

**Institutional Review Board (IRB)
Standard Operating Procedure (SOP)
The Pennsylvania State University
Penn State College Of Medicine
Penn State Milton S. Hershey Medical Center**

RESEARCH ACTIVITIES IN EMERGENCY SITUATIONS

- Emergency Use of Test Articles
- “Compassionate Use”
- Protocol Deviations
- Planned Emergency Research

I. Prior Consultation with IRB Chairperson

Institutional policy requires that, whenever possible, investigators will 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), so-called “compassionate” use situations, protocol deviations, and planned emergency research.

Nothing in the federal regulations or in this institutional policy is intended to limit the authority of a physician to provide emergency care to the extent the physician is permitted to do so under applicable Federal, State or local law.

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
 - For studies involving investigational *drugs*, “compassionate use” is often used erroneously to refer to emergency situations where it is not possible to obtain IRB review and approval. The requirements for the emergency use of test articles apply to these situations.
 - 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 Test Articles.
- 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) without prior IRB review and approval and possibly without the informed consent of the patient-subject or the patient-subject’s legally authorized representative

- Life threatening – in the emergency use context, life-threatening means a high likelihood of death unless the course of the patient-subject’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.
- Emergency protocol deviation – a change to an IRB-approved research protocol that is made to eliminate an apparent immediate hazard to a research subject where there is insufficient time to obtain IRB review and approval
- Planned emergency research – research taking place in an emergency setting in which it is anticipated that some or all of the subjects will need to be enrolled without the informed consent of the subject or the subject’s legally authorized representative
 - Planned emergency research always requires prospective review and approval by the IRB.

III. Federal Regulations

Nothing in the federal regulations or this institutional policy is intended to limit the authority of a physician to provide emergency care to the extent the physician is permitted to do so under applicable federal, state, or local law.

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 Department of Health and Human Services (DHHS) regulations (45 CFR 46) do not permit *research* activities to be started, even in an emergency, without prior IRB review and approval. Whenever emergency use of a test article is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a prospectively conceived, DHHS-supported research activity, except as required under the Food and Drug Administration (FDA) regulations. (Reference: OHRP Compliance Activities: Common Findings and Guidance #13: IRB Review in Emergency Situations)

IV. Duties and Responsibilities of Principal Investigator

Whenever possible, investigators will 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), so-called “compassionate” use situations, emergency protocol deviations, 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, “compassionate” uses of medical devices, emergency protocol deviations, 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 and compassionate uses of test articles and all emergency protocol deviations will be 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 or “compassionate” use of a test article or of a proposed emergency protocol deviation, it is the IRB Chair’s responsibility to review the relevant regulatory requirements with the investigator and provide appropriate advice and counsel as to the acceptability of proceeding with the proposed activity.

- A. Emergency Use of a Test Article.** In the specific case of a proposed emergency use of a test article, the IRB Chair will review the circumstances of the proposed use and advise the investigator on whether an exception from IRB requirements [21CFR56.104(c)], and where applicable, if an exception from the general requirements for informed consent [21CFR50.23(a)] appear to be satisfied.

The IRB Chair will document these actions in writing for the IRB records. 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 will determine whether the relevant regulatory and institutional requirements appear to have been satisfied. If there is any doubt about the acceptability of the emergency use, the Chair or designee will followup as needed with the investigator to clarify the events surrounding the use. Where necessary, the IRB Chair or designee will educate the investigator as to the relevant regulatory and institutional requirements.

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

- B. Compassionate Use of a Medical Device.** In the case of a ‘compassionate use’ of a medical device without prospective IRB approval and possibly without informed consent, the IRB Chair will follow the same procedures as outlined above for the emergency use of a test article.
- C. Emergency Protocol Deviations.** Upon notification of a protocol deviation made to avoid immediate hazard to a human subject, the IRB Chair or the Chair’s designee will review the situation and determine if the applicable regulatory and institutional requirements appear to have been satisfied. If there is any doubt about the acceptability of the deviation from the protocol, the Chair or designee will followup as needed with the investigator to clarify the events surrounding the event. Where necessary, the IRB Chair or designee will educate the investigator as to the relevant regulatory and institutional requirements.

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

The IRB Chair or the Chair’s designee will also make a determination (i.e., no action or change in protocol or consent document required) regarding the need for a modification to the protocol or informed consent document in light of the reported deviation or change.

The IRB Chair or the Chair’s designee will document these actions in writing for the IRB records. The Chair’s or the Chair’s designee’s determinations do not constitute IRB approval for the deviation from the protocol. However, the IRB members will be informed of the outcome of the Chair’s or designee’s review in the same manner in which they are informed of expedited reviews.

- D. Reporting Responsibilities.** It is the responsibility of the IRB Chair to provide timely notification to institutional officials and federal departments or agencies as required under applicable regulatory and institutional requirements.

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

Although the IRB has no regulatory responsibilities relative to the emergency or ‘compassionate’ use of test articles, the IRB members will be informed of these uses in the same manner in which they are informed of expedited reviews.

For emergency protocol deviations or changes made to avoid apparent immediate hazards to subjects, the IRB will be informed if the matter can be resolved under expedited review procedures. Where the matter cannot be resolved under expedited review procedures, the IRB

will review the matter as referred by the Chair based on the Chair's review of the reported deviation or change.

In the case of planned emergency research, a convened IRB will ensure that all conditions for such research under the applicable FDA regulations for exception from the informed consent requirement for emergency research [particularly 21 CFR 50.24] apply or if a DHHS Secretarial Waiver under 45 CFR 46.101(i), or other waiver by the Secretary of a Common Rule Agency have been satisfied.

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 will be reported in writing to the IRB within five weekdays (such reporting should not be construed as IRB approval for emergency use). This written report will include 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 subject 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 will be 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 will include 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 Test Articles

Although commonly used, the term "compassionate use" does not appear in the federal regulations.

A. Drugs

For studies involving investigational drugs, the term 'compassionate use' is often used erroneously to refer to emergency situations where it is not possible to obtain IRB review and approval and/or informed consent. The requirements for the emergency use of a test article apply in these situations.

B. Devices

'Compassionate use' of an investigational device may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious, albeit not life-threatening, condition or disease who does not qualify for the trial.

Such use, which is considered a protocol deviation (21 CFR 812.35), ordinarily requires that the sponsor obtain prior FDA approval before the device is used. If there is no IDE/HDE for the device, compassionate use may occur if the physician submits the compassionate use request directly to the FDA for review and approval.

IRB review and approval and informed consent of the patient (or legally authorized representative) are generally 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, institutional policy requires that the IRB Chair concur with the proposed use and that the conditions for emergency use of an investigational device without informed consent be satisfied.

IX. Emergency Deviation from an Approved Protocol

All changes to IRB-approved research require prospective review and approval by the IRB, except where needed to eliminate apparent immediate hazard to subjects or to protect the life or physical well-being of a subject in an emergency. Any such protocol deviations must be reported in writing to the IRB within five weekdays using the Protocol Deviation Report Form.

X. Publication or Presentation of Emergency Use Outcomes

On occasion, it may be beneficial to future patients, medical practice, or scientific knowledge to share the outcome of an emergency use. Where the emergency use has been properly invoked in accordance with all FDA requirements, the investigator may propose, and the IRB may approve, a retrospective study of the information obtained from the use. The usual requirements for review and approval of such retrospective research (and where appropriate waiver of informed consent and/or privacy rule authorization requirements) shall apply.

XI. 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 subjects or their legally authorized representatives.

Planned emergency research that is not FDA-regulated is also permitted by DHHS and 45 CFR 46 when the relevant department or agency takes action to exercise the waiver provision at 45 CFR 46.101(i). This waiver is not applicable to research involving prisoners.

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 Human Subject Signatory Official, Legal Counsel, and Compliance Officer 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 subjects 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 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.
 - b. Obtaining informed consent is not feasible because:
 - i. The subjects will not be able to give their informed consent as a result of their medical condition;
 - ii. The intervention under investigation must be administered before consent from the subjects' 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 subjects because:
 - i. Subjects are facing a life-threatening situation that necessitates intervention;
 - ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
 - 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 subject 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 subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.
 - g. Additional protections of the rights and welfare of the subjects will be provided, including , at least:
 - i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
 - ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation of plans for the investigation and its risks and expected benefits;
 - iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population and its results;
 - iv. Establishment of an independent data 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 subject's family member who is not a legally authorized representative, and asking whether he/she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
2. The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family

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

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 subjects 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:

- 1) 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 subjects who are unable to consent, and
- 2) 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 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.
- ii. Obtaining informed consent is not feasible because:
 - 1) The subjects 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 subjects' 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 subjects because:
 - 1) Subjects 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 subjects; and
 - 3) 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.
- 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 subject 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 subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.
- vii. Additional protections of the rights and welfare of the subjects 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 subjects will be drawn;
 - 2) 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;
 - 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 subject's family member who is not a legally authorized representative, and asking whether he/she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

2. 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 clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into 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.

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 subject 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.

Dates Approved: _____ (Social Science and Biomedical IRBs - UP)
May 23, 2004 (IRB Executive Committee - College of Medicine)