

Docket Number 01N-0322
**Institutional Review Boards: Requiring Sponsors and Investigators
to Inform IRBs of Any Prior IRB Reviews**

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Comments of Barbara J. Evans, Ph.D., J.D.¹

Scope of Comments

These comments respond to one of the questions under Issue 1 of the Advance Notice of Proposed Rulemaking (ANOPR): "What issues lead to IRB shopping?"

Summary

Individual Institutional Review Boards (IRBs) exercise broad discretion in making decisions under 21 CFR Part 56. Decisions can vary widely from one IRB to the next. IRB shopping is a foreseeable response to the opportunities that this implies.

In evaluating the disclosure requirement that is the subject of this ANOPR, a threshold question is whether consistency of IRB decisions is to be desired. Would greater consistency advance the protection of human research subjects or limit it to a relatively low common standard around which consensus could coalesce? This comment does not advocate one position or another on that question. It merely urges the FDA to enunciate its position on this question, before formulating its response to the phenomenon of IRB shopping. The optimal response depends on whether consistency is a goal.

- A. If the FDA concludes that it is desirable for IRBs to continue exercising broad discretion when they make decisions, the proposed disclosure requirement could chill the exercise of that discretion and possibly limit innovation in protecting research subjects.

- B. If the FDA concludes that it would be beneficial to promote greater substantive consistency of IRB decisions, the proposed disclosure requirement may be a helpful measure but it is, at best, only a partial solution. Alternative approaches, such as the following, may also merit consideration:
 - 1) instituting a formal regulatory appeals process through which sponsors and investigators could receive timely review of adverse IRB decisions, to ensure that IRB decisions are not only clustered together but clustered around a properly reviewed standard;
 - 2) providing additional guidance to IRBs to promote greater consistency in the standards and methodologies that they apply; or
 - 3) pursuing deeper reform of certain provisions of 21 CFR 56 that invite inconsistency of IRB decisions and, hence, encourage IRB shopping.

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Discussion

Different IRBs, acting in good faith under similar circumstances, can arrive at widely differing conclusions about what needs to be done to protect human research subjects. IRB shopping is a response to this inconsistency. Few observers would be concerned, if sponsors and clinical investigators were shopping solely for the purpose of finding IRBs that render decisions more swiftly or at lower cost. The concern is that they are shopping for substantively different outcomes. That is the point of discomfort with IRB shopping.

IRB shopping is a “problem” that warrants a federal regulatory response only if inconsistent IRB decisions are regarded as a problem. To date, the relevant federal agencies have not taken the position that inconsistent IRB decisions are a problem. The Department of Health and Human Services recognizes that, in applying 21 CFR §56.111(a)(2), “different IRBs may arrive at different assessments of the risk/benefit ratio.”² This inconsistency cuts to the very heart of an IRB’s decisions: “Evaluation of the risk/benefit ratio is the major ethical judgment that IRBs must make in reviewing research proposals.”³ The ANOPR in this docket has not presumed that inconsistent IRB decisions are a problem.⁴ However, it does characterize IRB shopping as a “problem” and, in our view, this accords with general public sentiment.

This commentator believes that inconsistent IRB decisions are a significant problem and expose serious defects in the regulations—defects that cannot be repaired merely by “plugging the hole” of IRB shopping. We acknowledge, though, that there could be plausible policy arguments in favor of granting IRBs discretion to decide similar issues differently. Rather than use the loaded term “inconsistent” in referring to IRB decisions that diverge from one another, we hereafter refer to such decisions as “reflecting the exercise of broad discretion at the level of the individual IRB.”

A. If the FDA concludes that it is desirable for IRBs to continue exercising broad discretion when they make decisions, the proposed disclosure requirement could chill the exercise of that discretion.

As noted in the ANOPR, there is a risk of “ill-considered, ‘defensive’ acceptance or rejection”⁵ of proposals, if IRBs resort to a herd mentality after learning that fellow IRBs have previously considered a matter that comes before them.

² Institutional Review Board Guidebook, http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm See, Chapter III *Basic IRB Review*, Section A, under the Subheading *Determination That the Risks are Reasonable in Relation to Anticipated Benefits*.

³ *Ibid.*

⁴ See, e.g., paragraph 3 in the Introduction of the ANOPR: “It is important to note that the OIG never suggested that it was inappropriate to challenge a negative decision or to seek another IRB’s review.”

⁵ ANOPR, Issue 5, third paragraph.

B. If the FDA concludes that it desirable for IRB decisions to be less discretionary in nature than they now are, the proposed disclosure requirement may not constitute a full or optimal response.

If substantive consistency of IRB decisions is deemed to be desirable, other approaches may be worth considering. These could be considered in combination with or in place of the proposed disclosure requirement:

(1) Evaluate the possible advantages of instituting a formal regulatory appeals process through which sponsors and investigators could receive timely review of adverse IRB decisions.

The disclosure requirement that is the subject of the ANOPR may help promote a clustering of IRB decisions. However, there is no guarantee that it would cause them to cluster around desirable standards or methodologies.

If objectionable IRB decisions are the ones most likely to be shopped, it may be prejudicial to disclose those decisions to other IRBs without first inquiring why they were objectionable.

Requiring adverse IRB decisions to be appealed, rather than letting them be shopped, would create a body of publicly accessible rulings to guide IRBs in the exercise of their discretion. This would promote increased consistency of IRB decisions yet ensure that the consistency is based on an appropriately reviewed set of standards and methodologies.

(2) Provide additional guidance to IRBs to promote greater consistency in the standards and methodologies that they apply.

IRBs could benefit from additional guidance on the question of how their discretion under 21 CFR 56 should be exercised. Specific guidance could help improve the general consistency and predictability of IRB decisions.

For example, the IRB Guidebook currently states that the risk/benefit ratio in 21 CFR §56.111(a)(2) “is a judgment that often depends upon prevailing community standards and subjective determinations of risks and benefits.”⁶ There is no specific guidance concerning how community standards shall be ascertained: Is a statistically valid public survey required, or is it sufficient for an IRB to ask a few community groups of its own selection or to rely on one or two self-selected volunteers? There is little guidance in defining the relevant community to be considered: In evaluating the benefits of research, some IRBs may define it as the

⁶ IRB Guidebook, *supra* note 2.

locality, while others may equate it to all who may have access to the improved treatments that flow from the research, *i.e.*, the nation or mankind. Different tacit assumptions could produce divergent IRB decisions. Finally, this guidance, as worded, allows the possibility that subjective determinations—presumably the IRB’s own—may be substituted entirely for the community standard. As guidance for calculating the important risk/benefit ratio, this is disturbingly close to “anything goes.”

The Office of Inspector General has noted that IRBs, in an effort to cope with heavy workloads, may rely on one reviewer to examine and summarize issues for the entire IRB. Some IRBs may spend only one to two minutes of review per study.⁷ IRBs and, potentially, their individual members wield their discretion in haste and with little specific guidance. IRB shopping is a consequence of that fact.

(3) **Consider deeper reform of the regulations in 21 CFR 56 to address the underlying causes of inconsistent IRB decisions.**

The original delegation of decision-making authority to IRBs under 21 CFR 56 may in certain respects have been inappropriate. This contributes to the problem of inconsistent IRB decisions and, hence, IRB shopping.

21 CFR 56 delegates multiple responsibilities to IRBs. Although related in their overall objective of protecting research subjects, these regulatory tasks are conceptually distinct. Their optimal performance may call for differing degrees of centralization of the decision-making process.

- At one level, 21 CFR 56 is a procurement regulation that sets forth procedures through which institutions may obtain a valuable “raw material” for producing research, *i.e.*, research subjects.
- It is also a safety regulation, through which IRBs intervene at the outset to ensure risks to research subjects are minimized and monitor ongoing compliance through continuing review.
- It is also an economic regulation aimed at preventing wasteful use of a resource, again, the human research subjects. “Waste” in this context refers to the exposure of research subjects to risks that are not justified by the marginal scientific value of the research in question. The risk/benefit ratio in 21 CFR §56.111(a)(2) serves as the measure of marginal scientific value, for this purpose.

A decentralized “regulator,” such as an IRB, is in a fairly good position to perform the first two tasks listed above, since they depend to a large

⁷ DHHS, Office of the Inspector General, Institutional Review Boards: A Time for Reform, OEI-01-97-00193 (June, 1998), page 6. <http://oig.hhs.gov/oei/reports/a276.pdf>

degree on information available locally within the institution. A decentralized approach is less suitable for the third task, which requires broader trade-offs of risks and benefits to ascertain whether a given activity is a worthy use of resources. As a general matter, regulations aimed at preventing waste typically require a fairly high degree of centralized regulatory responsibility. This ensures that resources are consistently deployed to the highest-valued uses, taking many possible alternative uses into account.

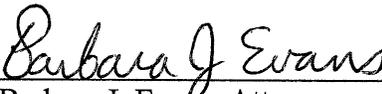
By decentralizing the cost/benefit analysis to individual IRBs, 21 CFR 56 invites inconsistent decisions. If Institution A has a large portfolio of “high-valued” research studies and Institution B does not, then their respective IRBs may, in good faith, reach widely differing conclusions regarding the merit of proceeding with a given research protocol. Context matters and no amount of methodological guidance would alter that fact. The regulations require IRBs to make certain judgments which, by their nature, call for a broader context than is available to individual IRBs.

The cause of IRB shopping lies not with individual IRBs that are issuing divergent decisions, nor with the sponsors and clinical investigators who take advantage of that fact. The cause lies in 21 CFR 56 itself. The question is whether a disclosure requirement is an adequate “patch” for what appears to be an inherently defective regulation.

Conclusion

It merits repeating that IRB shopping is a “problem” only if inconsistent IRB decisions are deemed to be a problem. If so, then requiring sponsors and clinical investigators to disclose prior review by other IRBs does not constitute a full or optimal response. Even an explicit ban on IRB shopping would not address the problem. If sponsors were limited to a “one-shot” review by a single IRB, sponsors would, in the course of time, gain experience to guide them in selecting the most hospitable IRB for a given type of research proposal. IRB shopping would not be necessary. Experienced shoppers quickly learn which stores sell what they want.

The potential for inconsistent IRB decisions is built into the regulations in their current form. If IRB shopping calls for a federal regulatory response at all, the response may need to be directed, in whole or in part, at this underlying problem.


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