

National Institutes of Health Comments on
 FDA Part 15 Conduct of Emergency Clinical Research Public Hearing
 November 2006

The National Institutes of Health (NIH) appreciates the opportunity to comment on the regulatory framework that provides exception from informed consent procedures in emergency research, codified at 21 CFR 50.24. The NIH has funded studies conducted under §50.24 and has recently created several emergency research networks to advance clinical investigations on this important public health topic. Consequently, we anticipate an increase in the number of NIH-funded emergency research clinical trials, including studies that will not be feasible without the exception from informed consent procedures. Thus, the NIH supports FDA's continued efforts to support the development of safe and effective interventions for life-threatening emergent conditions while ensuring the ethical conduct of research. We are pleased to provide input on issues related to FDA's current criteria for human subjects protections in emergency research conducted without individual informed consent and appreciate FDA's interest in gathering broad perspectives on §50.24.

V. Issues for Discussion

(1) Are the criteria for allowing studies conducted under §50.24 adequate to protect human subjects and to promote scientifically rigorous research? Are any additional criteria warranted?

The current criteria under §50.24 provide a rigorous threshold to justify conducting studies where obtaining informed consent from the subjects may not be possible. Thus, no additional criteria are warranted at this time. At the same time, additional research on effective ways to implement these existing criteria under §50.24 (e.g., community consultation) is critically needed. The results of such research may indicate that changes to the criteria are warranted.

(2) Are the following criteria easily understood and, if not, how can they be clarified?

- (a) "Available treatments are unsatisfactory or unproven" (§50.24(a)(1))
- (b) "Prospect of direct benefit" (§50.24(a)(3))
- (c) "Practicably" (§50.24(a)(4))

(a) While "unproven" is generally understood to refer to treatments that lack a scientific evidence, "unsatisfactory" is a much more ambiguous term. We recommend the adoption of the consensus definition of "unsatisfactory" developed at the May 2005 Academic Emergency Medicine Consensus Conference, "Ethical Conduct of Resuscitation Research," which stated:

"Existing therapies should be considered "unsatisfactory," even if partially effective, when serious risk of morbidity or mortality remains, even with the best available treatment or when the adverse effects of the best available treatment are serious. Emergency exception from informed consent should not be used to test experimental treatments that are expected to be no better than existing therapies."¹

(b) The term "prospect of direct benefit" has long been used in the context of human subject protections in clinical research and does not, in our view, need further clarification.

¹ Watters, D. et al. Research conditions that qualify for emergency exception from informed consent. 2005. *Acad Emerg Med*. 12(11):1040-4.

(c) Further clarification of the term “practicably” in criteria 4 (“...the clinical investigation could not practicably be carried out without the exception from informed consent.”) is needed. We suggest that the FDA provide examples of the criteria that will be used to determine whether a trial cannot practicably be carried out without the waiver. These criteria might include, but are not limited to, the length of delay in trial completion, the feasibility of expanding the trial to additional sites, and the degree of potential bias introduced in the subject population by restricting the study to consenting subjects (who are typically less severely impaired, but who may not derive the greatest benefit from the intervention).

(3) Are there other criteria in the regulation, besides those identified in criteria (2)(a) through (c), that need to be clarified?

The definition of “legally authorized representative” (§50.24(a)(2)(ii) and elsewhere) in the context of research involving human subjects needs clarification. The lack of a consistent definition across states and local jurisdictions creates challenges in implementing §50.24. Any steps to increase awareness of this issue and to facilitate the adoption of a uniform definition across the U.S. would be helpful to emergency research studies as well as protocols involving subjects with impaired decision-making capacity.

(4) Are there challenges that have not been explicitly addressed in the regulation in designing scientifically rigorous and ethically sound emergency research protocols (e.g., pediatric protocols)? If there are such challenges, should they be addressed and how?

In reference to criteria 1 and 3(a), which require subjects to be in a “life-threatening situation,” we suggest that the FDA consider expanding the scope to include emergency conditions that, while not immediately life-threatening, have a significant risk of serious morbidity (e.g., severe cognitive impairment or paralysis).

In the case of emergency research on substance abuse, mental health, and aging patient populations, among others, subjects may be conscious but may have questionable capacity to consent (e.g., are unable to provide valid consent). In these cases, the FDA should clarify whether these populations could (or should) qualify under §50.24.

B. Additional Human Subject Protections

Community Consultation

(5) What are the costs, benefits, and feasibility of community consultation as currently required under §50.24?

While the NIH recognizes the value and supports the process of community consultation, we are concerned about the significant additional time and effort required by this process. For example, the cost of community consultation for one NIH-funded study conducted under §50.24 totaled approximately one quarter of the overall grant award. Without appropriate outcome measures, it is difficult to assess the cost-benefit of community consultation activities.

Further, even after such efforts, it is not always clear whether the appropriate “communities” have been consulted. Even when considerable efforts have been made to effect consultations, it is not always clear whether the appropriate community has been reached. For instance, should interstate traffic accident victims who are not from the community be excluded from a study underway at the trauma center to which they are transported? How should “community” be defined for large trauma centers that cover a broad region? Local IRBs grapple with the appropriate action to take in these cases: allow the research to

proceed without consent or consultation with the subjects' communities, require that such subjects be excluded from the study, or require the investigator to undertake a broader consultation scheme. Guidance from the FDA on this issue would be highly beneficial, including information on how IRBs have handled similar challenges in the past.

(6) What aspects of community consultation as currently practiced are effective mechanisms for human subject protection? Are there additional practices that could enhance human subject protection?

The FDA should consult with IRBs that have experience in reviewing emergency research trials and community consultation efforts to learn more about aspects that have been found effective for human subject project. Additional research, such as studies on determining the effectiveness of outreach methods, identifying and engaging "relevant" communities, understanding how IRBs incorporate community feedback, and adapting approaches to particular communities, would be useful.

Multifaceted approaches to community consult, rather than a single model (e.g., a town meeting) should be encouraged. Call-in radio shows, focus groups, random digit dialing surveys and the like might be appropriate. Combining several types of community consultation schemas would likely be the best way to reach the largest audience with the most information. Additional research is required in this area.

(7) Are there elements of community consultation, both procedural and substantive that should, at a minimum, be required (e.g., types of information presented, number and types of meetings or interactions, number of people reached)?

Differences among communities make it difficult to develop a single set of detailed minimum requirements for the process and content of the community consultation. However, it is important to ensure that all communities are sufficiently informed about the nature and purpose of the study. Current minimum requirements in §50.24 provide an adequate framework for community consultation. Therefore, the implementation of community consultations (e.g., numbers of meetings, types of information presented) will need to vary based on factors such as community situations and settings.

(8) Would opt-out mechanisms (e.g., advanced directives, jewelry similar to medical alert bracelet/necklace, and driver's license indicators) to identify individuals who do not wish to be included as subjects in particular emergency research studies provide a necessary protection for human subjects? If so, are they feasible?

While there are logistical and scientific drawbacks to using opt-out mechanisms to identify individuals who do not wish to participate in emergency research, the option to "opt out" should continue to be used until better mechanisms are developed indicating individual preference. The use of opt-out mechanisms like medical alert jewelry or driver's license indicators may provide additional protections for prospective subjects who can not provide informed consent as a result of their medical condition and do not wish to participate in emergency research. However, the feasibility of these methods depends on their appropriateness for the population and the degree to which the community is aware of and utilizes them. In a trial involving car accident-related traumas, driver's license indicators might be sensible only for prospective subjects who drive and hold valid driver's licenses. Scientifically, opt-out mechanisms can affect the ability to obtain a representative study cohort, thereby introducing bias.

(9) Who should use the information obtained from the community consultation process and how should they use it? Should the regulation be more specific on this point, and if so, what should it provide?

The information should be used by the IRB and the investigative team to determine whether there are additional community concerns that have not been addressed in the protocol. The IRB should determine whether these concerns are significant enough to justify prohibiting the study at the local site, or whether changes can be made to the protocol to address the concerns without compromising the scientific value of the study. Additional research on community consultation methods and outcomes is needed before the FDA decides whether to make changes to the regulation. The NIH would welcome the opportunity to collaborate with the FDA to facilitate research on community consultation.

(10) Are there others besides the IRB (e.g., sponsors, clinical investigators, community leaders, advisory committees, ethicists) who should play a role in determining the adequacy of the plan for community consultation and the material to be publicly disclosed?

The IRB is in the best position to carry out this role. They have the most experience in ensuring adequacy of recruitment materials. In addition, the IRB may choose to consult or work closely with community leaders and advocacy groups on the adequacy of the consultation and disclosure plans.

(11) The community consultation process typically includes meetings and discussions about the study with the community.

(a) Should the regulation require documentation of meeting activities and discussions in sufficient detail to show the information that was disclosed and the community reaction to the clinical investigation? If so, who should be responsible for such documentation (e.g., clinical investigator, sponsor)?

To increase transparency, it is appropriate to require that the IRB document the information that was disclosed and the community reaction to the clinical investigation. This responsibility is consistent with the IRB's role in objectively overseeing the research and should be undertaken in collaboration with the clinical investigator and sponsor.

(b) The regulations (see 21 CFR 312.54(a) and 812.47(a)) currently require the sponsor to submit the information publicly disclosed prior to study initiation and after completion to FDA Docket Number 1995S-0158 (formerly 95S-0158). Should the regulation also require that documentation of community consultation activities be submitted to FDA, for example by being placed in the public docket? If so, who should be responsible for doing this?

The FDA should make the IRB-approved plan for community consultation available on the public docket. This would assist researchers in designing future community consultation activities. Sponsors should be responsible for providing this additional information.

(c) Should this information also be available elsewhere such as on clinicaltrials.gov?

Yes, §50.24 trials should be flagged in ClinicalTrials.gov and a link provided from the appropriate protocol summary to additional information available through the FDA public docket. Additional sources of such information would be useful for investigators, IRBs, and sponsors in designing, reviewing, or considering emergency research of their own.

Public Disclosure Prior to Initiation

(12) Are there certain types of information (e.g., adverse event reports, study protocol, informed consent document) that should, at a minimum, be publicly disclosed to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn?

Summary protocol information (e.g., study purpose, nature of the condition, and experimental intervention) should be publicly disclosed prior to initiation of the study (e.g., many of the data elements required for registration at ClinicalTrials.gov (<http://prsinfo.clinicaltrials.gov/definitions.html>) could be used). In addition, a summary of the criteria for reviewing exception from informed consent for emergency research studies and the additional human subject protections afforded under §50.24 should be provided to help people in the community understand what might happen if the emergency research study is initiated in their community (e.g., information about the community consultations, opt-out mechanisms).

(13) Should the full protocol, or other information such as the investigator's brochure, for emergency research be available (e.g., through FDA's public docket, clinicaltrials.gov) to the general public before initiation of the clinical investigation? If so, should protocols or other information be available for all emergency research or only for certain emergency research?

It would be appropriate to provide a protocol or protocol summary, such as the information available in trial records at ClinicalTrials.gov. The investigator's brochure contains technical information that may be more confusing than helpful to members of the community and should not generally be available.

Such information should be made available via a website and other accessible locations for the specific community for a reasonable amount of time prior to the community consultation meeting. This will provide interested community members with sufficient time to obtain and review the information. Further, this information should remain available throughout the course of the study and after study completion (e.g., ClinicalTrials.gov, FDA Docket site).

Requiring the same amount and type of information for all emergency research in a standard format (e.g., study summary format from ClinicalTrials.gov) will provide consistent disclosure of information across all such studies and prevent protracted discussions about what should be disseminated for each new research proposal.

Public Disclosure Following Completion

(14) Is there information regarding study results that, at a minimum, should always be disclosed after the clinical investigation is completed? If so, what is that information?

The current requirements of the regulation (disclosing study results and demographics of the study population) are adequate. By study results, we include a summary primary outcomes and relevant serious adverse events related to the study intervention, similar to what would be published in a journal or submitted in support of an IND/NDA.

(15) How can this disclosure best be accomplished? Who should be responsible for this disclosure?

Requiring sponsors to provide a link to this information in ClinicalTrials.gov would be an appropriate mechanism. In addition, the sponsor should use similar mechanisms for disseminating the results as during the initial public disclosure (e.g., mass media). It is particularly important for those individuals

closely associated with the research, either as study participants and their families or integral parts of the community consultation, to be made aware that study results are available.

(16) When should a clinical investigation be considered “completed?” How soon after a clinical investigation is completed should the results be disclosed?

The study should be considered “completed” after all data are collected, primary analyses are completed, and the results are published in a peer-reviewed journal. In the case where the results are not published (e.g., negative results), the information should be disclosed within a reasonable period of time (e.g., as defined by pending legislation on clinical trials results databases). An exception should be made when the public needs to be informed as soon as possible to protect public safety.

(17) How can we assure timely disclosure of study results after completion of a study?

Establish a timeframe that would require results to be disclosed, even if they are not available in a peer reviewed journal article, and “build in” specific check points with the existing FDA review process to ensure timely disclosure. The timing for disclosure could be modeled on the policy implemented by the NIH to ensure public access to the results of NIH-supported research (NIH Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research, *Federal Register Docket No. 05-2542*. Available online at <http://publicaccess.nih.gov/policy.htm>).

Public Discussion of Emergency Research

Currently, all emergency research protocols are subject to IRB review and community consultation. FDA has received some suggestions that it may be important, at least in some cases, to have additional public discussion, such as during an open meeting of an advisory committee or other expert panel. We invite comment on the following questions. Is there a need for such additional review and public discussion? If so, what criteria would be used to determine which protocols should be subject to this additional review and discussion?

The NIH agrees that additional public discussion of emergency research protocols in some cases could be very helpful for investigative teams and the field. For example, a national advisory committee or panel could be established to provide supplementary public discussion of selected §50.24 studies. Selection of protocols for such review should be based on criteria such as the novelty of the intervention and the risk it poses to subjects and the extent to which the protocol raises unusual or controversial ethical issues, which may be anticipated to generate public controversy. In such cases, additional discussion in a public forum could be highly beneficial. However, such a national review process should be optional for §50.24 studies that do not meet these criteria.

(18) What type of venue would be best for this additional review and public discussion?

Possible advantages of a national advisory committee or panel include increased transparency in the review of §50.24 protocols that present significant novel scientific, ethical, or regulatory issues, facilitated local IRB review of such studies with recommendations by nationally recognized domain experts knowledgeable about §50.24 regulations, and greater “standardization” in any subsequent review of §50.24 protocols that present similar types of issues. A number of national panels with different domains and purposes exist and could provide informative models. These include the NIH Recombinant DNA Advisory Committee (RAC), the NCI Central IRB, the FDA Pediatric Advisory Committee (PAC), and other FDA Advisory Committees. Since the RAC was established to address scientific and public concerns about the ethics of recombinant DNA technology, its open meetings have played an important role in increasing public awareness and confidence in the oversight of gene transfer studies. An

emergency research advisory committee or panel for some §50.24 protocols could similarly increase public awareness and confidence in exception from informed consent emergency research. However, considerable consultation and careful deliberation with stakeholders and the public is required to ensure that any proposed mechanism would be effective and not pose any undue burden for stakeholders.

(19) What information should be included in this review?

At a minimum, the protocol, including plans for addressing the §50.24 requirements, should be included in the review.