



Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. 01N-0322 Advance Notice of Proposed Rule Making (ANPRM)
Institutional Review Boards: Requiring Sponsors and Investigators to inform IRBs of Any Prior IRB Review

Introduction

This ANPRM must be viewed in context of two new factors in drug development. The first is increased reliance upon information technology (IT) to track information. The second is the dispersion of early stages of biotechnological drug development to many "out of industry" sources – to the academic "medical scientist-investigators" who use their expertise in medicine for designing molecular approaches to curing disease and who are essential to developing biotechnology. The most promising new approaches are coming from these new drug developers. Many of these individuals utilize NIH funding to get through preliminary studies and the first stages in drug development. They therefore fall under both 21 CFR 56 and 45 CFR 46 when they deal with the IRB.

I am addressing this ANPRM from the perspective of just such a small operation. We rely primarily on paper copies of documents and manual document control. We cannot yet fully leverage IT to reduce the cost of these components of compliance to FDA and NIH regulations.

My concern with the proposed new regulation is that it is based upon several assumptions that are implicit in the conceptual framework of the ANPRM and are not all true. The proposed new regulation has three underlying assumptions with corollaries, as follows:

First. "Shopping around" for a favorable IRB review is easily recognized when it occurs.

- *Corollary:* Human research projects are each unique, clearly defined and traceable.

This assumption is implicit in the decision to collect and share more data – with the use of a matching paradigm to sift through masses of project data to reliably match projects to themselves so that "IRB shopping" is detected when it occurs.

Second. Those submitters (sponsors/investigators) who do not like an unfavorable review are wrong to seek re-review of the same project by a new IRB.

- *Corollary:* By "IRB shopping" submitters are inherently increasing the risk of harm to the participants in the study by withholding information.

The OIG report that underlies this ANPRM uses anecdotal evidence, but the regulation will rely upon these anecdotes to be indicative of a larger reality. In the third paragraph of the ANPRM introduction, this assumption is denied, but it is there or the additional reporting would not serve any purpose.

Third. IRBs always benefit from, and wisely use, any new information about a study.

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- *Corollary 1*: Providing more information and opinion about a project is good.
- *Corollary 2*: IRB members have an infinite capacity for including new information in their review process.

Increasing the amount of information that is provided to the IRB, as this regulation would do, has to be good if this proposed new regulation is to reach its objective. If the IRBs could not benefit from or usefully utilize this information, this proposed new regulation would not achieve its goal.

Discussion

In the announcement, you have divided the subject into eight broad issues. All the issues listed in the ANPRM are addressed in the discussion below; they are not dealt with individually. I have found four reasons why this regulation should not be developed as proposed.

1) *This proposed new regulation would decrease the harmonization between 21 CFR 56 and 45 CFR 46.* IRBs must meet both the regulations of 21 CFR 56 and 45 CFR 46. If all IRBs are required to track the entire history of review for every project that falls under 21 CFR 56, but are not required to track that information for the studies that fall under 45 CFR 46, these distinctions will increase the workload of IRBs. Regardless of what information is defined in this regulation, the need to track information differentially will make function within the IRB more difficult (issue 6). It will also increase the confusion for medical scientist-investigators who do not have corporate backing (i.e. those who sometimes conduct studies that lead to INDs and sometimes conduct studies that do not) as they try to meet all the federal regulations.

2) *Little is known about the frequency or significance of the “IRB shopping.” That fact makes the proposed new regulation premature (issue 1).* When information gathering is mandated before it is known to be useful, it is difficult to de-regulate later. If, as information is collected, it indicates that “IRB shopping” does not relate to human subject risk, then IRBs should not be required to waste resources to track and evaluate this behavior. The IRBs’ primary purpose according to 21CFR 56.102.g is “to assure the protection of the rights and welfare of the human subjects.” If we are uncertain about the significance of “IRB shopping,” then the regulation is not needed. If it is not a problem, it does not need “fixing.”

3) *Requiring IRBs to collect tracking information about previous reviews increases the scope of the function of IRBs, and may endanger human subjects.* Giving the IRB previous review information implies that the “previous review record” must be included in the risk analysis of the study, regardless of the actual relevance of this information. This proposed new regulation would require IRBs to make a judgment about other IRBs’ ability to evaluate the study (issues 4, 5, & 6). Having IRBs review other IRBs’ decisions expands the roll of every IRB. IRBs do not have hard and fast rules about precedence, or anything but anecdotal evidence for evaluating the behavior of other IRBs and the sponsor/investigators who submit protocols to more than one IRB. They are not equipped to use this information. The proposed new regulation would increase the burden of paperwork especially for those IRBs that already have difficulty tracking evaluations¹ because the matching process is much more costly and difficult in a paper based system. Increasing their burden of information filtering will not improve their performance. The third assumption is not true.

4) *Defining a “project” in order to develop a project history is not clear-cut.* The first assumption is not true. All projects tend to be modified through time. In fact, it is not infrequent

¹ *Compliance Oversight Branch, Division of Human Subjects Protections, Office of Human Research Protections. OHRP Compliance Activities: Common Findings and Guidance – 11-30-2001. pg 1-5. accessed on-line through <http://ohrp.osophs.dhhs.gov/references/findings.pdf> 3-11-02 by Aleta Crawford*

for the design of the study to be radically changed between the time the study specific aims are first defined and the time that the study is approved by the IRB and initiated. This is especially true for medical scientist-investigators whose projects begin as grant proposals and undergo review by many funding and regulatory committees before they reach IRB review. This process of modification results in changes in scale, scope, named investigators, institution, title of the project, grant support, and even in sponsorship. This proposed new regulation could not be easily implemented because tracking a “single” project is not actually a clear-cut process, so defining which reviews are of “the same” project is not clear. How many parts of proposed research need to change before it is considered a new project?

Cursory cross matching of projects, when they are defined by only a few features, are unreliable. Those “IRB shoppers” who are intent on getting a new review could easily subvert any matching paradigm, unless all projects are forced to be much more tightly controlled. It would not be “good enough” to have project managers do the matching, because then subterfuge would be impossible to detect. Any new regulation would have to make the degree of change that defines a new project very clear or it would be unenforceable and would not stop “IRB shopping.”

Conclusion

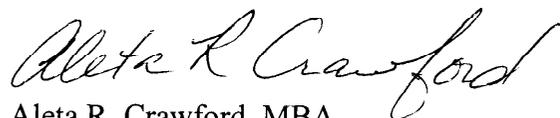
The growth of IT gives the FDA the prospect of better regulation enforcement because it provides an automated means of filtering. It is important to remember that the exact features of the information pool are critical to IT’s ability to perform reliably (i.e. variability in project definitions must be confined to subtypes whose components are well defined). If project definitions end up being infinitely variable and subject to entry or translation errors (due to a process of manual entry of printed material) the IT analysis of the data will suffer. The result will be that the FDA will not be able to reliably detect the same protocol appearing in more than one IRB. Attempting to codify all parts of all possible research designs is counter-productive to research as a process. Codification limits the information that studies can collect by reducing project variability.

It is very seductive to think that one more regulation can eliminate what is seen as problem behavior. This proposed new regulation must only be developed if it will result in greater safety for human trials. As it is conceived, it is based upon several false assumptions. The proposed new regulation **will** reliably increase the workload of IRBs, and decrease their sense of purpose.

In the future, the FDA will be dealing with more individual medical scientist-investigators, as the promise of biotechnology is fulfilled. These individuals have limited resources to use, and tend to be locked into single product life cycles, unlike larger multi-product drug companies. Gene transfer researchers would suffer inordinately from a regulation that increases information tracking for projects because of the need to meet both NIH and FDA regulations differentially. Those regulations will be diverging with this proposed new regulation.

Thank you for considering these facts.

Respectfully submitted by,



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