

Human Research Protection Program Policies & Procedures



Research on Emergency Medical Practices

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BACKGROUND

A core ethical principal for the approval of any proposed human subject research is ensuring that respect for persons is being upheld through the voluntary informed consent process. Institutional Review Boards (IRBs) are required to ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative and that it will be appropriately documented. Depending on the level of risk of the study, the regulations make provisions for waiving and altering consent and the requirement to document consent. However, until about a decade ago, a waiver of consent was not allowable for any research that was considered greater than minimal risk. This lack of ability to allow a waiver for greater than minimal research created an obstacle to scientific advances in the care of traumatic injuries. In 1996, the Food and Drug Administration (FDA) codified, in 21 CFR 50.24, the exception from informed consent requirements for emergency research.

The regulations allow for an exception to the requirement to obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in a clinical investigation. The exception applies to emergency research involving human subjects who cannot give informed consent because of their emerging, life-threatening medical condition, for which available treatments are unproven or unsatisfactory, and where the intervention must be administered before informed consent from the subjects' legally authorized representative is feasible. Studies involving an exception from informed consent requirements may proceed only after a sponsor has received prior written permission from FDA, and the IRB has found and documented that specific conditions have been met.

The emergency research permitted under 21 CFR 50.24 involves a particularly vulnerable population: persons with life-threatening conditions who can neither give informed consent nor actively refuse enrollment. This 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 of subjects are protected to the maximum extent possible. The regulations for emergency research therefore contain specific human subject protection requirements to account for these concerns. These include specific requirements that representatives of the community(ies) in which the research will take place and from which the subjects will be drawn be consulted about the study and that information about a study be publicly disclosed before the study may proceed. This is often referred to as the community consultation and disclosure process.

SCOPE

This policy and procedure applies to planned research which is not covered under the Emergency Use of an Investigational Drug, Device or Biologic.

II. POLICY

- A. There are special cases under emergency care research in which it is not feasible to obtain informed consent. In order to allow such research to proceed, there are special provisions for exception from informed consent requirements. Research conducted in an emergency setting when there is more than minimal risk to the participant, but the research holds out the prospect of direct benefit to the subject, may qualify for exception to informed consent requirements.
- B. OHSU Investigators may only conduct research on Emergency Medical Practices 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.
- C. A new IND or IDE must be provided to the OHSU IRB in order for this research to be approved by the OHSU IRB. These device exemptions must specify that the planned emergency research protocol may include participants who are unable to consent. An existing IDE or IND for the same drug or device will not be sufficient for this planned emergency research.
- D. The OHSU IRB may approve a study under the exception to informed consent requirements in emergency situations where the subjects cannot give informed consent due to a life-threatening medical condition and in which the legally authorized representative cannot be reached within the therapeutic window. The OHSU IRB may approve the study without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB Committee (which includes a member who is a licensed physician and who is not otherwise participating in the clinical trial) finds that all of the criteria of 21 CFR 50.24 have been met (see II.B below).

III. PROCEDURES

A. Principal Investigator Responsibilities

- 1. Investigators are encouraged to consult with the IRB Chair in preparing their applications. Investigators who are planning emergency research should contact the OHSU IRB for assistance at least 6 months before the desired start date.
- 2. The following is a short summary of the major points that will need to be considered carefully and discussed in depth in the protocol in order to conduct emergency research
 - a. *Detailed Discussion in Protocol:* The issues raised below will need to be discussed and documented in the appropriate sections of the protocol. The five points which need to be discussed are summarized as follows:
 - (i) the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions;
 - (ii) obtaining informed consent is not feasible, for three reasons (see below);
 - (iii) participation in the research holds out the prospect of direct benefit to the subjects, for three reasons (see below); the study could not practicably be carried out without the waiver of informed consent; and

(iv) the study defines the length of the potential therapeutic window and the investigator has committed to attempting to contact a legally authorized representative to ask for consent for each subject within that window of time.

3. *Community Consultation:*

- a. This is one of the most resource (time, labor and financial) intense requirements for conducting planned emergency research, and it must be met prior to full approval by the OHSU IRB. The community in which the research is to take place and the persons that would likely be affected by the research must be consulted in order to begin the research.
- b. 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 regarding the research and obtain their input regarding implementation of the research.
- c. 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.
- d. During the community consultation process, first responders will have to be engaged and consulted as well.
- e. The OHSU IRB cannot approve Planned Emergency Research without this part of the process being completed in a thorough manner. The consultation plan must be submitted with the initial IRB application and approved by the IRB with the protocol. Once the consultation plan is approved, it may be initiated.
- f. After the community consultation process is complete, the PI must present a written report to the IRB citing any and all issues raised through the process and conclusions, with modifications to the protocol as necessary.

4. *Public Disclosure:*

- a. A plan must be submitted 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.
- b. The plan must outline how this will be communicated and should be adjusted per the community consultation process.

5. *Ongoing Attempts to Obtain Consent:*

- a. Researchers planning to conduct research that does not include the informed consent of all subjects must be committed to providing information and attempting to obtain the consent from the subjects and/or the appropriate relatives or legally authorized representatives on an ongoing basis throughout the conduct of the research and at the conclusion of the research.
- b. Several types of consent forms will need to be prepared in order to assure that information is provided and that appropriate consent is obtained during the various phases of the research.

- c. It is also required that information be provided about the clinical investigation to the subject's legally authorized representative or to a relative, if feasible, if the subject dies before consent has been obtained.
6. *Summaries of Attempts to Obtain Consent:*
 - a. Investigators will need to document and summarize their attempts to contact family members to obtain their consent if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available. This information will need to be submitted to the IRB at the time of continuing review.
7. A separate IND or IDE may be required.
8. An independent data monitoring committee must be established

B. OHSU IRB Responsibilities

1. The OHSU IRB will approve a protocol for planned emergency research only after review of the protocol and finding each of the following elements:
 - a. Concurrence by an Independent Physician
 - (i) The OHSU IRB must obtain the documented concurrence of a physician, licensed in the state where the research will occur.
 - (ii) This MD must be a member of or consultant to the OHSU IRB but who is not otherwise connected to the study or involved in the research before approving an exception to informed consent for planned emergency research.
 - b. Life Threatening Situation
 - (i) The OHSU IRB must find that the subjects will be in life-threatening situations, which means, for purposes of this policy, diseases or conditions in which the likelihood of death is high unless the course of the disease or condition is interrupted.
 - (ii) 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 planned emergency research. In that case, the research intervention requires consent by a legally authorized representative of the subject.
 - c. Informed Consent Not Feasible
 - (i) The OHSU IRB must find that informed consent is not feasible because:
 - The subjects will not be able to give their informed consent as a result of their medical conditions;
 - The intervention under investigation must be administered before obtaining consent from a subject's legally authorized representative is feasible; and
 - There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

- (ii) Feasibility considerations include risk to the subject, due to delayed care, to seek consent.
- b. Prospect of Direct Benefit** - The OHSU IRB must find that participation in the research holds out the prospect of direct benefit to the subjects because:
 - (i) They are in life-threatening situations that necessitate intervention;
 - (ii) Data from animal and preclinical studies support the potential for direct benefit to individual subjects; and
 - (iii) Risks associated with the investigation are 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.
- c. Research Impracticable in Absence of Waiver** - The OHSU IRB must find that the clinical investigation could not practicably be carried out without the waiver.
- d. Therapeutic Window** - The OHSU IRB must find that the proposed investigational plan defines the length of the potential therapeutic window based on available scientific evidence.
- e. Plan to contact Legally Authorized Representative**
 - (i) The OHSU IRB must find that the investigator has committed to attempting to contact a legally authorized representative within the therapeutic window and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.
 - (ii) The investigator will summarize efforts made to contact the legally authorized representative and make this information available to the OHSU IRB at the time of continuing review.
- f. Informed Consent Procedures and Documents**
 - (i) The OHSU IRB must review and approve informed consent procedures and informed consent documents. These procedures and documents are to be used with subjects or their legally authorized representative in situations where use of such procedures and documents is feasible.
 - (ii) The OHSU IRB must also review and approve procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.
- g. Additional Protections** - The OHSU IRB must find that additional protections for subjects will be provided, including the following:
 - (i) consultation with representatives of the community(ies) in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - (ii) public disclosure to the community(ies) in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits;

- (iii) public disclosure of sufficient information following completion of the protocol to apprise the community(ies) and researchers of the study, including the demographic characteristics of the research population, and its results;
- (iv) establishment of an independent DMC to exercise oversight of the research; and
- (v) if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the OHSU IRB at the time of continuing review.

2. Required Information for Subject (or Legally Authorized Representative or Family Member):

- a.** The OHSU IRB is responsible for ensuring that the investigator has procedures in place:
 - (i) to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative 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;
 - (ii) to inform the subject as soon as possible, if a subject's condition improves, and if a legally authorized representative or family member is informed of the above;
 - (iii) to provide information about the research protocol to the subject's legally authorized representative or family member, if feasible, if a subject is entered into a planned emergency research protocol and dies before a legally authorized representative or family member can be contacted; and
 - (iv) to obtain signed informed consent from the subject, or if the subject remains incapacitated, the subject's legally authorized representative, when research interventions are required after the emergency intervention and/or when subsequent data is collected for longitudinal purposes.
- b.** The OHSU IRB Must Notify the Investigator and the Sponsor if it Does Not Approve the Planned Emergency Research:
 - (i) If the OHSU IRB disapproves the proposed planned emergency research protocol, the findings must be documented in writing and provided promptly to the investigator and the sponsor of the study (if different from the investigator).
 - (ii) 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.

C. DEFINITIONS

Community Consultation: Community Consultation means providing the opportunity for discussion with, and soliciting opinions from, the community(ies) in which the study will take place and from which the study subjects will be drawn. These communities may not always be the same; when they are not the same, both communities should be consulted.

Data Monitoring Committee (DMC): A data monitoring committee, sometimes called a data and safety monitoring board (DSMB), is an independent group of experts without OHSU affiliation, established by the sponsor of a research protocol to assess periodically the progress of a clinical trial (the safety data and the critical efficacy endpoints), and to recommend to the sponsor whether to continue, modify, or stop a trial. In some instances, the OHSU IRB may permit people with OHSU affiliations to be members of a DMC so long as the majority of the membership is not affiliated with OHSU.

Family Member: For purposes of this policy, any one of the following legally competent persons: spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship. [21 C.F.R. § 50.3(m)]

Legally Authorized Representative: An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the research.

Public Disclosure: (a) Before a planned emergency research protocol begins, the dissemination of information in the community(ies) in which the study will take place and from which the subjects will be drawn sufficient to allow a reasonable assumption that the communities are aware that the study will be conducted, and its risks and benefits; and (b) after the study has been conducted, the dissemination of information to the community(ies) in which the study was conducted and to scientific researchers sufficient to describe the study's demographic characteristics and the study's results.

Test Article: Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under 42 U.S.C. §§ 262 and 263b-263n.

Therapeutic Window: The time period, based on available scientific evidence, during which the intervention under investigation in the planned emergency research might reasonably produce a demonstrable clinical effect.

D. Authority

The Secretary of Health and Human Services (HHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i) per (Federal Register, Vol. 61, pp. 51531-51533), with provisions identical to those of the FDA except that there is no IND/ IDE requirement and the definition of family member includes spouses of brother/sisters. The waiver is not applicable to research involving prisoners because of the limitation at 45 CFR 46.101(i) & 46.306(b).

Most planned emergency research involves the use of a FDA regulated test article and therefore is subject to FDA regulations [21 CFR 50.24]. The Oregon Health and Science University Institutional Review Board (OHSU IRB) adheres to the FDA Planned Emergency Use requirements and the requirements for HHS Emergency Research Consent Waiver for all studies.