

I. PURPOSE

The purpose of this SOP is to outline the investigator's responsibilities related to the use of an unapproved test article in emergency use situations. This SOP defines the limits on physicians to provide emergency medical care to patients when FDA regulations apply, such as when care involves investigational test articles.

Notes:

- The FDA Information Sheets also refer to emergency use of a test article as Emergency Exemption from Prospective IRB Approval. This phrase emphasizes that IRB notification does not constitute IRB approval.
- The FDA regards emergency use of a test article, other than a medical device, as a clinical investigation and may require data from an emergency use to be reported in a marketing application. However, OHRP/45 CFR 46, has advised that "emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity." Thus, a patient receiving a test article under the emergency use mechanism provided by FDA is not considered a research participant under 45 CFR 46 and therefore emergency use is not considered research covered under 45 CFR 46.

II. POLICY STATEMENT

An investigator may use an unapproved test article without prior IRB review and approval in situations that meet the appropriate FDA regulations and qualify as emergency use.

III. SCOPE

This policy applies to use of investigational drugs, biologics, diagnostics, devices or other interventions that are regulated by the FDA. This policy does not regulate or interfere with the clinical practice of medicine.

IV. DEFINITIONS

Chair, CPHS: The Chair functions as the executive chair of all of the IRB committees and subcommittees and provides input for IRB policies and educational training requirements. The Chair works with the Director, Human Subjects Research and the VP, Research Compliance and Regulatory Affairs on procedural matters pertaining to the IRB. The Chair serves as Chair or Vice-Chair for one or more of the CHOP IRBs.

Emergency Use: The use of a test article with a human subject in a life-threatening situation in which no standard approved or generally acceptable treatment is available and in which there is not sufficient time to obtain IRB approval or concurrence by the IRB chair or other IRB member [21 CFR 56.102(d)].

Immediately Life-Threatening Disease or Condition: A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

IND: An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.

Investigational Device Exemption (IDE): IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and the requirements under 21 CFR 812, as applicable, are met. An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

Serious Disease or Condition: A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent (e.g., blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke). Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Test Article: A 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 the jurisdiction of the Food and Drug Administration.

Vice-Chair, CPHS: The Vice-Chair functions is responsible for assisting the Chair, CPHS and serving as a Chair or Vice-Chair of one or more of the CHOP IRBs.

V. PROCEDURES

A. Limitations of Emergency Use without Prior IRB Approval

An investigator may exercise the emergency exemption from prior IRB approval to use a test article once without prospective IRB review, provided that the use qualifies as emergency use. Any subsequent use of the test article at CHOP is subject to IRB review

(21 CFR 56.104), unless requiring prospective review would inappropriately deny emergency treatment to a second individual.

B. Investigator's Responsibilities When Using an Investigational Drug or Biologic:

1. Prior to the emergency use, an investigator, who must be a licensed physician, is required to do the following:
 - (a) Confirm that the disease or condition is either serious or immediately life-threatening;
 - (b) Contact the Chair or Vice-Chair CPHS, if time permits, to confirm that there is insufficient time for the IRB to review and approve the investigational use (if there is sufficient time, a submission will be reviewed in accordance with SOP 413);
 - (c) Obtain an IND from the FDA as required under 21 CFR 312.310;
 - (1) If the use of the unapproved test article does not meet the criteria of an existing study protocol or if an approved study protocol does not exist, the investigator/clinician must contact the manufacturer of the test article and determine if it can be made available for emergency use under the manufacturer's IND.
 - (2) If the manufacturer is unwilling to sponsor the emergency use through its IND, and there is no time for the investigator to submit an IND, the investigator must obtain the FDA's authorization and the manufacturer's agreement to ship the unapproved test article.
 - (d) Obtain and document informed consent from the subject or the subject's legal representative. When legally effective consent cannot be obtained, the investigator must, if time permits, obtain an independent assessment by an uninvolved physician who must certify in writing with the investigator that:
 - (1) The subject is confronted by a serious or immediately life-threatening disease or condition (i.e., requiring intervention before IRB Chair concurrence or review at a convened meeting is feasible) necessitating the use of the unapproved test article;
 - (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
 - (3) Time is not sufficient to obtain consent from the subject's legal representative; and

- (4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If the investigator cannot obtain the independent assessment of a physician to certify the above, then within five days after the use of the test article a physician who is not otherwise participating in the clinical investigation must certify with the investigator, in writing, that the above criteria were satisfied.

- (e) Notify the CHOP Pharmacy that the test article will be sent by the manufacturer.
- (f) If the manufacturer or CHOP pharmacy requires a letter from the IRB prior to release of the test article, the investigator should contact the IRB Office as soon as possible to obtain an acknowledgement letter. Notification may be by telephone, email or via the electronic IRB management system.
2. After emergency use, the investigator is required to:
- (a) Within 5 working days of the emergency use, submit a report describing the emergency use and initial outcome to the IRB. This report will be reviewed by the Chair or Vice-Chair CPHS.
- (b) Evaluate the likelihood of a similar need for the unapproved test article occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval of a study protocol to permit clinical use of the investigational drug.
- (c) If an unanticipated problem involving risk to subjects or others (e.g., an SAE that was unexpected and related) occurred in connection with the emergency use, submit reports consistent with the reporting requirements of the IRB (**SOP 408**), the FDA, and the manufacturer of the test article.
- (d) If the manufacturer agreed to sponsor the emergency use through its IND, provide the manufacturer with a written summary of the conditions constituting the emergency, subject protection measures, and the results of the emergency use. In these cases, the manufacturer is responsible for corresponding with the FDA
- (e) If the manufacturer did not agree to sponsor the emergency use through its IND, provide the FDA and the manufacturer with a written summary of the conditions constituting the emergency, subject protection measures, and the results of the emergency use within a formal IND application within 15 business days.

Notes:

- (1) If the investigator submits a formal IND application, they must submit annual reports per FDA regulations.
- (2) If the investigator does not plan to write a formal protocol for use of the test article, they must submit a final report requesting withdrawal of the IND per FDA regulations.

C. Investigator's Responsibilities for Emergency Use of an Unapproved Device

An investigator, who must be a licensed physician, may treat a patient with an unapproved medical device in an emergency situation if they conclude that: (1) the patient has a life-threatening condition that needs immediate treatment (the criteria of "life-threatening condition" include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity); (2) no generally acceptable alternative treatment for the condition exists; 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.

The investigator should contact the Chair or Vice-Chair CPHS, if time permits, to confirm that there is insufficient time for the IRB to meet and approve the investigational use. If there is sufficient time, a submission will be reviewed in accordance with **SOP 413**.

1. Prior to the emergency use, an investigator should meet as many of the following requirements as is practicable given the urgency of the clinical situation:
 - (a) Obtain the informed consent from the patient or their legal representative;
 - (b) Obtain the concurrence of the Chair or Vice-Chair CPHS. At CHOP the concurrence of the Chair or Vice-Chair CPHS satisfies the requirement to obtain clearance from the Institution (See **Institutional Clearance for the Emergency Use of an Investigational Device** policy);
 - (c) Obtain the assessment, in writing, of a physician who is not participating in the study or in the care of the patient that concurs with the planned usage; and
 - (d) Authorization from the IDE sponsor, if an IDE exists for the device.
2. If any of the requirements listed in C.1 cannot be met due to the urgency of the clinical situation, the investigator must document in writing their reasons for proceeding.

3. If the informed consent of the subject cannot be obtained prior to use of the device, the investigator must certify that all of the following have been documented in writing in the subject's medical record:
 - (a) The subject is confronted by a life-threatening situation necessitating the use of the test article (device);
 - (b) Informed consent cannot be obtained because of an inability to communicate with or obtain legally effective consent from the subject;
 - (c) Time is not sufficient to obtain consent from the subject's legally authorized representative;
 - (d) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
4. The emergency use of the test article must be reported to FDA by the IDE sponsor within 5 working days from the time the sponsor learns of the use. The report should contain a summary of the conditions constituting the emergency, patient outcome information, and the patient protection measures that were followed.
 - (a) If the investigator is the IDE holder the FDA must be notified by the investigator and provided with a written summary of the conditions constituting the emergency, subject protection measures, and results.
 - (b) A second use of an unapproved device may not take place until approval of an IDE for the proposed use has been issued by the FDA.
5. The emergency use of the test article must be reported to the IRB within 5 working days of its use.
 - (a) If it was not possible to obtain informed consent prior to the emergency use, the determination to proceed must be reviewed by a physician independent of the clinical investigation.
 - (b) The report of the independent physician's findings must be submitted to the IRB along with the investigator's report.

D. IRB Responsibilities

1. If time permits for the IRB to review the emergency use, then the conditions of 21 CFR 56.102(d) are not met, and the IRB must review the use in accordance with **SOP 413**.
2. If there is insufficient time for the IRB to review, the investigator may invoke the Emergency Exemption from Prospective IRB Review.

- (a) The Chair and Vice-Chair, CPHS will provide advice and assistance regarding interpretation of FDA regulations.
 - (b) If required by the sponsor, a letter from the IRB acknowledging the intended emergency use will be provided.
3. Review of 5-Day Reports of Test Article and Emergency Exemptions from Prospective IRB Approval for Drugs and Biologics. The Chair or the Vice-Chair, CPHS, will:
 - (a) Review reports of the emergency use (including the consent document used);
 - (b) Review exemptions from the requirement to obtain consent;
 - (c) Determine if the use met FDA regulatory requirements. If the requirements were not met, inform the investigator of the appropriate processes for future uses and evaluate the use in accordance with **SOP 901** and **SOP 907**.
4. For Emergency Use of an Unapproved Medical Device, the Chair or Vice-Chair CPHS will review the investigator's request for use and make a determination that the request meets the requirements of 21 CFR 56.102(d) and those outlined in Section C of this document. The investigator will be provided with a statement of concurrence or non-concurrence (via email or electronic submission system).

VI. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.102(d)	21 CFR 56.104(c)
21 CFR 50.23(a)	21 CFR 50.23(c)
21 CFR 50.24	21 CFR 812
FDA Information Sheets: Frequently Asked Questions: Emergency Use of an Investigational Drug or Biologic. 1998	OHRP Compliance Activities: Common Findings and Guidance #13 and #72
Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions About Medical Devices. January 2006	FDA Expanded Access to Investigational Drugs for Treatment Use— Questions and Answers: Guidance for Industry. October 2017

VII. REFERENCES TO OTHER APPLICABLE SOPS

SOP 105: IRB Review Processes	SOP 901: Non-Compliance with Human Subjects Research Policies
SOP 408: Unanticipated Problems Involving Risks to Subjects	SOP 907: Reporting to Regulatory Agencies & Sponsors
SOP 413: Expanded Access: Individual Patient Expanded Access IND (Drugs) and Compassionate Use (Devices)	Institutional Clearance for the Emergency Use of an Investigational Device

VIII. RESPONSIBILITIES

Title	Responsibility
Director, HSR	Responsible for monitoring changes to regulations and communicating such changes to IRB staff, IRB members, and investigators.
Chair, CPHS	The Chair or Vice-Chair is responsible for ensuring compliance with regulations pertaining to emergency use of unapproved drugs, biologics, or devices including review of 5-day reports.
Investigator	Responsible for securing the sponsors approval, the FDA's approval and the informed consent of the patient or the permission of the parent/guardian. The investigator must also notify the IRB within the proscribed time limit.

IX. REVISIONS:

- 08-11-2006 Initial approval date
- 05-05-2008 Revised to incorporate changes in IRB staff responsibilities; added Section C, Emergency Use of Unapproved Devices; Section D, Compassionate Use of Unapproved Devices
- 03-24-2010 Revised to clarify that investigators must contact the IRB, when time permits, to ascertain whether or not the IRB has sufficient time to meet prior to use of the investigational test article.
- 06-09-2010 Revised to correct minor grammatical issues for consistency across SOPs and to remove URLs that were no longer correct.
- 07-08-2010: Revised to reflect AAHRPP's recommendations including listing of individuals who should be consulted prior to emergency use.
- 03-07-2013: Revised to reflect 21 CFR Subpart I, compassionate use reporting requirements
- 05-29-2013: Revised to clarify FDA versus Common Rule definition of research/clinical investigation
- 09-25-2018: Revised to update definitions and minor edits.
- 06-28-2021: Revised to remove reference to compassionate use of an unapproved device (now addressed in IRB SOP 413)
- 12-13-2022: Minor administrative edits

X. APPROVAL:

Approval Indicator: Approved by Amy Schwarzhoff and Barbara Engel on 12/13/22
Amy Schwarzhoff, Director, Human Subjects Research and Barbara Engel, Chair, CPHS