FDA Issues Draft Guidance for IRBs, Clinical Investigators and Sponsors Regarding the Exception from Informed Consent Requirements for Emergency Research

On August 29, 2006, the U.S. Food and Drug Administration (FDA) released draft guidance to assist IRBs, clinical investigators and sponsors in interpreting and complying with regulation 21 C.F.R. 50.24, which sets forth an exception for emergency research from the requirements of informed consent. The draft guidance clarifies and elaborates on the language of the regulatory exception and on the FDA Information Sheet on this topic previously issued in 1998. For the full text of the draft guidance, please click here. The draft guidance is subject to revision following the public hearing and comment opportunities described below, and may or may not be finalized as formal FDA guidance. If finalized, this guidance would represent current FDA thinking on the topic, but would not be binding.

Background:

In October, 1996, FDA issued its final regulation (effective November 1, 1996) providing a narrow exception to the informed consent requirements for subjects in need of emergency medical intervention who cannot give informed consent because of their life-threatening medical condition (e.g., head trauma, cardiac arrest, stroke) and whose legally authorized representative cannot be reached in sufficient time to give consent. Because this type of research involves a particularly vulnerable population, the regulation imposes additional safeguards, including consultation with community representatives, public disclosure prior to commencing and following completion of the study, establishing an independent data monitoring committee, attempting to contact a subject's legally authorized representative or family member regarding the subject's participation in the research, and obtaining the concurrence of a licensed physician not involved in the research.

In the nearly ten years since this regulation was implemented, FDA has received approximately 60 requests to conduct clinical investigations under this exception. In light of its experience with these requests and comments informally received from the research community, FDA seeks to provide further guidance concerning these additional safeguards and to determine whether they ensure adequate protection of subjects without interfering with important research. The highlights of the draft guidance are described below.

IRB Responsibilities:

IRB Selection: FDA anticipates that emergency research usually will be performed at an institution with an internal IRB responsible for reviewing the study at that institution. While independent IRBs may also review these studies, FDA cautions that such IRBs need to be knowledgeable about local conditions in order to evaluate adequately the plans for community consultation and public disclosure.

Contact with Legally Authorized Representatives and Family Members: IRBs must review proposed plans and procedures for attempting to contact the subject's legally authorized representative to obtain an informed consent, or a family member (if no legally authorized representative is available) to provide the family member opportunity to object to the subject's participation. The IRB must determine whether the specified period of time for making these attempts before the test

article may be administered is appropriate. The effect of delaying administration of the test article should be taken into account when determining the portion of the therapeutic window to be devoted to seeking contact with these individuals. If a family member objects to an individual's participation, the individual should not be entered into the study. A family member's objection may be verbal, but should be documented in the individual's medical record.

Community Consultation and Public Disclosure: The draft guidance enlarges the IRB's role in community consultation and public disclosure activities. The guidance also makes explicit FDA's expectation that the community consultation will occur prior to the convened meeting at which the IRB reviews the emergency research, and will be taken into account in the IRB's own decision-making as to whether the research should be approved, modified, or disapproved. Specifically, with respect to community consultation IRBs:

- have the responsibility to ensure that the community consultation is adequate;
- should review, request appropriate modifications in, and approve or disapprove the sponsor/investigator's plans for community consultation;
- may wish to be directly involved in the community consultation to hear firsthand the concerns expressed; and
- should discuss community opposition to, or concern about, the emergency research and specifically document in the IRB meeting minutes what these concerns are and how the IRB resolved them.

With respect to public disclosure IRBs:

- are responsible for determining the adequacy of the pre-study disclosure plans submitted by the sponsor/investigator, and may determine that it is appropriate to require additional disclosure at subsequent times; and
- must find and document that the sponsor's post-study disclosures are sufficient to apprise the community of the study results.

Notice of Disapproval: If an IRB disapproves a clinical investigation because it does not meet the requirements of the emergency exception or because of other relevant ethical concerns, the IRB must notify the sponsor, who in turn must notify other IRBs that are reviewing the same investigation or a substantially equivalent investigation by that sponsor. This notification requirement, while not new, represents the only circumstance in which one IRB's disapproval of a study must be communicated to all of the other IRBs considering the same study.

Documentation: Because of the controversial nature of studies performed without receiving subjects' informed consent, the FDA strongly recommends that IRBs summarize their discussions and decisions regarding the required elements of the exception, including summaries of controverted issues and their resolution, in the IRB's written meeting minutes.

Clinical Investigator Responsibilities:

Community Consultation and Public Disclosure: Clinical investigators and sponsors have the primary responsibility for (i) planning and conducting the process of community consultation, hearing the concerns and making appropriate changes in the research plans; and (ii) arranging pre- and post-study public disclosures that will effectively reach the community. The guidance provides detailed examples of appropriate community consultation activities (including content, type and frequency) and public disclosures (including timing, content and medium).

Contact of Family Members: Clinical investigators should record in the subject's case history the efforts made within the therapeutic window to contact legally authorized representatives or the subject's family members so that this information may be easily retrieved, analyzed and reported to the appropriate IRB, and is accessible if FDA conducts an inspection.

Sponsor Responsibilities:

Defining Length of Therapeutic Window: The sponsor is responsible for defining the length of the potential therapeutic window, based on scientific evidence, during which the investigational product is to be administered.

Community Consultation and Public Disclosure: See above section under same title in "Clinical Investigator Responsibilities." Although FDA does not dictate who should bear the costs associated with community consultation and public disclosure, the agency anticipates that the sponsor would normally bear the costs because these activities are requirements for conducting the research.

Additional Guidance:

The informed consent exception is applicable to:

- *in vitro* diagnostic device (IVD) studies;
- trials that have morbidity endpoints, rather than mortality endpoints, if subjects are at risk of death from the condition and severe morbidity that is closely associated with mortality is being evaluated; and
- investigations in which the study objective is to determine whether some aspect of standard treatment is in fact useful.

Public Comment Opportunities:

FDA is seeking public input on its draft guidance through two opportunities:

- A public hearing scheduled for October 11, 2006 at the University of Maryland. The public hearing is designed to solicit comments from any individuals and groups who have encountered challenges in the conduct of emergency research in the absence of informed consent. Presenters must submit abstracts of their presentation by September 20, 2006.
- Written or electronic comments to be submitted to FDA by October 30, 2006. In the Federal Register notice of the draft guidance, FDA has posed a number of specific questions regarding aspects of emergency research on which the agency is interested in receiving feedback.
- For details on the public hearing and request for comments, click here and here.

FDA has committed to consider all comments received on this draft guidance to determine whether the current framework is adequate for the ethical conduct of emergency research, or whether modifications may be appropriate.

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