EMERGENCY USE OF AN INVESTIGATIONAL DRUG, BIOLOGICAL PRODUCT OR DEVICE IN HUMAN SUBJECTS RESEARCH

POLICY

This policy does not limit the authority of a physician to provide emergency medical care outside of the research context.

The Institutional Review Board (IRB) must approve the use of a test article in human subjects research except when:

- a life threatening emergency does not allow the IRB to review and approve the use of the test article by usual processes prior to its administration, and
- the researcher follows applicable Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) regulations for use of a test article in emergencies. The emergency use of an investigational drug or biological product, or unapproved medical device meets the FDA definition of a clinical investigation involving human subjects, but does not meet the DHHS definition of research involving human subjects. DHHS regulations do not permit data obtained from patients to be classified as human participants research or permit the outcome of such care to be included in any report of research activity subject to DHHS regulations.

DEFINITIONS

Emergency Use: The use of a test article on a single human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].


Planned Emergency Research: A research study that will include participants in life-threatening situations, where a test article must be used before consent can be obtained, and the researcher cannot know in advance who the participants will be.

Test Article: Any drug, biological product or medical device intended for human use that is subject to FDA regulations.

IND Investigational New Drug
IDE Investigational Device Exemption
**Unplanned Emergency Use of Drugs or Biologics**

Under usual circumstances, the use of an investigational drug or biologic requires prior approval of the IRB. Rarely there are emergency circumstances where it is in the best interest of a patient for an investigational drug or biologic to be used without IRB review and approval. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at an institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

**Investigators should do the following:**

1. Determine if the proposed use meets the regulatory definition for emergency use of an investigational drug or biologic [21 CFR 56.102(d)]. Emergency use must meet ALL of the following criteria:
   - The subject has a disease or condition which is life-threatening (e.g., the likelihood of death is high) or severely debilitating (e.g., may cause irreversible morbidity, such as blindness, loss of limb, loss of hearing, paralysis or stroke);
   - The subject's disease or condition requires intervention with the investigational drug or biologic before review at a convened meeting of the IRB is feasible; and
   - No standard acceptable treatment is available.

2. Contact drug/biologic manufacturer to determine if it can be provided under an existing IND or, if not available through the manufacturer, contact the FDA for an Emergency IND.

   If a drug or biologic will be used, the investigator must obtain an emergency IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND. If there isn’t time to apply for an IND, the FDA may authorize shipment
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of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means to the FDA.

- **Drug Products**: Division of Drug Information (888) 463-6332; (301) 796-3400
- **Biological Blood Products**: Office of Blood Research and Review (301) 827-3518
- **Biological Vaccine Products**: Office of Vaccines Research (301) 827-3070
- **On Nights and Weekends**: Office of Crisis Management & Emergency Operations Center (866) 300-4374; (301) 796-8240

3. If time permits, notify the Human Research Protection Program (HRPP) of the intended Emergency Use. Investigators may contact the HRPP via phone (513) 558-5259 or email (irb@uc.edu).

The IRB Chair/designee is responsible for either concurring with the intended emergency use or determining that the proposed use does not meet the criteria for an emergency exemption from prospective IRB approval. The IRB Chair/designee may request additional information or review by an independent physician when determining whether the criteria for an emergency exemption are met. The IRB Chair/designee is responsible for informing the investigator of his/her concurrence or disagreement with the emergency exemption. When the reviewer disagrees with the emergency exemption, the proposed use will be scheduled for review at the next available convened meeting of the IRB.

This notification should not be construed as an IRB approval. Notification will be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process do not apply. The IRB must convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to obtain quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB
Chair/designee can prepare a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c).

**Unplanned Emergency Use of an Unapproved Device**

Emergency use of an unapproved device occurs when a human is in a life-threatening situation where an unapproved device may offer the only possible life-saving alternative but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE.

The IRB allows for the emergency use of an unapproved device if the FDA requirements for emergency use are met and the HRPP is notified (in advance whenever possible) of an intent to use an unapproved device.

All of the following conditions must exist: the patient is in a life-threatening condition that needs immediate treatment; no generally acceptable alternative for treating the patient is available; and because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

If an IDE exists, authorization from the IDE holder must be obtained. If an IDE for the use does not exist, the sponsor is to be notified of the emergency use. If an IDE does not exist the FDA Center for Devices and Radiological Health must be notified of the emergency use (—(301)-594-1190 and provided with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Any subsequent emergency use of the investigational device requires an IDE and prospective IRB review and approval. If it is anticipated that the investigational device may be used on subsequent subjects, the IRB will require the IRB application, Informed Consent Form, clinical protocol, investigators brochure, and any supporting information deemed necessary for review, be developed and submitted so that an approved protocol would be in place when the next need arises. These documents must be submitted for full board review.
Informed Consent

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative

- If the holder of the IND or IDE (i.e., sponsor or other local or distant physician) has an existing consent form that is made available, that form may be used. The IRB would prefer to review these forms in advance of their use, if time permits, though this may not be possible in an emergency.
- If there is no existing consent form available from a sponsor or other IND holder, a clinical consent form should be used. Physicians should discuss with patients, or legally authorized representatives, the investigational nature of the proposed emergency treatment, the risks and benefits, and document these discussions in the medical record, in clinical notes, and in a clinical consent form.

The requirement for informed consent may be waived if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- The subject is confronted by a life-threatening (or severely debilitating) situation necessitating the use of the investigational product;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject;
- Time is not sufficient to obtain consent from the subject's legal representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

INVESTIGATOR RESPONSIBILITIES AFTER THE TEST ARTICLE IS USED

1. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)]. The notification should describe;
   a) The test article that was used, including any IND or IDE numbers
   b) The conditions necessitating the emergency use,
   c) The status of the patient,
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d) How written informed consent was obtained,
e) If written consent was not obtained, provide written certification from the investigator and a physician who was not otherwise participating in the clinical investigation that
i. The subject is/was confronted by a life-threatening situation necessitating the use of the test article.
ii. Informed consent was not/could not be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
iii. Time is/was not sufficient to obtain consent from the subject's legal representative.
iv. No alternative method of approved or generally recognized therapy is/was available that provides an equal or greater likelihood of saving the subject's life.

2. For IDEs, the emergency use should be reported to the FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed and patient outcome information.

3. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. If the investigator believes the investigational product may need to be used again, a new protocol submission should be submitted to the IRB. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Planned Emergency Research

Planned emergency research is not synonymous with “emergency use of a test article”. Planned emergency research refers to research planned for emergency settings, including the planned use of a test article (i.e. drug, device, biologic). Planned emergency research involves an extensive approval process: FDA approval, prospective IRB approval, approval and consultation with the communities where the research will be conducted and from where participants will be drawn. Community consultation includes a presentation of the risks and benefits associated with the research. An independent data monitoring committee must be established to exercise oversight of the research.

For emergency research under 21 CFR 50.24, 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 whether the investigation satisfies the criteria
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in 21 CFR 50.24(a)(1) through (7) and whether the investigation may be approved under this section.

All of the following conditions must be met:

- The human subjects are in a life-threatening situation that necessitates urgent intervention;
- Available treatments are unproven or unsatisfactory;
- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention;
- Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition;
- The intervention must be administered before consent can be obtained from the subject’s legally authorized representative;
- There is no reasonable way to identify prospectively individuals likely to become eligible for participation;
- Participation in the research holds out the prospect of direct benefit to the subjects; and
- The clinical investigation could not practically be carried out without the waiver.
- 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.

The IRB will assess and document whether or not the research is subject to regulations codified in 21 CFR 50. This will include the following:

- The research participants 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.
- Obtaining consent is not feasible because:
  - The participants are not able to give their consent as a result of their medical condition.
  - The intervention involved in the research is administered before consent from the participants’ legally authorized representatives is feasible.
There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

- Participation in the research held out the prospect of direct benefit to the participants because:
  - Participants are facing a life-threatening situation that necessitated intervention.
  - 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 participants.
  - The risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

- The research could not practicably be carried out without the waiver.
- 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 participant within that window of time and, if feasible, 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.
- The IRB has reviewed and approved consent procedures and a consent document in accord with 45 CFR 46.116 and 46.117. These procedures and the consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documented 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 participant’s participation in the research consistent with the paragraph of this waiver.

Additional protections of the rights and welfare of the participants are provided, including, at least:

- Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research is conducted and from which the participants are drawn.
- Public disclosure to the communities in which the research is conducted and from which the participants are drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits.
- Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic
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- Establishment of an independent data monitoring committee to exercise oversight of the research.
- If obtaining 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 participant’s family member who is not a legally authorized representative, and asking whether he or she objects to the participant’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. The IRB will ensure there are procedures in place to inform, at the earliest feasible opportunity, each participant, or if the participant remained incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, of the participant’s inclusion in the research, the details of the research and other information contained in the consent document. The IRB will ensure that there is a procedure to inform the participant, or if the participant remained incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, 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. If a legally authorized representative or family member is told about the research and the participant’s condition improves, the participant is also informed as soon as feasible. If a participant is entered into research with waived consent and the participant dies before a legally authorized representative or family member can be contacted, information about the research is provided to the participant’s legally authorized representative or family member, if feasible. For the purposes of this waiver “family member” means any one of the following legally competent persons: spouses; 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 participant is the equivalent of a family relationship.

If the study involves an FDA-regulated product, and is conducted or supported by HHS, both the FDA regulations and HHS human subject protection regulations apply. In order for an exception from the informed consent requirements to be granted for a study that is subject to both FDA and HHS regulations, the study may not involve pregnant women or prisoners as subjects, and the provisions of 21 CFR 50.24 must be satisfied. When an exception from the informed consent requirements for such a study is granted, all other applicable requirements of 21 CFR Parts 50 and 56, and 45 CFR 46 must be satisfied.
Planned emergency research is usually not eligible for “emergency use of a test article”. The IRB and/or PI will provide advance notice of these protocols to the Office for Human Research Protections (OHRP) pursuant to federal regulation 45 CFR 46.101(i). Investigators who wish to conduct planned emergency research should consult with HRPP staff prior to submission of the protocol to the IRB.

Planned research in life-threatening emergent situations where NOT obtaining prospective informed consent is permitted by 21 CFR 50.24. An exception of informed consent may be allowed under 21 CFR 50.24, 45 CFR 46.101(i), or 45 CFR 46.116(f), depending on whether or not the research is subject to FDA regulation, given that all required IRB determinations under these provisions can be made. Under these regulations, the IRB may permit planned research in an emergency setting without the informed consent of the participants or their legally authorized representatives (LARs) in a limited class of emergent situations where the participant is in need of an emergency experimental intervention but cannot give informed consent due to a life-threatening medical condition and there is not sufficient time to obtain consent from the participant’s legally authorized representative.

In addition, advance notice of such planned emergency research protocols will be provided to the Office for Human Research Protections pursuant to 45 CFR 46.101(i).

**VA Research**
For VA research, the IRB cannot waive the requirement to obtain consent for planned emergency research.

**Applicable Regulations and Guidelines**
21CFR46
21 CFR 50.23
21 CFR 50.24
21 CFR 56
21 CFR 312
21 CFR 812
45 CFR 46.101
45 CFR 46.116-117
March 2011 FDA Guidance for IRBs, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research:

OHRP Guidance Informed Consent Requirements in Emergency Research
http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm

HRPP Procedure 202 Exception from Informed Consent in Clinical Research

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<td>L. Harpster</td>
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<td>M. Linke</td>
<td>Revision has been made to differentiate between emergency research that was FDA regulated and research that was not FDA regulated.</td>
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<td>J. Gerlach</td>
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<td>C. Norman</td>
<td>Revise wording and format to be consistent with other HRP policies. Remove language that more appropriately belongs in other documents.</td>
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<td>M. Linke</td>
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