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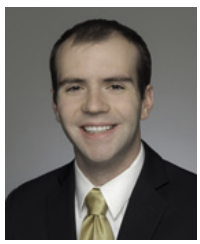
Single IRB Review: Legal and Policy Perspectives


By Haley Bavasi, David Peloquin and Mark Barnes

I. Introduction

On Sept. 8, 2015, the U.S. Department of Health and Human Services (HHS) proposed significant revisions to the Federal Policy for the Protection of Human Subjects (the ''Common Rule''), which is the set of federal regulations governing the conduct of clinical research involving human subjects.[1] HHS's Notice of Proposed Rulemaking (NPRM), joined by 15 other federal departments and agencies that subscribe to the Common Rule (thereby holding the Rule ''in common,'' the derivation of the ''Common Rule'' appellation), marks the first systematic attempt to overhaul the Common Rule since its promulgation in 1991.

One of the most significant changes set forth in the NPRM is the proposal to mandate that all domestic sites in a multi-site study rely upon a single institutional review board (IRB) as the IRB of record. Currently, institutions involved in multi-site research are permitted, but not required, to use joint review by a single IRB. In recent years, however, the regulatory atmosphere has favored moving toward single IRB review as a way to reduce duplication of effort and streamline research. While the advantages of single IRB review are well documented, commentators have noted that taking the additional step to *mandate* single review could be problematic: elaborating on the complexities of mandatory adoption, some say that eliminating local IRBs could actually degrade meaningful review by curtailing consideration for local, site-specific factors, among other concerns discussed below.

In this article, we describe the current regulatory landscape for single IRB review, the perceived advantages and disadvantages of joint review and responses to the recent shift toward mandating a central IRB for domestic multi-site research.

[1] Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53,933 (Sept. 8, 2015).

The authors are attorneys at Ropes & Gray LLP. Mr. Barnes is the faculty co-director of the Multi-Regional Clinical Trials Center of Harvard and Brigham & Women's Hospital and is a visiting lecturer at Yale Law School.

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II. Regulatory Landscape for Single IRB Review

HHS and FDA Regulation and Guidance

Current Food and Drug Administration (FDA)[2] and HHS[3] regulations governing human subjects research explicitly permit the use of joint review in multi-institutional studies. In offering this affirmative permission, the agencies have identified that at least one major goal of single IRB review is reducing the duplication of effort implicated in the traditional, de-centralized, local IRB review process. In fact, the preamble to HHS's 1979 proposed regulations protecting human subjects, the predecessor to the current Common Rule, contemplated single IRB review as a way to ''reduce duplicative review of multi-institutional studies.''[4]

In March 2006, FDA announced a pro-single IRB position in guidance for industry titled ''Using a Centralized IRB Review Process in Multicenter Clinical Trials.'' In this guidance, FDA stated that it ''hopes sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research will consider the use of a single IRB . . . , especially if using centralized review could improve the efficiency of IRB review.''[5] The intent of FDA's nonbinding guidance is threefold: it clarifies how interested parties can meet IRB requirements through central IRB review;[6] explicitly encourages reliance on single IRB review to avoid inefficiencies caused by de-centralized review,[7] including delay and increased costs associated with such coordination; and addresses certain concerns about single IRB review in the multi-site research community.[8] To these ends, FDA issued specific recommendations to assure that single IRB review complies with IRB requirements under 21 C.F.R. Part 56, including: outlining the roles and responsibilities of principal parties (*i.e.*, the institution, institution's IRB, sponsor and central IRB), including written procedures to implement the single IRB review process; addressing meaningful consideration of local factors related to the communities where the research will take place, including issues of cultural background, community attitudes about the nature of the proposed research, ethical standards of the local community, mechanisms for equitable study selection, minimizing risks to vulnerable populations and adequacy of the informed consent process; helping IRBs comply with requirements of adequate documentation, including authorization agreements documenting responsibilities between the IRB of record and participating sites; and exploring existing models and organizational arrangements for distributing IRB review responsibilities.[9] For multi-site studies interested in pursuing joint review, the guidance provides a detailed roadmap for using a single IRB without jeopardizing regulatory compliance.

Following the release of FDA's guidance, the Office for Human Research Protections (OHRP), which is the agency responsible for enforcing the Common Rule, published a ''Letter on Use of a Centralized IRB'' on April 30, 2010.[10] The letter was written in response to a medical center that was seeking guidance on the current state of regulations regarding the use of central or external IRBs. In the letter, OHRP clarifies that it ''fully agrees with the [FDA's] position on the benefits of relying on a single central IRB for multicenter research.''[11] OHRP also stated that the Advance Notice of Proposed Rulemaking it released on March 5, 2009, proposes to address precisely this issue.[12] Specifically, the 2009 Advance Notice sought to address concerns about regulatory liability for the acts or omissions of an external IRB

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[2] *See* 21 C.F.R. § 56.114 (''In complying with these [Part 56 Institutional Review Boards] regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.'')

[3] *See* 45 C.F.R. § 46.114 (''Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.'')

[4] *See, e.g.*, Proposed Regulations Amending Basic HEW Policy for Protection of Human Research Subjects, 44 Fed. Reg. 47,688, 47,700 (Aug. 14, 1979) (proposed rule), stating that the purpose of the regulation is ''to explicitly reduce duplicative review of multi-institutional studies.'' FDA has subsequently interpreted regulation 21 C.F.R. § 56.114 to establish that the ''[u]se of a centralized IRB review process is consistent with the requirements of existing IRB regulations.'' *See* FDA Guidance for Industry, *Using a Centralized IRB Review Process in Multicenter Clinical Trials* (March 6, 2006), http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127013.pdf.

[5] *See* FDA Guidance for Industry, *supra* note 4.

[6] *Id.* at 1, (''This guidance is intended to assist sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research in meeting the requirements of 21 CFR part 56 by facilitating the use of a centralized IRB review process (use of a single central IRB), especially in situations where centralized review could improve efficiency of IRB review.'').

[7] *Id.* (''Such multiple reviews by multiple IRBs can result in unnecessary duplication of effort, delays, and increased expenses in the conduct of multicenter clinical trials. Greater reliance on a centralized IRB review process, in appropriate circumstances, could reduce IRB burdens and delays in the conduct of multicenter trials.'' (internal citations omitted). ''[T]he goal of the centralized process is to increase efficiency and decrease duplicative efforts that do not contribute to meaningful human subject protection.''

[8] *Id.* (''The guidance (1) describes the roles of the participants in a centralized IRB review process, (2) offers guidance on how a centralized IRB review process might consider the concerns and attitudes of the various communities participating in a multicenter clinical trial, (3) makes recommendations about documenting agreements between a central IRB and the IRBs at institutions involved in the centralized IRB review process concerning the respective responsibilities of the central IRB and each institution's IRB, (4) recommends that IRBs have procedures for implementing a centralized review process, and (5) makes recommendations for a central IRB's documentation of its reviews of studies at clinical trial sites not affiliated with an IRB. This guidance applies to clinical investigations conducted under 21 CFR part 312 (investigational new drug application, or IND regulations).'').

[9] *Id.*

[10] Letter from Jerry Menikoff, Director, Office for Human Research Protections, to James T. McDeavitt, Senior Vice President, Carolinas Medical Center, Office of Human Rights Protection (April 30, 2010), http://www.hhs.gov/ohrp/policy/Correspondence/mcdeavitt20100430letter.html.

[11] *Id.*

[12] *Id.*

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by proposing to hold IRBs, and the institutions or organizations operating them, directly accountable for meeting certain regulatory requirements.[13] In the absence of regulations, OHRP said it was taking steps to clarify its perspective on the matter of joint review, for example, by archiving prior guidance documents that suggested OHRP favored local review, a position that it no longer holds.[14]

2011 HHS, FDA Advance Notice of Proposed Rulemaking

On July 26, 2011, HHS and FDA released an Advance Notice of Proposed Rulemaking (ANPRM) proposing to significantly overhaul the Common Rule.[15] Among other things, the purpose of the 2011 ANPRM was to request comments on the feasibility, advantages and disadvantages of *mandating* that all domestic sites in a multi-site study rely upon a single IRB as their IRB of record. The proposal would only affect which IRB would be designated as the IRB of record for institutional compliance with the IRB requirements of the Common Rule; it would not relieve any site of its other obligations under the regulations to protect human subjects.[16] Specific comments and recommendations were requested on the following issues: What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies? How does local IRB review of research add to the protection of human subjects in multi-site research studies, and how might mandating centralized review impair consideration of valuable local knowledge that enhances human subject protections? To what extent are concerns about regulatory and legal liability contributing to institutions' decisions to rely on local IRB review for multi-site research and would the proposed changes adequately address these concerns? How significant are the inefficiencies created by local IRB review of multi-site studies? And, how should a single IRB of record be selected, and could the process lead to inappropriate forms of ''IRB shopping''?[17] The ANPRM also referenced the accountability issue addressed in OHRP's 2009 ANPRM (described above), explaining that ''[t]o address institutions' concerns about OHRP's practice of enforcing compliance with 45 CFR part 46 through the institutions that are engaged in human subjects research, appropriate accompanying changes would be made in enforcement procedures to hold external IRBs directly accountable for compliance with certain regulatory requirements.''[18]

NIH Draft Policy

Continuing the trend of movement toward use of a single IRB, on Dec. 3, 2014, the National Institutes of Health (NIH) issued for comment a draft ''Policy on the Use of Single Institutional Review Board (IRB) for Multi-Site Research.''[19] While the details on scope, timing and implementation of a final policy remain uncertain, the draft policy establishes a probable directional strategy for NIH-funded studies: ''the NIH generally expects all domestic sites of multi-site, NIH funded studies to use a single IRB of record.''[20] Supporting this movement, the draft policy stakes out a strong pro-single IRB review stance for multi-site studies funded by NIH and encourages their use as a way to streamline and enhance the IRB review process, suggesting that the current practice of de-centralized review is antiquated because it follows regulations that were drafted when most clinical research was primarily conducted at a single site.[21] While the NIH Draft Policy is nonbinding, it represents the agency's current thinking and likely policy direction on the topic of single IRB review.

2015 HHS Notice of Proposed Rule Making

In the NPRM published on Sept. 8, 2015, HHS, joined by 15 other government agencies, proposed to depart from the permissive stance it has henceforth taken on the issue of single IRB review: Under the NPRM, any institution located in the U.S. that is engaged in ''cooperative research'' must rely on approval by a single IRB for the portion of the research conducted domestically.[22] The reviewing IRB would be selected by the federal department or agency supporting or conducting the research, or, if there is no funding agency, by the lead institution conducting the research.[23] The NPRM does not state explicitly whether the requirement for single IRB review in cooperative research applies to all cooperative research at an institution that receives any federal funding or only to those cooperative research projects that themselves are federally funded. The fact that the NPRM contemplates the single IRB being selected by the lead institution in the instance in which there is no federal agency funding the research suggests that the single IRB requirement is not limited to federally funded cooperative research. This may be referring to the NPRM's expansion of the Common Rule to apply to non-federally funded ''clinical trials,'' as defined in the NPRM,[24] that are not covered by another body of fed-

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[13] *Id.*

[14] *Id.*

[15] Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512 (July 26, 2011).

[16] *Id.* at 44,522.

[17] *Id.*

[18] *Id.*

[19] Policy on the Use of Single Institutional Review Board (IRB) for Multi-Site Research, Nat'l Inst. of Health (Dec. 14, 2014), http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html.

[20] *Id.*

[21] *Id.* (''The purpose of this Policy is to increase the use of single Institutional Review Boards (IRB) for multi-site studies funded by the National Institutes of Health (NIH). Its goal is to enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed efficiently without compromising ethical principles and protections.'').

[22] 80 Fed. Reg. at 53,937 (Sept. 8, 2015).

[23] *Id.* at 53,984 (''Cooperative research'' is defined as ''projects covered by this policy that involve more than one institution.''). This requirement would *not* apply to (1) cooperative research for which more than single IRB review is required by law (*e.g.*, FDA-regulated devices); or (2) research for which the federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular study.

[24] *Id.* at 53,990 (''For purposes of this policy, the NPRM proposes at § __.102(b) that a clinical trial be a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the intervention on biomedical or behavioral health-related outcomes.'')

eral human subject protections regulations, such as FDA's human subject protections oversight, but that take place at a domestic institution that receives funding for non-exempt and non-excluded research.[25] In such a case, the Common Rule would apply to the clinical trial, and thus presumably the requirement for single IRB review would also apply.[26] However, for cooperative research that is neither federally funded nor subject to this ''clinical trial'' expansion of the Common Rule, the single IRB requirement presumably would not apply.[27]

As in the 2011 ANPRM, the NPRM would make changes to allay institutions' concerns about OHRP's practice of enforcing compliance with human subject protection regulations through the institutions that are engaged in human subjects research by holding external IRBs directly accountable for compliance with certain regulatory requirements. Notably, however, as originally proposed in the 2011 ANPRM, the change would affect only which IRB would be designated as the IRB of record for purposes of institutional compliance with the IRB review requirements of the Common Rule; it would not relieve any site of its other obligations to protect human subjects and abide by the Common Rule.[28] The NPRM also would not prohibit institutions from conducting additional internal ethics reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule or binding affect on the IRB of record.[29]

III. Response to Mandatory Single IRB Review

As noted above, regulatory agencies and stakeholders alike are in agreement that single IRB review has the demonstrated potential to, among other things, increase efficiency, reduce costs and actually enhance the protection of human subjects.

However, single IRB review is not without some noted disadvantages, and the NRPM's proposal to *mandate* joint review elevates these concerns. The HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) has been at the forefront of articulating some of the most salient concerns. In its comments to the 2011 ANPRM, SACHRP stated that single IRB review for domestic sites ''assumes that all domestic sites are sufficiently similar such that a single IRB could assess the research appropriately for Common Rule purposes, and conversely assumes that all non-U.S. sites are sufficiently different that a single IRB should not similarly be required for studies that involve only those sites,'' opining that these assumptions are simultaneously over- and under-inclusive.[30] The assertion that differences among sites matters also underlies SACHRP's and other commentators' concern that consideration of local and regional variations is ''critical to assuring welfare of subjects.''[31] In other words, how can an IRB with few (if any) affinities with the potential subject populations adequately review the research and be competent to undertake meaningful consideration of the concerns and attitudes of the various communities involved in a multi-site clinical trial? Especially sensitive are those issues of equity in subject selection, risk to vulnerable populations and the adequacy of the informed consent process, which may require the expertise and input of local community representatives and study teams to navigate effectively.

In addition to these ''widely different'' subject population factors, according to SACHRP, significant variations among sites also include state laws governing categories of subjects and research data (*e.g.*, genetic testing and privacy, health information laws, mental health information and consent requirements); investigator conflicts of interest requiring varying management strategies; ''emergency research'' undertaken without subject consent, for which the FDA requires local community consultation; disparate cultural norms among populations targeted for recruitment; and varying investigator and research team experience.[32] Given these challenges, SACHRP suggests that selection of the central IRB is critical: while the 2015 NPRM ameliorates a concern that has been raised regarding ''forum shopping,'' it is unclear whether its alternative proposal to have the federal department or agency supporting or conducting the research select the reviewing IRB will guarantee that IRB has the appropriate expertise and capacity SACHRP recommends.[33]

Following the ANPRM, SACHRP provided comments to NIH's 2014 Draft Policy, which emphasized the need for more data.[34] It noted that the Draft Policy only identifies one research paper in support of the statement that single IRB use is more cost effective, and that more data are needed to assess the cost impact of joint review. It also noted that most institutions *involved* in multi-site trials are not necessarily designed for or equipped to *manage* multi-site research, and therefore

[25] *Id.* at 53,989 (''Note that the purpose of the clinical trials extension is to ensure that the clinical trials that would otherwise not be covered by some body of federal research ethics regulations are covered. To that end, if a clinical trial is already subject to FDA oversight but not Common Rule oversight, since that clinical trial is subject to human subjects protection regulations, this change would not affect it.'')

[26] *Id.* at 53,990 (''[T]he NPRM proposes changes . . . to state that the policy extends to all clinical trials defined by this policy, irrespective of funding source, that meet all three conditions: (1) The clinical trials are conducted at an institution that receives support from a federal department or agency for human subjects research that is not excluded from this policy under § __.101(b)(2), and the research does not qualify for exemption in accordance with § __.104; (2) The clinical trials are not subject to FDA regulation; and (3) The clinical trials are conducted at an institution within the United States.'')

[27] *Id.* at 53,989 (The 2011 ANPRM ''discussed the possibility of the Common Rule's being applied to *all* studies, regardless of funding source, that are conducted by a U.S. institution that receives some federal funding for human subjects research from a Common Rule agency.'' Alternatively, the ANPRM considered ''requir[ing] domestic institutions that receive some federal funding from a Common Rule agency for non-exempt research with human subjects to extend the Common Rule protections to all human subjects research studies conducted at their institution.'') Neither of these proposals was adopted in the NPRM.

[28] *Id.* at 53,984.

[29] *Id.*

[30] Letter from Barbara E. Bierer, Chairperson, SACHRP, to Kathleen Sebelius, Secretary of Health and Human Services, p. 9 (Oct. 13, 2011), http://www.hhs.gov/ohrp/sachrp/commsec/.

[31] *Id.*

[32] *Id.*

[33] *Id.* at 10.

[34] Letter from Jeffrey R. Botkin, SACHRP, to the Sylvia M. Burwell, Secretary of Health and Human Services, at Attachment F (April 24, 2015), http://www.hhs.gov/ohrp/sachrp/commsec/attachmentf:letter4/24/15.html.

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service as a central IRB would require substantial resources and costs, especially in the context of the informational technology needed to ensure adequate review, communication and oversight. Furthermore, these ''reliance arrangements'' among a central IRB and study sites require ''complex coordination and communication'' to manage how the central IRB would interact with local IRBs with respect to a host of issues. SACHRP recommends that if NIH (and by analogy, HHS) were to mandate single IRB review, a standardized process and tools need to be provided to the research community to ensure ''consistent and reasonable approaches.''[35]

While SACHRP supports the increased use of single IRB review, it has stated that a uniform mandate of single IRB review for all domestic multi-site studies is ''premature.''[36] Instead, it recommended in 2011 that a ''more measured and careful process of encouraging single IRB use, accompanied in a step-wise way by issuing guidance on critical issues involved in the use of single IRB review, would result in less disruption of the research enterprise and eventual improvements in a single IRB process that is anchored in deep collective experience.''[37]

[35] *Id.*
[36] *Id.*
[37] *Id.*

IV. Summary

There is wide agreement among regulatory agencies and stakeholders that use of single IRB review is, in general, a positive development, and research sponsors and funders already have the ability to require a central IRB for sites in a multi-site study. Moving to joint review for multi-site studies may increase efficiencies, decrease duplication of effort and institutional conflicts and allow for the differing issues that arise across study sites to be translated into insights that can lead to better science and safety for human subjects. However, for now, increased single IRB review should be facilitated using a voluntary approach in which joint review is incentivized and further data are collected and analyzed to refine and inform the adoption process. These incentives should encourage research sponsors and funders and research institutions to take advantage of the benefits of single IRB use, while ensuring that sites also have the opportunity, on a case by cases basis, to evaluate the drawbacks and costs of using a central IRB. These incentives could be tied to data and reporting requirements, so that NIH, HHS and other stakeholders can leverage valuable insights to develop effective solutions to on-the-ground problems, including the particular challenge of accounting for and addressing local variation. Without this careful planning, implementation of mandated single IRB review, as SACHRP pointed out, will likely be more complex, and could degrade the quality and effectiveness of the human subject protections that IRBs, as local review mechanisms, were designed to ensure.