Confronting Ethical and Regulatory Challenges of Emergency Care Research With Conscious Patients

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Barriers to informed consent are ubiquitous in the conduct of emergency care research across a wide range of conditions and clinical contexts. They are largely unavoidable; can be related to time constraints, physical symptoms, emotional stress, and cognitive impairment; and affect patients and surrogates. US regulations permit an exception from informed consent for certain clinical trials in emergency settings, but these regulations have generally been used to facilitate trials in which patients are unconscious and no surrogate is available. Most emergency care research, however, involves conscious patients, and surrogates are often available. Unfortunately, there is neither clear regulatory guidance nor established ethical standards in regard to consent in these settings. In this report—the result of a workshop convened by the National Institutes of Health Office of Emergency Care Research and Department of Bioethics to address ethical challenges in emergency care research—we clarify potential gaps in ethical understanding and federal regulations about research in emergency care in which limited involvement of patients or surrogates in enrollment decisions is possible. We propose a spectrum of approaches directed toward realistic ethical goals and a research and policy agenda for addressing these issues to facilitate clinical research necessary to improve emergency care. [Ann Emerg Med. 2016;67:538-545.]

A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2015.10.026

INTRODUCTION

Rigorous research is essential to improving care for acute conditions, but conducting clinical trials in emergency settings is difficult. Patient eligibility must be verified, an enrollment decision made, and treatment allocated rapidly to deliver timely treatment. Involving patients in consent discussions in this context is further complicated by physical symptoms, stress, and cognitive impairment.

US federal regulations, and similar regulations internationally, allow an exception from informed consent for certain studies in emergency settings.[1,2] These regulations have facilitated important trials in conditions such as cardiac arrest, status epilepticus, and traumatic brain injury.[3-5] In most of the conditions in which the exception from informed consent regulations have been applied, patients are unconscious and an acceptable surrogate cannot be identified in an appropriate timeframe. Emergency care research, however, spans a wide range of conditions and can take place in numerous clinical contexts, from the out-of-hospital setting to emergency departments, inpatient wards, and ICUs. In most emergency care research, patients are not unconscious and surrogates are often available, but barriers to informed consent exist. Patients with ST-segment elevation myocardial infarction (STEMI), for example, or severe sepsis require rapid treatment and exhibit widely varying symptoms and ability to engage in decisions.[6] Stroke patients are usually awake but neurologically impaired, and time constraints and emotional stress complicate surrogate consent.

There is neither clear regulatory guidance nor established ethical standards in regard to informed consent for emergency care research with conscious patients. Disagreement over the right approach has been highlighted by heated debate over the absence of prospective consent in a recent STEMI trial.[7-9] Establishing a coherent approach to consent-related challenges in emergency care research is essential to improving care for numerous conditions while respecting patients and maintaining public trust.

These issues were a focus of a workshop convened by the National Institutes of Health (NIH) Office of Emergency Care Research and Department of Bioethics.[10] The 35 participants in the workshop included leading scholars and representatives from government agencies (NIH, Food and Drug Administration, the Office of Human Research Protections, and the Office of Assistant Secretary for Preparedness and Response), clinical research, and bioethics. The workshop was dedicated to the following

topics: comparative effectiveness research, community consultation, centralized ethics review, and informed consent. All participants took part in each session. At the conclusion of the workshop, participants generated a set of key concepts for each topic and divided into writing groups. Writing group members then participated in subsequent telephone meetings and e-mail discussions to refine the content. All writing group members have had the opportunity to review and edit the final report.

This report focuses on consent processes for emergency care research. We clarify important potential gaps in ethical understanding and federal regulations in this area. We then propose a spectrum of practical approaches directed toward realistic ethical goals and a research and policy agenda to promote progress in emergency care research.

BARRIERS TO CONSENT AND REASONS TO INVOLVE PATIENTS IN DECISIONS

There is a clear ethical imperative to conduct clinical research to improve care of acutely ill patients, but barriers to obtaining informed consent in emergency settings are multiple and unavoidable. First, enrollment decisions must take place quickly. Prolonging evidence-based time targets for percutaneous coronary intervention for STEMI, thrombolytic administration for ischemic stroke, or antibiotic initiation for severe sepsis to obtain consent would compromise care. Second, many conditions are associated with severe symptoms and physiologic states such as pain, respiratory distress, and hypotension that can impair decisionmaking capacity and judgment. Neurologic emergencies in particular directly affect communication and cognition. Third, emergency illness is stressful and frightening for patients and surrogates. Finally, research is unfamiliar to most people. Patients or surrogates are unlikely to have preformed, well-defined values about trial participation to guide rapid decisions.

Available evidence suggests enrollment decisions in these contexts are frequently minimally informed. Patients asked to enroll in STEMI[11-13] and stroke trials[14,15] have demonstrated limited understanding and prevalent confusion about distinctions between clinical treatments and research. Moreover, surrogate decisionmakers have limited ability to predict research preferences of acutely ill patients.[16,17] In summary, barriers to consent in the emergency setting appear prevalent and are intrinsic to the clinical context. Conducting essential clinical trials to address these conditions involves confronting rather than eliminating these barriers.

An important part of confronting this challenge is to recognize that there are important reasons to consider involving patients in enrollment decisions, even if decision quality is often low. First, the ability to engage in decisions exists on a spectrum and depends on patients' symptoms, past experiences, baseline personality, and cognitive state. It may be possible to explain major risks and benefits of a trial to some participants through brief conversations. Moreover, consent processes are imperfect even in the best of circumstances.[18] The fact that some participants will not make fully informed decisions is not a reason to abandon consent altogether, and involving patients with decisionmaking capacity in enrollment decisions as much as possible is an important part of respecting their autonomy.

Second, consent processes serve multiple purposes, not all of which depend on understanding or capacity. For example, they offer an opportunity to decline enrollment. Although some have argued that patients may at times have an obligation to participate in research because of strong societal interests,[19] it is generally accepted, especially in the United States, that there is not an overriding obligation to enroll in clinical trials. In this context, refusals to participate in clinical trials are almost always respected without requiring demonstration of capacity or a substantial reason for refusal. In addition to promoting autonomy, providing an opportunity for refusal advances the beneficence-based obligation to avoid the harm of unwanted enrollment. Asking permission may also constitute an expression of respect and concern for patients, promote transparency, and help to foster trust among patients, surrogates, and the public. Which strategies best advance each of these goals is unknown, but success in these domains may not hinge on understanding of all elements required in US regulations (Figure) or emphasized in most ethical analysis.

Third, the presumption that some involvement in decisions is better than none is reflected in US regulations and international guidance. For example, the Declaration of Helsinki and Council for International Organizations of Medical Sciences guidelines suggest assent in research with cognitively impaired individuals.[20,21] Similarly, US exception from informed consent regulations require offering family members of incapacitated patients the opportunity to object to inclusion, even if they cannot provide consent.[22] The latter requirement in particular reflects the view that involvement should be sought even in circumstances in which it is ethical to enroll patients without prospective consent.

Fourth, available data from the United States and Western Europe support patient involvement despite potential impairment. Patients with acute myocardial infarction, for example, have indicated a preference for being asked about enrollment and seem to believe they can participate meaningfully in decisions.[12,23] Although refusal rates may be low,[24] refusals can express authentic desires