



STANDARD OPERATING PROCEDURE RESEARCH ACTIVITIES IN EMERGENCY SITUATIONS

Emergency Use of Test Articles
“Compassionate Use”
Planned Emergency Research

I. Prior Consultation with IRB Chairperson

Institutional policy requires that, whenever possible, investigators consult an IRB Chair for guidance prior to conducting research activities in emergency situations. This includes the emergency use of FDA-regulated test articles (i.e., unapproved drugs, biologics and devices) and planned emergency research.

II. Clarification of Terms

- Test article – an unapproved FDA-regulated product (i.e., unapproved drug, device, or biologic)
- Compassionate use – this term does not appear in the federal regulations; however, for studies involving investigational *devices*, FDA guidance includes limited provisions for compassionate use in serious, but not life-threatening, situations. The requirements for such compassionate use are described under Compassionate Use of Investigational Devices (Section VIII)
- Emergency use of test article – the situation in which a physician-investigator wishes to use an unapproved FDA-regulated product (i.e., unapproved drug, device, or biologic) 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.
- Life threatening – in the emergency use context, life-threatening means a high likelihood of death unless the course of the patient-participant’s condition is interrupted
 - It includes diseases or conditions with potentially fatal outcomes, where the end point of trial analysis is survival. Immediacy of death is not required.
 - “Life-threatening” in this context also includes “severely debilitating” circumstances, i.e., diseases or conditions that cause major irreversible morbidity (e.g., blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke). Reference: FDA Information Sheet, “Emergency Use of Investigational Drug or Biologic”
- Planned emergency research – research taking place in an emergency setting in which it is anticipated that some or all of the participants will need to be enrolled without the informed consent of the participant or the participant’s legally authorized representative.
 - Planned emergency research always requires prospective review and approval by the IRB.

III. Federal Regulations

Research activities in emergency situations are addressed in federal regulations.

- The emergency use of a test article is addressed in 21 CFR 56.102(d) and 21 CFR 56.104(c).
- Emergency use without informed consent is addressed in federal regulations, 21 CFR 50.23.

- Planned emergency research is addressed in federal regulations, 21 CFR 50.24 and 45 CFR 46.101(i).

The emergency use regulations may only be used to treat a patient in an emergency and may not be used as a mechanism to bypass the requirements for IRB review. Other than providing information to the sponsor and FDA, the data may not be used without prior review and approval by the IRB

IV. Duties and Responsibilities of Principal Investigator

Whenever possible, investigators consult an IRB Chair for guidance prior to conducting research activities in emergency situations. This includes the emergency use of FDA-regulated test articles (i.e., unapproved drugs, biologics and devices) and planned emergency research.

It is the duty of the principal investigator (lead investigator at this institution) to ensure that all emergency uses of a test article and planned emergency research are conducted in strict compliance with all regulatory requirements and institutional policies, including those addressed in the following sections of this policy.

In any case, all emergency uses of test articles are reported in writing, with appropriate documentation, to the IRB within 5 weekdays of the event.

Planned research in an emergency setting requires an application for prospective review and approval by the IRB.

V. Duties and Responsibilities of the IRB Chairperson

When approached by an investigator regarding a proposed emergency use of a test article, it is the IRB Chair's responsibility to review the proposed use and determine that the proposed use meet the federal regulatory requirements for emergency use of a test article in a life-threatening situation where there is no time for prior IRB review. The Chair will also determine that FDA requirements for informed consent will be met, or that the use meets the FDA exemption from the requirements to obtain informed consent.

The IRB Chair's actions do not constitute IRB approval for the emergency use. However, the Chair may acknowledge notification if so requested by the investigator or the holder of the applicable IND/IDE/HDE, and may state that the circumstances of the proposed use appear to comply with the applicable regulatory requirements and guidance.

Under institutional policy, the IRB Chair is NOT eligible to serve as the independent physician whose concurrence is required for certain emergency situations.

Upon notification in writing of an emergency use that has already taken place, the IRB Chair or the Chair's designee determines whether the proposed use met the federal regulatory requirements for emergency use of a test article in a life-threatening situation where there is no time for prior IRB review. The Chair will also determine whether FDA requirements for informed consent were met, or that the use met the FDA exemption from the requirements to obtain informed consent. If there is any doubt about the acceptability of the emergency use, the Chair or designee may refer the report to the convened IRB for a determination. The IRB may follow-up as needed with the investigator to clarify the events surrounding the use.

If the IRB Chair or designee or the convened IRB determines that the applicable requirements do not appear to have been met, and the situation appears to reflect non-compliance, the matter is processed following the IRB policies and procedures for non-compliance.

VI. Duties and Responsibilities of the Institutional Review Board (IRB)

The convened IRB is informed of an emergency use of a test article in the IRB Agenda. In the event that the IRB Chair or designee cannot determine the acceptability of the emergency use, the report is referred to the convened IRB for a

determination. In this situation, copies of the report submitted by the investigator regarding the emergency use of a test article and any relevant supporting materials are sent to IRB members for review and a determination.

In the case of planned emergency research, a convened IRB determines whether the proposed use meets the federal regulatory requirements for emergency use of a test article in a life-threatening situation where there is no time for prior IRB review. The Chair will also determine whether FDA requirements for informed consent were met, or that the use met the FDA exemption from the requirements to obtain informed consent.

Compassionate uses of investigational devices, however, require prospective IRB review and approval.

The duties and responsibilities of the convened IRB for planned emergency research with exception from informed consent are described in Section IX.

VII. Emergency Use of Test Articles

A. Emergency Use of a Test Article without IRB Review

An exemption under FDA regulations at 21 CFR 56.104(c), exemption from IRB requirements, permits the emergency use of an investigational drug, device, or biologic on a one time basis per institution without IRB review and approval.

Whenever possible, it is the responsibility of the investigator to consult the IRB Chair for guidance prior to any emergency use of a test article.

If it appears probable that similar emergencies will require subsequent use of the test article at PSU, the investigator is advised to make every effort to develop a study for future use of the article at this institution. The study will require prospective review and approval by the IRB. If a situation occurs whereby emergency use of the test article for a second patient is requested, either by the same or a second physician, subsequent emergency use should not be withheld for the purpose of gaining IRB approval. This policy is not intended to limit the authority of a physician to provide emergency care in a life-threatening situation.

1. Requirements

All of the following conditions must be met for this type of emergency use:

- A patient is in a life-threatening situation.
- No standard acceptable treatment is available.
- There is insufficient time to obtain IRB approval.
- Ordinarily, the investigator must obtain the informed consent of the patient for such an emergency use, except as described in “Emergency Use of a Test Article without Informed Consent” (see below). For emergency use situations the consent form provided by the sponsor may be used for obtaining the informed consent of the patient.
- The emergency use is reported in writing to the IRB within five weekdays (such reporting should not be construed as IRB approval for emergency use). This written report includes a cover letter with the name of the investigational test article, an explanation of the medical condition and its reason for use, date and time administered, any adverse events or unanticipated problems to the recipient or others and outcome if known; a copy of the informed consent document; and any manufacturer information available on the product (e.g., protocol, drug brochure or device information).

2. Additional Requirements: Emergency Use of Drugs

Emergency use of an unapproved drug requires an Investigational New Drug review and number (IND) from the FDA applicable to the intended use. The sponsor (holder of the IND) should be consulted to verify such applicability. If no applicable IND exists, use of the drug in the emergency situation requires a request to the

FDA to authorize shipment of the drug for emergency use. Such authorization is conditioned on the sponsor making an appropriate IND submission as soon as practicable (21 CFR 312.36).

3. Additional Requirements: Emergency Use of Devices

Emergency use of an unapproved device requires an Investigational Device Exemption review and number (IDE) or Humanitarian Device Exemption review and number (HDE) from the FDA applicable to the intended use. The sponsor (holder of the IDE/HDE) should be consulted to verify such applicability. Follow-up reports should be provided to the sponsor.

Where (1) an IDE/HDE for the device does not exist, or (2) a physician wants to use a device in a way not approved under an existing IDE/HDE, or (3) the physician is not an investigator under the existing IDE/HDE, the device may be used with the prior approval of the FDA. Follow-up reports should be provided to the FDA.

If there is not sufficient time to obtain FDA approval, the device may be used provided that the physician later justifies to the FDA that an emergency actually existed. Each of the following conditions must exist to justify emergency use:

- 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 obtain FDA approval for the use.

In this situation, the physician must follow as many participant protection procedures as possible. These include: (1) obtaining informed consent of the patient or a legal representative; (2) notifying institutional officials as specified by institutional policies; (3) concurrence of an IRB Chair; (4) an independent assessment of an uninvolved physician; and (5) authorization from the IDE/HDE sponsor, if an IDE/HDE exists.

B. Emergency Use of a Test Article without Informed Consent

An exception under FDA regulations at 21 CFR 50.23, exception from general requirements [for informed consent], permits the emergency use of an investigational drug, device, or biologic without informed consent where the following conditions are met.

1. Requirements

The investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions. (The IRB Chair is not eligible to serve as the independent physician.) If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within five working days.

- The patient is confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the patient.
- Time is not sufficient to obtain consent from the patient's legally authorized representative.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

The emergency use is reported in writing to the IRB within five weekdays (such reporting must not be construed as IRB approval for the emergency use). This written report includes a cover letter with the name of the investigational test article, an explanation of the medical condition and its reason for use, date and time administered, any adverse events or unanticipated problems to the recipient or others and outcome if known; documentation of the unfeasibility of obtaining consent as described above; report of the independent

physician; and any manufacturer information available on the product (e.g., protocol, drug brochure or device information).

VIII. Compassionate Use of Investigational Devices

The FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious or life-threatening condition (hereinafter referred to as “compassionate use”). Unlike emergency use of an unapproved device discussed above, prior FDA approval is needed before compassionate use occurs. In order to obtain FDA approval, the sponsor submits an IDE supplement requesting approval for a protocol deviation in order to treat the patient. (See CFR 812.35(a)).

If the request is approved by the FDA, the attending physician must devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient is monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report is submitted to the FDA in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, they are discussed in the supplement and are reported to the IRB.

IRB review and approval and informed consent of the patient (or legally authorized representative) are required for the compassionate use of a medical device. However, should medical necessity require the use of the device by a physician-investigator without IRB review and approval or without informed consent, the policies and procedures for the Emergency Use of Test Articles apply (See Section VII above).

IX. Planned Emergency Research

An exception under FDA regulations (21 CFR 50.24), exception from the informed consent requirement for emergency research, permits planned research in an emergency setting without the informed consent of the participants or their legally authorized representatives. Planned emergency research that is not FDA-regulated is also permitted by DHHS.

The requirements for planned emergency research without informed consent are extremely complex and require much consultation within this institution, within the community, and within the federal agencies involved. Investigators should contact the IRB Chair well in advance if they wish to conduct planned emergency research.

It is the responsibility of the IRB Chair to provide prompt written notification to the institution’s Institutional Official, Legal Counsel, and the Office for Research Protections or Human Subjects Protection Office should the IRB receive a proposal for planned emergency research.

A. FDA Requirements for Planned Emergency Research with Exception from Informed Consent

1. The IRB may review and approve a clinical investigation without requiring informed consent of all research participants be obtained if 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) finds and documents each of the following:
 - a. The human 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.
 - b. Obtaining informed consent is not feasible because:
 - i. The participants 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 participants’ 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.
- c. Participation in the research holds out the prospect of direct benefit to the participants because:
 - i. Participants 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 participants; and
 - iii. Risks associated with the investigation 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.
- d. The clinical investigation could not practicably be carried out without the waiver.
- e. 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 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.
- f. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and 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. 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.
- g. Additional protections of the rights and welfare of the participants 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 participants will be drawn;
 - ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the participants 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 and safety monitoring board 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 must commit to attempting to contact within the therapeutic window, the participant's family member who is not a legally authorized representative, and asking whether he/she objects to the participant'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.

2. The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each participant or if the participant remains 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 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 participant, or if the participant remains 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 clinical investigation and the participant's condition improves, the participant is also to be informed as soon as feasible. If a participant is entered into a clinical investigation with waived consent and the participant dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the participant's legally authorized representative or family member, if feasible.
3. All clinical investigation records, including regulatory files and IRB files, must be maintained for at least 3 years after the completion of the clinical investigation and will be accessible for inspection and copying by the regulatory authorities, as applicable.
4. Clinical investigations 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 participants who are unable to consent. The submission of these clinical investigations to the FDA for 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 this IND/IDE may not be submitted as an amendment to the existing IND/IDE.
5. If the IRB determines it cannot approve a request for exception from informed consent requirements in emergency research because the clinical investigation does not meet the criteria according to Federal regulations, IRB policies and procedures, or other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator who will forward these to the sponsor of the clinical investigation. The sponsor must promptly disclose this information to the FDA, and to all other IRBs and investigators who have reviewed and are participating in the trial (or a substantially equivalent investigation) or who have been or will be asked to review and participate in the trial (or a substantially equivalent investigation).
6. For research involving direct patient care that will be conducted by Emergency Medical Services (EMS) providers, the research study must be approved by the Pennsylvania Department of Health and Safety before study initiation.
7. For the purposes of this waiver of consent, "family member" means any one of the following legally competent persons: spouses, parents, children (including adopted children), brothers and sisters.

B. Requirements for DHHS Planned Emergency Research with Emergency Research Consent Waiver

1. The general requirements for informed consent at 45 CFR 46.116(a) and (b) and 46.408 can be waived for a class of research consisting of activities, which meet the following strictly limited conditions under either (a) or (b) below:
 - a. **Research subject to FDA regulations**

The IRB responsible for the review, approval, and continuing review of the research activity has approved both the activity and a waiver of informed consent and found and documented:

 - i. that the research activity is subject to regulations codified by the FDA and will be carried out under an FDA IND or IDE, the application for which has clearly identified the protocols that would include participants who are unable to consent, and

- ii. that the requirements for exception from informed consent for emergency research detailed in 21 CFR 50.24 have been met relative to those protocols **or**

b. Research not subject to FDA regulations

The IRB responsible for the review, approval and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research is not subject to regulations codified by the FDA at 21 CFR 50, and (ii) found and documented and reported to the OHRP that the following conditions have been met relative to the research:

- i. The human 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.
- ii. Obtaining informed consent is not feasible because:
 - (1) The participants will not be able to give their informed consent as a result of their medical condition;
 - (2) The intervention under investigation must be administered before consent from the participants' legally authorized representatives is feasible; and
 - (3) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- iii. Participation in the research holds out the prospect of direct benefit to the participants because:
 - (1) Participants are facing a life-threatening situation that necessitates intervention;
 - (2) 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 participants; and
 - (3) 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.
- iv. The research could not practicably be carried out without the waiver.
- v. 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, to asking the legally authorized representative 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.
- vi. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 45 CFR 46.116 and 46.117. These procedures and 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. 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.
- vii. Additional protections of the rights and welfare of the participants will be provided, including , at least:
 - (1) 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 participants will be drawn;

- (2) Public disclosure to the communities in which the research will be conducted and from which the participants will be drawn, prior to initiation of the research of plans for the research and its risks and expected benefits;
 - (3) 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;
 - (4) Establishment of an independent data and safety monitoring board to exercise oversight of the research; and
 - (5) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator must commit to attempting to contact within the therapeutic window, the participant's family member who is not a legally authorized representative, and asking whether he/she objects to the participant'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.
2. The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each participant or if the participant remains 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 informed consent document. The IRB shall also ensure that there is a procedure to inform the participant, or if the participant remains 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 clinical investigation and the participant's condition improves, the participant is also to be 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 to be provided to the participant's legally authorized representative or family member, if feasible.
 3. 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.
 4. For research involving direct patient care that will be conducted by Emergency Medical Services (EMS) providers, the research study must be approved by the Pennsylvania Department of Health and Safety before study initiation.

Institutional Review Board The Pennsylvania State University Penn State College of Medicine Penn State Milton S. Hershey Medical Center	
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