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IRB Help Sheet

Exception from Informed Consent (EFIC) for Research on Emergency Medicine Practices

Introduction

For certain types of research on emergency medicine practices, the regulations allow for an exception to the requirement to obtain informed consent from each subject, or the subject's Legally Authorized Representative (LAR), prior to enrollment ("Exception from Informed Consent," EFIC). The exception applies to emergency research where subjects cannot give informed consent because of their emerging, life-threatening medical condition, for which available treatments are unproven or unsatisfactory, and where the research intervention must be administered before informed consent from the subjects' legally authorized representative is feasible.

These subjects' lack of autonomy creates a special need for the FDA, study sponsors, IRBs, and clinical investigators to work closely together to ensure that the interests of this vulnerable population are protected to the maximum extent possible. Such studies may proceed only when conducted in accordance with the regulatory requirements of 21 CFR 50.24 and 45 CFR 46.101(i), the approval of the OHSU IRB, community consultation, and pursuant to an IND/IDE specific to the planned emergency research.

This Help Sheet is a supplement to "HRP-301 CHECKLIST: Waiver of Consent Emergency Research."

The IRB uses this Checklist in determining whether emergency research under the EFIC regulations meets the criteria for approval. This Help Sheet provides additional guidance on certain elements listed in the Checklist. You can help your review go smoothly by ensuring that all of the items on the Checklist are addressed in your protocol or other study documents, and by communicating with the IRB early in the development of your project.

Key Issues in Emergency Research under EFIC

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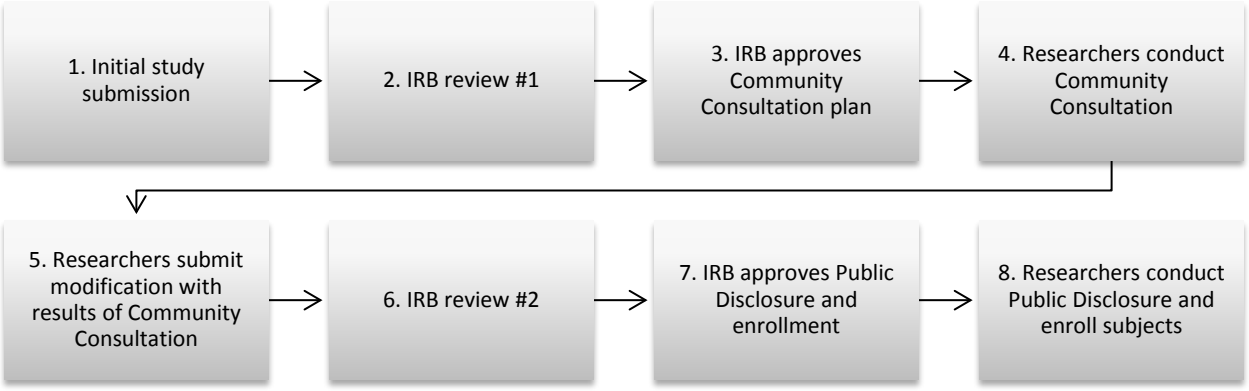
1. IRB review process for EFIC studies

The IRB reviews emergency research under EFIC in two steps. The first review determines whether the basic EFIC criteria are met and whether the Community Consultation plan is appropriate. The second review happens after the Community Consultation is conducted. The IRB reviews the findings of the Community Consultation process, along with any changes to the study that resulted from that process, and decides whether Public Notification and enrollment may begin. The basic steps of the review process are as follows:



If the research is FDA-regulated, it must be conducted under an IND or IDE that specifically covers the emergency research study. While the IND/IDE process and the IRB review process happen independently, the IRB will not grant final approval to enroll subjects until the IND or IDE is in place. It is often best to begin the IND/IDE process well before the IRB review process.

If the OHSU IRB disapproves the proposed protocol, the findings will be documented in writing and provided promptly to the investigator and the sponsor of the study (if different from the investigator). The sponsor must promptly disclose the disapproval to the FDA, to other investigators who have been asked to participate in this or a substantially similar study by the sponsor, and to other IRBs that have been asked to review this or a substantially similar study by the sponsor.

2. Guidance on addressing EFIC requirements in the protocol

a. Appropriateness of the research and the use of the EFIC provision

The criteria for approval under the EFIC provisions are complex. In addressing these criteria in your protocol, pay particular attention to the following:

<u>Life-Threatening Situation</u>

- Subjects must be in life-threatening situations, which means they have diseases or conditions in which the likelihood of death is high unless the course of the disease or condition is interrupted.
- An individual is not considered to be in a life-threatening situation when the situation is not emergent. For example, research involving an individual who has been in a coma for a long

period of time and whose condition is not rapidly deteriorating is not considered emergency research that is eligible for EFIC.

Available Therapy is Unproven or Unsatisfactory

- Available therapy includes therapy that is specified in the approved labeling of regulated products, as well as non-FDA-regulated therapies such as surgery and, rarely, some off-label uses of drugs or devices when supported by compelling evidence in the medical literature.
- Unproven means that there is not substantial evidence that the treatment is effective for the condition of interest. This may reflect the absence of any data or the absence of studies of acceptable quality.
- Unsatisfactory means that the available therapy is effective, but there are concerns about safety, low or partial efficacy (such as a low survival rate), or practical limitations on the use of the therapy.
- The OHSU IRB will consider the following in determining whether this element is satisfied. Describing these in your protocol will assist the IRB in making the necessary determinations:
    - The current standard of care
    - The available treatments and whether scientific evidence of efficacy is lacking (unproven) or whether the treatments are of questionable safety, limited efficacy, or suffer practical limitations (unsatisfactory)
    - Whether a study could be done to support approval for a product that is not approved but widely used

Informed Consent Not Feasible

- Subjects must not be able to give their informed consent as a result of their medical conditions.
- There must be a need for the intervention under investigation to be administered before obtaining consent from a subject's legally authorized representative is feasible. Feasibility considerations include risk to the subject, due to delayed care, to seek consent.
- There must be no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

Prospect of Direct Benefit

- Subjects must be in life-threatening situations that necessitate intervention.
- Data from animal and preclinical studies must support the intervention's potential for direct benefit to individual subjects.
- Risks associated with the investigation must be reasonable in relation to what is known about the medical conditions of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

Research Impracticable in Absence of Waiver

The OHSU IRB must find that the clinical investigation could not practicably be carried out without the waiver. If the results obtained in consenting subjects could be generalized to subjects who are unable to provide consent or if the research would not be unduly delayed by restricting it to consenting subjects, the OHSU IRB will not likely find that the investigation could not practically be carried out without the waiver.

Therapeutic Window

The protocol must clearly define the length of the potential therapeutic window based on available scientific evidence. This means the time period during which the intervention under investigation might reasonably produce a demonstrable clinical effect.

b. Community Consultation process

This is one of the most resource (time, labor and financial) intense requirements for conducting emergency care research. The community in which the research is to take place and the persons that would likely be affected by the research must be consulted before the research may begin.

The community will be defined by the nature of the research, taking into consideration disease or condition being studied, geographic catchment areas, and other demographic considerations. Every effort must be made to engage a representative sampling of persons or organizations in the affected community consultation process in order to educate them about the research and obtain their input regarding implementation of the research. Emergency first responders should be engaged and consulted as well.

Depending on the nature of the research, community consultation consists of any number of the following activities: survey(s); questionnaire(s), focus groups and community meetings. The information that should be presented to the community during consultation activities is detailed in "HRP-301 CHECKLIST: Waiver of Consent Emergency Research," Footnote 6.7.

After the community consultation process is complete, the PI must present a written report to the IRB by submitting a modification. The report should cite any and all issues raised through the process and conclusions, with modifications to the protocol as necessary. The IRB will consider issues raised in the community consultation process before granting approval to initiate the main portion of the investigation.

c. Public Disclosure plan

Investigators must submit a plan for public disclosure to the community that the research will be taking place in their area and who could potentially be a participant in emergency research without consent. The information that must be disclosed to the community before beginning the study is detailed in "HRP-301 CHECKLIST: Waiver of Consent Emergency Research," Footnote 6.8.

Following completion of the investigation, the investigator must submit a plan to disclose to the public information about the study design and its results, both positive and negative. This should include information about the primary outcome of the study, adverse events associated with the test article, and the basis for a decision to terminate the study.

The plan must outline how the information will be communicated and should be adjusted per the Community Consultation process.

d. Informed Consent and ongoing attempts to obtain consent

If informed consent of an individual subject or the subject's LAR is feasible prior to enrollment in the research, it must be sought, even if the study is approved under the EFIC provisions.

Where informed consent of the subject or an LAR is not feasible, researchers must be committed to providing information and attempting to obtain consent on an ongoing basis throughout the conduct of the research and at the conclusion of the research.

Specifically, the investigator must have procedures in place to:

- Attempt to contact an LAR within the therapeutic window and, if feasible, ask the LAR for consent within that window rather than proceeding without consent.
  - The investigator is not required to exhaust the entire therapeutic window before the test article may be administered.
  - In determining whether the plan to contact the LAR is appropriate, the OHSU IRB will assess whether the portion of the therapeutic window to be devoted to seeking informed consent is appropriately balanced against the loss of potential benefit caused by delaying administration of the test article.
- Inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, an LAR of the subject, or if such a representative is not reasonably available, a family member:
  - Of the subject's participation in the research, the details of the research protocol, and other information contained in the informed consent document; and
  - That the subject may discontinue participation in the study at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- Inform the subject as soon as possible, if a subject's condition improves, if a legally authorized representative or family member has been informed of the above.
- Obtain signed informed consent from the subject, or if the subject remains incapacitated, the subject's LAR, when research interventions are required after the emergency intervention and/or when subsequent data is collected for longitudinal purposes.
- Provide information about the clinical investigation to the subject's LAR or to a relative, if feasible, if the subject dies before consent has been obtained.

Several types of consent forms and information documents may need to be prepared in order to ensure that information is provided and that appropriate consent is obtained during the various phases of the research.

Investigators must document and summarize their attempts to contact family members to obtain their consent if obtaining informed consent is not feasible and an LAR is not reasonably available. This information must be submitted to the IRB at continuing review.

3. Vulnerable Populations: Children, Prisoners, and Pregnant Women

Children

Children may be included in EFIC studies provided that the additional criteria for involving children in research are met (see "HRP-310 CHECKLIST: Children"). Most emergency research that meets the criteria for EFIC will also meet the criteria for inclusion of children because the research is greater than minimal risk, but holds out the prospect of direct benefit to the subjects. If the study involves children, the Community Consultation and Public Disclosure plans should carefully consider how to reach parents of children who would potentially be included and, if appropriate, the children themselves.

Prisoners

Per DHHS regulations, prisoners may not be included in federally-funded emergency research under EFIC. However, given the emergent circumstances under which subjects are enrolled these studies, it may not be apparent that a subject is a prisoner at the time of enrollment. Likewise, a subject could become a prisoner following enrollment and during the study period (including long-term follow-up periods).

Therefore, the protocol should be clear that known prisoners will not be enrolled and should address either: (1) the plan for safely removing subjects from the study who become prisoners after enrollment; or (2) how the protocol meets the criteria for approval of research with prisoners with respect to the study procedures that take place after the emergency intervention (see "HRP-308 CHECKLIST: Prisoners" and "HRP-309 CHECKLIST: Unexpected Incarceration").

Pregnant Women and Fetuses

Per DHHS regulations, pregnant women and fetuses may not be included in federally-funded emergency research under EFIC. However, given the emergent circumstances under which subjects are enrolled in these studies, it may not be apparent that a subject is pregnant.

Investigators must carefully consider the impact that the study intervention could have on a pregnant woman or fetus where the pregnancy is not identified at the time of enrollment. A plan for pregnancy testing prior to enrollment (if feasible and appropriate) or follow-up to ensure the safety of pregnant women and fetuses after incidental enrollment should be described in the protocol. Any study procedures performed after pregnancy is identified must meet the criteria in "HRP-305 CHECKLIST: Pregnant Women."

Additional Resources

FDA Guidance: Exception from Informed Consent Requirements for Emergency Research (2013)

DHHS Federal Register Notice: Informed Consent Requirements in Emergency Research (1996)