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Robert Klitzman
Columbia University

Ekaterina Pivovarova
University of Massachusetts Medical School

Charles W. Lidz
University of Massachusetts Medical School

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VIEWPOINT

Single IRBs in Multisite Trials

Questions Posed by the New NIH Policy

Robert Klitzman, MD
Columbia University,
New York, New York.

Ekaterina Pivovarova, PhD
University of
Massachusetts Medical
School, Worcester.

Charles W. Lidz, PhD
University of
Massachusetts Medical
School, Worcester.

On June 21, 2016, the US government announced changes that are arguably the most significant of the last quarter century concerning the protection of human research participants—a requirement for use of central or single institutional review boards (IRBs) in multisite National Institutes of Health (NIH)-funded research. Specifically, the NIH announced a new policy (effective September 25, 2017) to mandate that nonexempt multisite research with humans funded by the NIH be reviewed by a single IRB.¹ On January 19, 2017, final amendments to the federal human research participant protection regulations (the Common Rule) were also published, requiring use of a single IRB,² although implementation will be delayed until January 20, 2020. The NIH directive seems straightforward, but effective implementation will require that institutions, researchers, and policy makers decide how to address a number of critical issues. The Common Rule amendments explicitly recognize that further guidance will need to be developed, necessitating that these stakeholders confront several dilemmas.²

Underlying the NIH single-IRB policy is the belief that the use of single IRBs for multisite studies avoids duplicate and possibly conflicting IRB reviews and thereby streamlines and accelerates the review process. Studies of local IRBs have been conducted,^{3,4} but research data supporting the benefits of single IRBs and information on how they operate and the difficulties they face remain very limited, adding to these challenges.

Of all the issues raised by the NIH single-IRB policy, the relationship between the single IRB and the participating sites is possibly the most complex. There are 3 critical aspects that academic institutions, researchers, and policy makers will have to resolve before implementation of the new policy: (1) the relationship between the single IRB and the local institutions, including the local IRBs; (2) the collection and incorporation of local knowledge in the single-IRB review; and (3) the relationship between the single IRB and local researchers. These issues involve fundamental legal, ethical, institutional, and policy tensions that will profoundly shape the costs and effectiveness of future multisite research involving human research participants.

Relationship Between the Single and Local IRBs

The NIH single-IRB policy outlines responsibilities between single and local IRBs that will apply only to NIH-funded research as of September 25, 2017, and similarly to all research with humans, through the changes to the Common Rule, as of January 20, 2020. Single IRBs will be expected to carry out the ethical review of the study and the functions required for institutional compliance with the Common Rule; whereas local IRBs will be responsible for meeting other regulatory obligations, overseeing implementation of the approved protocol, and reporting unan-

anticipated problems. However, the single and the local IRBs both retain regulatory responsibilities. Separation between the more formal Common Rule–required regulatory functions and the local responsibilities associated with broader protections of research involving humans (eg, reporting unanticipated problems, managing investigators' and institutional conflicts of interest, ensuring training in research ethics, and dealing with noncompliance) is not clearly differentiated. Decisions will need to be made regarding which responsibilities will be shared, how responsibilities will be determined, and how conflicts between the single and local IRBs will be resolved.

It is also unclear whether local IRBs will have input into single-IRB reviews, and if so, at what stage, and who will have the final say. What if the local IRB disagrees with the single IRB? The Common Rule amendments indicate that institutions may still conduct additional local-IRB reviews, but such reviews "would no longer have any regulatory status."² What this means and how such reviews might affect single-IRB reviews are uncertain.

Local IRBs and the institutions they represent will use reliance (or authorization) agreements, which cede review of research to the single IRB and its larger institution. These reliance agreements will need to address the aforementioned issues but currently vary greatly in scope and content—often to account for the practical concerns of the relying institutions, the needs of specific studies, and single IRBs' concerns about risks and attendant liabilities. Few standardized models of reliance agreements exist. Yet with limited models, the negotiation with multiple sites could take as much or more time as multiple local-IRB reviews. A national model or template might help, but whether one such agreement could work with all types of research and research institutions is unclear.

Recently, the NIH National Center for Advancing Translational Sciences proposed use of a single master reliance agreement that can be used across institutions and studies (SMART IRB platform).⁵ This reliance agreement allows for flexibility among the participating institutions and leaves the specifics of many issues to be determined on a study-by-study or protocol-by-protocol basis. However, few data exist on how the agreement would be used nationally.

Collection and Incorporation of Local Knowledge

Many issues in IRB reviews reflect state or local laws, institutional policies and resources, information about local medical standards of care, investigators' past experiences, and the demographics and vulnerabilities of the local study populations. These issues may involve small details in standards of care practices or the circumstances in which potential research participants can be approached for consent to participate in research. Single-IRB

Corresponding Author: Robert Klitzman, MD, Columbia University, 1051 Riverside Dr, Mail Unit 15, New York, NY 10032 (rlk2@columbia.edu).

members are likely to be unaware of these kinds of information that local IRB members routinely acquire in their clinical or research work.

Even though the new NIH regulations state that participating sites are expected to communicate “relevant information necessary for the single IRB to consider local context issues and state and local regulatory requirements;”² this formulation is vague and requires more specification. Delineation of the type of information that single IRBs need to have, development of mechanisms to collect and transmit local knowledge effectively and efficiently, and clarification of the roles of such contextual information in single-IRB reviews are critical.

Relationships Between the Single IRB and Local Researchers

Another issue that will need to be addressed is how single IRBs will replace the ongoing relationships and close interactions that many local IRBs have with local researchers. Currently, local-IRB members and local investigators often know each other well, enabling curbside consults and hallway conversations that help investigators understand IRB concerns and also help IRBs to appreciate investigators' needs and constraints. Visits by investigators to local IRB offices can often resolve questions and facilitate protocol reviews. Removing reviews to a remote single IRB is likely to reduce or eliminate these important informal interactions and possibly increase the time needed to approve research. If these interactions are valuable, consideration should be given to how they could be incorporated into the single-IRB model without diluting the potential efficiencies of centralized review.

Will single IRBs offer the kind of prospective help in crafting protocols that local IRBs often provide—interactions that may not always be most efficiently handled through formal mechanisms? Will single IRBs have mechanisms for responding to investigators' requests for individualized assistance regarding IRB concerns post review? If so, what kinds of mechanisms? Will investigators only be able to interact with the single IRB through their local IRB, and if so, will this change entail possible additional delays? Best practices should be developed to support single IRBs' interactions with investigators (eg, scheduled times for teleconferences between investigators and the single IRB; hotlines or other communication mechanisms). Developing, assessing, and implementing best practices will prevent each single IRB from having to reinvent these measures. Researchers may also face many expectations and demands from various single IRBs, including required use of different information technology plat-

forms, and need to provide different types of information. Development of workable communication practices could help preempt further complications and delays in protocol reviews.

Implications for a System of Single-IRB Review

If the complexities and burdens of serving as a single IRB become too great for academic or other nonprofit institutions, the NIH policy could result in a substantial increase in the number of studies being reviewed by for-profit IRBs, which may currently have the most experience serving as the IRB in multisite studies. Critics have argued that for-profit IRBs may emphasize speed rather than thoroughness of review.^{6,7} Large for-profit IRBs may do an excellent job, but no published data have been found regarding their procedures, quality, or effectiveness, and they may be resistant to undergoing outside examination.

In addition, the NIH has recognized that no system will work for all circumstances, and it has acknowledged the need for exceptions to the single-IRB requirement. The NIH stated that it will make exceptions if a “compelling justification” exists,² but it did not specify the standards or circumstances for such exceptions. The Common Rule amendments also permit a federal department or agency to determine that single IRBs are not appropriate for certain contexts, permitting local IRB review with local variations, but again, the specific criteria to be applied are unstated.

In summary, although the NIH single-IRB policy is designed to improve IRB review of multisite studies by accelerating the review process, given the number of public comments that were generated prior to the policy being finalized and the fact that the policy has been developed in the absence of the systematic collection of data, significant issues remain unresolved. These obstacles are not insurmountable, but the NIH, academic institutions, researchers, and others should begin to consider how best to address these challenges. Data regarding the process and outcomes of a single-IRB system should be collected and analyzed to formulate best practices for defining the relationships and boundaries between local IRBs and single IRBs, developing standardized ways for single IRBs to account for local practices, and establishing working relationships between single IRBs and investigators. Appropriate implementation of the NIH single-IRB policy will be key to developing an efficient research-friendly process for multisite IRB reviews that continues to ensure the protection of human research participants.

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