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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2006D-0331
Draft Guidance for IRBs, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research

I am an interested party who submitted a public comment to the docket for the interim final rule in 1996. I have followed the uses of emergency research since then, and have worked intensively over the last 2 years to foster public discussion about the PolyHeme trial and the application of the emergency consent waiver rule in that trial.

The FDA is to be commended for its progress on this draft guidance, which in a number of respects expands usefully on the previous draft version (released for comment on March 30, 2000). However, there are still gaps and deficiencies in the guidance.

Most glaringly, the draft guidance fails to address most of the questions asked in the Part 15 questions on emergency research, which were promulgated for the October 11, 2006 hearing and which will remain open for public comment after the comment period for this draft guidance has closed. It is essential to incorporate the guidance offered by the answers to those questions into the final version of this guidance, as those questions address key concerns of investigators, IRBs, and sponsors.

Re: Docket No. 2006D-0331
Nancy M. P. King, JD

The key concerns that are raised in the Part 15 questions but not adequately addressed in this draft guidance include the following:

- The meaning of operative terms in the regulations, including in particular: “unproven or unsatisfactory”; “prospect of direct benefit”; and “practicably”.
- Minimum required publicly available information, before approval and after completion of research
- Suggested consultation on the adequacy of community consultation plans (e.g., community advisory board, expanded ethics advice, local community leadership)
- Minimum required elements for community consultation
- Experience with effective and ineffective community consultation
- How to use the information obtained from community consultation to modify, approve, or disapprove of proposed emergency research
- Types of effective opt-out mechanisms

My comments on specific aspects of the draft guidance follow.

II. Study Design: Prospect of Direct Benefit (draft p. 3). What should count as a prospect of direct benefit is ill-defined throughout the federal regulatory research oversight scheme. Thus, the meaning of the concept is in dire need of elaboration here, since the conditions permitting a consent waiver ought to be narrower than those applicable to research with consent. Condition 2 requires that prior research “support the potential for the intervention to provide a direct benefit” – with no further discussion of what would meet that condition. Given the example of the PolyHeme trial, where research prior to the phase III waived-consent trial was thin at best, my concern is that this condition could be too easily satisfied. Many investigators, sponsors, and even IRBs might argue that the line of research is promising and the subjects are patients with the condition of interest and for whom nothing else is very effective – thus, simply by definition they could benefit. And this would be as true for a phase I first-time-in-humans study as for a definitive phase III RCT. In my view, the potential for direct benefit should be reasonably likely, and the benefit itself should be reasonably significant, in order to justify use of the emergency waiver – and investigators and IRBs should be required to make an affirmative case to the IRB to that effect. It is not enough to say “nothing else has worked” – a type of “theoretical possibility” reasoning that has all too often been used to describe even phase I interventions as directly beneficial to subjects with the disease or condition of interest.

Study Design (draft p. 4). The guidance says only that “the study design should be adequate to the task of evaluating whether the investigational drug or device has the hypothesized effect.” Given that the design of the PolyHeme trial, to the extent that it is known, seems to have been utterly inadequate to the task, I believe that elaboration on the nature and meaning of adequacy of statistical design is called for here.

Re: Docket No. 2006D-0331
Nancy M. P. King, JD

IV. IRB Responsibilities: General (draft p. 6). The second paragraph here notes that the IRB “has authority to . . . require modifications in . . . a proposed clinical investigation.” This authority appears to be incompatible with the issuance of a Special Protocol Assessment. Given the use of an SPA in the PolyHeme trial, and its detrimental effect on the IRB process, the relationship between IRB review and the existence of an SPA should be clarified. Indeed, SPAs should not be permitted in emergency research.

In the same section, on draft p. 7, the elaborated discussion of IRB review of the planned process and content of community consultation is helpful. However, it should be explicitly noted that review of all community consultation materials should be undertaken using the same standards as are applied to study recruitment materials (ads, letters, etc.), telephone scripts and other ancillary materials, and consent forms. Investigators should also be required to distribute copies of an IRB-approved version of the consent form at community consultation sessions. The consent form should be labeled Draft – For Community Review and Comment, and could be revised as needed in response to community consultation. The final version should then be widely distributed as part of the public disclosure process.

On draft p. 8, reference is made to the IRB’s review of “information that the investigator or sponsor will publicly disclose”. As noted, this should include the final, IRB-approved consent form.

More significantly, this guidance document should make clear that investigators and sponsors are expected to make as much information as possible publicly available, both for community consultation purposes and as a matter of public disclosure. At a minimum this should include not only the consent form but also the protocol itself, as well as IRB-approved FAQ sheets and information sheets. Claims of commercial confidentiality should not be countenanced in this context. It is also important to underscore the IRB’s need for vigilance in assessing and addressing language that promotes the therapeutic misconception – whether in draft consent forms, information sheets, or investigator presentations to community groups.

Re: Docket No. 2006D-0331
Nancy M. P. King, JD

VI. Sponsor Responsibilities (draft p. 10). The bullet referring to the sponsor's responsibility to report "information related to an IRB's determination that it cannot approve" proposed emergency research is in desperate need of elaboration. As was seen in the PolyHeme study, if "cannot approve" is construed narrowly, as synonymous with "disapproves", this reporting requirement will be rarely invoked – and opportunities for IRBs to share important information will be lost. "Cannot approve" should be interpreted broadly in this guidance, to include all instances in which the IRB asks questions or requests modifications, even when the investigator withdraws the application without responding. Because it is certainly true that many such withdrawals are benign and unrelated to the substance of the IRB's questions or modifications, this reporting requirement should be seen as analogous to a hospital "incident report", which ascribes no causality or blame, but simply reports what has occurred. Such "cannot approve" reports would then afford IRBs the opportunity to follow up with questions to the involved IRBs – or not. The critical issue here is information-sharing among IRBs, who can then, properly informed, judge for themselves the significance or nonsignificance of the information.

VIII. Community Consultation and Public Disclosure (draft pp. 12-17). The draft guidance has gone a long way toward making clear the important differences between community consultation and public disclosure – distinctions that, in practice, have been far better honored in the breach. As in earlier sections, it is crucial to emphasize that the IRB should review and approve the content of community consultation and public disclosure materials.

The draft guidance offers good suggestions about effective community consultation, but could very easily provide more assistance to IRBs, sponsors, and investigators regarding effective models for community consultation. There is a substantial and growing scholarly literature on community consultation, which should be known to and consulted by all responsible parties. Answers to the Part 15 hearing questions on community consultation should be incorporated into this guidance as well. In addition, the guidance should offer the suggestion that investigators approach the IRB well in advance of beginning the IRB application process for a waived-consent study. Many IRBs are in the position to make available pre-application consultation to the investigator. For example, at UNC School of Medicine, investigators considering emergency waived-consent research are able to meet and work with IRB members and their colleagues who have knowledge of the literature, the regulations, and the issues, and can assist investigators in pre-application planning and assessment.

Re: Docket No. 2006D-0331
Nancy M. P. King, JD

There is one significant problem with the draft's discussion of community consultation; it appears on draft p. 14. This is the discussion of how the "opt-out" provision should be presented in community consultation. Introducing the availability of an opt-out mechanism in the community consultation setting is likely to signal to the community that the only way to object to a waived-consent study is to opt out. Instead, mention of the opt-out mechanism at the community consultation stage should be clearly and specifically explained as a means of asking the community whether the chosen mechanism would be adequate if the study were approved, whether any changes are needed, and how to publicize the availability of the opt-out mechanism. When I attended a community consultation meeting for the PolyHeme trial, instead of being able to discuss a proposed opt-out mechanism, meeting attendees were shown opt-out bracelets and offered an opt-out sheet to sign (with their Social Security numbers). This conflation of community consultation and public disclosure left essentially no opportunity for consultation at all. The proper place for discussion of informing communities about opt-out mechanisms (as opposed to consulting with them about the most appropriate ways to opt out) is found on draft p. 17 of the guidance, and should be highlighted there.

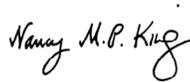
Post-study disclosure to communities, mentioned briefly on draft p. 19, should be expanded with discussion of what time frame is reasonable, in light of the Part 15 hearing questions on how much information should be made available and within what time frame.

Re: Docket No. 2006D-0331
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In conclusion, I believe that emergency waived-consent research is ethically appropriate, but only under carefully limited circumstances – not simply because bypassing consent is more convenient for investigators and sponsors. Responsible use of the waiver should be undertaken with care and serious attention, not simply to the letter of regulatory compliance but to the significance of waiving consent when there is great need and real justification. Only meaningful guidance can help investigators, sponsors, and IRBs use this extraordinary option in ways that properly respect and protect communities and subjects.

I trust that the FDA is up to this important task, and I look forward to its prompt, thorough, and continuing attention to regulatory revision and guidance on emergency waived-consent research.

Sincerely, _____

A handwritten signature in black ink that reads "Nancy M.P. King". The signature is written in a cursive style with a small dot above the letter 'i' in "King".

Nancy M. P. King, JD
Professor of Social Medicine