

Before The
FOOD AND DRUG ADMINISTRATION
and
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Conduct of Emergency Clinical Research
71 F.R. 51143, [Docket No. 2006D-0331]

Comment Submitted By: Michael J. Conrad
299 North Spring Mill Road
Villanova, PA 19085
mconrad@law.villanova.edu

Comment Submitted By E-mail and Direct Mail.

Comment Submitted To: Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

<http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm?AGENCY=FDA>

Date: November 27, 2006

I. INTRODUCTION

I respectfully submit the following comment concerning suggested amendments to 21 C.F.R. § 50.24 as discussed at the Food and Drug Administration's (hereafter "FDA") public hearing on "Conduct of Emergency Clinical Research" that took place on Wednesday, October 11th. I am commenting in response to the Notice of Public Hearing that appeared in the *Federal Register* on August 29, 2006. It is my hope that the FDA will consider this comment when making a final decision on the proposed amendments.

I am currently a third-year law student at Villanova University School of Law. I submit the following comment exclusively on my own behalf. Therefore, the following comment reflects only my personal opinions and insights, and not those of Villanova University School of Law. Moreover, nothing in this comment should be considered legal advice of any kind, as I have not yet earned my Juris Doctorate or become a member of any Bar. I appreciate the opportunity to be heard on this issue, and I thank the FDA for its time in reading my comment.

Several members of my extended family are medical professionals, while others are directly involved in medical research. Therefore, I have a personal interest in greater

clarification of this regulation in order to better facilitate their abilities to engage in emergency research for the benefit of others. A dear friend of the family was also part of a clinical study that arguably saved his life. The study was not emergency research per se, and informed consent was obtained. However, I often wonder how the situation would have turned out had the study been deemed emergency/experimental research and consent was not obtainable. Without a properly clarified regulation in place, the hypothetical experimental research may not have taken place. For all of these reasons, I would like to see a greater clarification of the rule in order to encourage more emergency research while maintaining adequate protections of all human subjects involved in the investigations.

II. BACKGROUND

Approximately ten years ago, the FDA promulgated 21 C.F.R. § 50.24. This rule allows for an exception to the requirement of obtaining and documenting informed consent from human subjects prior to initiation of clinical investigations.¹ Without this exception, informed consent must be obtained from each human subject involved in the clinical investigation. The intent of the rule is to provide a balance between the facilitation of emergency research and the protection of human subjects.² Since the issuance of this regulation, the FDA has received approximately sixty requests to conduct a clinical investigation under § 50.24 with an exception from the informed consent requirements.³

In the same ten-year period of time, many researchers have conveyed to the FDA that there are some problems with the rule. The most common criticism is that the rule's safeguards are not well-defined in terms of human subject protections. Others claim that the rule creates a bar too high to meet for successful and effective emergency research. There were other criticisms as well, and as a result, the FDA decided to hold a public hearing in order to determine how best to address all of these concerns. Ultimately, the goal will be to redefine § 50.24, if necessary, in order to better serve both the research community and the human subjects. The most important aspect of the rule is to strike an effective balance between the protection of human subjects and the encouragement of emergency research.

III. SCIENTIFIC ASPECTS OF EMERGENCY RESEARCH AND HUMAN SUBJECT PROTECTION

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?

¹ 71 F.R. 51143 (August 29, 2006)

² 61 F.R. 51498 (October 2, 1996)

³ 71. F.R. 51143 (August 29, 2006)

The regulations as they stand are appropriately crafted in order to balance the dual requirements of human subject protection and the promotion of scientific research. The current procedure for obtaining informed consent is sound. To the contrary, the procedure may sometimes be too difficult and hamper emergency research that might otherwise benefit the lives of the subjects, as well as others. Moreover, there may be additional subclasses of human subjects who may or may not necessarily require their own set of appropriate regulations. If they do not require their own set of regulations, exceptions should be carved out from the current regulation. (Please see additional challenges)

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))*

The terms “unsatisfactory” and “unproven” are too vague. There should be a greater clarification of these terms. With respect to “unsatisfactory”, an appropriate definition is any treatment that possesses a moderate to high level of risk of injury or death, as well as a moderate to low chance of improving the subject’s condition. This is the most common definition in the medical and scientific community. The available treatments should also be compared to the emergency research treatments to determine their respective risk/success ratios. An “unproven” available treatment is simply one that lacks any scientific evidence of a positive effect. Any treatment that possesses even a scintilla of positive effect should not be considered “unproven”.

(b) *“Prospect of direct benefit” (§50.24(a)(4))*

What exactly is a “direct benefit”? This term is unclear as well and should be clarified. A mathematical bar, whereby an emergency research treatment would have a success rate of more than 1% higher than the standard treatment would be an acceptable definition. This is provided, of course, that the emergency research treatment does not have a higher rate of risk than the standard treatment. Any experimental treatment that has a higher rate of success and equal or lower rate of risk should satisfy “prospect of direct benefit”. However, if the experimental treatment has a “significantly higher” rate of success than the standard treatment, even with a “moderately higher” rate of risk, the experimental treatment should be deemed to have a “prospect of direct benefit”.

(c) *“Practicably” (§50.24(a)(4))*

Provided that practicability measures the economics, logistics, and benefit of scientific research, this criteria is acceptable as is. To further clarify, however, the FDA should specifically define “practicably” as situations where obtaining informed consent is not possible and the emergency research treatment will clearly improve the chances of survival. Therefore, the “prospect of a direct benefit” should exist before determining whether “practicably” is satisfied in the research.

IV. ADDITIONAL HUMAN SUBJECT PROTECTIONS

a) Community consultation

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

The general consensus from the presentations at the hearing and the affected medical community appears to be that community consultation, if anything, has been difficult. The core problem is that there is a lack of proper representation from the affected community at public meetings. Moreover, less than a dozen studies have examined the methodology of community consultation and have been poorly undertaken and published sporadically. As Dr. Michelle Biros illustrated by an example, in a study initiated involving cocaine addicts, not one single cocaine addict could be recruited for community consultation.⁴ So the question then becomes, who represents them in this consultation? Indeed, who in the “community” is listening to these proposals and providing feedback when the target group is underrepresented or nonexistent at these meetings? Who counts as a community member? What is the purpose of this consultation? All of these questions, at present, have unclear answers.

In cases where the affected community is reached, how does it assist the process if they do not understand the specific facets of the study? Again, as Dr. Biros and others in the medical community have pointed out, less than 5% knew of or understood protocols in many studies.⁵ The information should be tailored depending upon the education level of the respective audience. At a bare minimum, the protocols and practical effects of the investigations should be reduced to language that non-medical individuals can understand without diminishing their true meaning.

The only viable options available are to either scrap the public meetings all together or increase their overall effectiveness. The latter is far more desirable, and can be facilitated with a greater emphasis on advertising and public awareness of the meetings. With greater input from those affected by clinical studies, the study will be more effective and perhaps yield more accurate results.

One final point with respect to community consultation is the aspect dealing with placebo-controlled investigations. This is something of a division within the medical community, some believing that the use of placebo controls should be disclosed while others believe it would not be prudent to do so. If a placebo-controlled investigation is slated to take place, the placebo aspect of the investigation should not be disclosed. Primarily, this will ensure the integrity and common double-blind scenario of the investigation. The more individuals that are informed that a placebo is involved, the more likely that the placebo portion of the investigation will fail to yield the results that it otherwise should. Information concerning placebos should be compartmentalized and

⁴ Presentation from Society for Academic Emergency Medicine (SAEM).

⁵ Ibid.

kept confidential prior to and during the investigation. Disclosing this information to the community after the investigation is perfectly acceptable. While this is something of an ethical quandary, the concerns for an accurate and successful investigation far outweigh the ethical concerns. This is particularly true when informed consent has already been waived for the subjects involved.

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?

Opt-out mechanisms are feasible, particularly in the sense of applying a statement on driver's licenses akin to those who wish to donate their organs. As driver's license applications allow for people to designate whether or not they wish to donate their organs, applications could also ask the same question about participation in emergency research studies. With this simple addition to licenses, the concern for obtaining informed consent can be eliminated. Medical alert bracelets and necklaces can also be another feasible mechanism for those who are chronically ill, as well as children. However, the optimal situation is giving each and every patient the opportunity to directly respond to a request for research. If they refuse, then the inquiry should end there. The protection of the human subject, when they have specifically refused participation, should always trump any other concerns.

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 discussed?

In terms of the dissemination of the community consultation plan, it would be prudent to recruit and utilize those experienced in advertising and advocacy. As many public meetings have either been largely unattended or unsuccessful, a more aggressive advertising campaign could increase local awareness. These individuals should work closely with community leaders in order to increase participation and therefore create a more effective public forum.

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?

Clinical investigators should, at a minimum, disclose the primary details of the clinical investigation, particularly the class of human subjects that will be affected (e.g. terminal brain tumor patients), as well as the proposed experimental treatment(s) to the community. With respect to the proposed experimental treatments(s), there should be full disclosure of the expected level of success, as well as the level of risk involved. While the primary purpose of this rule and the investigations attached to them is due to the lack of

informed consent, it would nevertheless be prudent to disclose the informed consent document to the community so that they are aware of the nature of the investigation. It should not be taken for granted that the community is aware of the lack of informed consent, thus the release of this form is recommended. Full disclosure of all technical details is not necessary, as most of the community are likely non-medical personnel who would only be confused by the information. Disseminating the essential facts is important, as input from the community may call for changes to the clinical investigation. Ultimately, the knowledge passed on to the community should be as honest and accurate as is scientifically possible.

b) Additional challenges

20. Are there any additional challenges to the conduct of emergency research that have not been identified in the preceding question?

Yes, several additional challenges should be addressed, which will be described below. The challenges deal with the need for a central IRB, specialization for children, and concerns over publication of studies.

21. If so, what are they and how should they be addressed?

Institutional Review Boards (“IRBs”) have given limited guidance and very little, if any, feedback. Some IRBs are very reluctant to allow an exception. A central IRB might need to be established for a network study. As many in the medical community have indicated, a national institutional review board would be desirable in this instance. 51 studies in 10 years is not an overwhelming workload for a national body, assuming of course this trend is to continue. Local IRBs vary in their interpretations of such requests and in this way, there is a severe lack of uniformity. A central IRB can remedy this issue by dealing exclusively with requests for emergency research where informed consent is not obtainable. The central IRB can also coordinate such requests with the appropriate local IRBs. With a central IRB established and successful coordination with local IRBs, emergency research studies will occur on a more uniform basis.

There is a need for specialization to incorporate children, with respect to the regulation. Whether the regulation itself should be amended or a new set of regulations should be drawn up in order to meet the unique challenges that minor human subjects present remains to be seen. In either case, children are clearly a different class of subjects than adults and the requirements for waiving informed consent should be increased. On the other hand, young children can also be more fragile, especially physically, and treatments may have to be administered more quickly than they are with adults. The FDA should take both of these issues into consideration. A new set of regulations would yield a more effective result and should be explored as soon as possible.

One additional point is that only studies that produce positive results are published. This does not present a clear picture of the overall success of emergency research investigations and studies. Studies that produce negative or null results should

also be published in order to provide an accurate depiction of the status of emergency research as a whole. Indeed, despite large successes in emergency research, it is disingenuous to fail to publish the studies that have either produced negative results or have had no effect. While this may be an additional financial burden, the benefits of public dissemination far outweigh this concern.

V. CONCLUSION

The tension between encouraging emergency research and ensuring adequate human subject protections will always exist, but it is my hope with these suggestions, as well as those of others in the medical community, a more effective balance can be struck. § 50.24 in its current form is an impressive regulation. With some additional tweaks and modifications, this regulation will better serve the medical community, while continuing to protect human subjects. Overall, protections for human subjects are adequate, while some modifications can be made to increase the likelihood and effectiveness of future investigative research. Protecting human subjects is paramount, but not to the extent that it will unreasonably frustrate or completely obstruct research that will benefit the subjects as well as the community at large. Finally, I would like to thank the FDA for holding a highly successful and insightful public hearing as well as its time in reading this comment.