Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

BIROS SECTION ON RESEARCH ETHICS

Balancing Ethical Goals in Challenging Individual Participant Scenarios Occurring in a Trial Conducted with Exception from Informed Consent

Michelle H. Biros, MD, MS, Neal W. Dickert, MD, PhD, David W. Wright, MD, Victoria M. Scicluna, MPH, Deneil Harney, MPH, MSW, Robert Silbergleit, MD, Kurt Denninghoff, MD, and Rebecca D. Pentz, PhD

Abstract

In 1996, federal regulations were put into effect that allowed enrollment of critically ill or injured patients into Food and Drug Administration (FDA)-regulated clinical trials using an exception from informed consent (EFIC) under narrowly prescribed research circumstances. Despite the low likelihood that a legally authorized representative (LAR) would be present within the interventional time frame, the EFIC regulations require the availability of an informed consent process, to be applied if an LAR is present and able to provide prospective consent for patient enrollment into the trial. The purpose of this article is to describe a series of unanticipated consent-related questions arising when a potential surrogate decision-maker appeared to be available at the time of patient enrollment into a trial proceeding under EFIC.

ACADEMIC EMERGENCY MEDICINE 2015;22:340–346 © 2015 by the Society for Academic Emergency Medicine

In 1996 federal regulations were put into effect that allowed enrollment of critically ill or injured patients into U.S. Food and Drug Administration (FDA)-regulated clinical trials using an exception from informed consent (EFIC).[1] These regulations are applicable under narrow clinical circumstances when the critical condition of the patient and the rapidity with which the intervention must be initiated make it impracticable to obtain prospective informed consent from the patient or his/her legally authorized representative (LAR). Other criteria, such as lack of adequate alternative therapies, acceptable risk to benefit profile, and possible direct benefit to the patient, are also required.

The FDA understood that the EFIC regulations would be applied infrequently and in trials in which the patient populations, interventions, and situational constraints vary. The rules therefore allow substantial latitude for investigators and institutional research boards (IRBs) and require considerable interpretation. In 2011, the FDA released a guidance document on EFIC that incorporated examples from accumulated experience (which was minimally updated in 2013).[2] Challenges remain, however, in development of optimal approaches to EFIC trials and application of these regulations. The purpose of this article is to describe a series of unanticipated consent related questions arising when a potential surrogate decision-

From the Department of Emergency Medicine Hennepin County Medical Center and University of Minnesota (MHB), Minneapolis, MN; the Division of Cardiology (NWD), the Department of Emergency Medicine (DWW), and Department of Hematology and Oncology (RDP), Emory University School of Medicine (VMS), Atlanta, GA; the Department of Epidemiology, Emory University Rollins School of Public Health (ND), Atlanta, GA; the Department of Emergency Medicine, University of Michigan (DH, RS), Ann Arbor, MI; and the Department of Emergency Medicine, The University of Arizona, and The Arizona Emergency Medicine Research Center (KD), Tucson, AZ.

Drs. Biros and Wright, both of whom are associate editors for this journal, had no role in the peer-review process or publication decision for this paper.

Received September 3, 2014; revisions received October 21, 2014; accepted October 22, 2014.

The authors have no relevant financial information or potential conflicts to disclose.

Supervising Editor: Joshua Goldstein, MD, PhD.

Address for correspondence and reprints: Michelle H. Biros, MD, MS; e-mail: biros001@umn.edu.

A related commentary appears on page 365.

ISSN 1069-6563
PII ISSN 1069-6563583

doi: 10.1111/acem.12602

maker appeared to be available at the time of patient enrollment into a trial proceeding under EFIC.

BACKGROUND

Although the conditions of studies covered under EFIC generally make prospective informed consent impossible, investigators are required to develop an informed consent process in the event that prospective informed consent can be obtained in an individual case. Consent in these severe critical circumstances would likely come from the subject's LAR, with the hierarchy of LARs established by state law. In many EFIC circumstances, prospective consent is not feasible from the LAR because the LAR is not present within the intervention's time window or the subject (and hence the LAR) is not identifiable. Occasionally, an LAR may be present, but the investigational agent or other study intervention must be given before an adequate consent discussion can be conducted and an informed prospective decision can be made by the LAR regarding enrollment of the subject in the trial.

In 2009, the Neurological Emergencies Treatment Trials (NETT) research network[3] began an interventional trial for patients with moderate to severe traumatic brain injury (ProTECT-III). The trial involved treatment with progesterone as a neuroprotective agent, initiated within 4 hours of injury (and with a goal of initiation within 2 hours of injury), and continued as an intravenous infusion for 96 hours. Participants were followed for 6 months. Patients eligible for this study were cognitively impaired (Glasgow Coma Scale 4 to 12) and not capable of providing meaningful prospective informed consent for research participation for themselves.

The investigators proposed a 1-hour window after the patient's ED arrival that would be dedicated to a good faith effort to locate the LAR so that the patient might be eligible for enrollment with prospective surrogate consent. If the LAR presented within the hour, an informed consent process took place, during which the LAR decided whether to enroll the patient in the trial. The 1-hour window was chosen keeping in mind the inherent delay inevitable in obtaining test results required to satisfy the inclusion criteria. Further, the allotment was felt to be respectful of patient autonomy and consistent with the spirit of the regulations. If no LAR was present within 1 hour of patient arrival, an eligible patient could be entered into the study under EFIC. Consent for continued participation was then pursued from the subject or from an LAR as soon as feasible. Previous work by the study investigators indicated that suitable surrogates are often not present and available to participate in consent processes within the narrow treatment window for this intervention.[4] Therefore the FDA approved an investigational new drug application for this trial that allowed subjects to be enrolled under EFIC. The consenting mechanism of the trial is shown in Figure 1.

The NETT clinical coordinating center has a dedicated human subjects coordinator and a human subjects working group (HSWG) tasked with overseeing human subjects protection issues related to all NETT trials.[5] The case studies presented here are cases reported to the HSWG for discussion of ethical challenges that arose during the conduct of the ProTECT-III trial. The cases present the complexities of consent by an LAR within the context of an EFIC study. In addition, each case also describes the challenges that arise when attempting to determine how the case fits into the established (and approved) consenting paradigm for the study itself and how the case, as it was resolved, satisfies the regulatory requirements for surrogate consent when it is possible within an EFIC study.

CASE STUDIES (TABLE 1)

Case 1: "Like a Brother"

A severely injured patient arrived at the emergency department (ED) after a motorcycle crash. The patient met inclusion criteria for the ProTECT-III study. Shortly afterward, within the 1-hour time frame established for the physical presence of an LAR, a man arrived who identified himself as the patient's brother, and the site study coordinators considered him to be the patient's available LAR. The LAR was informed of the study and agreed to provide prospective informed consent for the patient's enrollment. Several hours later, it was discovered that the consenting individual was not the patient's biological sibling, but rather the subject's "Harley brother."

Discussion. In this case, the Harley brother was thought to have a legally recognized relationship with the patient that he in fact did not have. When it became clear that the Harley brother was not the patient's LAR, pursuit of a valid consent from a real LAR was sought, but no LAR was immediately found. The ProTECT-III hotline was notified and the HSWG determined that the enrollment should be considered an EFIC enrollment,

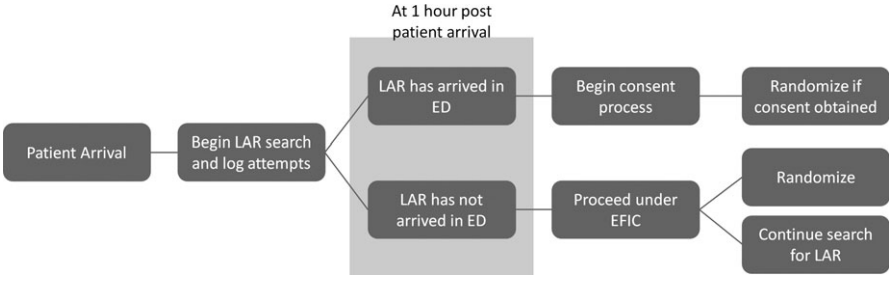

Figure 1. Consenting paradigm for ProTECT-III. LAR = legally authorized representative; EFIC = exception from informed consent.

Table 1
Summary of Cases and Ethical and Practical Challenges

Case	Barrier to Effective LAR	Core Tension	Guiding Principle(s)	Ethical Challenge(s)/ Questions
Harley brother	• Lacks legal status • Patient's preferences unknown	• Ethical vs. legal surrogacy	• Respect legitimate refusals • Ensure surrogate has appropriate ethical standing	• No criteria for relying on a non–legally recognized surrogate, particularly in context of "opportunity to refuse"
Intoxicated LAR	• Intoxication impairs LAR's capacity to serve as a surrogate	• Desire for surrogate decision-making vs. desire not to act on decisions in context of incapacity	• Recognize patients' wishes as expressed by LAR • LAR must have capacity to make meaningful decision	• If an incapacitated potential LAR wants to refuse participation, are criteria for honoring refusal different than those for providing consent?
Refusal to be LAR	• LAR is capacitated but reluctant • LAR believes the significant other should make decisions.	• Preference for surrogate decision-making rather than EFIC vs. forcing someone to act in a capacity in which they are uncomfortable	• Do not enroll if consent is "possible" but not obtained. • Avoid incentivizing "opting out" of decision-making.	• Cannot force people to act as a surrogate decision-maker • Refusal of an LAR to serve in that role may reflect patient's preferences regarding research enrollment
Geographically distant LAR	• LAR is identified but there is a communication barrier based on geographic distance	• Desire to act on individuals' wishes (as expressed by LAR) versus a suboptimally informed decision	• Opportunity to object should be offered unless communication barrier prevents adequate discussion to meet criteria for acceptable refusal	• Uncertainty regarding necessary level of understanding for refusal to be ethically valid • Uncertain/unknown whether stress imposed by discussion over the phone or involvement in decisions is preferred by patients/ surrogates

LAR = legally authorized representative.

since the assumed LAR was not a true LAR. Ultimately, the subject himself was able to give meaningful consent for continued participation, 11 days after enrollment.

The EFIC regulations default to EFIC enrollment whenever there is a question of the presence or identity of an LAR. In this case, the enrollment was deemed an EFIC enrollment just as it would have been had the Harley brother not been present. EFIC studies are unique in this respect, differing from standard clinical research, because enrollment does not depend on prospective consent; the default of enrollment is in large part justified by the additional protections built into the EFIC regulations.

Tension related to the EFIC regulations might, however, have arisen in this case of the "false" surrogate if, for example, a true LAR or the patient himself disagreed with the decision made by the false surrogate. For example, the patient would not have been enrolled into the study if the Harley brother, assumed to be the true LAR, had declined enrollment. By the time the discovery was made that a true LAR was not present, the time frame for study enrollment had passed.

Most states have statutes that define the hierarchy of LARs related to clinical decision-making for incapacitated patients and describe how this should be documented. States may vary in their interpretation of who constitutes an appropriate potential decision-maker. In some, state law provides LAR status to friends or close friends as the last resort (see for example Georgia state law O.C.G.A 31-9-2[6]).

Further, even in states where no statute exists, many hospitals honor a friend's greater knowledge of the intent of the patient. However, it is not clear if the same rules of hierarchy would hold for research study enrollment (rather than clinical care) of an incapacitated patient. In emergency research situations, where time is limited, it is important to communicate clearly with the presumed surrogate what they are claiming and agreeing to. When a true LAR is not present within the allotted time frame, the EFIC regulations allow enrollment of the patient into the trial.

This case thus raises important conceptual questions about the role of surrogates in EFIC research. If a close and long-term established relationship exists between the potential surrogate and the patient, what role should that person play in enrollment decisions when the default in EFIC studies is enrollment in the absence of an LAR? The EFIC regulations state that an LAR can provide consent for research enrollment for the incapacitated patient and that investigators should offer the family an opportunity for refusal when appropriate.[1] Would nonenrollment based on objection by a non–

family member such as the Harley brother be considered appropriate if it was deemed that the non–family member was legitimately aware of patient preferences? If so, how would this knowledge be verified and what would be the consequences? What if the extent of the connection was unclear? Tensions between legal and ethical authorization as a surrogate are well known, but their specific implications in the context of EFIC research have not been fully addressed.

Case 2: "Too Drunk to Say"

A patient was transported to the ED shortly after sustaining a severe TBI. The study team had been notified prior to his arrival, so the team was able to immediately screen him for study eligibility. It was determined that the patient was eligible, pending the confidential serum alcohol level results. During the preliminary screening process, the on-duty ED social worker was asked to help contact family and the LAR. The social worker notified the study coordinators that the patient's mother and girlfriend were at the bar with the patient at the time of the incident and were on their way to the hospital. Since the family's arrival was anticipated to be within 1 hour of patient arrival, the study team proceeded under the protocol with the intent to seek prospective consent upon LAR arrival.

When the family arrived, the charge nurse informed the study team that the LAR appeared to be intoxicated. The social worker, who also interacted with the family, concurred that the family members, including the LAR, were all intoxicated and, further, that they were too inebriated to participate in any meaningful decision-making or consent process. Based on this information, the family was not approached by the study team. The ProTECT-III hotline was contacted for guidance and a decision was made to enroll the patient under EFIC. The team therefore enrolled the patient with EFIC despite the presence of an LAR within the study's 1-hour time frame for LAR consent.

Discussion. In subsequent discussions, the HSWG agreed with the study team that an LAR who is impaired from intoxication obviously cannot engage in a meaningful conversation and participate in an informed consent process. This case raises the issue of capacity assessment of LARs and how this may result in tension within the context of an EFIC study. What should be done if an LAR is present but is deemed incapable of making an informed decision to accept or decline study enrollment? How can it be determined that EFIC is the correct default in this circumstance?

It must be acknowledged that there are many circumstances when family members and LARs lack capacity to provide informed decisions. Examples of this include when the family members are also critically injured in the same accident, when they are minors, when they are demented or developmentally delayed, or when they are very intoxicated. Allowing EFIC enrollments when family members and LARs lack capacity avoids exclusion of eligible subjects from enrollment. At the same time, the temptation to enroll patients can lead to a thoughtless and rapid determination of incapacity when, in fact, more careful scrutiny and effort may resolve the question of the capacity of the LAR. Tension exists for the investigator, who obviously wants to enroll the patient and whose research intervention is very time-sensitive, but who also is required and expected to follow ethical procedures, to adhere to the regulations that govern ethical research, to apply the patient safeguards inherent in the EFIC regulations, and to act in a manner that respects and protects the incapacitated patient's rights. Indeed, this tension may be perceived as a conflict of interest for the investigators, but it is not. Because EFIC enrollments are followed as soon as possible by notification and consent to continue, there is no advantage to the investigator to enroll under EFIC someone who will withdraw immediately thereafter. While the tension is largely mitigated by this requirement, determination of LAR capacity in emergency research circumstances remains an uncertain and unstudied challenge.

Determination of incapacity or competence is rarely straightforward, even in the best of situations. These decisions are often subjective and can place the research team in a difficult situation. Ideally, other non-study personnel should determine the capacity of the LAR to give prospective consent. In the acute care setting, this may not be possible. If the study team begins the discussion of the study with the LAR who is then determined to be incapacitated, what should be done if that person declines the study? Is this refusal truly informed? How informed does informed refusal need to be? What constitutes an adequate assessment of capacity?

The HSWG recommended that the study team itself be responsible for ensuring careful capacity assessment before determining that someone is not capable of being an LAR. Such a determination should be based on reliable historical or clinical information. Taking the word of another without the research team's own assessment may raise questions about the team and overeagerness to enroll the patient without attending to the capacity assessment of the LAR. In addition, to avoid the perception that study teams determine incapacity in order to enroll patients, we suggest that the threshold be high for determining incapacity, but low for honoring refusals. As a further protection against perceived conflict of interest, and to be sure these decisions are highly transparent and can be tracked, the study team should notify the on-call principal investigator prior to enrolling using EFIC. The HSWG also recommended that, because it is ubiquitous, emotional impairment alone not be considered as a basis for incapacity (although this will be discussed below). In addition, whenever a study team enrolls under EFIC in situations where the LAR was present but is felt to lack capacity, the case should be reviewed in detail by committees such as the NETT HSWG to track such enrollments and recommend improvements to this interpretation or implementation as needed.

Case 3: "Able and Authorized"

A man with a severe TBI was transported to the ED after a serious motor vehicle collision. His mother was present almost immediately (within the 1-hour time

frame for ProTECT-III LAR enrollment). She was approached to provide prospective consent for study enrollment. She had no objection to the patient being enrolled into the study, but felt that the patient's significant other, who was on the way to the hospital, should be the one to provide prospective surrogate informed consent.

Discussion. This case raises several important issues related to surrogate consent. What is the alternative if an LAR is reluctant to act in that capacity? How can capacity of an LAR be assessed in the short time frame of an EFIC study? Should surrogate decision-making only be done by an LAR? Can investigators determine if an LAR's indecisiveness is due to situational incapacity, reluctance to take responsibility, or uncertainty regarding what the patient may want? Should an LAR's emotional distress be interpreted as making LAR-provided consent infeasible?

According to the EFIC regulations and the study protocol, if present within the established time frame, an LAR is expected to take responsibility for providing prospective consent for patient enrollment. The consenting LAR does not necessarily have to be the highest-ranked LAR in the state-defined hierarchy; however, if there is conflict among multiple LARs who may be present, the person highest in the state's hierarchy should be approached for decision-making.[1] The LAR can seek input from a significant other without LAR standing, but it is not clear if an LAR can abdicate or reassign the legal authority and responsibility of being the LAR.

By the protocol of the study, the patient could not be enrolled under EFIC because an LAR was present within the 1-hour window, even though she was unwilling to act in that capacity. At first glance, it would seem that an LAR who refuses to act in that capacity is equivalent to no LAR at all, and that in both cases, the default should be to EFIC enrollment. However, the study protocol was explicitly written to remove any incentive on the part of the study team to consider an LAR inappropriate to enroll the subject under EFIC. Therefore, this patient was not enrolled in ProTECT-III.

The FDA's guidance on EFIC does not address the issue of the present but reluctant LAR. Consultation with the hospital or IRB attorney may provide guidance, if practicable in a timely fashion. A more feasible approach may involve having a very short, focused conversation with the LAR (in this case the mother), designed to identify whether the subject is someone who would generally not want to be included in this or any research study. Such a process of "informed refusal" has been suggested as a possible approach to consent challenges in other kinds of acute care research[7] and may provide a balance between respecting the subject's autonomy and the mother's desire not to serve as an LAR. This process may be appropriate if there is real reason to believe that the mother is simply not in a position to comprehend the necessary information and make a fully informed decision at that moment, but may be willing to make an informed refusal that enrollment would be against the son's wishes.

Informed refusal or some lower level of involvement in the enrollment decision is consistent with the EFIC regulatory provisions. EFIC regulations have established a lower threshold of legitimacy for objections to enrollment than is accepted for consenting to enrollment. Family members, regardless of position on the state hierarchy of LARs, are required to have the opportunity to object to study enrollment for their family member (if feasible), but non-LAR family members cannot consent to enrollment.[2] A case such as this one, with an LAR who does not appear to object to enrollment, but does not want to act as an official surrogate, is not explicitly covered in the regulations.

Of course, the LAR could refuse to engage in an informed refusal discussion as well, forcing the team to decide whether to exclude the patient from the study or to enroll under EFIC. Because the clinical conditions that qualify for EFIC research are exceedingly stressful on families, and research decisions often are foreign, circumstances in which potential LARs do not feel they can act as a surrogate (due to emotional stress or otherwise) warrant careful consideration. Is this mother refusing to act as an LAR because she does not feel knowledgeable enough to speak on behalf of the patient? Although challenging for investigators, this in and of itself is not enough to preclude an informed consent discussion, and it is important to discuss the role of the LAR and what she needs to know or understand to function as an LAR. Is she unable or reluctant to focus on the research issues because she is distraught over the severe life-threatening circumstances her adult child is in? How can study teams separate situational impairment from other causes of incapacity?

Most family members are expected to have some situational impairment related to the rapid pace and strong emotional content of communication and decision-making in the emergency setting, just after being notified of a loved one's life-threatening condition. However, situational impairment itself should not be the sole determinant of defaulting to EFIC enrollment rather than obtaining LAR prospective consent. In some circumstances, situational impairment may likely interfere with the ability to have a meaningful informed consent discussion, but the HSWG felt that EFIC should not be used as a default in the setting of purely "emotional impairment," even if the emotional state of the LAR delays the informed consent discussion.

Like the first case, this case also illustrates the question of who is the best surrogate decision-maker. In this case, the significant other may have had greater knowledge of the patient's wishes, but since the significant other was not a family member or LAR, the significant other could neither consent nor decline enrollment. Is there any justification for handling surrogate decision-making in such situations differently in the context of an EFIC study? If so, who would determine this? The conflict between the legal and ethical representative creates a difficult conflict between respect for autonomy within the framework of the study, included to address the spirit of the regulations, and the need to follow the letter of the law.

Case 4: "Remote and Minimally Informed"

The patient was on a motorcycle trip with a friend when he sustained a TBI. He was from another state, but was

brought to the local ED where he was treated and found to be eligible for inclusion in ProTECT-III. The subject's friend was not his LAR and therefore was not asked for consent for or given the opportunity to object to the study enrollment. Because no LAR was immediately available, as the friend was not a relative and the patient's wife was out of state, the patient was enrolled under EFIC.

Most hospitals restrict the information provided to family members by telephone about acutely critically ill or injured patients, so that such information can be communicated in the hospital in a more controlled and supportive environment. However, most institutions allow some clinical information to be communicated by telephone when relatives are remote and unlikely to be able to arrive immediately. However, in this case, the hospital policy was to provide minimal clinical information over the phone, so the friend (and not a clinician) relayed the patient's clinical information to the patient's wife. Since the wife had not been provided any clinical information from the treating team, the investigators felt that it was inappropriate to describe the study and her husband's eligibility for enrollment until her anticipated arrival the next day. In fact, the study protocol explicitly excluded a phone discussion prior to clinical notification by the treating team. She was therefore also not provided the opportunity to object prior to the enrollment. Consent was eventually obtained for continued ProTECT-III participation from the wife, after she was able to travel by airplane to the treating hospital. Although she had no concerns about the patient's treatment or enrollment, she expressed some resentment about the lack of clinical information she received and not being informed of the research study over the phone in advance of enrollment.

Discussion. In most clinical trials, in-person consent for enrollment is required because of ethical concerns about the quality of consent conversations that may take place over the telephone and legal concerns about the ability to document the appropriateness of the surrogate when that person is not present.[8] In these situations, if signed consent documenting the informed consent process cannot be obtained in person from the patient or a suitable surrogate decision-maker, an individual is simply not enrolled in the trial. When a trial is approved for EFIC, however, a unique situation arises. The default position is to enroll the patient rather than not to enroll the patient.

Consistent with these general regulatory requirements regarding signed consent to document the informed consent process, the EFIC regulations do not contain any provisions that allow for consent discussions to occur with an LAR over the telephone.[1,2] However, the EFIC regulations do clearly state that where possible a family member should be given the opportunity to object prior to study enrollment and that such an objection does not have to be in writing.[2] Specific allowable communication modalities by which this conversation can occur are not specified. In the case presented here, the investigators felt that the severe clinical condition of the patient and the LAR's lack of direct communication with the treating team created an uncomfortable situation that precluded a meaningful discussion of research options.

In the context of the EFIC regulations, and subsequently knowing that the wife was upset about not being informed, the role of a potential telephone conversation with the patient's wife warrants reexamination. There are, in fact, two ways to view this conversation: 1) as a true informed consent discussion or 2) as an opportunity for refusal of enrollment. This distinction is important, because the standards for refusal are generally accepted to be lower than the standards for consent.[7,9] While there are reasons to question whether a consent conversation conducted over the phone is sufficiently informed and ethically valid, there are some reasons to believe that a refusal in this context may be. If, for example, the patient's wife had told investigators that her husband would not want to be included in any research protocols in the context of acute TBI and there was no reason to question the legitimacy of this preference, the patient should probably not be enrolled. In contrast, if the patient's wife did not voice objections to enrollment after an appropriate telephone explanation of the patient's status and a very brief summary of the ProTECT-III trial, enrollment under EFIC seems justifiable.

This case was complicated by the hospital's policy not to release clinical information over the phone, but this is an extreme interpretation of a common hospital practice. This policy created ethical tension for the investigators. The HSWG suggests that when important research-related discussions need to occur and the default in the absence of an LAR is enrollment using EFIC, disclosure should probably take place to allow the opportunity to object to enrollment, as is consistent with the EFIC regulations. Ideally, depending on the expected delay until the LAR's arrival, the patient's clinical status would have been provided by the treating team to the wife over the phone. This would have been followed by a very brief description of the ProTECT-III study and an opportunity for her to ask questions and decline participation if that is what she wanted to do. If she did not object, the patient would be enrolled with EFIC, based on absence of true consent (but no objection). The wife would then go through a formal, in-person consent process for continued study participation upon arrival at the site. This practice allows for maximal respect for the patient's wishes but recognizes the limitations of telephone conversations.

It could, however, also be argued that the need to allow opportunity for objection to an EFIC enrollment should be dependent on the nature of the study itself. For example, some experimental interventions are known to present little additional medical risk at the time of intervention and have no known dangerous complications. In these circumstances, a telephone communication simply to provide an opportunity to object may be less important than when a study intervention carries a greater risk.

From a practical standpoint, however, any conversation about research enrollment is difficult if the patient's clinical status has not yet been described by the treating team and the investigator cannot directly assess the capacity of the LAR to understand the research discussion in the face of serious and stress-producing circum-

stances. Clinical policy and research policy need to be harmonized. In this cases, the clinical policy of not disclosing information resulted in a suboptimal approach to EFIC research enrollment. Research enrollment in an EFIC study should be considered an extenuating circumstance if a hospital does not have a policy to allow disclosure of clinical information over the phone when the LAR is coming from a long distance.

Another related ethical challenge raised by this case relates to the proper role of the patient's friend. Can the friend serve as a "suboptimal" but available LAR? Can the wife authorize the friend to give consent on her behalf? Can the friend refuse enrollment? Although common sense and ethical theory may permit a good faith answer, the legal requirements do not address these unusual circumstances. There may be relevant state laws, and legal consul may help ascertain how they apply in similar circumstances.

CONCLUSIONS

These cases describe challenges arising when prospective informed consent appeared to be possible in the context of an exception from informed consent study. Each case created an unanticipated ethical tension related to the legally authorized representative. The tension typically involved some form of trade-off between less informed, lower-quality consent decisions at the present time and more informed, higher-quality decisions later. Although these cases are related to a single research protocol and arose because of the trial-specific consent paradigm of ProTECT-III, the ethical issues and tensions that are described are mostly generalizable to other exception from informed consent studies.

When the regulations and their guidance were written, the nuances described above could not have been anticipated. It is likely that many other such cases have occurred in other studies, but there has been little reporting of such issues. Best practices for exception from informed consent studies have not been established, but the development of a human subjects working group allowed thoughtful discussion and deliberation of cases to inform a consistent subsequent practice.

References

1. U. S. Code of Federal Regulations. 21 CFR 50.24: protection of human subjects; informed consent–FDA; final rule. Fed Regist 1996;61:51498–533.
2. Guidance for Institutional Review Boards. Clinical Investigators, and Sponsors; Exception From Informed Consent Requirements for Emergency Research. Washington DC: U. S. Food and Drug Administration, 2013.
3. Cearnal L. The birth of the NETT: NIH-funded network will launch emergency neurological trials. Ann Emerg Med 2006;48:726–8.
4. Wright DW, Clark PL, Pentz RD, Hertzberg V, Kellermann AL. Enrolling subjects by exception from consent versus proxy consent in trauma care research. Ann Emerg Med 2008;51:355–60.
5. Silbergleit R, Biros MH, Harney D, Dickert N, Baren J; NETT Investigators. Implementation of the exception from informed consent regulations in a large multicenter emergency clinical trials network: the RAMPART experience. Acad Emerg Med 2012;19:448–54.
6. State if Georgia. State law O.C.G.A 31-9-2. Available at: http://dch.georgia.gov/sites/dch.georgia.gov/files/imported/vgn/images/portal/cit_1210/37/13/182745096Questions_About_Proxy_Caregiving_March2012.pdf. Accessed Dec 7, 2014.
7. Dickert NW, Llanos A, Samady H. Re-visiting consent for clinical research on myocardial infarction and other emergent conditions. Prog Cardiovasc Dis 2012;55:251–7.
8. U.S. Code of Federal Regulations. 21 CFR 50.27. Documentation of informed consent. Fed Regist 1981;46 FR 8951.
9. Faden RR, Beauchamp TL, King NM. A History and Theory of Informed Consent. New York, NY: Oxford University Press, 1986.