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Public Comments on the Proposed Common Rule Mandate for Single-IRB Review of Multisite Research

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Abstract

We reviewed the public comments submitted in response to the Department of Health and Human Services' (DHHS's) original and revised proposal for mandated single-IRB review of federally funded multisite research to see who responded to the proposed mandate and to determine what they said and how the agency addressed the public comments in its revised proposal. Our analysis indicates that support for the single-IRB mandate was limited. The most common argument against the proposed mandate came from those concerned with the loss of site-specific institutional review board (IRB) review of the protocol for a multisite study to address issues relevant to local context. Concerns were also raised that the single-IRB approach would replace one inefficient system (that entails, for example, multiple reviews of a single study) with another potentially inefficient system (involving the negotiation and management of multiple interinstitutional agreements). Empirical research about the implementation of DHHS's final rule—and the separate rule of the National Institutes of Health—mandating single-IRB review is needed to determine whether the single-IRB model achieves the stated goals.

Keywords

multisite studies; single IRBs; local IRBs; Common Rule; research ethics; human subjects research

Several studies indicate that the human subjects review process for multisite research is inefficient when multiple institutional review boards (IRB) are involved.¹ Multisite studies are most often phase III trials designed to test the efficacy of the investigational intervention in a large number of participants. Delay in the initiation or completion of these trials may result in a delayed translation of findings (whether positive or negative) to clinicians and their patients. Consequently, delay in approval at a single institution among the multiple research sites delays the opportunity for individuals to enroll in the trial at that site, which limits the fair distribution of the benefits and burdens of research across the population of eligible participants. In addition, handling routine protocol amendments and changes across multiple sites and IRBs requires administrative capacities and costs at coordinating centers that do not translate into tangible benefits for study participants, scientists, or society. And

little is known about whether reviews by multiple IRBs enhance human subjects protections.
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Adopting a central approach for IRB review has been endorsed as a way to potentially expedite the review and oversight of multisite studies.³ The term “central institutional review board” has been used to describe a number of different models of collaborative review and oversight (in whole or in part) in which the multiple study sites rely on a single IRB of record. This IRB would be at one of the participating institutions or would be an IRB unaffiliated with the participating institutions. Different models of centralized IRB review of protocols for multisite studies have been implemented, though this approach is not yet the norm.⁴ That may change as two new federal policies mandating a single-IRB approach for multisite research are fully implemented. As of January 25th, 2018, the National Institutes of Health (NIH) has required the use of a single IRB of record for most domestic NIH-funded multisite research.⁵ And recent changes by the Department of Health and Human Services (DHHS) to the regulations governing research with humans (the Common Rule) include a provision that all domestic, federally funded cooperative research studies be reviewed by a single IRB.⁶ This change to the Common Rule goes into effect on January 20, 2020.

For this study, we examined the public comments submitted to DHHS when it first proposed in July 2011 to require the use of a single IRB for multisite studies. In an Advance Notice of Proposed Rulemaking (ANPRM) that proposed a host of changes to the Common Rule,⁷ DHHS requested public comments regarding five questions about the single-IRB approach (see table 1). There were three important caveats in the ANPRM about the proposed mandate. The single-IRB requirement would not relieve local institutions (those relying on single-IRB review) of other Common Rule requirements regarding the protection of human subjects. It also would not prohibit the IRB at each research site to provide additional local ethical review, since only review by the IRB of record would serve as evidence of regulatory compliance. And under the proposed policy, the single IRB of record would be liable for noncompliance with all review-related regulations. Local institutions would remain responsible for noncompliance of all other regulations relevant to local conduct of the studies reviewed and approved by the single IRB of record.

After reviewing the comments submitted in response to the ANPRM, DHHS (joined by 15 other federal agencies) issued a Notice of Proposed Rule Making (NPRM) on September 7, 2015,⁸ which is the last step the agency takes before deciding whether to issue a final rule. The final revisions to the Common Rule were published on January 19, 2017,⁹ with an effective date of January 19, 2018, the exception being the January 2020 date for the new requirement for single-IRB review of multisite studies. The purpose of our study was to find out who submitted comments in response to the questions DHHS posed in the ANPRM about the single-IRB approach, to learn what they thought about the proposed mandate, and to address how DHHS responded to those concerns in its NPRM and, ultimately, in the final regulation.

STUDY METHODS

We identified 1,142 public comments relevant to the ANPRM posted on the website Regulations.gov.¹⁰ Of those comments, 321 addressed the proposed single-IRB mandate as either (1) responses to Item 2 presented in the “Background” narrative in the ANPRM 2, “Utilization of a single IRB review of record for domestic sites of multisite studies”;¹¹ or (2) a general response to Item 3, “Streamlining IRB Review of Multi-Site Studies”;¹² or (3) a direct response to questions 30 to 34 (of the 72 questions asked; see table 1) specific to the proposed single-IRB mandate.¹³

Thirty-three of 321 comments about the single-IRB mandate were found to be duplicate comments; in other words, the text for each pair was identical. We found 5 comments in triplicate, and 1 in quadruplicate. The relevant text of the remaining comments (n = 275) were categorized by the type of respondent (e.g., university or pharmaceutical or biotech industry). One author (HAT) open coded the text. Open codes were further refined to develop a coding scheme that was applied to all comments related to single IRBs. The codes reflected topics covered in the specific questions that DHHS posed (e.g., advantages of adopting the mandate) and topics that emerged from the comments (e.g., concerns about the adoption of the proposed single-IRB mandate). Comments were coded only once per respondent (i.e., if a respondent indicated endorsement of the single IRB more than once, their endorsement was counted only once when tallying responses).

STUDY RESULTS

Table 2 summarizes the affiliation of the 275 respondents. Those who did not provide a professional affiliation or stated an affiliation but were not speaking on behalf of an organization were categorized as individuals. Most respondents were individuals (31%), with “university” the category given to 25% of the respondents. Other respondents included disease, professional, and pharmaceutical organizations.

Support for the single-IRB mandate.

Of the 275 respondents, 239 (87%) included a statement of support or opposition to the single-IRB mandate. We coded 75 statements (27%) as conveying support for the single-IRB mandate and 164 (60%) as opposed to it. The remaining 36 responses were coded as “unclear”; they made points for or against the mandate but did not take a side (see table 3 for sample quotations). In contrast to our findings, the NPRM states that public comments were evenly divided on the question of whether a single IRB ought to be mandated.¹⁴ The NPRM also noted that “IRB and institutional representatives tended to be opposed to the possible requirement.”¹⁵ Our results confirm this conclusion. As noted in table 2, 25% of the responses came from universities (including university human research protection programs), and respondents from this group were the least likely to endorse the mandate (12% favored the mandate).

Importance of local IRB and local context (question 31).

In answers to question 31, 137 respondents (48%) said that local IRB review is an important component of the review and oversight of multisite research. As one university respondent noted,

There are ethnic, cultural, and regional variations in issues relevant to research activities. To remove discretion from the local IRB would run roughshod over these matters, which is certainly not compatible with respect for persons. Furthermore, not all IRBs are as thorough in their examination of the protocol as others are. We have had several instances in which protocols which had been approved by one or more other IRBs were discovered to contain egregious errors.

An additional 39 (14%) respondents further specified that expertise in local and state laws would be lost in the absence of local review.

The NPRM reiterated statements from the ANPRM that mandating a single IRB does not prohibit a local IRB from conducting its own review of the research. Nor did the NPRM free the local sites from their obligations to protect the human subjects participating at their institution. The NPRM said that local considerations can inform the conduct of human subjects research but that these considerations can be addressed through mechanisms other than the IRB. The NPRM did not provide any examples of how this could occur.

Universities expressed limited support for the single-IRB mandate, raising concerns that the single-IRB approach would replace one inefficient system with another potentially inefficient system.

Regulatory and legal liability (question 32).

One-quarter of the ANPRM respondents (68) noted that a failure to clearly assign liability for regulatory noncompliance was a barrier to wider adoption of the single-IRB approach, with many adding that in a final rule DHHS should indicate with whom regulatory responsibility lies: either the local IRB or the single IRB of record that conducts the review.

While the NPRM noted that some respondents to the ANPRM pointed out that assigning liability to the single IRB may be a disincentive for IRBs to be willing to serve in that role, the DHHS also said that “[a] majority of commenters expressed an opposing view; that is holding IRBs [of record] directly accountable for compliance with the [review related] regulations would increase the comfort level of institutions in accepting the regulatory review of an external review.”¹⁶ This claim is not fully supported by our analysis of the respondents’ comments. By our count, DHHS is correct that “some” respondents (n = 10) indicated that assigning liability to the single IRB may be a disincentive for an institution to permit its IRB to be the IRB of record. However, only 13 of the 68 (19%) directly endorsed assigning liability for noncompliance with regulatory review to the IRB of record. The other 45 respondents who commented on liability did little more than affirm the statement that was embedded in the question asked; that is, they agreed that “concerns about regulatory and legal liability contribut[e] to institutions’ decisions to rely on local IRB review for multi-site research.” The proposed regulatory language in the NPRM addresses liability concerns directly. Enforcement of noncompliance with IRB-related regulations will be directed at the

single IRB of record, including independent IRBs unaffiliated with any of the institutions participating in the multisite study.

Inefficiencies of local IRB review (question 33).

More than half of the respondents (57%; 158) commented on the inefficiency of the current system of multiple IRB reviews, with the majority simply stating that the current system is inefficient. Four respondents referred to previous literature on the inefficiencies of multiple-IRB review.¹⁷ Three other respondents cited data from their own institution in support of the claims of inefficiency, with only one of these people providing data from a systematic assessment. The NPRM refers to commentators' citing long delays in the review and approval of behavioral and social science research, but only these three respondents supported this claim with reference to the empirical literature or provided data of their own to support the claim.¹⁸

Selection of the single IRB and IRB shopping (question 34).

A minority of respondents (31; 11%) indicated that IRB shopping would likely be a problem if DHHS mandated the single-IRB approach. Concern about incentives to seek out an IRB known to provide a "quick" and "lenient" review was noted by about one-third of these 31 respondents (n = 9, 5%). Seven respondents noted that clear guidance from the Office for Human Research Protections about how a single IRB would be selected could address this concern.

On a related matter, the NPRM said that the single IRB ought to be selected by the agency funding the research or, in absence of a funder, by the lead institution among those in the multisite study. Our review of the public comments indicates that only five respondents suggested that the funding agency ought to be responsible for selecting the IRB of record (see table 3). The NPRM also said that the funding agency could solicit recommendations about which IRB ought to be selected and public comments on "how this will work in practice."¹⁹ Respondents to the ANPRM provided a number of suggestions for criteria that could be used to guide the funding agency selection.

DISCUSSION

DHHS explained in the NPRM that the proposed rule was based on feedback received from many sources, including the public comments on the ANPRM. According to our analysis of the ANPRM comments alone, support for the single-IRB mandate was limited. Of particular concern, the least enthusiastic group of stakeholders for the mandate were universities, which are typically sites where research is conducted. At least one reason behind this lack of enthusiasm was concern that the single-IRB approach would replace one inefficient system (that entails, for example, multiple reviews of a single study) with another potentially inefficient system (involving, for example, the negotiation and management of multiple interinstitutional agreements). There is no empirical evidence in the academic literature—or evidence provided by any of the respondents commenting on the ANPRM—that a single-IRB approach would improve the efficiency of the IRB review process or that it would

protect the welfare of human subjects as well as or better than the existing system involving multiple IRB reviews of a protocol for a multisite study.

We also previously conducted a review of the public comments submitted in response to the NIH's proposal for the single-IRB requirement.²⁰ While the NIH's proposal was similar in intent to the policy DHHS proposed, there were some differences. The NIH proposal mandated coverage only for domestic multisite studies the agency funded; allowed applicants to identify the single IRB (subject to NIH approval); was silent on the assignment of liability but addressed cost; and, with some limitations, allowed investigators to include direct costs related to the establishment of a single IRB in grant budgets. We found 108 of the 167 (65%) responses supportive of the NIH's proposed policy, whereas 75 (27%) of the ANPRM responses were supportive of DHHS's single-IRB proposal. It is interesting to note that while the percentages of the total responses in support of the changes were very different (65% v. 27%), the absolute number of responses (108 v. 75) was not that different. Assuming that similar stakeholder groups would have known about the two proposed federal policies for the single-IRB approach, it may be that the proposed changes to the Common Rule attracted many more respondents given the breadth and scope of the changes in DHHS's proposal.

The most common argument against a single IRB in response to the proposed changes to the Common Rule came from those concerned with the loss of local IRB review, that is, review at each research site where the IRB could address concerns relevant to its local context. University-based stakeholders noted that an institution's human research protection program involves more than IRB review of protocols and ongoing studies; these stakeholders raised concerns that eliminating the IRB process at each research site would result in the loss of expertise related to state and local laws as well as familiarity with the local community from which research participants would be recruited. Yet there is no empirical evidence in the academic literature nor was any evidence provided in any of the comments that knowledge of the local community enhances the review of research or correlates with better protection of research participants. The adoption of public policy ought to be supported by the relevant stakeholders as well as be based on empirical evidence that the proposed actions will result in the intended goal—a more efficient system of human subject review that does not compromise the welfare of human subjects.²¹

At least one message was heard loud and clear from the respondents, as articulated clearly in the NPRM: that the IRB of record will be liable for any noncompliance with relevant human subjects regulations. While this clarification may come as comfort to institutions that were reluctant to cede their review responsibility to a single IRB, it is unclear how this assignment of liability will affect the willingness of a local institution, such as an academic medical center, to have its IRB assume the role of the single IRB of record. Moreover, the new policy is essentially an unfunded mandate for an IRB to assume additional administrative responsibilities. If the IRBs at academic and other not-for-profit institutions decline to serve as the single IRB of record, the federal mandates for the single-IRB approach may result in commercial IRBs' serving in this capacity.

In at least one area, the NPRM was nonresponsive to the suggestions of ANPRM respondents. Although the ANPRM did not directly ask what criteria ought to be used when selecting the single IRB, respondents offered a number of suggestions about this. The adoption of such criteria was recommended by a small number of respondents in direct response to the ANPRM query about how to prevent IRB shopping. The NPRM proposed that the funder of the research designate the single IRB of record. Only five of the ANPRM respondents suggested the funder as the stakeholder who ought to designate the IRB of record. The most common suggestion was that the principal investigator of the project designate the IRB of record.

Several ANPRM respondents also asked about how the single-IRB effort would be financially supported. This may be especially relevant if the funder designates the principal investigator's home institution as the single IRB of record. Taking on the role of a single IRB will likely require an investment of funds not addressed by the ANPRM or NPRM, though, as noted above, it was a lingering question posed in the NPRM.

The concerns that respondents to the ANPRM raised about a single-IRB mandate for multisite studies suggests that there are lingering empirical questions to consider. While there is no requirement that federal research ethics policy be evidence based, having such evidence might have alleviated the concerns of those who were unconvinced that a single-IRB approach will lead to efficiency while not jeopardizing the protection of human subjects. Now that a single-IRB approach is mandated by the NIH and the Common Rule for most federally funded multisite studies, generating empirical data about the implementation of these policies will be critical for determining whether the single-IRB model achieves the stated goals, as well and for guiding the adoption of the model for non-federally funded multisite studies.

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Table 1.**ANPRM Questions Specific to Mandate for a Single IRB for Multisite Studies**

Question 30: What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies?

Question 31: How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution's specific perspective or the needs of their population, or that a centralized IRB may not share an institution's views or interpretations on certain ethical issues?

Question 32: To what extent are concerns about regulatory and legal liability contributing to institutions' decisions to rely on local IRB review for multi-site research? Would the changes we are considering adequately address these concerns?

Question 33: How significant are the inefficiencies created by local IRB review of multi-site studies?

Question 34: If there were only one IRB of record for multisite studies, how should the IRB of record be selected? How could inappropriate forms of "IRB shopping"—intentionally selecting an IRB that is likely to approve the study without proper scrutiny—be prevented?

Table 2.

Affiliation of Single-IRB Mandate Respondents

Affiliation	N (%)
Individual	85 (31%)
University	69 (25%)
Disease organization	32 (12%)
Professional organization	31 (11%)
Hospital system	23 (8%)
Independent research organization	14 (5%)
Pharmaceutical or biotech industry	11 (4%)
State or local health department	5 (2%)
Advocacy organization	3 (1%)
International society	2 (1%)
Total	275

Table 3.

Criteria for Identifying the Single IRB

Characteristic	Number ^a	Percentage
"Institution of study principal investigator" ^b	29	39%
"Single IRB should be accredited." ^c	21	35%
"Sponsor of research should select the single IRB." ^d	5	7%
"IRB with the most experience among those participating in the multicenter trial should be selected as the single IRB."	5	7%
"IRB with relevant disease specific expertise should be the single IRB."	3	4%
"Institutions and investigators involved in the multicenter trial should together select the single IRB." ^e	3	4%
"Institution of the data coordinating center should be selected as the single IRB."	3	4%
"The IRB at the institution expected to enroll the most participants should be the single IRB."	3	4%
"OHRP and/or the NIH should select the single IRB."	3	4%
"A 'virtual' IRB made up of representatives from all sites should be created and serve as the single IRB."	2	3%
"OHRP should identify a small group of the best IRBs in the country and one of them selected as the single IRB"	2	3%

^aSome commentators had more than one suggestion.

^bTwo commentators suggested that the institution with which the PI is affiliated should not be the single IRB.

^cTwo commentators indicated that accreditation is cost prohibitive for some institutions and should not be required for an IRB to serve as the single IRB.

^dThree commentators suggested that the sponsor should not select the single IRB.

^eTwo commentators suggested that the institution and investigators involved in the multisite trial should not be the single IRB.