Research in Emergency Settings

Overview

Revised federal regulations allow certain human research activities to be conducted in emergency settings and include *subjects unable to consent for themselves when more than minimal risk is involved*.

These regulations help facilitate potentially life-saving and life-enhancing research while protecting the rights and welfare of subjects. They were developed with input from a number of national organizations and physicians, including those involved in the treatment of cardiac arrest, stroke, head trauma, spinal cord injury, gunshot wounds and poisoning.

Most research in emergency settings falls under FDA regulations because it involves FDA regulated drugs, biologics or devices, but non-FDA regulated research may fall under OHRP requirements [1] almost identical to the FDA regulations.

VA and DoD Exceptions: The Department of Veterans Affairs does not permit use of a waiver of informed consent for planned emergency research. The Department of Defense does not permit such a waiver unless a waiver is obtained from the Secretary of Defense.

IRB Application Requirements

If you wish to conduct research in an emergency setting when there may be more than minimal risk but participation in the research holds out the prospect of direct benefit to the subject, review the regulations below very carefully to make sure that the proposed research qualifies for a waiver of consent. As appropriate, also review the following guidelines on Surrogate Consent [2], Those with Cognitive Impairments [3], and Emergency Use and Compassionate Use of Experimental Drugs and Devices [4].

The following is a short summary of the major points that you will need to consider carefully and discuss in depth in the IRB Application/protocol in order to conduct the research. We encourage you to consult with the IRB when preparing your application.

1. Detailed Discussion of Regulatory Issues: Discuss and document the issues raised in section 50.24 (a) (1) through (5) in the IRB Application and protocol, when/where applicable.

Summary of the five points

- 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.
- Obtaining informed consent is not feasible, for three reasons (see below).
- 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.
- 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.

2. Community Consultation: Consultation with appropriate community representatives will need to occur before the research begins (see paragraph 50.24 (a) (7) (i) below).

3. Public Disclosure: Appropriate public disclosure will need to occur prior to the initiation of the study, as well at the completion of the study (see paragraphs 50.24 (a) (7) (ii) and (iii) below).

4. Ongoing Attempts to Obtain Consent: Researchers conducting research that does not include the informed consent of all subjects should commit 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.

More information

The FDA and OHRP require that at the earliest feasible opportunity, the subject, a legally authorized representative, or a family member be given all of the information contained in the consent form and be told that he or she may withdraw the subject from the research without penalty or loss of benefits. UCSF asks that the willingness to continue be documented with a signed consent form as soon as possible; this requirement is in accord with the ICH-GCP 4.8.12.

Therefore, 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. Please refer to the information above in section G.6.b of this Appendix labeled Providing Subjects with Additional Information and Types of Consent Documents Needed.

In addition to the types of consent forms discussed in the information above, 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 (see section 50.24 (b) below).

5. Summaries of Attempts to Obtain Consent: 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 (see paragraph 50.24 (a) (7) (v) below).

6. Separate IND or IDE: A separate investigational new drug application (IND) or investigational device exemption (IDE) will be needed (see section 50.24 (d) below).

7. Independent Data Monitoring Committee: An independent Data Monitoring Committee will need to be established (see paragraph 50.24 (a) (7) (iv) below).

Regulatory Requirements

Below are FDA regulations [5]. See OHRP guidance on Emergency Research Informed Consent Requirements [1] for research that is not regulated by the FDA. Provisions are essentially identical to the FDA regulations. However, the OHRP waiver does not apply to research involving prisoners, fetuses, pregnant women or in vitro fertilization; these restrictions are not included in the FDA regulation.

Regulatory Text (21 CFR 50.24)

21 CFR 50.24 (a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Obtaining informed consent is not feasible because:

i. The subjects will not be able to give their informed consent as a result of their medical condition.

ii. The intervention under investigation must be administered before consent from the subject's legally authorized representatives is feasible; and

iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3. Participation in the research holds out the prospect of direct benefit to the subjects because:

i. Subjects are facing a life-threatening situation that necessitates intervention;

ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition 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.

4. The clinical investigation could not practicably be carried out without the waiver.

5. The proposed investigation plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact a legally authorized representative and make this information available to the IRB at the time of continuing review.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved 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 consistent with paragraph (7)(v) below.

7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:

i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and

from which the subjects will be drawn;

ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

iv. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; 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 clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

50.24 (b) The IRB is responsible for ensuring that procedures are in place 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 inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the 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, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

50.24 (c) The IRB determinations are to be retained by the IRB for at least 3 years after completion of the clinical investigation and the records accessible for inspection by the FDA.

50.24 (d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

50.24 (e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the

clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

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Links
[1] http://www.hhs.gov/ohrp/policy/hsdc97-01.html
[2] https://irb.ucsf.edu/surrogate-consent
[3] https://irb.ucsf.edu/enrolling-individuals-cognitive-impairments-and-assessing-decisional-capacity
[4] https://irb.ucsf.edu/emergency-use-and-compassionate-use-experimental-drugs-and-devices
[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24