Guidance on
Planned Emergency Research, Exception from Informed Consent, and Waiver of Applicability of Informed Consent

The objective of this guidance document is to assist investigators in planning, and the IRB in reviewing, protocols meeting the requirements for research that is designed for life-threatening, emergency situations, including the requirements that must be met for exception from, or waiver of applicability of, informed consent in these situations.

Planned Emergency Research

The term "Planned Emergency Research" refers to human subjects research designed to test medical interventions, drugs, or devices in urgent, life-threatening situations.

The UTHSCSA IRB will accept applications for planned emergency research using the UTHSCSA IRB application and processes for initial review. However, prior consultation with the UTHSCSA IRB office is strongly recommended to ensure all details in this guidance are covered. Note that all planned emergency research is reviewed by the UTHSCSA IRB regardless of funding source. Research that is planned emergency research requires strict attention to regulations found in 21 CFR 50.24 for FDA regulated research, which describe the process for 'exception to informed consent.' There is also a separate provision for waiving the 45 CFR 46 requirement to obtain prospective informed consent for emergency research that is not FDA-regulated. FDA and OHRP provide guidance documents to inform the planning and implementation of planned emergency research. These are followed closely by the IRB, and the PI is expected to incorporate their guidance into protocol design. This guidance document is an adjunct to the FDA and OHRP guidance and will be used in conjunction with their guidance and regulations. Reference to these documents are listed in the reference section below.

IRB review of FDA-regulated Planned Emergency Research – Exception from Informed Consent (EFIC)

A. Approval in principle of the protocol and subsequent informed consent procedures

The IRB reviews the protocol and subsequent informed consent procedures to ascertain 'approvability.' 'Approval in Principle' by the IRB means that the study will likely be approved when and if community consultation demonstrates a positive consensus in the community. For this step, the IRB must find and document the following, as per 21 CFR 50.24(a):

1. The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring prospective 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' LARs 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 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.
f. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.

2. The IRB is responsible for ensuring the following with regards to informed consent :
    a. 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.

b. 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.
c. 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.
d. 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. If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly (no longer than within 30 days) in writing to the clinical investigator and to the sponsor of the clinical investigation.

Tips for preliminary review and approval by the IRB:

- The IRB evaluates the relative risk of the research based on standard of care locally and in other regions. Areas to include in a risk assessment include, but are not limited to, the following: medical risk, risk of standard of care in a research context, risk of using investigational drugs and devices in the setting, risks of offending the cultural sensibilities of the community, etc.
- The PI is to provide information about the prevalence of the particular condition being studied. Such information should include the frequency of presentation to the affiliated institution's Emergency Department (ED) as well as to the EDs of other institutions with which UTHSCSA is collaborating. If the research begins in the field, provide geographic references and frequencies for emergency intervention.
- The IRB should ask for PI clarification about whether the ambulance, after picking up the patient/subject, is directed to the nearest ED or bypasses in favor of an ED participating in the research. If the latter occurs, the IRB should consider how and whether emergency treatment is impacted and how research risk is affected.
- For EFIC studies originating in the field, the PI provides information about human subjects and protocol training for first responders. Collaborating first responder organizations are to have an FWA (for federally-funded research) in place and provide their own IRB review, or request to defer to the UTHSCSA IRB.
- If children are included in the research, ensure that additional regulatory criteria is addressed, i.e. Subpart D, 21 CFR 50.50. Pregnant women and prisoners are excluded from this type of research.
- The inclusion of children and other scientific aspects of the study may require that the IRB consult with experts. Such consultation is carefully documented.

A. Approval of a community consultation plan and its implementation (this step is done in conjunction with the Approval in Principle)

The required community consultation aspect for EFIC research has ethical goals that include enhanced protections and benefits for the community participants, and legitimacy and shared responsibility for the conduct of the research by informing the impacted community and soliciting its views. The 'community' may have a geographic identity as well as a condition-specific identity that need not depend on living in the research catchment area.

The submitted protocol must include a plan for community consultation. Community consultation activities are "designed to help ensure that the communities in which the emergency research will be conducted and from which subjects will be drawn are adequately informed about the risks and expected benefits of the research and are given the opportunity to ask questions about it as well as express their views prior to the IRB making a determination about the research." (March 2011 Guidance Document). Section VIII of the FDA Draft Guidance Document provides extensive information about community consultation. For this step, the IRB must find and document the following, as per 21CFR50.24(a):

a. 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 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 monitoring committee 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 has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

<u>Tips for investigators and the IRB about community consultation:</u>

- Consider goals of community consultation:
    - Show respect for persons by informing the community about the study in advance;

- Show respect for the community by allowing representatives of the community to identify potential community-level concerns and effects of the research;
- Show respect for subjects' autonomy. Respect may be shown by including in community consultation activities individuals who may have, or be at risk for, the condition under study (and thereby obtain input from a group that is expected to be similar to the eventual study subjects).
- Provide a means for affected communities to provide meaningful input to the IRB before its decision to approve, require modifications to, or disapprove the study; and
- Identifying group 'leaders' who are willing to function as intermediaries for continued communication with the community about the study is helpful. PI and/or IRB consultation with the group 'leaders' is encouraged.

- Community consultation activities can include:
  - Standing meetings. Standing meetings, such as local civic public forums, may be better attended because such meetings are already on community members' calendars.
  - Plan for at least 10 meetings with affected groups, depending on the risk of the research and the size of the community potentially impacted by the research. Meetings can be town hall style or can be added onto a regularly scheduled meeting of the group. The latter generally ensures a larger number of participants. The number of meetings and additional susceptible populations may be further identified by the IRB.
  - Plan to advertise the meetings via mainstream and alternative media, if possible. Publicity that asks for feedback about the study is also solicited via websites, material distributed in faith communities or other settings frequented by identified susceptible groups. A multi-faceted approach is recommended. Random digit dialing, as a method to survey large portions of the community, is another way to solicit opinion and feedback. However, it is not required.
  - Public community meetings or other special meetings specifically organized to discuss the research. Such meetings may be valuable in attracting participation from individuals with strong interest in the research.
  - Local radio and/or television talk shows. Such programs allow viewers to "call in" to express their views and concerns.
  - Interactive websites, focus groups and surveys.
- The contribution of non-affiliated IRB members is very important in this endeavor. If possible, a non-affiliated member should serve, in addition to the primary and secondary reviewer, as a reviewer on the protocol.
- The plan for community consultation requires full board approval. Outside meetings with the PI/research staff may be necessary to facilitate the process. A designated IRB representative should be the primary contact with the PI/staff about matters related to community consultation.
- All materials utilized in community consultation, including presentations and tools designed to elicit feedback, are to be IRB approved prior to their use.

- Community consultation should make every effort to reach out to limited-English proficient individuals who may be susceptible to becoming research subjects in the study. All materials designated for community consultation activities must first be IRB approved in English. Translations by duly qualified translators are subsequently submitted for IRB approval by way of an Amendment.
- When the study receives an Approval in Principle, the community consultation plan has also been approved, and the PI implements the plan. The PI/Research team are expected to present the study at these meetings in a way that is understandable to a lay audience. Transcripts and other feedback, such as anonymous survey results, are provided to the IRB for review for approval of the research to begin enrollment. IRB members are encouraged to attend one or more community consultation meetings.
- The IRB must approve that community consultation has been 'adequate.' 'Adequacy' generally means that an acceptable number of individuals have been directly exposed to consultation activities and the preponderance of the feedback has been positive toward the research. Plan on 'touching' at least 100 individuals who could be potential subjects. This number is highly fluid and subject to IRB request.

B. Approval of public disclosure before the study begins and after the completion of the study:

Public disclosure means dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware of the plans for the investigation, its risks and expected benefits. The public disclosure phase requires a positive response by the community before the IRB can grant approval of the research to begin enrollment; a largely negative response to public disclosure by the community may cause the IRB to require additional actions.

- Additional protections of the rights and welfare of subjects will be provided, including, at least:
    - 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;
    - 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;

See Section XI in the FDA Draft Guidance document for specific information about methods suggested by the FDA for public disclosure.

<u>Tips for investigators and the IRB on Public Disclosure:</u>

- Plan to send public disclosure materials to many, if not most, of the same venues receiving community consultation materials. Utilize identified group 'leaders' if possible.
- Public disclosure activities may include:
    - Multiple forums

- Media resources
- Targeted mailings to households in the communities with information about how to obtain further details;
- Advertisements and articles in the English language, and if appropriate, foreign language, newspapers (Public outreach documents should be translated into languages that are common in the area served by the facility where the investigation is being conducted and in the communities from which subjects will be drawn.);
- Clearly marked links and information on the sponsor's and participating hospitals' Internet web sites;
- Summary materials that are accessible to non-English speaking or homeless populations who reside in the community from which research subjects are likely to be drawn;
- Presentation or distribution of information at meetings of community, local government, civic, or patient advocacy groups;
- Letters to local and regional community leaders and first responders (e.g., police, paramedics);
- Announcements to local/regional hospital staff(s);
- Public service announcements and interviews or discussions on "talk" radio or television programs;
- Press conferences and briefings; and
- Meetings or activities provided by hospitals' and institutions' existing community outreach programs.

- A lengthy description of risks and expected benefits may not be feasible in all of the disclosure materials. If a website is used, ensure that the website:
  - Points community members to location where additional information can be obtained; and
  - Provides contact information (telephone number and email addresses) so community members may contact for additional questions.
- The IRB approves the public disclosure plan to occur before the study begins, prior to the plan's publication and dissemination.
- The PI provides a summary of the information that was disclosed, which is approved by the IRB as having been adequate. In some cases, pieces of the disclosure plan may not have been implemented due to unforeseen circumstances. The summary must explain these exceptions.

Tips for investigators and the IRB on Public Disclosure after Study Completion:

- Submit a plan for public disclosure to take place after completion of the study. This plan may include many of the same features as the plan for disclosure prior to the initiation of the study and must be approved by the IRB. Any meetings can be town hall style or can be added onto a regularly scheduled meeting of the group, perhaps revisiting some of the same groups or venues. Since study completion may not occur for years, the plan may need re-review by the IRB before its implementation at the completion of the study.

- The information disclosed should provide sufficient detail to allow a clear understanding of the study design and its results, both positive and negative, including:
    - Information about the primary outcome(s) of the study
    - The number and nature of adverse events associated with the test article
    - Whether the study was terminated and the basis for that decision.
- At the IRB's discretion, the PI may be asked to provide plans for continued public disclosure at intervals during the course of the research, especially if the research will continue for a year or more. Such plans may be required and approved at the IRB's request. The PI is expected to provide a public disclosure summary of each implementation during the course of the research.

C. IRB approval of the research to begin enrollment

The IRB must also find and document the following, as per 21CFR50.24(a):

- Additional protections of the rights and welfare of subjects will be provided, including, at least:
    - Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
- The protocol is performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identified such protocols as protocols that might include participants who are unable to consent.
    - The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

See especially Sections II, III, IV, V, VIII, IX, and, X in the EFIC FDA Draft Guidance for full information on these regulatory requirements.

<u>Tips for the IRB in approving the research to begin enrollment:</u>

- Ensure that all regulatory aspects are considered before final approval. For example, the EFIC criteria at 50.24 must be fully addressed, in addition to regulatory criteria for children.
- Ensure that a licensed physician concurs with the initiation of the study and with continuing review. The licensed physician member's affirmative vote or licensed physician consultant's concurrence should be recorded in the minutes.
- The IRB should consider the frequency of continuing review.
- The IRB promptly provides to the sponsor, by way of PI in writing, a copy of the information that has been publicly disclosed about the initiation of the study under 50.24a7ii and 21CFR56.109g
- Any site additions or modifications to the protocol must be approved by the IRB prior to implementation, including site-specific community consultation and public disclosure.

- Protocol violations have the potential to lessen public support for the research if they are numerous or become widely known. The PI must act very promptly with a corrective action plan whenever violations of enrollment or treatment occur. This will be stated on the IRB approval letter to the PI.

IRB review of research not subject to FDA regulations according to the waiver of applicability of the requirement in 45CFR46 to obtain and document informed consent

As noted above, this provision in emergency setting research is seldom used at UTHSCSA. Nonetheless, the PI and IRB should know that it is available. Although there are many similarities with EFIC requirements for FDA-regulated research, the OHRP guidance document should be consulted for further information (The 1996 OPRR (now, OHRP) Report titled, "Informed Consent Requirements in Emergency Research.")

References

1. The 2011 Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors " Exception from Informed Consent Requirements for Emergency Research,"
2. The 1996 OPRR (now, OHRP) Report titled "Informed Consent Requirements in Emergency Research"
3. 21 CFR 50.24
4. 45 CFR 46.116(c)2

Overview of Planned Emergency Research Review and Approval Process