



PLANNED RESEARCH IN AN EMERGENCY SETTING

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Planned emergency research is research conducted in emergency settings with subjects who cannot provide informed consent because of their life-threatening medical conditions and who do not have an available legally authorized representative. The participant or the participant's legally authorized representative must be informed about the clinical trial as soon as possible and provide consent if the participant wishes to continue. Unlike emergency uses, planned emergency research must be approved in advance by FDA (or DHHS) and the IRB, and publicly disclosed to the community in which the research will be conducted.

The exception to the requirement for obtaining informed consent applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized representative present to represent them. The intent of these regulations is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections for safe and ethical studies. The lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of such research. The exception from the informed consent requirement permitted by the rule is conditional upon documented findings by the IRB.

A. Definitions

Family Member: defined by both FDA (21 CFR 50.3(m)) and OHRP (OPRR Report 97-01) as 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.

Legally Authorized Representative: (See DUHS IRB Legally Authorized Representative Policy)

Life Threatening: diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted (21 CFR 312.81).

B. IRB Procedures and Investigator Responsibilities

The IRB, with the concurrence of a licensed physician "who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation," must find and document each of the criteria in this section in order to permit a waiver of consent for research in an emergency setting.

Because the majority of research conducted in emergency settings involves FDA regulated drugs, biologics, or devices, the FDA regulations most frequently apply (21 CFR 50.24). Non-FDA regulated research may fall under similar requirements based on a waiver of applicable DHHS requirements, with the restriction that the waiver is not applicable to research involving prisoners, fetuses, pregnant women, or *in vitro* fertilization. While FDA regulation (21 CFR 50.24) and guidance documents, and OHRP policy (OPRR Report 97-01) do not make provisions for the inclusion of prisoners, pregnant women and fetuses in such planned emergency research, OHRP policy and recent FDA guidance (cited below) specifically include children, for whom applicable Subpart D requirements must be met. The IRB must determine if research is subject to FDA or DHHS regulations, and whether additional restrictions apply.

Under 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 finds and documents the following seven key elements:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which might include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions (21 CFR 50.24 (a)(1)).
2. Obtaining informed consent is not feasible because: the subjects will not be able to give their consent as a result of their medical condition; the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation (21 CFR 50.24 (a)(2)).
3. Participation in the research holds out the prospect of direct benefit to the subjects because: (21 CFR 50.24 (a)(3))
 - a. The subjects are facing a life-threatening situation that necessitates intervention;
 - b. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supported the potential for the intervention to provide a direct benefit to the individual subjects; and
 - c. 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 (21 CFR 50.24 (a)(4)).
5. The proposed investigational 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 participant

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 legally authorized representatives and make this information available to the IRB at the time of continuing review (21 CFR 50.24 (a)(5)).

6. The IRB has reviewed and approved consent procedures and a consent document consistent with the FDA elements of informed consent (21 CFR 50.24 (a)(6) and 21 CFR 50.25).
 - a. These procedures and the informed consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documents is feasible.
 - b. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a participant's participation in the clinical investigation consistent with the item 7e below:
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least: (21 CFR 50.24 (a)(7))
 - a. 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;
 - b. 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;
 - c. 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;
 - d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
 - e. 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 IRB will also ensure that:
 - i. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
 - ii. Procedures are in place for the investigator 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 participant's inclusion in the investigation, the details of the investigation and other information contained in the consent document, including that that he or she may discontinue

- the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
- iii. 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.
 - iv. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

The IRB must determine, based on the specific details of the individual clinical investigation (including the window of opportunity for treatment), the procedures the investigator must follow to attempt to obtain informed consent before enrolling a subject in an investigation without such consent.

The investigator will be notified of these special directives in writing by the IRB Chair/Vice-Chair following the convened meeting where the directive was approved. The investigator must comply and notify the IRB of each directive's implementation and its outcome either in response to a specific request by the IRB or at the time of periodic continuing review of the study.

C. New IND or IDE

For research subject to FDA regulation, a separate IND or IDE must be submitted to ensure that FDA reviews the application before the study may proceed (21 CFR 50.24). Such submission must clearly identify 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 and IDE for the same device already exists. The IRB must receive a copy of the FDA approval letter to the sponsor that indicates the IND or IDE number related to this study approved under this regulation.

FDA guidance also describes how an *in vitro* diagnostic device may be an investigational device under emergency use evaluation, in which the diagnosis of a life-threatening condition cannot be confirmed by an approved product or well-established procedure (e.g., research involving an investigational test for a neurotoxin that when inhaled or in contact with skin, can cause patients to become sick within minutes and at high doses, to lose consciousness, develop seizures and die).

D. Notice to the North Carolina Medical Care Commission

When the IRB reviewing the research study has authorized the start of the community consultation process, but before the beginning of that process, notice of the proposed research study must be provided to the North Carolina Medical Care Commission (10A NCAC 13B .3302, Minimum Provisions of Patient's Bill of Rights). This notice is required regardless of whether a study is regulated by FDA or DHHS. The notice shall include at a minimum:

1. The title of the research study;
2. A description of the research study, including a description of the population to be enrolled;
3. A description of the planned community consultation process, including currently proposed meeting dates and times;
4. An explanation of the way that people choosing not to participate in the research study may opt out; and
5. The contact information for the IRB and the principal investigator.

The Medical Care Commission may publish all or part of the above information in the North Carolina Register, and may require the institution proposing to conduct the research study to attend a public meeting of the Commission to present and discuss the study or the community consultation process proposed.

E. Report to the Community

The scientific community: A comprehensive summary of data from the completed trial must be provided to the research community in order to permit other researchers to assess the results of the clinical investigation. Sufficient information may be contained in a scientific publication of the results of the completed investigation; in other instances, a publication may need to be supplemented by additional information. Information to be disclosed must include the demographic characteristics (age, gender, and race) of the research population.

The broader lay community: Both before and after publication of the scientific report, the IRB will be responsible for determining appropriate mechanisms for providing information about the outcome of the research to the community from which research subjects were drawn.

The information disclosed should provide sufficient detail to allow a clear understanding of the study design and its results, both positive and negative, including:

- information about the primary outcome(s) of the study;
- the number and nature of adverse events associated with the test article;
- whether the study was terminated, and the basis for that decision.

F. IRB Disapproval

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under 21 CFR 50.24 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 is obligated to 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 IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor. Other clinical

investigation would be "substantially equivalent" if it proposes to invoke this exception from informed consent and involves basically the same medical conditions and investigational treatments.

If the IRB determines that it is not appropriate to waive the requirement for informed consent because there is a reasonable way to identify prospectively the individuals likely to become eligible for the study, then the exception under 21 CFR 50.24 would not apply. In that case, only a subject with the condition (or his or her legally authorized representative) who gave prior consent may be enrolled in the study. If scientifically sound research can be practicably carried out using only consenting subjects (directly, or with the involvement of the subject's legally authorized representative), then the research must be carried out without involving non-consenting subjects. The term *practicably*, as used here, means, for example, (1) that recruitment of consenting subjects does not bias the science, and the science is no less rigorous as a result of restricting it to consenting subjects; or (2) that the research is not unduly delayed by restricting it to consenting subjects.

G. Research not subject to FDA regulations

Research that is not subject to FDA regulations is subject both to the specific DHHS (OHRP) provisions and to the requirements summarized below. The IRB responsible for the review, approval, and continuing review of the research must find and document that the research *is not subject* to FDA regulations at 21 CFR 50.24, and find and document and report to the Office of Human Research Protections (OHRP) that the following conditions have been met relative to the research:

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:
 - a. the subjects will not be able to give their informed consent as a result of their medical condition;
 - b. the intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - c. there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
 - a. subjects are facing a life-threatening situation that necessitates intervention;
 - b. 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

- c. risks associated with the research 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 research could not practicably be carried out without the waiver.
5. The proposed research protocol 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 representatives 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 in accord with Sections 46.116 and 46.117 of 45 CFR Part 46. 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 research consistent with item (b)(7)(e) below.
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
 - a. consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
 - b. public disclosure to the communities in which the research 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;
 - c. public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
 - d. establishment of an independent data monitoring committee to exercise oversight of the research; and
 - e. 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 IRB at the time of continuing review.

In addition, 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 research, the details of the research 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 research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

The investigator proposing to conduct research under this provision must do so in full compliance with federal regulations and guidance, IRB policies and procedures and additional IRB directives specifically related to this research.

The investigator will be notified of these special directives in writing by the IRB Chair/Vice-Chair following the convened meeting where the direct was approved. The investigator must notify the IRB of each directive's implementation and its outcome either in response to a specific request by the IRB or at the time of periodic continuing review of the study.

References:

Food and Drug Administration Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research, March 2011, updated April 2013.

<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/emergency-research-informed-consent-requirements/index.html>

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