Uninformed refusals: objections to enrolment in clinical trials conducted under an Exception from Informed Consent for emergency research

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ABSTRACT

Clinical trials in emergency situations present unique challenges, because they involve enrolling individuals who lack capacity to consent in the context of acute illness or injury. The US Department of Health and Human Services and Food and Drug Administration regulations allowing an Exception from Informed Consent (EFIC) in these circumstances contain requirements for community consultation, public disclosure and restrictions on study risks and benefits. In this paper, we analyse an issue raised in the regulations that has received little attention or analysis but is ethically complex. This challenge is when to solicit and honour objections to EFIC trial enrolment, including from non-legally appointed representatives. We address novel questions involving whose objections should be honoured, what level of understanding is necessary for objections to be considered valid and how hard investigators should work to offer an opportunity to object. We present a set of criteria that provide conceptual and practical guidance. We argue that objections should be honoured if they undermine one of the key assumptions that allows for the permissibility of EFIC trials: that individuals would likely not object to enrolment based on their values or preferences. We then clarify the practical implications of this approach through examination of three cases of refusal in an EFIC study.

INTRODUCTION

In recognition of the need for clinical trials to advance emergency care for acute illness and the fact that informed consent is often impossible, regulations in the USA and other countries allow an Exception from Informed Consent (EFIC) for research in emergency settings.[1–3] Investigators and institutional review boards (IRB) have gained substantial experience conducting EFIC trials of interventions for cardiac arrest, traumatic brain injury, and other life-threatening injuries. There has also been significant discussion in the literature about EFIC research, especially US requirements for community consultation and public disclosure. One interesting challenge has received little attention: when to solicit and honour objections to EFIC enrolment.

In non-emergency settings, patients lacking capacity for informed consent or a suitable legally authorised representative (LAR) are typically not enrolled in clinical trials. Most countries' emergency research regulations also require that prospective consent be sought when possible; however, the default position becomes enrolment when no LAR is available. US regulations also encourage offering individuals other than the LAR an opportunity to object to enrolment. 'If no LAR is available, the clinical investigator must commit to contact a family member to provide an *opportunity to object* to the participation of an individual, before administering the test article without informed consent, if feasible.'[1] US regulations are unique in distinguishing opportunity to object from consent, but the need to exclude people who would not want to be included is widely recognised. The European Commission Clinical Trials Directive, for example, requires that a research subject 'has not previously expressed objections known to the investigator,' though it does not mention objections by others.[2 3]

Offering an opportunity to object in EFIC trials raises novel and important ethical and practical questions. It has not been defined whose objections count, what level of understanding is necessary for objections to be valid, or how hard investigators should work to offer opportunities to object. US regulations and guidance documents also provide no details regarding whether this objection can be solicited remotely (eg, by telephone) or how investigators should handle unsolicited objections that arise if people accompanying a patient find out the patient is being included in a trial. These issues are not merely academic. One recent publication described related challenges during a traumatic brain injury trial.[4] Investigators encountered surrogates who were misrepresented, intoxicated, reluctant, and geographically distant. It is important to consider how to respond if these individuals object to enrolment. This paper examines the ethical basis for honouring objections in EFIC research. Through consideration of key scenarios, we propose criteria to guide decisions about when EFIC investigators should solicit or follow objections.

Framing the issue

The threshold for honouring objections in research is low

There are two strong reasons for having a low threshold for honouring objections to EFIC research. First, while some have argued that limited obligations to participate in some research may exist, it is widely accepted and ensconced in international guidelines and regulations that participation in clinical research—especially with novel interventions—is generally non-obligatory and is not like public health efforts, for example. As a result, informed consent by a patient or surrogate is usually required for enrolment, and refusals are typically honoured, regardless of whether a patient or surrogate understands the study. In other words, capacity for consent must be

demonstrated in order to *allow* enrolment, a requirement traditionally grounded in the principle of respect for persons.[5 6] There is generally no threshold for honouring objections to enrolment.

Second, EFIC is permitted in emergencies because consent is not *possible*, not because consent is not *important*. If consent could be practicably obtained for enrolment in a randomised trial of a new drug for cardiac arrest or traumatic brain injury, it would be required. Most EFIC studies typically involve an investigational intervention and are rarely what most IRBs would consider to be minimal risk.[7] It is true that US EFIC regulations contain additional protections; they require that risks be reasonable, that a prospect of direct benefit be present, that a situation be life threatening, and that existing therapy is in some way inadequate. However, the EFIC mechanism is ultimately allowed when studies cannot be conducted with capacitated patients.[8] If consent were possible, the default position would become non-enrolment as in other settings.

Recognising that EFIC is grounded in practical considerations makes it clear that a low threshold for honouring objections to enrolment in EFIC studies is ethically appropriate. However, an objector may be uninformed, have marginal capacity or lack a connection to the patient that would provide insight into the patient's wishes regarding enrolment. Some individuals should not be given an opportunity to object, and some objections should not be honoured. Identifying these situations will be the focus of this paper.

The relevance of the research-clinical care distinction

In clinical emergency medicine, interventions are often performed over objections of incapacitated patients or surrogates. An agitated patient with haemorrhagic shock from a gunshot wound might be taken to surgery against his will because it is known that the operation is necessary to save his life and it is unclear whether his objection is genuine. These decisions are governed by determinations of the patient's best medical interests.[9] Some may argue that the EFIC trial scenario is analogous. Because EFIC trials require a potential for direct benefit in order to be approved, and because existing therapy must be considered unsatisfactory or unproven, EFIC enrolment may be considered to be in a patient's best interests.

We agree that EFIC trial participation, in some circumstances, may represent the best chance for a good outcome. However, the distinction between clinical care and research is relevant. EFIC trials must have a favourable risk-benefit ratio and, in the presence of equipoise, may be *consistent* with clinical obligations, but they remain trials. Study interventions are typically not standard of care, and sufficient uncertainty must be present for randomisation to be ethical. In other words, all treatment arms must be considered consistent with patients' interests; all patients must receive care consistent with standard practice. Despite a prospect of benefit, enrolment in an ethical randomised trial—in which legitimate uncertainty exists—over an objection by a patient (or someone who knows the patient) is difficult to justify based on best interests grounds. If the treatment being tested were known to be in patients' best interests, the trial would not be ethical to conduct in the first place.

Objections should be honoured when they undermine the assumption that participation does not conflict with enrolled patients' values or interests

The most promising answer to when objections should be honoured lies in the underlying ethical justification for EFIC research. Interestingly, the EFIC regulations do not offer an explicit ethical argument for why EFIC is acceptable other than to articulate that emergency research is important and that consent is impractical. The regulations do incorporate protections related to risk and benefit and require community engagement. However, addressing objections to enrolment requires an understanding of the ethical basis of EFIC enrolment.

Several accounts have been put forth regarding the justification of EFIC. Some have emphasised clinical equipoise and the absence of significant non-therapeutic research risks.[10 11] If these conditions apply, there are unlikely to be strong reasons why most patients would object to enrolment. In a comprehensive analysis of the ethical justification for EFIC, Largent *et al* argue more explicitly that an important condition is that 'there is no compelling reason to think that participation in research conflicts with enrolled patients' values or interests.'[12] This condition, we believe, offers instructive guidance regarding how objections should be approached. The additional protections in the EFIC regulations help to ensure that approvable trials are ones to which most patients are unlikely to object. However, this assumption is probabilistic. If a patient, LAR, family member or friend expresses an objection, this assumption may be undermined for that patient, and the justification for enrolment may not hold.

The key question in addressing objections to EFIC enrolment is thus whether the objection overturns the assumption that participation does not conflict with the patient's values or interests. We consider three different cases of objection in order to examine when this assumption is or is not undermined.

Case studies

Case 1

A patient with suspected myocardial infarction is eligible for a prehospital EFIC study. The patient is conscious and awake but is having active chest pain. After being told that patients in this system are routinely being enrolled in a study testing a new treatment for heart attack, he states he does not want to be included.

This situation is straightforward. With a responsive patient, investigators need not depend on the assumption that he is *unlikely* to object. His objection undermines that assumption, even if his understanding is minimal. For these reasons, some EFIC studies have offered patients the opportunity to opt out of inclusion and honour all refusals. In the Out-of-Hospital Administration of Intravenous Glucose-Insulin-Potassium in Patients with Suspected Acute Coronary Syndrome trial,[13] for example, investigators incorporated a brief assent script to allow refusal in a prehospital acute coronary syndrome trial. In addition to being conceptually sound, this approach has empirical support. Although some may believe that patients may not want to make such decisions in the context of stressful emergencies, evidence suggests they value the opportunity to refuse, even in emergency situations with diminished understanding.[14 15]

While this case may not seem controversial, this approach is not universal, and few attempts to offer opportunities to object have been described. In a recent trial of anticoagulation in acute myocardial infarction in the UK, for example, no opportunity to object was offered despite potentially capacitated patients.[16–18] Honouring this patient's refusal thus requires acceptance of the view that uninformed refusals have ethical force. After all, this patient's refusal is not rooted in any understanding of this trial, and it is far from clear that he is capacitated to provide consent. Willingness to honour the refusal thus establishes an important baseline for cases that are not as intuitively obvious.

Case 2

There is no LAR available for a patient with traumatic injury and haemorrhagic shock, but a non-LAR family member is contacted

via phone. When telling the family member what is occurring, should the investigator offer an opportunity to object over the phone?

The US regulations specifically state that an opportunity to object to trial enrolment should be offered if a family member (not an authorised surrogate) is present at the hospital within the therapeutic window for an EFIC trial. This case asks whether geographic proximity matters. Having accepted in the last case that uninformed refusals can be appropriate, it is not clear why the fact that the family member is not physically present should affect a decision about whether to offer an opportunity to object or to honour a refusal of enrolment. An available family member allows investigators to involve someone with potential knowledge of the patient's wishes in the enrolment decision rather than relying on a population-based assumption of non-objection. There is no clear reason why the lack of physical presence of the family member is ethically determinative.

The challenge in this case is more about practicality. The opportunity to object to a trial should not be offered without some discussion of relevant clinical information. An investigator should not say 'your family member is going to be included in a study of a new treatment unless you object, but we can't tell you what is happening medically.' This is an important detail, as some hospitals have restrictive policies regarding sharing of clinical information over the phone. These policies are grounded in the view that remote communication may pose risks to the family member (eg, driving to the hospital) and may not be in patients' interests. Clinical disclosure policies are outside the scope of this paper, but addressing incompatibilities between such policies and the desire to engage surrogates in research decisions is important for hospitals doing EFIC research to confront.[4]

An additional challenge is that investigators should make clear to family members that they are not being asked to provide informed consent but that patients are being enrolled in this trial at that institution. The default position in an EFIC study when an authorised surrogate is not present remains enrolment. The family member is simply given the ability to opt out on behalf of the patient if they believe the patient would not want to be included. Follow-up discussion and an informed consent must happen with an LAR or patient as soon as possible.

How best to communicate the nuances of offering an opportunity to object (as opposed to asking for consent) has not, to our knowledge, ever been studied, and there are logistical challenges related to contacting family members who are not present. Research teams should not delay care or enrolment inappropriately and can only make reasonable efforts. Moreover, the nature of the intervention being studied—particularly its potential risks—factor into assessing the ethical importance of contacting a family member immediately. These concerns may affect the approach in a given trial, but they do not detract from the basic ethical argument that remote family members (or other appropriately connected individuals) should be given the opportunity to object when feasible.

Case 3

A patient has suffered traumatic brain injury, and her roommate is present at the hospital. The investigator is talking with the roommate about what is happening and discloses that the patient is being enrolled in a clinical trial. The roommate states that the patient would not want any kind of experimental drug.

In many places, a roommate or friend does not have a legally defined relationship with the patient and does not qualify as an authorised surrogate. The decision regarding whether to involve these individuals in decisions and whether to honour objections on behalf of the patient can thus become complicated. The EFIC guidance document only discusses family members and gives no recommendations regarding other friends and bystanders.[1] Two related but separable issues arise: whether to offer the friend the opportunity to object and whether to act on an objection raised spontaneously.

Whether to offer the roommate an opportunity to object is highly contextual. Some roommates are little more than acquaintances and are inappropriate to act as an agent for the patient in any capacity. Others are deeply connected—more than most family members—and may be ethically valid surrogates. Unfortunately, figuring out the context of the roommate's relationship to the patient may be impossible in emergency settings. For this reason, it is reasonable for investigators to default to local legal standards of surrogate authority as a matter of policy. This avoids placing healthcare decision-making responsibility on an individual who may have little knowledge about the patient's wishes and interests and gives investigators a consistent default practice. That said, if it is immediately clear that a roommate's relationship is substantial, it seems ethically justifiable to offer an opportunity to object to enrolment.

Even if an opportunity to object is not solicited, the roommate may learn about EFIC trial inclusion (through actions of staff or direct communication) and state an objection to enrolment that suggests the trial does not align with the patient's values or interests. To take an extreme example, one can imagine that the patient had a parent who died while participating in a clinical trial and swore never to enrol in research. We believe there is an ethical responsibility to honour that objection. A policy of not honouring such objections—based purely on the roommate's lack of LAR status—seems inconsistent with the EFIC justification and likely to generate problematically unwanted enrolment. Moreover, it may create situations in which investigators practise diminished transparency in order to avoid a confrontational situation. A lack of transparency and perception of secrecy by investigators and clinicians could have negative implications for public trust in healthcare and research.

Concerns about offering or honouring the roommate's objection are legitimate. The roommate may make a decision that is later discovered not to reflect the patient's wishes. That decision may have real consequences if the study intervention is beneficial. However, there are three reasons why this does not constitute a reason to over-ride the objection. First, though EFIC creates a default of enrolment, it does not create an obligation to enrol an individual in a clinical trial or ground a best interests argument to over-ride an objection. As articulated earlier, despite a prospect of benefit, randomised trials are only justified when sufficient uncertainty (clinical equipoise) exists. A patient receiving the current standard of care is not deprived of known effective therapy. Second, enrolment over the objection of someone who knows the patient violates a component of the ethical justification for EFIC (that enrolment does not likely conflict with the patient's values or interests). Finally, research occurs in a public context, and practices that involve over-riding objections to enrolment by individuals like this roommate seem likely to jeopardise the trust on which the research enterprise depends.

DISCUSSION

The regulatory requirement to offer an opportunity to object presents infrequent but real potential challenges for EFIC researchers. We have argued that the key to addressing objections in an EFIC study is recognition of the fundamental

difference between clinical care and clinical research and the distinction between consent and refusal.[19] As reflected in the US regulations, the threshold for honouring objections to enrolment should be low. A patient who is not enrolled in a trial due to an objection (offered by the patient or someone else) has not been deprived of the best known medical therapy. Even when EFIC trials provide the best hope for a successful outcome, this does not justify over-riding objections when the trial is premised on uncertainty.

There are numerous practical issues that must be addressed in implementing opportunities to object in practice. One important issue is the decision of when that opportunity should be explicitly *offered*. As demonstrated by the differences between case 2 and case 3, this determination is different from whether an objection should be *honoured*. There are individuals to whom one should not offer an opportunity to object. However, 'unsolicited' objections are meaningful when they provide evidence that an assumption of EFIC enrolment—that enrolment is not likely to conflict with the individual's values or interests—is invalid. Investigators may have to make difficult determinations regarding the legitimacy of objections. We believe that a general policy of deference to objections/refusals represents the best practice, in part due to the potential effects of alternative policies on public trust that is essential to EFIC research. There are few data to guide this practice, but it is easy to imagine how enrolment of patients in research over objections from family or friends could be perceived by the public as an abuse. Moreover, fear of unsolicited objections to enrolment should not restrict research teams from practising transparency with patients, family and friends.

There are two important further considerations regarding objections to EFIC enrolment. First, the consequences of the initial enrolment decision may vary in different studies. This affects the 'stakes' of offering or not offering an opportunity to object. For example, in a trial of emergent operative versus medical management of a traumatic injury, all trial-associated risks and benefits occur immediately on enrolment (when the patient goes or does not go for the operation). In contrast, in a study involving an infusion of a generally well-tolerated drug over several days, there may be very little risk involved in the first few hours of administration. In the former case, providing an opportunity to object to family members over the phone may be of substantial importance. In the latter case, a higher quality conversation with a true LAR several hours after initiation may be much more meaningful and appropriate than a minimally informed conversation offering an opportunity to object. In the latter case, it may be reasonable to consider not offering the opportunity to object over the phone if it is clear that family members will be arriving soon and a robust consent process can happen at that time. In this respect, it is important to tailor the approach to offering opportunities to object to the individual study.

Second, any approach must be consistent with local laws and regulations. Unfortunately, we are aware of no specific laws or jurisprudence of relevance to the involvement of non-LAR surrogates in objecting to clinical research. However, we suspect that, from a liability perspective, it is likely that there is a stronger argument for erring on the side of honouring rather than overriding refusals given that non-enrolment does not deprive anyone of known effective therapy.

CONCLUSION

The opportunity to object is an important aspect of the EFIC regulations that has been sparsely discussed but is important to consider. Its existence is grounded in an important distinction between clinical medicine and clinical research; however, complex cases can arise. We offer a practical approach to deciding whether to provide an opportunity to object and deciding when to honour objections. We believe this approach is consistent with regulations, appropriately respects potential participants, and promotes transparency and trust in emergency research. The complexity of this issue in practice also highlights the need for research teams to develop protocols specifically for interacting with non-LARs regarding enrolment decisions for EFIC research, and it highlights the need for empirical scholarship to define optimal approaches.

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