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Jerry A. Menikoff, MD, JD
Department of Health and Human Services
Division of Policy and Assurances
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: Use of a Single Institutional Review Board for Cooperative Research Draft Guidance, Docket No. HHS-OASH-2022-0011

Submitted electronically at www.regulations.gov

Dear Dr. Menikoff:

The Association of American Medical Colleges (AAMC) appreciates the opportunity to comment on the draft guidance from the Office of Human Research Protections (OHRP) related to the requirement that federally funded multisite research use a single institutional review board (IRB) review. This Cooperative Research provision (45 CFR 46.114) continues to stimulate discussion across the research community on how to meet the requirements and implement best practices for quality IRB review. We appreciate OHRP's efforts to clarify specific aspects of the provision.

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.

Since the 2018 publication of the revisions to subpart A of 45 CFR Part 45, known as the Common Rule (2018 Requirements), OHRP has released several resources to assist the regulated community with implementation and compliance (e.g., decision charts or FAQs).¹ In AAMC's comments to OHRP on the *Delay of the Revisions to the Federal Policy for the Protection of Human Subjects*, we emphasized the need for the immediate issuance of agency guidance given the complexity of the revised regulations.² We continue to encourage OHRP to issue additional guidance on other key requirements that are of importance to the research community.

¹ See also, *Exploratory Workshop, Practical and Ethical Considerations for Single IRB Review*; Office for Human Research Protections, Department of Health and Human Services (September 2020).

² AAMC Comments, *Federal Policy for the Protection of Human Subjects: Delay of the Revisions to the Federal Policy for the Protection of Human Subjects*, Docket Number HHS-OPHS-2017-0001; <https://www.aamc.org/media/12251/download?attachment> (March 2018).

Research Not Supported or Conducted by a Common Rule Agency (Section 2)

The Common Rule requires that “each institution engaged in research that is covered by [the Common Rule] [...] shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements of this policy.”³ The Federalwide Assurance (FWA) is the only assurance accepted by OHRP and approved for use across other Common Rule departments and agencies. In an attempt to provide additional clarity on the assurance process, the Draft Guidance notes that “research that is not supported or conducted by any Common Rule agency is not subject to the single IRB requirement even if one (or more) of the institutions [has checked the FWA box].” We note that in the final rule announcing the revisions to the Common Rule, OHRP included the following announcement:

“[...] [a]n additional, a nonregulatory change that was described in the NPRM will be made to the assurance mechanism. The prior option that enabled institutions with an active FWA to ‘check the box’ (described in section IV.A above) is being eliminated. Importantly, institutions could, if they so desire, continue for purposes of their own internal rules to voluntarily extend the regulations to all research conducted by the institution, but this voluntary extension will no longer be part of the assurance process and such research will not be subject to OHRP oversight. We expect this change to have the beneficial effect of encouraging some institutions to explore a variety of flexible approaches to overseeing low-risk research that is not funded by a Common Rule department or agency, without reducing protection of human subjects, thus furthering the goal to decrease inappropriate administrative burdens.”⁴

We recommend that OHRP clarify whether this nonregulatory change was implemented, and if not, whether it will be eliminated in the future or if the agency has changed its recommended approach to “checking the box.”

Notably, in the Assurance Process FAQs (2018 Requirements), OHRP states that “[i]nstitutions engaging in research conducted or supported by non-HHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question.”⁵ The Draft Guidance goes a step further, with helpful clarification on the specific application of the single IRB requirement on research not supported or conducted by any Common Rule agency. While it is clear in this Section that research not supported by a Common Rule department or agency does not need to follow the single IRB requirements, it would benefit from an example, such as research under the jurisdiction of the Food and Drug Administration (FDA) but not federally funded.

Although not a specific topic of this guidance, the AAMC notes that despite the mandate from the 21st Century Cures Act,⁶ the relevant FDA regulations are not yet harmonized with the Common Rule. Related, while the FDA’s guidance *Using a Centralized IRB Review Process in Multicenter Clinical Trials* encourages the use of a single IRB to avoid duplication of effort,⁷ FDA multi-site research does not currently require a single IRB review. Until the FDA aligns its regulations on human subject protections with the 2018 Regulations, the regulated community is subject to differing requirements causing potential confusion and an increase in administrative burden. In the AAMC’s comments to OHRP in response to

³ 45 CFR 46.103(a).

⁴ United States, Department of Health and Human Services, et. al. *Federal Policy for the Protection of Human Subjects*, 82 FR 7149 (<https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects#p-443>, last visited August 25, 2022).

⁵ Department of Health and Human Services, Office for Human Research Protections, *Assurance Process FAQs*, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/assurance-process/index.html> (last visited July 28, 2022).

⁶ Section 3023 of the 21st Century Cures Act (P.L. 114-255).

⁷ 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).

both the *Common Rule Notice of Proposed Rulemaking*⁸ and *Delay of the Revisions to the Federal Policy for the Protection of Human Subjects*,⁹ we encouraged the swift initiation and finalization of rulemaking to harmonize HHS and FDA human subjects protection regulations. If aligned, the single IRB requirement is one that would have an appreciable benefit on the research community. We would like to use this opportunity to encourage OHRP to coordinate with the Secretary's Advisory Committee on Human Research Protections (SACHRP) Subcommittee on Harmonization and the FDA to swiftly move this process forward.

Decision-Making for Purposes of Regulatory Compliance (Section 3)

We appreciate that the process for identifying and selecting the single IRB of record is complex, requiring consideration for institutional procedures, policies, capacity, and expertise, among other factors. It is clear there is not a “one size fits all approach” to the determination process (45 CFR 46.114(b)(1)) and appropriately, in this Section, the Draft Guidance does not prescribe how Federal departments, agencies, or institutions should make these decisions providing ample flexibility. However, as suggested in our response to the Common Rule NPRM, we would like to reiterate here that OHRP should “create or fund resources and tools that facilitate collaboration, cooperation and greater efficiencies, perhaps allowing the central review of multi-site studies through an online platform.”¹⁰ There is a continued need for large scale community discussions, webinars, and town hall meetings to ensure Common Rule departments and agencies, as well as institutions are able to share best practices and efficiently navigate the single IRB review process.¹¹ An example convening that is worth emulation is the 2020 *OHRP Exploratory Workshop, Practical & Ethical Considerations for Single IRB Review*.¹²

Additional Internal IRB Review (Section 5)

The Draft Guidance states that “an institution may conduct additional internal IRB reviews of the research activities in which the institution is engaged, although such reviews would not have any regulatory status in terms of compliance with the 2018 Requirements.” While OHRP recommends a mechanism for communicating with the single IRB (i.e., “the institution conducting the additional internal IRB inform the single IRB about the decision and determinations”), we believe an “additional internal IRB review[]” would cause confusion, potential duplication of effort, and unnecessary burden on both the institution’s human research protection program as well as the single IRB. We recommend removal of this statement from the Draft Guidance.

Local Context (Section 8)

The Draft Guidance states that “[w]hile the phrase ‘local context’ is not a regulatory term nor is it defined by the 2018 or the Pre-2018 Requirements, OHRP regards ‘local context’ for proposed research as generally referring to local circumstances, preferences, and variability, and could include such factors as culture and language, geography, socioeconomic factors, the professionals conducting the research, the institutions where the research will be conducted, or local standards of care.”

⁸ 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); <https://www.aamc.org/media/11936/download?attachment> (January 4, 2016).

⁹ Supra Note 2.

¹⁰ Supra Note 8.

¹¹For example, this might include discussions regarding local context; impact of state and local laws; training and education efforts; financial considerations; implementation and updates to electronic systems; communication with relying sites, staff qualification and expertise.

¹² Supra Note 1.

We appreciate OHRP’s inclusion of local context in the Draft Guidance, especially given the growing recognition across the research community with respect to the importance of incorporating local circumstances and variability in study design and conduct. Notably, there was extensive discussion at the July 2022 SACHRP meeting on local context as it relates to this Draft Guidance. The Committee noted that while local context is not formally defined in the 2018 regulations, OHRP accounted for local context in the drafting of the revisions to the regulations.¹³ The Committee also recommended elaboration on the ways local context could be accounted for in the single IRB review process, particularly in the approval decision for a study. We support SACHRP’s request for further articulation in the Draft Guidance, and as an example, the following could also be addressed:

- **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 or opinions**
 - Community standards that impact local context might include population characteristics, language, literacy, and cultural views
 - Consideration of the variation in these standards and impact on participant recruitment and retention, informed consent, safety monitoring and standards of care

Finally, in reference to single IRB membership, the Draft Guidance states that “[t]he single IRB membership must also include sufficient diversity of race, gender and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of the research subjects, which may be part of local context (§ 46.107(a)).” While we strongly support the promotion of diversity of IRB staff and committee members and agree with OHRP that diversity plays a critical role in addressing local context issues, we believe it is *only one* mechanism to ensure local context issues are appropriately addressed in order to “safeguard[] the rights and welfare of the research subjects.”

State and Local Law (Section 9)

Under the 2018 Requirements, IRBs must assess the applicability of state and local law on proposed research to make determination requirements (45 CFR 46.111). We agree with OHRP that while there are “multiple approaches” IRBs can utilize to acquire information on state and local law, IRBs “should have the flexibility to obtain this information in the most efficient manner [...]”

In consideration of the need for flexibility and efficiency, we believe there is a corresponding need for greater access to this information. In SACHRP’s comments to OHRP on the *Consideration of Local Context with Respect to Increasing Use of Single IRB Review (2013)*, the Committee recommended HHS develop and maintain a compendium of state law and other resources pertaining to human subjects research due to the “critical need.”¹⁴ We also encourage the development of a compendium or common

¹³ For example, the 2018 Regulations apply only to institutions based in the United States. *Also see*, exception for research governed by tribal law (45 CFR 46.114(b)(2)(i)).

¹⁴ Attachment A: *Consideration of Local Context with Respect to Increasing Use of Single IRB Review* <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2013-january-10-letter-attachment-a/index.html> (last visited August 25, 2022).

resource that can be used as a reference aid when assessing the effect of state and local law on research, especially given the rapidly changing landscape of state privacy laws.¹⁵

The AAMC supports OHRP's efforts to provide Draft Guidance on an important aspect of the 2018 Requirements and recommends continued stakeholder engagement to expand on areas in this Draft Guidance that would benefit from additional clarification and precision (e.g., delegation and definition of roles and of responsibilities, especially pertaining to local context issues). We also recommend OHRP prioritize the development of a plan to routinely evaluate the effectiveness of the single IRB approach, a suggestion that was also offered in our response to the Common Rule NPRM.¹⁶

We would be happy to discuss these comments or provide additional details on any of our recommendations. If we can be of assistance, please do not hesitate to reach out to me or my colleagues Daria Grayer (dgrayer@aamc.org) or Heather Pierce (hpierce@aamc.org).

Sincerely,

A handwritten signature in blue ink that reads "Ross E. McKinney, Jr., MD". The signature is written in a cursive style with a large initial "R" and "M".

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

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

¹⁵ Per the 2018 Requirements, "when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data" (46.111 (a)(7)).

¹⁶ Supra Note 8.