Docket number 2006D-0331: Conduct of Emergency Clinical Research; Public Hearing.

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I am requesting time to make an oral presentation during a public hearing scheduled for October 11, 2006, on emergency research conducted without informed consent under FDA's emergency research rule. My comments will address aspects of questions 1-4, 6-8, 10-13, and 18-19. Although I will be speaking for myself, my comments are informed by the work that I have conducted over the past two years with my colleagues Nancy King of the University of North Carolina and Ken Kipnis of the University of Hawaii. Together we will be submitting written comments that will address the questions in more detail by the November 27, 2006 deadline.

Abstract of Presentation:

I and my colleagues are supportive of the concept of research conducted under an exception from informed consent but remain concerned that a lack of clarity in the interpretation and application of the criteria, along with a failure to conduct a robust and transparent process of community consultation, will undermine public trust in the conduct of emergency research.

The primary source of ongoing controversy is the interpretation of the criteria that available treatments are either "unproven or unsatisfactory." The criterion "unproven" is fairly straightforward, and should be interpreted simply as the absence of any proof of effectiveness. However, the criterion "unsatisfactory" is subject to a range of possible interpretations. This criterion should be stricter than the ethical requirement for equipoise that serves as the basis for controlled clinical trials. Rather, as suggested in the preamble to the 1995 proposed rule, the criterion "unsatisfactory" should mean that the available treatment fails to "prevent a significant proportion of deaths or permanent disabilities." We are concerned that extending the exception from informed consent to include clinical trials between treatments that are in equipoise would, in effect, eliminate informed consent as a moral requirement for research whenever obtaining consent is not feasible (even if available treatments are both safe and efficacious).

We support the clear distinction between community consultation and public disclosure that is found in the FDA draft guidance. However, we believe that the moral acceptability of research conducted under the emergency exception from informed consent rests on a robust process of community consultation and on the transparency of this process and of the conduct of the research. Unfortunately, we believe that many forms of community consultation that are currently practiced do not satisfy the moral requirement for two-way communication, nor for this communication process to be open to the possibility that changes may need to be made in the protocol and/or other aspects of the research. We believe that the research protocol as well as informed consent documents should be available to all members of the community on a routine basis. In addition, the requirement for an "opt out" mechanism should not be used as an excuse to withhold such documents from members of the community who have expressed doubts about the research. The moral requirement for transparency in the process of community consultation

suggests that the adequacy of such consultation should be readily apparent to all members of the community, including regulatory authorities such as FDA and OHRP.

There are two procedural issues that we do not see addressed either in the FDA draft guidance or in the questions posed in preparation for this public hearing. First, the regulations require that an IRB which "cannot approve" the research report this to the sponsor who then must report this to FDA and to other involved IRB's. We believe that this requirement is consistent with the moral importance of transparency and community dialogue that serves as the foundation for this type of research. We are aware of instances when an IRB has raised questions about the appropriateness of certain research under this regulation, only to have the investigator at the behest of a sponsor withdraw the protocol from IRB consideration. Since the IRB had not taken a final action, the concerns of the IRB were not reported directly to the sponsor nor to FDA or other involved IRB's. We believe that any action by an IRB, including a failure to take action based on concerns raised subsequent to the submission of the protocol, should be reported via the sponsor to FDA and other involved IRB's. Second, we are also aware of emergency research under an exception from informed consent taking place after a Special Protocol Assessment has been granted by FDA. It is our understanding that such an assessment means that there can be no changes in the protocol based on subsequent ethical concerns that are raised during the process of community consultation. We believe that such an assessment is contrary to the spirit of transparency and to the two-way communication which FDA cites in its own draft guidance.

Before concluding, as a pediatrician who has conducted research on the application of an exception from informed consent to parental permission, I should add one comment about pediatric research. The feasibility of informed and voluntary parental permission remains an issue even if the parent is physically present at the child's bedside. Although parents want there to be a process of communication, our research supports the view that a narrow therapeutic window such as 30 minutes may not provide sufficient time for a parent to make an informed and voluntary choice to permit a child's enrollment in emergency research. Nevertheless, there should still be a carefully thought out process by which the parent can opt out of having the child to participate in such research. Although the criteria for such research remain the same, the practical application of these criteria in the context of pediatric research need to be evaluated on a case-by-case basis. In addition, there needs to be active involvement of parents drawn from the appropriate communities in the design and conduct of such research.

Finally, we support the view that research to be conducted under an exception from informed consent be subject to an initial public discussion of the appropriateness of the proposed research under the existing regulations. Such a discussion is even more essential when there are substantive differences of opinion about the interpretation and applicability of such criteria as "unsatisfactory" and "practicably." Depending upon the sponsor, such public discussion could occur before either an FDA advisory committee (four research involving an FDA-regulated product) or under the auspices of an NIH Council (for research funded by NIH). The questions that could be productively addressed in such a public discussion include whether the research meets the criteria for being conducted under an emergency exception from informed consent, the communities that should be involved in the consultation, the appropriate processes for conducting such consultation, mechanisms for opting out, and other issues. In effect, such a meeting could serve as the first event in a robust and transparent process of community consultation. We do not hold to the position that all such research would, over time, require such a review. However, the use of such a review process would establish a public tradition of the interpretation and application of the regulations that would allow for the identification of protocols that would not require such a process based on past discussions. Although we

believe that there can be greater clarity and guidance about the criteria for conducting research using an exception from informed consent, and improvement about the process of community consultation and the overall transparency of research conducted under such an exception, we do not believe that either the guidance or the process can be specified with such precision to obviate the need for ongoing public discussion and review of protocols conducted with an exception from informed consent.

Thank you for the opportunity to present to you today.