

NIH Comments on FDA Draft Guidance for
Institutional Review Boards, Clinical Investigators, and Sponsors:
Exception from Informed Consent Requirements for Emergency Research
November 2006

The National Institutes of Health (NIH) appreciates the opportunity to comment on FDA's August 2006 draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. NIH recognizes the importance of the regulations in 21 CFR 50.24, and the conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814, that ensure the protection of human subjects who are involved in emergency research protocols that have been exempted from the requirement to obtain a subject's informed consent. In general, the document provides helpful definitions, examples, and lists of IRB, sponsor, and clinical investigator responsibilities. We do, however, have a number of specific comments that reflect the experience and concerns of NIH researchers who conduct emergency research studies and provide suggestions for enhancing the utility of the document.

While the recent call for comments on the draft Guidance and the public hearing are very important mechanisms for FDA to solicit input from the stakeholder community, we recommend that the FDA collaborate with stakeholders on a more frequent basis (it has been a decade since 21 CFR 50.24 was implemented) and employ other mechanisms such as focus groups or roundtable forums. This will enhance the research community's understanding of the rules and FDA's expectations and broaden FDA's understanding of the needs and concerns of the stakeholders, such as researchers, IRBs, and members of the public whose communities may be asked to participate in 50.24 studies.

Organization of the Guidance

While the organization of the draft document clearly defines the individual responsibilities of IRBs, sponsors, and investigators, it lacks a detailed, integrated overview of the 21 CFR 50.24 process and contains duplicate information. The flowchart in Appendix B ("Suggested Flow Chart for 50.24 Studies") provides a high-level view of the process, but does not provide sufficient detail. We would suggest that the following steps be taken to enhance the level of detail about the process:

- Reorganize the Guidance by process and move the current "responsibilities" sections for IRBs, sponsors, and clinical investigators to the appendix (i.e., in a checklist format);
- Add a table that displays the responsibilities across the three groups for each step in the process (i.e., a process-by-responsibility matrix); and,
- Add references in the flowchart (Appendix B) to sections in the Guidance that describe the process in greater detail.

Highlighting "Optional Practices"

The Guidance lists a number of suggestions and examples to illustrate ways to interpret 21 CFR 50.24. Some of these examples may extend beyond "minimum standards" required under the regulations. It would be useful to highlight or otherwise distinguish those "optional practices" in FDA's current thinking.

Discussion of Intent

In general, the guidance would be more understandable and useful if it discussed the underlying intent of the regulation and the main provisions of the guidance. For example, under the “Study Design” section, two kinds of placebo-controlled trials are discussed: 1) “intervention + standard care” versus “placebo + standard care” when usual care is effective and 2) “standard care” versus “placebo” where the effectiveness of usual care is questioned.

The guidance appears to reflect a general principle that requires the effectiveness of “standard care” to be carefully considered in designing placebo-controlled studies under 21 CFR 50.24. Further, if “standard care” is known to be effective in preventing serious harm (e.g., irreversible injury) or death, then such care must be provided (at a minimum) in each interventional arm. Is this interpretation correct? In this context, does “standard care” refer to “usual care” (i.e., common practice) or something more definitive (e.g., formal clinical guidelines)? For example, would a drug labeled for a particular intervention be considered “standard care” exclusively even if a similar drug with a similar level of supporting data was frequently used in a similar context, but was not approved for that indication? Or does FDA intend to require that any “usual care,” regardless of the evidence, be provided? Since there are several ways to interpret the term, it would be helpful to clarify the intent of this provision and meaning of “standard care.”

Investigational Use of “Off-label” Products and 50.24 Studies

“Off-label” uses of approved products are sometimes investigated in emergency research protocols. The FDA Information Sheet, *Guidance for Institutional Review Boards and Clinical Investigators – 1998 Update* (<http://www.fda.gov/oc/ohrt/irbs/offlabel.html>), indicates that the intention to “invoke 21 CFR 50.24” for studies of “off-label” uses of marketed drugs, biologics, and medical devices may require the submission of an IND or IDE under 21 CFR 312.2(b)(1). We request that the draft Guidance clarify circumstances under which 50.24 studies using “off-label” marketed products would need to be submitted under an IND/IDE.

Timing of IND/IDE Submission

The draft Guidance is unclear about when a sponsor should submit INDs/IDEs for 50.24 studies and when “FDA written authorization” for a study would be sent to the sponsor. This is especially important with respect to submission of the research protocol for IRB review (e.g., does the “...written determination 30 days after FDA receives the IND or earlier” specified in 21 CFR 312.20(c) apply here?).

It would be useful to indicate the likely timing of these events, both in the text of the Guidance as well as in the flowchart (Appendix B).

Overall, a separate section outlining FDA’s role and recommendations (parallel to those for IRBs, sponsors, and investigators) would be helpful. In the current draft, this important information is sprinkled throughout the document. Also, the roles of other Federal agencies (e.g., OHRP) should be described or, at a minimum, referenced, as appropriate.

In Vitro Diagnostic Device (IVD) Study Example

We recommend that the Guidance use a different example of the IVD study in the Introduction (p. 3), such as an IVD study to distinguish between subtypes of stroke or another commonly encountered

problem. The diagnosis of a neurotoxin is likely to be an extremely rare occurrence and may create confusion with the FDA's new exception from informed consent for investigational IVDs used in public health emergencies (71 FR 32827).

“Research would not be unduly delayed”

The second example of “practicable” (p. 4) states “that the research would not be unduly delayed by restricting it to consenting subjects.” The example is amplified with the following point: It may not be possible to obtain consent in advance from patients likely to be “at an extremely high risk for the event to be treated” because of a low incidence of the event under study. It is not clear to us, however, whether “unduly delayed” in this example refers to the accrual of individual subjects, the accrual of all subjects required for completion of a study, or both.

Emergency Research in Pregnant Women, Fetuses, Neonates, and Children

Subparts B and D of the Common Rule (45 CFR 46) provide for additional safeguards for pregnant women/fetuses/neonates and children in clinical investigations, respectively. It would be useful for the Guidance to discuss how Subparts B and D relate to 50.24 studies.

Study Sites in Multi-Center Trials

It would be helpful to clarify whether it would be possible to conduct a single multi-site study that includes both some sites that require the exception of informed consent requirements for emergency research and some sites that do not, such as those where legally authorized representatives (LARs) are readily accessible. For example, because of different local requirements and laws about research LARs, different sites may or may not need to use an exception for informed consent within the same emergency research study, based on their local, legal and regulatory conditions. In addition, regional differences in emergency medical care infrastructure can also contribute to regional differences in the ability to enroll LAR-consented subjects into a study within the therapeutic window.

Therapeutic Window

We recommend clarification of the definition of “therapeutic window” in the Guidance. For example, is the therapeutic window defined as the longest time period, based on scientific evidence, for which the investigational test article has a “potential clinical effect” or is there flexibility to adjust the length of the window based on other scientific evidence, such as “effect size” or “optimal time” for intervention? That is, both uncertainty and variability in defining the therapeutic window need to be addressed. For instance, even if an intervention might have some clinical effect over a period of 6 hours, would it be permissible to define the therapeutic window as 3 hours, based on biostatistical evidence that the effects of the intervention are optimized within the shorter time period?

Summarizing Efforts to Contact LARs/Family Members

It would be helpful to clarify that such summaries are required for **each subject**, rather than an overview for the entire group of subjects enrolled in the study (first bullet, top of p. 12).

It would also be useful to repeat the last sentence from the “Records” subsection (p. 22) here: “FDA suggests that clinical investigators record this information in the subjects’ case histories (e.g., study records, subjects’ medical records, or other files) so that it may be easily retrieved, analyzed, and reported to the IRBs, and so that it is accessible if FDA conducts an inspection.”

Community Consultation and Public Disclosure

The Guidance should further highlight patient advocacy groups and voluntary health organizations as examples of resources to use during the “outreach” phases. These groups often have well-organized communications networks for disseminating information and support regular meetings of members of a disease population within specific geographic locations. In addition, the Guidance should reference and highlight research conducted and/or funded by a number of Federal agencies (e.g., CDC, NIH, EPA) on approaches to and evaluation methods for community consultations and related areas (e.g., perception of risk) reported in the peer-reviewed literature.

Access to Public Disclosure Information

In addition to making the publicly disclosed information available through the FDA’s Dockets Management Branch or through a Freedom of Information Act (FOIA) request, researchers (and other members of the public) would benefit from learning more details about approved 50.24 studies. For example, when such information from Docket Number 95S-0158 has been made public through a FOIA request, we urge FDA to make that information broadly available through a posting on the FDA Website. Alternatively, posting of summaries or “best practices” would help inform the design of subsequent 50.24 studies.

Responsibilities of the Data Monitoring Committee (DMC)

The fact that Section X (p. 22) refers only to the existing FDA Guidance on DMCs suggests that there are no additional responsibilities for DMCs specific to 21 CFR 50.24. If this is the case, it would be helpful to say so explicitly.

Formatting the Flow Chart

To make the flow chart easier to read, we suggest that the boxes surrounding “Yes” and “No” be eliminated and the text placed directly next to the appropriate arrows (see “approves study” and “disapproves study” labels above the arrows out of the “IRB reviews study” box). This will not only reduce the number of boxes in Appendix B, but may also allow for more white space, both of which will enhance the readability of the chart.

Color-coding the flow chart according to the responsibilities in each box would be a way to more clearly and readily show what steps IRBs, sponsors, and investigators are responsible for in the overall process.