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ALERT

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The U.S. Government Accountability Office Recommends Actions to Improve Federal Oversight of Institutional Review Boards for Human Research

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On June 16, 2020, Senators Elizabeth Warren, Bernie Sanders, and Sherrod Brown issued a letter (the "2020 Letter") to the U.S. Government Accountability Office (the "GAO") requesting that the GAO investigate the operations of so-called "commercial" institutional review boards ("IRBs").[1] The 2020 Letter asked the GAO to address a series of questions regarding the market dynamics in the IRB industry, the adequacy of existing processes and procedures utilized by "commercial IRBs," how federal agencies can "address any shortcomings" in existing IRB standards, and to compare "commercial IRBs" to "academic IRBs."[2]

The GAO accepted the request on August 10, 2020[3] and conducted an investigation focused on the following: (i) composition of the IRB market; (ii) practices IRBs have implemented to strengthen the quality of their reviews; and (iii) oversight of IRBs by the Office for Human Research Protections ("OHRP") and the U.S. Food and Drug Administration ("FDA").[4] The investigation obtained information through review of relevant laws, regulations, guidance documents, research articles, and other secondary literature and discussions with key stakeholders.[5] Specifically, the GAO interviewed or collected written information from officials at FDA, OHRP, and the National Institutes of Health ("NIH") as well as other IRB experts and stakeholders.[6] The GAO also reviewed IRB registration, drug applications, inspection data, and other information maintained by FDA and OHRP relating to IRBs, including information not available to the public.

The GAO memorialized its review in a written report titled *Institutional Review Boards: Actions Needed to Improve Federal Oversight and Examine Effectiveness,* which was issued to Senators Warren, Sanders, and Brown on January 17, 2023 and then released to the general public on February 16, 2023 (hereinafter, the "Report"). The Report classifies IRBs into five categories: independent IRBs (defined as "review boards with no affiliations with organizations that conduct or sponsor research"); university IRBs (including college and academic medical center IRBs); hospital or healthcare IRBs; private IRBs (e.g., independent research foundations that do not provide medical care); and government IRBs.[7] We refer to these categories for purposes of this alert.

Overview of the Report

The Report provides (i) details regarding the increasing reliance by research institutions and study sponsors on independent IRBs; (ii) viewpoints of expert researchers and ethicists, IRB organizations, and other clinical research stakeholders about the advantages and disadvantages of review by independent IRBs; and (iii) an overview of the practices and standards used by IRBs of all types to help strengthen the quality of their reviews. The Report describes the role of FDA and OHRP in overseeing IRBs, focusing on what the GAO believes are two primary gaps in these agencies' current approaches to inspecting IRBs and assessing their effectiveness. Finally, the Report concludes with high-level recommendations regarding additional measures that FDA and OHRP can undertake to "help provide assurance that that IRBs are successful in protecting human subjects."[8]

Key Information Regarding the Existing IRB Landscape

As noted above, one focus of the Report is to provide a detailed summary of the existing IRB landscape. Key issues discussed in this portion of the Report include the following:

- *The Report summarizes data not available to the public regarding the increase in the use of independent IRBs over time.* It is widely understood in the human subject research community that the percentage of research being reviewed by independent IRBs has been increasing over the past few decades and, in particular, over the past decade. As indicated in the Report, recent federal policy shifts have contributed to this increasing use of independent IRB services, including federal requirements to use a single IRB for certain types of multi-site research.[9] The Report provides summary statistics to help the research community understand the increasing use of independent IRBs with greater precision: specifically, from 2012 to 2021, the share of protocols involving FDA-regulated drugs reviewed by independent IRBs increased from 25 percent to 48 percent; and 2021 was the first year in which independent IRBs overtook university-based IRBs in reviewing the largest share of FDA-regulated research protocols.[10]

- *The Report explains the trend toward the consolidation of the independent IRB market and describes some of the advantages and disadvantages of consolidation.* The Report notes that the independent IRB market began a shift towards consolidation in 2007.[11] As of 2021, independent IRBs make up only two percent of IRBs in the United States, even though these entities reviewed 48 percent of protocols involving FDA-regulated drugs during the same year.[12] The GAO has attributed the increasing use of independent IRBs to several key factors, including an increase in the growth rate of industry-sponsored clinical trials compared to that of government-funded trials, federal actions (including requirements for single IRB review), and private capital investment in independent IRBs.

- *The Report discusses private capital investment in independent IRBs.* The 2020 Letter from Senators Warren, Sanders, and Brown focused on questions and concerns regarding private capital investment in independent IRBs. In response, the Report describes some of the effects of private capital investment in IRBs, focusing on qualitative feedback relayed by IRB officials and other experts and stakeholders interviewed or surveyed by the GAO during its review. The Report notes that private capital investment "has led to several positive changes to the IRB industry," including that staff at IRBs supported by private investment firms are well trained and resourced and that the high quality of training and resources at these IRBs has led to positive spillover effects across the IRB landscape, including "increased professionalization of, and educational opportunities for, IRB staff at both independent and other types of IRBs" and an increase by all types of IRBs in hiring IRB staff with relevant experience and certifications.[13] The report emphasizes that the growth in independent IRBs has led to greater specialization, including, for example, that hospital-affiliated IRBs "may send later-stage clinical trials (i.e., Phase 2 or above) to independent IRBs, but keep other investigator-initiated studies or clinical trials for review in-house."[14] The Report also opines about some "potential negative effects of private investment in IRBs," including that an emphasis on profit and/or faster protocol review may result in less focus on potential harms of research to human subjects and that "for-profit IRBs, in particular, may be more inclined to approve a protocol and do so expediently in order to satisfy a client."[15] The bottom line here, however, is that this Report does not appear to have fully validated the apparent skepticism toward private investment in IRBs expressed in the Senators' 2020 Letter to the GAO that triggered this Report.

- *The Report provides an overview of controls used to ensure the quality of IRB reviews.* The Report summarizes the practices utilized by the eleven IRBs that the GAO surveyed for purposes of its review.[16] This summary may be particularly helpful for smaller or less experienced IRBs that could benefit from insight as to the practices of their peer organizations to ensure a high level of review. Some of these recommended practices include managing various levels of conflicts of interest, monitoring research activity (including making site visits), and annual assessment of research operations. Despite the GAO's general endorsement of the practices highlighted in the report, the GAO was clear about the limited empirical evidence available about the effect of such practices, stating that there "is currently a lack of evidence to support that these practices contribute to more ethical decisions or greater protections for human subjects, according to some experts."[17]

FDA and OHRP Oversight of IRBs

The final section of the Report focuses on the role of FDA and OHRP in overseeing IRBs and recommendations for improving the oversight provided by these agencies. The Report emphasizes that both FDA and OHRP rely on inspections of IRBs as a key element of their oversight duties but that the effectiveness of agency inspections is limited by a lack of inspections and by shortcomings in the methodologies used by these agencies to select IRBs for inspection.[18] The Report points out that neither OHRP nor FDA conducts a risk-based assessment of IRBs[19] and that neither agency has examined the effectiveness of IRBs in promoting human subjects protections.[20]

Based on these perceived shortcomings in current oversight by FDA and OHRP, the Report concludes with the following recommendations:

- Recommendation 1: The Department of Health and Human Services ("HHS") should ensure that OHRP takes steps to ensure the accuracy of protocol data collected in OHRP's IRB registry. This could include updating instructions to IRBs and examining data accuracy for a sample of IRBs.

- Recommendation 2: HHS should ensure that OHRP conducts an annual risk assessment to determine whether the agency is conducting an adequate number of routine IRB inspections and to optimize the use of IRB inspections in the oversight of IRBs and protection of research participants.

- Recommendation 3: FDA should conduct an annual risk assessment to determine whether the agency is conducting an adequate number of routine IRB inspections and to optimize the use of IRB inspections in the oversight of IRBs and protection of research participants.

- Recommendation 4: HHS should ensure that OHRP and FDA convene stakeholders to examine approaches for measuring IRB effectiveness in protecting human subjects and implement the approaches as appropriate. These could include effectiveness measures; peer audits of IRB meetings and decisions; mock protocols; surveys of IRB members, investigators, and human research participants; or other approaches.[21]

Implications of the Report

The timing of the Report coincides with a number of recent regulatory changes in effect to harmonize and modernize the regulations and guidance applicable to human subjects research over which the federal government has jurisdiction. For example, on September 28, 2022, FDA issued two Notices of Proposed Rulemaking to harmonize FDA's regulations pertaining to human subjects research and the review of cooperative research by a single IRB.[22] Similarly, on December 29, 2022, President Biden signed into law the Consolidated Appropriations Act, 2023 (H.R. 2617), which included the Food and Drug Omnibus Reform Act of 2022 ("FDORA") and incorporated several provisions intended to promote diversity in clinical trial enrollment, encourage the growth of decentralized clinical trials, and to modernize clinical trials.[23] We anticipate that the overall increase in the number of decentralized clinical trials in which some or all study-related activities occur at a location separate from the investigators location will further expand the use of independent IRB review. Also of note, FDORA clarified FDA's authority to conduct bioresearch monitoring inspections of IRBs and directed FDA to issue draft guidance on this additional inspection authority within 18 months.[24] This authority may assist FDA in carrying out some of the recommendations in the Report.

The Report encourages OHRP and FDA to undertake efforts to improve the tracking and monitoring of IRB data being submitted to federal agencies so that the agencies, in turn, can make better decisions about which IRBs to inspect and when. For IRB organizations, these recommendations may result in an increase in the frequency of governmental audits and an expansion of the types of information that must be reported to OHRP and FDA on a regular basis. Currently, OHRP's IRB Registration Form only asks IRBs to report the "approximate" number of protocols reviewed over the last 12 months, the subset of those protocols relating to research conducted or supported by HHS or regulated by FDA, and

the types of FDA-regulated products involved in such protocols.[25] More detailed information capture, including, for example, the number of subjects associated with each protocol or the types of research and attendant risk levels, could inform a risk-based approach.[26]

The Report recommends that OHRP and FDA convene stakeholders to examine possible approaches for measuring IRB effectiveness. Appendix IV of the Report notes that OHRP and FDA officials "may incorporate recommendations made by the Secretary's Advisory Committee on Human Research Protections ("SACHRP") . . . in developing guidance documents." This observation suggests that the GAO may envision SACHRP, a federal advisory committee that provides recommendations to the Secretary of HHS on issues relating to the protection of human research subjects, as the best forum for developing guidance outlining how IRB organizations and federal agencies should seek to evaluate IRB effectiveness.[27] Appendix IV notes that SACHRP has provided guidance on other important topics of interest to IRBs, including an approach for navigating "pay-to-participate" research and that certain IRBs have indicated that they treat SACHRP recommendations as guidance to implement while carrying out IRB review.[28]

In sum, while the Report is the end result of a multi-year review process by the GAO, it is, in many ways, just the starting point for a more detailed discussion about how OHRP and FDA can enhance their processes for ensuring that IRBs are effective in maintaining protections for human subjects. That discussion will continue through fora like SACHRP, in which many diverse viewpoints and stakeholders across the research community are represented.

If you have any questions, please contact David Peloquin, Mark Barnes, Devin Cohen, Minal Caron, Leslie Thornton, or your usual Ropes & Gray advisor.

1. Letter from Sen. Elizabeth Warren, Sen. Bernard Sanders & Sen. Sherrod Brown, U.S. Senators, to Gene L. Dodaro, U.S. Comptroller General, Gov't Accountability Off. (Jun. 16, 2020), *available at* https://www.warren.senate.gov/imo/media/doc/2020.06.16%20Letter%20to%20GAO%20request%20on%20for-profit%20IRBs%20.pdf.
2. *Id.* at 4.
3. Letter from Orice Williams Brown, Managing Director, Gov't Accountability Off., to Sen. Warren, U.S. Senator (Aug. 10, 2020), *available at* https://www.warren.senate.gov/imo/media/doc/20-0731%20Warren%20GAO%20reponse.pdf.
4. U.S. Gov't Accountability Off., GAO-23-104721, Institutional Review Boards: Actions Needed to Improve Federal Oversight and Examine Effectiveness (Jan. 17, 2023), *available at* https://www.gao.gov/products/gao-23-104721 (hereinafter, the "Report") at 4.
5. Report at 4.
6. *Id.* at 4–5.
7. *Id.* at 2, 4.
8. *Id.* (introductory page).
9. *See* 45 C.F.R. § 46.114 (requiring single IRB review for all U.S. sites engaged in cooperate research subject to the Federal Policy for the Protection of Human Subjects, otherwise known as the "Common Rule"); National Institutes of Health, NOT-OD-16-094, Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (2016), *available at* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html (requiring single IRB review for multi-site research funded by NIH).
10. Report at 19.
11. *Id.* at 18.
12. *Id.* at 18, 19.
13. *Id.* at 28, 29.

14. *Id.* at 29.
15. *Id.* at 29.
16. *Id.* at 30–35 and Appendix II.
17. *Id.* at 30.
18. *Id.* at 40, 54.
19. *Id.* at 55–56.
20. *Id* at 56.
21. *Id.* at 63.
22. *See* Ropes & Gray LLP, *Harmonizing the Common Rule and U.S. Food and Drug Administration Human Subjects Research Regulations* (Sep. 30, 2022), *available at* https://www.ropesgray.com/en/newsroom/alerts/2022/september/harmonizing-the-common-rule-and-us-food-and-drug-administration-human-subjects-research-regulations (describing the FDA Notices of Proposed Rulemaking issued in September 2022).
23. *See* Ropes & Gray LLP, *Congress Enacts Legislation Requiring Guidance on Clinical Research Diversity and Modernization* (Jan. 9, 2023), *available at* https://www.ropesgray.com/en/newsroom/alerts/2023/01/congress-enacts-legislation-requiring-guidance-on-clinical-research-diversity-and-modernization (describing the relevant provisions of the Consolidated Appropriations Act, 2023).
24. H.R. 2617, § 3612.
25. IRB Registration Form, Office for Human Research Protections, *available at* https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/forms/irb-registration-form/index.html (Approved for use through June 30, 2025); *see also* IRB Registration Instructions, Office for Human Research Protections (Apr. 2022), *available at* https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/forms/irb-registration-instructions/index.html.
26. Report at 54.
27. *Id.* at 84.
28. *Id.* at 84–85.