum, the design makes it more difficult to ensure similar composition of comparison groups than in a randomized trial. This design is also more vulnerable to secular trends. We leave it to others to assess whether these limitations are significant for this particular clinical question. However, from an ethical perspective, it is notable that using a scientifically suboptimal research design conferred no additional protections for patients. In both the randomized trial initially proposed and the observational (or more accurately quasi-experimental) study actually conducted, treatment was assigned by protocol and not individualized. Risks to subjects were no different, and it is problematic if regulations promote scientific changes that do not enhance protection.

Regulations have prompted research “creativity” before. Before 1996, US investigators interested in advancing care for patients with severe, acute illness lacked an appropriate regulatory structure within which to conduct clinical trials when patients could not provide consent. As a result, investigators relied on the concept of “deferred consent” and regulations designed for emergency clinical use that were never intended for clinical trials.4 After an essential shutdown of emergency care research in the United States, the FDA and the US Department of Health and Human Services promulgated exception from informed consent regulations in 1996. These regulations have facilitated ethical conduct of important clinical trials during the past 22 years, but practical and ethical challenges persist. There has been extensive discussion about the exception from informed consent requirements for community consultation and public disclosure. There are also lingering questions about how exception from informed consent regulations should be applied when patients are conscious and conditions are less severe. The report by Klein et al prompts consideration of the latter set of issues.

Klein et al mention that part of the FDA’s rationale for placing the proposed randomized study on a full clinical hold related to “insufficient evidence that this population could not provide consent.” This raises an obvious question: how can an agitated patient possibly provide informed consent? Patients who require chemical sedation are typically not in a position to engage in a traditional research consent process. Almost by definition, they have altered decision-making capacity, and sedatives are frequently administered without consent for their safety and well-being. We share the investigators’ intuitions that it is difficult to imagine a substantial consent process in this context. Furthermore, requiring consent would likely result in a skewed or very small study population. The FDA, appropriately, does not take granting an exception from the
requirement for informed consent lightly, and exception from informed consent regulations are explicitly intended for situations in which consent is impracticable. However, it is difficult to see how agitation does not meet this standard.

Although we doubt that informed consent is possible among acutely agitated patients, more limited forms of involvement may sometimes be possible. Patients with acute coronary syndrome, for example, have consistently demonstrated a preference for prospective involvement in enrollment decisions despite relatively poor understanding of those studies in the emergency setting. Up-front involvement, through opt-out or assent processes, may provide transparency and allow patients opposed to research to exclude themselves, even in situations in which they don’t understand precisely what is being offered. The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial of out-of-hospital treatment for acute coronary syndrome, for example, was an exception from informed consent trial that explicitly incorporated an assent process allowing patients to opt out of participation. Nevertheless, even limited involvement may be difficult in acute agitation, since agitated patients may be distrustful of clinicians. However, it is essential to recognize that exception from informed consent studies can sometimes incorporate prospective involvement of patients or surrogates.

There is an additional potential reason for the FDA’s not approving the proposed trial under exception from informed consent: agitation is not typically life threatening. Exception from informed consent regulations require that the study condition be life threatening, reflecting that they were designed with conditions such as traumatic brain injury and cardiac arrest in mind. Acute agitation is not as lethal, but it is certainly a significant and prevalent problem for which evidence-based treatment is needed. Unfortunately, if consent is not possible but a condition is not life threatening, emergency care trials land in a regulatory no-man’s-land where they are essentially unapprovable. The motivation for the life-threatening requirement is understandable, but this requirement may foreclose the conduct of well-designed trials evaluating serious conditions.

It is also uncertain whether the life-threatening requirement does any ethical work. The exception from informed consent regulations already require that risks be reasonable in relation to the condition under study. It stands to reason that only studies of lower-risk interventions would be approved for conditions that carry lower background risks. The proposed trial by Klein et al is a good example. It presented very low risks, because it involved agents commonly used in practice and known to be relatively safe. It is indeed problematic if a regulatory structure does not permit low-risk comparative effectiveness trials of existing treatments for important emergency conditions.

In light of the challenges raised by this study, we must examine whether there are ways to harmonize regulatory, ethical, and scientific goals in the conduct of emergency care research with conscious patients who have serious but nonlife-threatening conditions. There are at least 3 important paths forward.

First, we encourage open communication between the FDA and investigators regarding what evidence is necessary to demonstrate impracticability of informed consent. It is unclear how much discussion took place in this case or what evidence would have resulted in approval of the proposed trial under an exception from informed consent. These discussions should also include the possible role of “partial involvement” strategies such as assent or opt-out processes (at enrollment) when appropriate. These may not be possible with agitated patients, but they can be a way to balance the desire to involve patients or surrogates with the recognition that traditional consent processes are impracticable. Exception from informed consent trials do, and should, include patients across a spectrum of capacities to consent. Indeed, the range of consent capacity within a population often reflects the heterogeneity of the disease or condition under study. Investigators and the FDA must collaborate to make the process match the context.

Second, the exception from informed consent regulations contain potentially problematic elements. The “life-threatening” condition requirement seems overly restrictive, because other regulatory provisions already limit and calibrate the risks to which subjects would be exposed. Related, the requirement that existing therapy be “unsatisfactory or unproven” may raise similar issues. If interpreted strictly, low-risk studies seeking to improve on existing treatments that are known to be effective may pose challenges. Carving out a clear path for regulatory approval—either through guidance or regulatory reform—of context-appropriate studies of less lethal emergency conditions and of comparative effectiveness research is critical. The FDA has previously clarified that morbidity endpoints are acceptable. They could further clarify that serious conditions that do not immediately threaten life may also be eligible for exception from informed consent if risk limitations are met. The key issue to a study’s ethical acceptability is careful evaluation of the risks posed within the context of the disease or condition and existing treatments. This is articulated already within the regulations.

Third, a promising avenue for comparative effectiveness research exists. The 21st Century Cures Act provides for
harmonization of FDA and US Department of Health and Human Services regulations in significant ways. Specifically, it allows the FDA to grant waivers or alterations of informed consent in trials posing no more than minimal risk. Although determining what constitutes minimal risk in the context of emergency illness may be difficult, the study proposed by Klein et al may be considered by many to fall into this category and may be appropriate for waived or altered consent. This provision may be a reasonable means for approving low-risk studies that are ruled out of current exception from informed consent regulations.

The goal of the exception from informed consent regulations is to advance science for emergency illness while protecting and respecting participants. We hope that one legacy of this trial is a robust discussion identifying potential policy paths for achieving this goal.

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