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OFFICE OF THE VICE PRESIDENT – RESEARCH AND INNOVATION

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Sent via https://www.regulations.gov/document/FDA-2019-N-2175-0001/comment

December 20, 2022

Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
North Bethesda, MD 20852

RE: Docket No. FDA-2019-N-2175 for "Institutional Review Boards; Cooperative Research." (September 28, 2022)

Dear Dr. Califf:

I write on behalf of the University of California (UC) system in regards to the Notice of Proposed Rulemaking (NPRM) titled "Institutional Review Boards; Cooperative Research" published in the Federal Register on September 28, 2022.

The UC system is comprised of ten research-intensive campuses, six medical schools, and three affiliated U.S. Department of Energy national laboratories. As a system, UC receives approximately $7 billion annually of extramural awards to support research conducted throughout all UC locations, with nearly half of the funds supported through federal funding.[1]

We appreciate the work of the Food and Drug Administration (FDA) to harmonize regulations pertaining to the review of cooperative research by a single institutional review board (IRB) with those of the Federal Policy for the Protection of Human Subjects ("Common Rule"). UC has extensive experience in single IRB reviews and was among the first in the country to offer the option of single IRB for multi-site studies that ordinarily would require separate IRB reviews at each participating site. All ten UC campuses and the Lawrence Berkeley National Laboratory signed an MOU to facilitate multi-UC single IRB review in 2009. Based on our experience, we offer to FDA some general feedback as well as specific input on the listed cooperative research exceptions.

[1] University of California Accountability Report 2022:
https://accountability.universityofcalifornia.edu/2022/chapters/chapter-9.html

General Feedback

1. Need for Updated Data on the Administrative Burden and Financial Costs of Single IRB

UC appreciates that the goal of implementing a single IRB requirement is to increase efficiency; however, little to no data exists that establishes the benefits and drawbacks of this approach. In UC's experience, single IRB review often results in a burden shift rather than a burden reduction, and can be at times more confusing and cumbersome for investigators and IRBs alike. To utilize a single IRB, study teams must learn a new IRB review process, likely including a new electronic submission system, coordinate single IRB processes and requirements at their participating institution, and maintain communication with their local IRBs. In addition, the Human Research Protection Program (HRPP) for the single IRB, is responsible for serving as the communication hub for all participating sites throughout the lifespan of a project. HRPPs for the single IRB need to determine a mechanism for communicating review decisions, reportable events, and local considerations to all collaborating sites and their investigators. Variances in administrative procedures or institutional requirements at participating sites cause delays and administrative burden. Thus, single IRB does not necessarily reduce IRB review time nor provide further protections for research participants.

The FDA's Preliminary Economic Analysis of Impacts states that "This proposed rule should reduce the administrative and coordination costs of conducting FDA-regulated cooperative research by: (1) reducing duplicative reviews; (2) facilitating an earlier start of cooperative research; and (3) reducing the need to reconcile variability in IRB review decisions for cooperative research conducted with a common protocol. Reducing the costs of conducting cooperative research should reduce the costs of FDA-regulated medical product development and facilitate an earlier start of cooperative research, which could contribute to a faster introduction of those products into commercial use." We find this information misleading as the FDA utilized data to estimate costs of the proposed rule based on information from 2017 or prior years. In fact, the strongest evidence that FDA utilizes for their economic impact analysis was from a study published in 2017 where Western IRB (a commercial entity) was selected as the single IRB. However, this was during a time period when federal policies did not mandate a single IRB, but rather awarded funding for developing new processes for single IRB review. (The Common Rule required compliance with the cooperative research rule in January 2020, and the NIH Single IRB Policy applied to grant applications on or after May 2017.) With references cited in the Regulatory Impact Analysis Report based on data prior to the mandated use of single IRBs, we find this misleading and not representative of the single IRB ecosystem where largely institutions of higher education, with varying electronic submission systems and institutional requirements, serve as the single IRB.

UC, therefore, requests that FDA gather current data to assess the single IRB process, and any associated administrative burden and cost. The information produced from this assessment can be utilized to add future exceptions to FDA's cooperative research rule that would not require a formal exception process.

2. Clarification on Scope of Cooperative Research Rule

It is unclear from the provided information whether the FDA intends to apply the proposed cooperative research provision for only Clinical Investigations or also ancillary projects that are reviewed by IRBs under the FDA's regulations, which do not traditionally qualify as "research" (e.g. expanded access, compassionate use, humanitarian use device, etc.). For example, 21 CFR 312.305(c)(4) states "In all cases of expanded access, investigators are responsible for… ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter." Would it be the FDA's interpretation that Individual Patient, Intermediate-Size Patient Populations, and Treatment Protocols would all be reviewed by a single IRB if more than one institution were participating? **To address this complication, UC recommends that the FDA have an exception from the cooperative research requirement for all single-patient expanded access INDs and single-patient compassionate use IDEs.**

Exceptions to the Cooperative Research Requirement

1. <u>Exception involving a highly specialized FDA-regulated medical product for which unique, localized expertise is required.</u>

UC believes that the exception for cooperative research involving a highly specialized FDA-regulated medical product undermines the efficiencies of single IRB review. If this exception were in place, local IRBs would still have to reach out to the same handful of experts and would ultimately place greater burden on the regulated community. As such, we do not believe the FDA should create an exception for research involving a highly specialized FDA-regulated medical product.

Connectedly, FDA is requesting comment on whether it is appropriate to include an exception for cooperative research for which use of a single IRB is unable to meet the needs of specific populations. UC recommends that the FDA reframe the exception for research involving a highly specialized FDA-regulated medical product as an exception for "Cooperative research for which a single IRB is unable to meet the needs of specific populations." There should be a high standard applied to enable access to this exception, so that the exception does not become so heavily used that it undermines the efficiencies of a single IRB mechanism. A local institutional IRB is best positioned to ensure the welfare and protection of subjects, such as when there are special needs of the subject population or when the research topic involves political, controversial, or sensitive issues. **As such, UC requests that local, institutional IRBs be allowed to have discretion to decline a reliance based on these grounds.**

2. <u>Exception for research on drugs exempt from IND regulations under 21 C.F.R. § 312.2(b) and exception for research on medical devices that meets the abbreviated requirements 211 under 21 C.F.R. Section 812.2(b)</u>

In agreement with SACHRP, UC urges FDA to omit the proposed exceptions for IND-exempt studies, NSR studies, and IDE-exempt studies. UC believes that such exceptions are likely to create new areas of confusion. In addition, UC is skeptical of FDA's reasoning that studies conducted under INDs or IDEs are more likely to benefit from the increased efficiencies of the single IRB process than studies not requiring a submission to FDA (i.e., IND-exempt studies, NSR studies, and IDE-exempt studies). We believe that the requirements for mandating single IRB should not be based on whether an IND or IDE application will be submitted to FDA. **As such, we ask that the FDA <u>not</u> include these two exceptions.**

3. Exception for research with a small number of investigational sites

FDAs asks whether it is appropriate to include an exception for cooperative research with a small number of investigational sites (e.g., five or fewer). **UC believes it would be appropriate to include an exception for cooperative research with a small number of sites.** In UC's experience, unfunded investigator-initiated collaborations in particular would benefit from this exception. This exception would also reduce administrative burden across the institution. We ask though that if the FDA were to allow for this exception that the FDA maintain the language that specifies a "small number of sites" rather than giving a definitive number of sites (such as "five or fewer"). We think that the IRB is in the best position to determine whether a small multi-site trial should warrant an exception to the cooperative research requirement rather than arbitrarily selecting a specific threshold for a number of sites. As a practical matter, if an exact limit is set, for example five sites, some may specifically choose to limit their study to only five participating sites in order to meet the exception. This would limit the applicability of the results of the study, and deter from the overall objective of the FDA.

4. Exception for unique challenges to use of a single IRB review model for FDA-regulated cooperative research that could not be addressed by FDA's proposed exceptions

FDA requests comments on whether there are unique challenges to use of a single IRB review model for FDA-regulated cooperative research that could not be addressed by FDA's proposed exceptions. **We ask that the FDA allow local IRBs the discretion to decline a reliance. For example, in cases where the lead researcher/ PI has prior compliance issues, the local IRB may want to be directly involved in the review process or review of investigator-initiated trials. In addition, we kindly request that IRBs of institutions of higher education who are closely familiar with the single IRB practices be given the latitude to request exceptions based on the efficiency of the established process and that those exceptions be granted with leniency and confidence in the IRB's ability to assess the situation.**

Reliance Agreements

UC appreciates that the FDA recognizes flexible ways in which reliance agreements can be achieved, such as through "a written agreement between the institution and the IRB" or "by implementation of an institution-wide policy directive." However, in UC's experience, reliance agreements are increasingly used as a vehicle to legally shield institutions from a range of unforeseen problems rather than focusing on delineating responsibilities between the reviewing and relying IRBs. We ask that FDA make clear that the purpose of a reliance agreement is to explain the respective roles of the participating institutions. Language beyond that is unnecessary and may create further delays in conducting single IRB reviews. **As such, we suggest that the FDA adopt the Common Rule language at 45.115(a)(9) without further additions or revisions.** The Common Rule language at 45.115(a)(9) is straightforward and well understood. We are concerned that some institutions will interpret the FDA's provision of additional verbiage as an indication that they should add additional requirements to reliance agreements.

Effective Date

The FDA proposes that the new rule be effective one year after the final rule is published in the Federal Register. Further, the final rule would only apply to cooperative research approved by an IRB on or after the proposed effective date. Ongoing research that an IRB approved before the proposed effective date would have the option – but not be required – to use a single IRB.
UC supports this approach.

If you have any questions concerning these comments, please contact me at agnes.balla@ucop.edu.

Sincerely,

Agnes Balla

Agnes Balla
Sr. Research Policy Manager
Research Policy Analysis and Coordination
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