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Food and Drug Administration
Dockets Management Staff (HFA-305)
5360 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted electronically at www.regulations.gov

Re: Institutional Review Boards; Cooperative Research, Docket No. FDA- 2021-N-0286

The Association of American Medical Colleges (AAMC) appreciates the opportunity to respond to the Food and Drug Administration (FDA) Notice of Proposed Rulemaking (NPRM), *Institutional Review Boards; Cooperative Research* (87 Fed. Reg. 58752 to be codified at 21 C.F.R. Part 56).

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members comprise all 156 accredited U.S. medical schools; 14 accredited Canadian medical schools; approximately 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and nearly 80 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools and teaching hospitals and the millions of individuals across academic medicine, including more than 191,000 full-time faculty members, 95,000 medical students, 149,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened the AAMC's U.S. membership and expanded its reach to international academic health centers.

General Comments

With this proposed rule, the FDA seeks to adopt the mandate that most multi-site or cooperative research use a single IRB, following the lead of the "Common Rule," regulations adopted by the Department of Health and Human Services (HHS) and fifteen other departments and agencies. Federal efforts to increase the use of single IRB review were also furthered by the National Institutes of Health's (NIH) January 2018 policy requiring the use of single IRB review for multi-site research funded by the NIH. The FDA has long engaged in efforts to encourage the use of a single IRB or "centralized IRB" for multisite research as in 2006 guidance, *Using a Centralized IRB Review Process in Multicenter Clinical Trials*.¹ In justification of the current regulatory action, the FDA states that it "agrees with the Common Rule Departments and Agencies that the benefits of single IRB review — including a streamlined review process, reduced administrative burdens, and increased efficiencies — are unlikely to be realized if reliance on a single IRB for review of cooperative research remains purely voluntary."² However, despite the support for mandating single IRB review, the FDA also raises concerns, noting that "for some types of research, we do not believe it is clear that the potential benefits of single IRB review outweigh the potential associated burdens in every circumstance."³

¹ Department of Health and Human Services, Food and Drug Administration, Guidance for Industry, Using a Centralized IRB Review Process in Multicenter Clinical Trials (March 2006).

² 87 Fed. Reg. 58756.

³ *Id.*

The AAMC shares these concerns about a sweeping single IRB mandate and has noted them in responses to the Common Rule ANPRM, NPRM, as well as the NIH single IRB draft policy, where we wrote: “Despite our support for the increased use of single IRBs for multi-site trials, we believe that the implementation of this policy as drafted will not accomplish the NIH’s laudable goals, but may instead increase costs, shift administrative burdens, and encourage the development of ‘shadow’ IRB reviews to fill in the gaps left by insufficient guidance on how to create many simultaneous reliance agreements and relationships.”⁴

The academic institutions that implemented the single IRB requirement embedded in the Common Rule and NIH policy now have a better sense of its costs, burdens, and benefits, and could provide the FDA with the opportunity to more fully understand whether the assumptions of increased efficiency and better protections of human subjects have been realized as a result. **Therefore, the AAMC recommends that the FDA adopt a two year implementation period prior to the effective date of the single IRB requirement and use that time to evaluate whether additional guidance, exceptions, or flexibilities are warranted.**

Activities to Support Data Collection and Regulatory Decision-Making

In gathering responses for this NPRM, AAMC has heard both appreciation for greater harmonization of the FDA human subjects regulations with the Common Rule and hesitation at whole-heartedly recommending that the FDA implement the requirement for, rather than facilitation of, single IRB review of cooperative research. In large part, this stems from the lack of data definitively supporting the assumption that single IRB review is in all cases more efficient, at least equally protective, and less administratively burdensome than local IRB review. This lack of data could be remedied through a collaborative effort. Notably, the FDA has expressed an interest in collecting data to inform its decisions about whether to adopt certain aspects of the revised Common Rule (such as the exceptions). We support the collection of this information, whether through a pilot study or survey. **While there are individual institutions and some organizations seeking to better understand the impact of single IRB review mandates through research, we recommend that the FDA, in partnership with OHRP, establish a formal evaluation project collecting experiential data related to single IRB review.**

The AAMC, in response to both the Common Rule NPRM and NIH single IRB draft policy, recommended HHS and NIH “run a pilot program with a select group of institutions and studies to measure the true costs, benefits and consequences of greater adoption of single IRBs.”⁵ We respectfully reiterate this recommendation and suggest that the FDA and HHS establish a formal pilot program to measure the costs, benefits, and consequences of the single IRB model and develop potential guidance based on the results instead of relying on anecdotal or insufficient evidence. The AAMC has experience with regulatory evaluation and would be happy to assist the FDA in this effort.⁶

Challenges and Impact of Exceptions on FDA and HHS-Regulated Research

With respect to exceptions from the single IRB requirement, the FDA has proposed adopting two exceptions from the revised Common Rule, and proposes three new exceptions that would allow multisite research to be reviewed by local IRBs: cooperative research involving a highly specialized the FDA-

⁴ AAMC Comments, Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, Notice number NOT-OD-15-026 (January 2016) <https://www.aamc.org/media/11776/download?attachment>.

⁵ AAMC Comments, Notice of Proposed Rulemaking: Federal Policy for the Protection of Human Subjects, published in the September 8, 2015 Federal Register (80 FR 53933), Number HHS-OPHS-2015-0008, <https://www.aamc.org/media/11936/download?attachment>.

⁶ See, AAMC Conflicts of Interest Metrics Project, <https://www.aamc.org/metrics-project> (Accessed Dec. 20, 2022).

regulated medical product, cooperative research on drugs exempt from the IND regulations under 21 C.F.R. Section 312.2(b), and cooperative research on medical devices that meets the abbreviated requirements or the requirements for exempted investigations. The FDA has asked for comment on the use of these exceptions and notes that both the revised Common Rule and the FDA’s proposed rule permit the use of a single IRB for review and approval of cooperative research even if an exception applies. We appreciate the difficulty in striking the right balance between increasing flexibility with respect to IRB review and ensuring consistency across related regulations. We note that any variation in exception language increases the chances that a multisite research project subject to both sets of regulations could have a local IRB review under one framework and a single IRB mandate under another. Unless there is a regulatory allowance under the Common Rule for honoring an exception made by the FDA, this result is untenable. **We understand the FDA’s rationale that single IRB is not appropriate or is impracticable for certain FDA-conducted or supported research. However, in the interest of reducing confusion and regulatory burden across the research community, we encourage the FDA to remain consistent with the revised Common Rule when developing exceptions, and work jointly with OHRP to expand the exceptions so that reasonable and practical exceptions to the requirement are implemented consistently by the FDA and OHRP.**

We note that the FDA has not proposed adopting the Common Rule exception providing that a “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 context” given its limited applicability to the FDA-regulated research.⁷ This exception in the Common Rule, however, could provide an opportunity to reduce confusion and have true harmonization. A blanket determination or guidance document from OHRP holding that a single IRB is not appropriate in the context of an exception granted by FDA under its regulations would circumvent the scenario described above.

SACHRP has also provided HHS with its thinking on “potentially appropriate exceptions to the single IRB requirement” in response to the OHRP’s single IRB draft guidance, suggesting that OHRP consider other possible exceptions to the single IRB requirement in addition to those recommended.⁸ The AAMC in response to the same draft guidance recommended OHRP develop a plan to evaluate the effectiveness of the single IRB approach. These and other recommendations made to both OHRP and the FDA could form the basis for truly harmonized exceptions.

Specific Populations and Local Context

The FDA has requested comment on whether it is appropriate to include an exception for cooperative research when a single IRB is unable to meet the needs of specific populations (“for example, [...] research that involves recruiting members of a distinct patient population or community [...] for which the local perspective is particularly important if the single IRB of record is unable to obtain sufficient supplemental information to consider that community’s needs.”⁹). The FDA also emphasizes that “mechanisms other than a separate local IRB review and approval can be used to address local contextual issues, such as the local site providing the single IRB of record with information on local context and updates, when appropriate.”¹⁰

We believe the FDA’s proposed exception is appropriate, especially given the unique role local IRBs play in the understanding of community perspectives that could impact research design or enrollment. However, while there are benefits to the use of local context to inform the single IRB

⁷ 87 Fed Reg. 58758.

⁸ SACHRP, *Recommendations on the Draft Guidance for Use of Single Institutional Review Board for Cooperative Research* (July 21, 2022).

⁹ 87 Fed. Reg. 58759.

¹⁰ 87 Fed. Reg. 58756.

process, the regulated community would need more guidance from the FDA on when this exception could be applied or when FDA expects that no exception would be granted but a single IRB would be provided with local context from individual sites. This lack of clarity complicates the implementation of an already complicated requirement.

As we highlighted in our comments to NIH on the single IRB draft policy: “there will undoubtedly be times when circumstances will warrant the local review to ensure the protection of human subjects.”¹¹ The issue of local context is also one whose importance is gaining wide recognition across the research community in light of the increasing relevance of cultural, religious, political, and sensitive/controversial issues in research.¹² Recent convenings on the use of single IRB review have highlighted both the benefits and challenges associated with local IRB review,¹³ and the AAMC in recent comments to OHRP has also noted several areas that could be further addressed, including:¹⁴

- Assessment of local context information across various trial sites
 - Identification of the appropriate entity or entities responsible for the collection, assessment, and dissemination of local context information (e.g., chief investigator, institution official)
 - Uniform communication of local context information across study sites
- Variation in community standards across study sites and mechanisms for resolution if there are differing standards, opinions, or state/local laws
- Community standards that impact local context might include population characteristics, language, literacy, and cultural views
- Consideration for the variation in these standards and impact on participant recruitment and retention, informed consent, safety monitoring and standards of care

The OHRP draft guidance on single IRB review dedicates a section to local context issues and additional guidance on single IRB review. **The FDA should join these efforts on how local context could be better incorporated into the single IRB review process, establishing clearer mechanisms for institutions to address these concerns.**¹⁵

IRB Expertise and Supplemental Knowledge

The NPRM requests comment on issues related to IRB competence, requisite expertise, and supplemental knowledge. Notably, both the revised Common Rule and the proposed FDA regulations have similar language regarding the appropriate and relevant expertise of IRB members and are clear that the IRB should invite individuals with expertise to assist in the review of issues beyond the expertise of the existing IRB membership.

The invitation of experts familiar with a specific type of research or issue area can be essential for an IRB’s understanding whether the risks of participation are reasonable in relation to anticipated benefits. In

¹¹ Supra Note 4.

¹² Klitzman, R., et al., “Local Knowledge and Single IRBs for Multisite Studies: Challenges and Solutions,” *Ethics & Human Research* 41, no. 1 (2019): 22-31. DOI: 10.1002/eahr.500003.

¹³ Exploratory Workshop, Practical and Ethical Considerations for Single IRB Review; Office for Human Research Protections, Department of Health and Human Services (September 2020).

¹⁴ AAMC Comments, Use of a Single Institutional Review Board for Cooperative Research Draft Guidance, Docket No. HHS-OASH-2022-0011 (August 26, 2022), <https://www.aamc.org/media/62301/download?attachment>.

¹⁵ Office for Human Research Protections, Use of a Single Institutional Review Board for Cooperative Research (July 1, 2022), <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-use-single-institutional-review-board-for-cooperative-research/index.html> (Accessed Dec. 20, 2022). In AAMC’s comments to OHRP, we also recommend HHS create additional opportunities to inform potential guidance such as an in person or virtual convening similar to the HHS Exploratory Workshop identified in Note 13.

some cases, a single IRB review would not be sufficient, especially if the subject population at different sites is distinct. We support the FDA entertaining an exception in these circumstances, and encourage the FDA to ensure that when research that falls under the Common Rule as well, there is a clear mechanism for FDA to communicate that this exception has been granted. Further, there might be instances where this exception is insufficient to address the needs of specific studies, such as when a “specialized IRB,” where a majority of a committee consists of such experts, is warranted.¹⁶

Similar to our previous recommendations related to specific populations and local context, it would be helpful if the FDA provided examples of specific circumstances to help the regulated community determine when this exception could be used as well as when an alternative avenue might be more suitable. Finally, we caution the use of the term “supplemental knowledge” to refer to the information or expertise needed in these situations. Specifically, the use of the word “supplemental” fails to take into account that local and community perspectives that are already integrated in the review process and are considered fundamental, not supplemental or additional.

Cooperative Research and Number of Investigational Sites

The AAMC agrees that with a small number of sites, requiring a single IRB review process could add complexity and inefficiency to the IRB review without an increase in research protections.¹⁷ The FDA has requested feedback about whether there should be an exception for a small number of investigational sites, citing SACHRP’s recommendation that “five or fewer sites should be considered as potentially appropriate for the exception to the single IRB review requirement.”¹⁸

As described above, there is insufficient data available to understand whether the benefits of single IRB are realized when there are two or more sites, five or more, or ten or more. We find the SACHRP recommendation to be a reasonable one but reiterate the recommendation that data from the institutional experiences of implementing the existing single IRB policies inform the decision about when an exception to the policy is warranted.

Effective Date

The AAMC recommends that the FDA single IRB requirement become effective two years after the final rule is published, rather than the one year as proposed. Notably, the compliance date for the cooperative research provision in the revised Common Rule was two years from the effective date. While the regulated community now has previous experience with single IRB implementation, they will need time to develop trainings and modify policies and processes as well as relationships with industry sponsors. This poses a significant burden on the research community and recommend extending the effective date to two years to enable meaningful transition and minimize foreseeable burden. The FDA also proposes that the single IRB requirement only apply to FDA-regulated cooperative research approved by an IRB on or after the proposed effective date, which we believe is appropriate.

¹⁶ We note that SACHRP has raised similar concerns in its comments to this NPRM: Recommendations on 87 FR 58752: Institutional Review Boards; Cooperative Research, <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/87-fr-58752-institutional-review-boards-cooperative-research/index.html> (Accessed December 20, 2022).

¹⁷ SACHRP, Recommendations on the Draft Guidance for Use of Single Institutional Review Board for Cooperative Research (July 21, 2022), <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-july-25-2022-letter/index.html> (Accessed Dec. 20, 2022).

¹⁸ *Id.*

Additional Considerations

The AAMC has received thoughtful feedback on this NPRM from its member institutions which has helped inform these comments. We note that the FDA has indicated that it plans to undertake additional rulemaking to harmonize its regulations with the revised Common Rule and encourage additional opportunities to engage the research community to ensure guidance and clarifications are in place prior to this rule's proposed effective date. It would also help ensure the FDA's goals to "streamline the review process without compromising human subject protections" and "reduce administrative burden in cooperative research" are met.¹⁹

The AAMC sincerely appreciates the opportunity to comment on this NPRM. We also appreciate the FDA's acknowledgment of the thoughtful comments from academic medical centers and research institutions describing the benefits and burdens of single IRB review.²⁰ If the FDA would like additional opportunities to hear directly from the academic medicine community, especially concerning the areas in the proposed rule where the agency has indicated a need for data and/or current examples to support its decision-making, such as local context or exceptions to single IRB review, the AAMC would be glad to assist in these efforts. Please feel free to contact me or my colleagues Daria Grayer (dgrayer@aamc.org) or Heather Pierce (hpierce@aamc.org) about these comments or other ways in which we can help.

Sincerely,

A handwritten signature in blue ink, appearing to read "Ross E. McKinney, Jr., MD". The signature is fluid and cursive, with a distinct "MD" at the end.

Ross E. McKinney, Jr., MD
Chief Scientific Officer

cc: David J. Skorton, MD, President and Chief Executive Officer

¹⁹ 87 Fed. Reg. 58755.

²⁰ *Id.*