



January 2023

# INSTITUTIONAL REVIEW BOARDS

## Actions Needed to Improve Federal Oversight and Examine Effectiveness

Accessible Version

## Why GAO Did This Study

IRBs review research studies involving human subjects to ensure that risks to subjects are minimized and participants have sufficient information to consent to participate. In the past, IRBs were based at research institutions, such as academic centers. Over time, independent IRBs have played a more prominent role in reviewing research on human subjects. Some policymakers and others have raised questions about the increased use of independent IRBs and the effects on protecting human subjects.

GAO was asked to examine independent IRBs, processes used to protect human subjects, and standards of IRB quality, among other things. This report describes the composition of the IRB market and examines OHRP and FDA oversight of IRBs, among other objectives.

GAO reviewed federal laws and regulations and articles published between 2010 and June 2021; analyzed IRB registration, drug application, and inspection data; and interviewed FDA and OHRP officials, experts and stakeholders, and 11 IRBs selected for variation in type, size, and other factors.

## What GAO Recommends

GAO is making four recommendations, including that HHS and FDA conduct annual risk assessments to determine if the agencies are routinely inspecting an adequate number of IRBs and to optimize the use of inspections in the oversight of IRBs and protection of research participants, and examine and implement approaches for measuring IRB effectiveness. HHS concurred with the recommendations.

View [GAO-23-104721](#). For more information, contact John Dicken at (202) 512-7114 or [dickenj@gao.gov](mailto:dickenj@gao.gov).

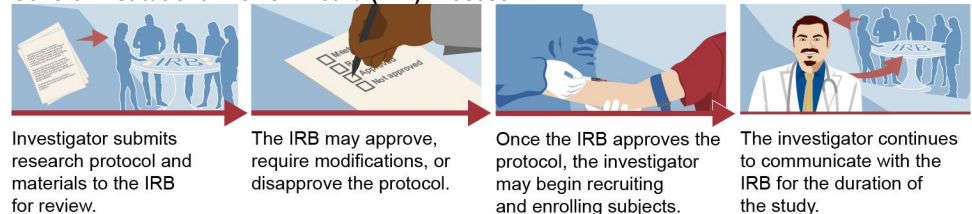
# INSTITUTIONAL REVIEW BOARDS

## Actions Needed to Improve Federal Oversight and Examine Effectiveness

### What GAO Found

Institutional review boards (IRB) are groups that review ethical and safety considerations for research involving human subjects, such as clinical trials.

#### General Institutional Review Board (IRB) Process



Source: GAO analysis of Department of Health and Human Services information. | GAO-23-104721

Most IRBs are based at universities, according to Department of Health and Human Services (HHS) data. University-based IRBs were also responsible for reviewing most research involving certain investigational drugs from calendar years 2012 through 2020, according to Food and Drug Administration (FDA) data. Some IRBs are independent, meaning they are not part of institutions that conduct or sponsor research. FDA data show these independent IRBs have reviewed an increasing share of investigational drug research: 25 percent of this research in 2012, and 48 percent in 2021. At the same time, the number of independent IRBs has decreased largely due to consolidation; this is, in part, related to private equity investment in IRBs.

FDA and HHS's Office for Human Research Protections (OHRP) oversee about 2,300 U.S.-based IRBs (operated by about 1,800 separate organizations, which may register and operate one or more IRB) through routine or for-cause inspections. These inspections assess whether IRBs follow federal regulations when reviewing research. FDA and OHRP consider several factors when selecting organizations for inspections, such as the volume of research reviewed. However, GAO found the agencies inspect relatively few IRBs. OHRP officials said they aim to conduct three to four routine inspections annually, while FDA conducted an average of 133 inspections annually between fiscal years 2010 and 2021. Neither agency has conducted a risk-based assessment of their IRB inspection program to help ensure they inspect enough IRBs annually and to optimize their responsibilities in protecting human subjects. Such an approach would be consistent with federal risk management principles.

While the agencies oversee IRBs to determine their adherence to regulations, OHRP and FDA have not assessed to what extent IRB reviews are effective in protecting human subjects. This is because the agencies have not determined the best approaches for doing so. Evaluating effectiveness is challenging in part due to an absence of validated measures and because IRBs are only one part of the framework of stakeholders responsible for protecting human subjects. Convening stakeholders to identify approaches for evaluating IRB effectiveness would be consistent with OHRP and FDA responsibilities and change management practices, and would help provide assurance that IRBs are successful in protecting human subjects.

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(OHRP) and the Food and Drug Administration (FDA)

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**Abbreviations**

AAHRPP	Association for the Accreditation of Human Research Protection Programs, Inc.
BMIS	Bioresearch Monitoring Information System
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
HHS-OIG	Department of Health and Human Services Office of Inspector General
IRB	institutional review board
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PRIM&R	Public Responsibility in Medicine and Research
SACHRP	Secretary's Advisory Committee on Human Research Protections
WHO	World Health Organization

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January 17, 2023

The Honorable Sherrod Brown  
United States Senate

The Honorable Bernard Sanders  
United States Senate

The Honorable Elizabeth Warren  
United States Senate

As of October 18, 2022, over 21,000 registered clinical research studies in the United States were actively recruiting human subjects, and, according to a recent publication, the number of studies involving human subjects has increased steadily each year since 2007.<sup>1</sup> Federal law provides protections for people who participate in certain research studies. These protections stem from the National Research Act, which was enacted in 1974 after actions taken by the U.S. federal government during the U.S. Public Health Service Syphilis Study at Tuskegee.<sup>2</sup> The Act required entities that applied for a grant or contract from the Department of Health and Human Services (HHS) for biomedical or behavioral research involving human subjects to establish a group, known

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<sup>1</sup>Data are of studies registered on ClinicalTrials.gov, a database of privately and publicly funded clinical studies conducted around the world, maintained by the National Library of Medicine at the National Institutes of Health. Certain studies are required to submit information to it. See 42 C.F.R. Part 11. See also U.S. National Library of Medicine, "Clinicaltrials.gov Trends, Charts, and Maps." Accessed October 19, 2022, <https://clinicaltrials.gov/ct2/resources/trends>; and Deborah A. Zarin et al., "10-Year Update on Study Results Submitted to Clinicaltrials.gov." *New England Journal of Medicine*, vol. 381, no. 20 (2019): 1966–1974.

<sup>2</sup>Pub. L. No. 93-348, 88 Stat. 342 (1974). In 1932, the U.S. Public Health Service worked with the Tuskegee Institute on a study to record the natural history of syphilis, which enrolled hundreds of African American men—some with syphilis and some who did not have the disease. By 1943, penicillin was identified as the standard of care for treating syphilis; however, the participants in the study with syphilis were not offered this treatment until an Associated Press article about the mistreatment of the study participants was published in 1972.

as an institutional review board (IRB), to review the research and its risks to human subjects.<sup>3</sup>

Research studies with human subjects are generally required to obtain IRB approval before the research begins. IRBs review how the research will be conducted in order to protect the rights and welfare of the research subjects. In their review, IRBs help ensure that research protocols meet certain requirements, such as demonstrating that human subjects will be adequately informed about a research study's risks and benefits.

HHS's Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) have requirements for IRBs related to the protection of human subjects.<sup>4</sup> HHS and other federal departments and agencies jointly establish regulatory requirements for IRBs related to the protection of human subjects, known as the Common Rule.<sup>5</sup> Within HHS, OHRP helps ensure the protection of participants in HHS-conducted and supported research, including ensuring such research complies with the Common Rule, establishing guidance regarding how IRBs reviewing such research should operate, and providing education.<sup>6</sup> In addition, FDA has established and oversees compliance with its own regulations for IRBs reviewing research involving the products it regulates, such as drugs and medical devices intended for human use.<sup>7</sup>

Historically, IRBs were affiliated with the same institution as the researcher and the location of the research, such as academic centers. Over time, researchers have relied increasingly on IRBs external to their

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<sup>3</sup>Pub. L. No. 93-348, § 212, 88 Stat. at 352 (codified at 42 U.S.C. § 289).

<sup>4</sup>A research institution may also establish its own requirements for IRBs, apart from federal requirements.

<sup>5</sup>The Common Rule was first adopted by HHS and other agencies in 1991. 56 Fed. Reg. 28,003 (June 18, 1991).

<sup>6</sup>OHRP addresses the protection of human subjects involved in research conducted or supported by HHS; in this report, we use HHS-supported to refer to both types of research. OHRP also provides leadership in cooperation with other federal departments and agencies. See generally 45 C.F.R. Part 46. OHRP is a division within the HHS Office of the Assistant Secretary for Health; we refer to OHRP as an "agency" throughout this report.

<sup>7</sup>See generally 21 C.F.R. Part 56.

organizations, such as independent IRBs—that is, review boards with no affiliation with organizations that conduct or sponsor research.<sup>8</sup>

Recent actions may further increase the use of independent IRBs. For example, in 2016, the National Institutes of Health (NIH) issued a policy stating it expected the use of a single IRB to review NIH-funded research studies involving multiple study sites.<sup>9</sup> Additionally, in 2020, the use of a single IRB became a requirement for HHS-supported research involving more than one institution, known as cooperative research, and, in 2022, FDA noted it was considering how a single IRB requirement could apply to research it regulates.<sup>10</sup> Since independent IRBs are thought to have more experience operating as single IRBs, researchers estimate that this policy could lead to an increased use of independent IRBs relative to other IRB types.<sup>11</sup> However, some policymakers have raised questions about whether certain independent IRBs have profit motives that may prioritize reviewing more studies—thus generating more revenue—at the possible expense of ensuring that research studies adhere to regulations that aim to protect human subjects.

Prior questions about the due diligence independent IRBs were exercising in their review of research protocols led us to conduct an

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<sup>8</sup>See, for example, Department of Health and Human Services Office of Inspector General, *Institutional Review Boards: The Emergence of Independent Boards*, OEI-01-97-00192 (Washington, D.C., June 1998).

<sup>9</sup>Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, 81 Fed. Reg. 40,325 (June 21, 2016). The term single IRB—also referred to as central IRB—is an IRB that conducts research protocol reviews on behalf of all institutions or sites in a clinical study instead of multiple IRBs conducting protocol review for the participating institutions or sites.

<sup>10</sup>Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7,149 (Jan. 19, 2017). This final rule updated the Common Rule. The single IRB requirement became effective in 2020. See HHS Policy for the Protection of Human Research Subjects, 84 Fed. Reg. 64,432 (Nov. 22, 2019). See also 87 Fed. Reg. 58,752 (Sep. 28, 2022).

<sup>11</sup>Sarah Babb, *Regulating Human Research: IRBs from Peer Review to Compliance Bureaucracy*, (Stanford, C.A.: Stanford University Press, 2020); Ann-Margret Ervin, Holly A. Taylor, and Stephan Ehrhardt, “NIH Policy on Single IRB Review—A New Era in Multicenter Studies,” *New England Journal of Medicine*, vol. 375, no. 24 (2016): 2315-2317; and Holly Fernandez Lynch and Stephen Rosenfeld, “Institutional Review Board Quality, Private Equity, and Promoting Ethical Human Subjects Research,” *Annals of Internal Medicine*, October 2020.



undercover investigation of the independent IRB review system.<sup>12</sup> In 2009, we reported that one of the three independent IRBs we contacted approved of a protocol for a fictitious medical device we created. Following the report, the IRB voluntarily agreed not to review any new FDA-regulated studies and not to allow new subjects to be added to ongoing FDA-regulated studies and later ceased its operations.<sup>13</sup>

To help Congress further understand independent IRBs and their operations, you asked us to describe the current IRB market structure, the processes and procedures independent and other IRBs have in place to protect human research subjects, and standards of IRB quality, among other things.<sup>14</sup> This report

- (1) describes the composition of the IRB market,
- (2) describes the practices selected IRBs have implemented to help strengthen the quality of their reviews, and
- (3) examines OHRP and FDA oversight of IRBs.

For all three objectives, we reviewed relevant federal laws and regulations related to IRBs and human research subject protections. We reviewed HHS and FDA documents, research articles, trade publications, and other documentation describing the different types of IRBs and changes to the composition of the IRB market, the research protocols

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<sup>12</sup>GAO, *Human Subjects Research: Undercover Tests Show that the Institutional Review Board System is Vulnerable to Unethical Manipulation*, [GAO-09-448T](#) (Washington, D.C.: March 26, 2009).

<sup>13</sup>Food and Drug Administration (FDA), "Questions and Answers on IRB April 14, 2009 Warning Letter," accessed August 10, 2022, <https://www.fda.gov/drugs/enforcement-activities-fda/questions-and-answers-coast-irb-april-14-2009-warning-letter>.

In [GAO-09-448T](#), we also reported that OHRP approved of a fictitious independent IRB we registered. In commenting on that report, HHS officials stated that the department did not review IRB registrations to assess whether the information submitted is factual, lacked the staff to do so, and did not consider such an examination worthwhile. Additionally, OHRP officials added that the registration process was not designed to provide a meaningful review of IRB registrations. Subsequent to this report, OHRP added disclaimers to its web pages noting that neither IRB registration nor an IRB assuring to OHRP that it complies with U.S. federal regulations on protecting human subjects should be taken as any indication that that OHRP has evaluated the competence of the IRB.

<sup>14</sup>Senator Sanders's June request was in his role as Chairman of the Senate Committee on the Budget in the 116th Congress.

they review, OHRP and FDA mechanisms for ensuring the protection of human research subjects, and IRB practices.<sup>15</sup> We obtained this information through federal agencies, a literature review, and external stakeholders. In addition, we interviewed or obtained written responses from OHRP, FDA, and NIH officials, and interviewed or collected written responses from 11 experts, seven stakeholder organizations, and 11 organizations that operate IRBs. The information we obtained from these entities cannot be generalized to experts and organizations we did not select and interview.<sup>16</sup> Information on how we selected these experts, stakeholder organizations, and IRBs is provided in appendix I.

To describe the composition of the IRB market, we obtained and analyzed data from OHRP, FDA, and NIH. Specifically, we analyzed OHRP's IRB Registry data to obtain information on the total number and types of IRBs in the United States registered with HHS as of April 2021, the most recent information at the time we began our review.<sup>17</sup> We used FDA Bioresearch Monitoring Information System (BMIS) data to analyze trends in the number and types of IRBs in the United States reviewing FDA-regulated research as well as the share of research studies being reviewed by different types of IRBs from 2012 through 2021, the most recent calendar year data available at the time of our review.<sup>18</sup> Finally, we obtained information from NIH on the use of IRBs outside of NIH for clinical trials conducted by NIH intramural research program investigators.

As part of our analysis of these data, we created five categories of IRBs and categorized IRBs into one of these five categories because neither OHRP nor FDA categorize IRBs in this way. We categorized IRBs as:

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<sup>15</sup>IRBs may also review research that is not subject to federal requirements, such as research involving new surgical techniques funded by a private organization. Such research was outside the scope of our review.

<sup>16</sup>In our report, we generally use the terms "some" to refer to a statement made by three or more experts, stakeholders, or IRB officials, and "most" to refer to a statement made by at least half of each group—that is, at least six experts, at least four stakeholder organizations, or officials representing at least six IRBs.

<sup>17</sup>Certain research conducted outside of the United States, including HHS-supported research, is also subject to U.S. law and regulation, including related to IRB review. However, we limited the scope of our work to IRBs operating within the 50 U.S. states and the District of Columbia.

<sup>18</sup>BMIS data captures information on the IRB that reviewed research involving regulated drugs and biologics under an investigational new drug application regulated by FDA's Center for Drug Evaluation and Research. In order to test an investigational drug on human volunteers in clinical trials, a sponsor must first submit an investigational new drug application to FDA.

university (which includes colleges and academic medical centers), hospital or health care organization, private, government, and independent. To do so, we developed an approach that involved assigning an IRB to a category based upon the IRB name or address, and by conducting additional research, such as identifying the mission of an organization from its website. We recognize that others attempting such a process might develop different categories and that our approach has limitations, which we describe in Appendix I.

To describe the practices selected IRBs have implemented to help strengthen the quality of their reviews, we conducted a literature search of articles published from 2010 through June 14, 2021, and interviewed the experts in our review to identify a set of recommended practices. We then reviewed information collected from our sample of IRBs (e.g., policies and procedures) to understand the extent to which the selected IRBs were using those recommended practices. These practices are not inclusive of all possible recommended practices identified in the literature or by experts. We also reviewed IRB standards and measurement tools developed by other entities such as the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) and the World Health Organization (WHO).

To examine OHRP and FDA oversight of IRBs, we reviewed IRB and human research protection program inspection manuals and guidance documents and reports from OHRP, FDA, and the Department of Health and Human Services Office of Inspector General (HHS-OIG). We also obtained and analyzed OHRP and FDA IRB inspection data for fiscal years 2010 through 2021—the most recent complete year of data at the time of our review—to describe the number and type of inspections during this time period, as well as the types of inspection findings. We categorized inspection findings by IRB type using the same approach as explained above, and reviewed letters OHRP and FDA issued to IRBs following inspections conducted from fiscal years 2010 through 2021. We analyzed OHRP IRB Registry data, including the volume of research IRBs reported reviewing, and asked the selected IRBs about the accuracy of the information they reported to OHRP. We also reviewed HHS documentation and reports by national advisory bodies describing approaches for ensuring IRB quality.

We also assessed information on OHRP and FDA's IRB inspection processes against federal internal control standards for information and communication and risk assessment, and Office of Management and

Budget guidance.<sup>19</sup> In addition, we considered OHRP and FDA's actions to examine IRB effectiveness in the context of OHRP's Statement of Organization and Functions, which outlines the office's responsibilities; the Federal Food, Drug, and Cosmetic Act; a 2018 memorandum of understanding between FDA and OHRP that describes how the two agencies collaborate; and key practices from our June 2018 report on agency reform efforts.<sup>20</sup>

To assess the reliability of data we analyzed from the OHRP IRB Registry, the FDA BMIS, and OHRP and FDA IRB inspection data, we obtained information from knowledgeable OHRP and FDA officials regarding the accuracy of the data. For these data sources and the Centers for Medicare & Medicaid Services Provider of Service File, we reviewed the published literature for how the data have been used, and we performed checks to identify missing or incorrect data. Based on these steps, we determined that the data were sufficiently reliable for the purposes of our reporting objectives. See appendix I for a more detailed discussion of our scope and methodology.

We conducted this performance audit from January 2021 to January 2023 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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<sup>19</sup>See GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: September 10, 2014); and Office of Management and Budget, *Management's Responsibility for Enterprise Risk Management and Internal Control*, Circular No. A-123 (Washington, D.C.: July 15, 2016). An internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

<sup>20</sup>See Department of Health and Human Services, Office of the Assistant Secretary for Health, *Statement of Organization and Functions for the Office for Human Research Protections (OHRP): Part I*, (March 6, 2002); Food and Drug Administration, *FDA Policy for the Protection of Human Subjects* (June 18, 1991); Pub. L. No. 75-717, 52 Stat. 1040 (1938) (as amended and codified at U.S.C. Title 21); Food and Drug Administration and Office for Human Research Protections, "Memorandum of Understanding between the Food and Drug Administration and Office for Human Research Protections," accessed January 10, 2022, <https://www.fda.gov/about-fda/domestic-mous/mou-225-18-014>; and GAO, *Government Reorganization: Key Questions to Assess Agency Reform Efforts*, [GAO-18-427](#) (Washington, D.C.: June 13, 2018).

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## Background

Each year, individuals participate as subjects in research studies covering a wide range of topics.<sup>21</sup> These include research studies in which investigators:

- learn about human behavior, including psychological, economic, political, social, and educational behavior, for example, by observing human subjects performing specific tasks under various conditions;
- analyze existing data and specimens, for example, by reviewing electronic health records to determine if a new medical model improves patient outcomes;
- observe human subjects, for example, by collecting blood from subjects to determine if a new laboratory test is a good predictor of a clinical condition; and
- test new ways to prevent, detect, or treat disease—also known as a clinical trial—for example, by testing whether a new drug is safe and effective.

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## IRB Review

Federal requirements define the composition and scope of review for IRBs.<sup>22</sup> For example, an IRB must have five or more individuals who meet to discuss the ethical considerations of research studies initiated by sponsors and conducted by research investigators.<sup>23</sup> Prior to initiating certain research involving human participants, an investigator must

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<sup>21</sup>Certain research conducted outside of the United States, including HHS-supported research, is also subject to U.S. law and regulation. However, we limited the scope of our work to IRBs operating within the 50 U.S. states and the District of Columbia.

<sup>22</sup>See generally 42 C.F.R. Part 46; 21 C.F.R. Part 56.

<sup>23</sup>The Common Rule does not include specific definitions for “sponsors” and “investigators.” FDA regulations define sponsors as individuals, pharmaceutical companies, governmental agencies, academic institutions, or private organizations that take responsibility for and may initiate research studies. They also define investigators as individuals who conduct a research study, which involves obtaining informed consent from study participants and providing immediate direction over the administration of the study. Sometimes, an individual both initiates and conducts a clinical research study. See 21 C.F.R. § 312.3.

submit a research protocol and related documents to the IRB for review.<sup>24</sup> One IRB organization may operate one or more IRBs, which are also known as boards.<sup>25</sup>

There are different types of IRBs that review research studies: four types that we refer to as affiliated IRBs, and independent IRBs.<sup>26</sup> For example,

- IRBs affiliated with universities (including academic medical centers);
- IRBs affiliated with hospitals or health care organizations, such as managed care organizations;
- IRBs affiliated with private organizations, such as research foundations or businesses that do not provide medical care;
- IRBs affiliated with government agencies, such as the Department of Veterans Affairs or a state public health agency; or
- Independent IRBs, which are IRBs that are not affiliated with organizations that conduct or sponsor research and do not fit one of the above categories.

In reviewing research protocols and other information, IRBs are responsible for considering, among other things, whether the proposed study ensures that

- risks to participants are minimized,
- participants will have sufficient information to decide whether to consent to the research, and
- participants will be selected fairly (e.g., not selected because of ease of availability or manipulability).

Based on the review, the IRB may approve the protocol, require modifications to the protocol, or disapprove the protocol. After the IRB approves the research study, the investigator may begin enrolling subjects, but must continue to communicate certain information to the IRB throughout the study. (See fig. 1.)

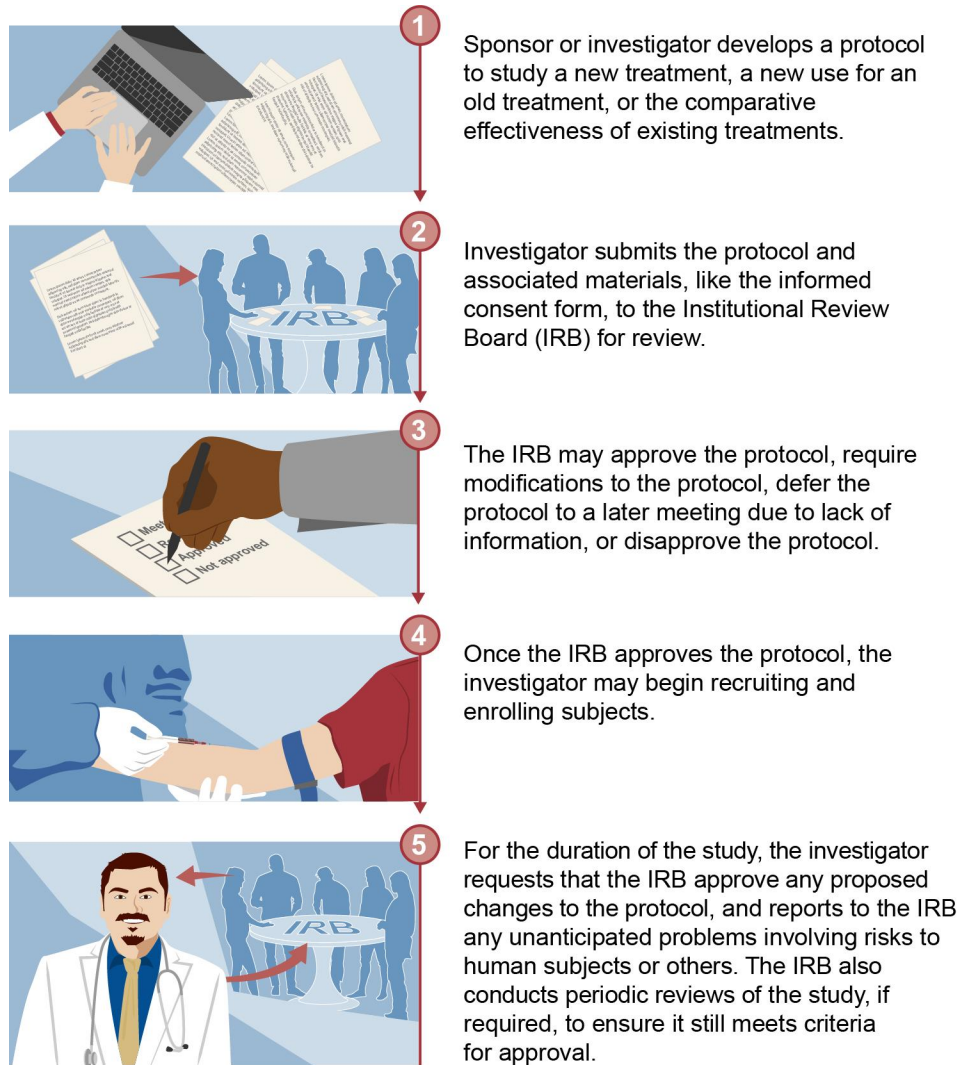
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<sup>24</sup>Some HHS-supported research activities involving human subjects are exempt from IRB review. These include research involving anonymous surveys. See 42 C.F.R. § 46.104.

<sup>25</sup>Throughout this report, we use the terms IRB and board interchangeably.

<sup>26</sup>Any IRB, regardless of its type, can review research conducted at sites of research not affiliated with the IRB.

**Figure 1: General IRB Process**



Source: GAO analysis of Department of Health and Human Services (HHS) information. | GAO-23-104721

Note: This figure depicts the process for reviewing research studies determined to present greater than minimal risk of harm to its human subjects, which requires the IRB to convene a board meeting to discuss.

Federal regulations require a majority of IRB members and at least one non-scientist member—a process known as full board review—to convene to review and approve studies that involve greater than minimal risk; investigational drugs, biologics, and devices; or certain procedures. Additionally, the IRB must re-review these studies at least once per year

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while the research is ongoing—a process known as continuing review.<sup>27</sup> Certain studies that present no greater than minimal risks to subjects may go through an expedited IRB review, in which one experienced board member conducts the review; such studies subject only to the Common Rule generally do not need to be re-reviewed by IRBs.<sup>28</sup>

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<sup>27</sup>Minimal risk refers to studies where the probability and magnitude of harm or discomfort are not greater in and of themselves than ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For the definition of minimal risk and descriptions of full board review and continuing review, see 45 C.F.R. §§ 46.102(j), 48.108(b); 42 C.F.R. §§ 46.109(e), 46.110; and 21 C.F.R. §§ 56.102(i), 56.108, 56.109(e)(f), 56.110.

<sup>28</sup>45 C.F.R. §§ 46.109–10; 21 C.F.R. §§ 56.109–10. Federal regulations specify the categories of HHS-supported and FDA-regulated research that are eligible for expedited review; these categories are published in the Federal Register. See 63 Fed. Reg. 60,364 and 63 Fed. Reg. 60,353 (November 9, 1998). 45 C.F.R. § 46.110, and 21 C.F.R. § 56.110. Although periodic reviews are not required for HHS-supported studies approved through an expedited review, FDA’s regulations require IRBs to re-review at least annually FDA-regulated studies approved through an expedited review. See 45 C.F.R. § 46.109(f) and Department of Health and Human Services, Food and Drug Administration, Office of Good Clinical Practice, *Guidance for Sponsors, Investigators, and Institutional Review Boards: Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations* (October 2018).



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## IRB Oversight Framework

### Ethical Principles Established by the Belmont Report

**Respect for persons:** This includes respect for individual autonomy and the protection of individuals with reduced autonomy, such as incarcerated individuals.

**Beneficence:** This refers to the obligations to protect individuals from harm and, when risks are present, to maximize possible benefits and minimize possible harms.

**Justice:** Equitable distribution of research burdens and benefits by, for example, ensuring some classes of individuals are not being systematically selected because of easy availability.

The Belmont Report states that these basic principles are addressed by the informed consent process, assessments of the study's risks and benefits to human subjects, and in how subjects are selected for research.

Source: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. (Washington, D.C.: DHEW Publication, April 1979). | GAO-23-104721

The IRB oversight framework evolved from the National Research Act. The act established a national commission to identify basic ethical principles that should underlie the conduct of research involving human subjects, develop guidelines to ensure that such research is conducted in accordance with those principles, and make recommendations to the Secretary.<sup>29</sup> The commission's findings culminated in a final report in 1979—the Belmont Report—which established that respect for persons, beneficence, and justice are the basic ethical principles that should be the focus of research involving human subjects.<sup>30</sup>

OHRP and FDA, the federal agencies within HHS charged with protecting human research subjects, enforce regulations that reflect the ethical principles of the Belmont Report. While not identical, the regulations set similar requirements for IRBs, and OHRP and FDA coordinate their IRB oversight efforts. Examples of OHRP and FDA requirements for IRBs include:

- **Board membership.** IRBs must have at least five members from varying and diverse backgrounds who are qualified to review research protocols and are not permitted to review protocols for which they have a conflicting interest.<sup>31</sup>
- **Functions, operations, and records.** IRBs must have sufficient staff to support IRB review and recordkeeping duties, follow written procedures for conducting reviews and reporting unanticipated problems or noncompliance, and prepare and maintain documentation of IRB activities, such as meeting minutes.<sup>32</sup>
- **Research review.** In order to approve research, IRBs must determine the research is consistent with specific criteria, which include ensuring

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<sup>29</sup>Pub. L. No. 93-348, tit. II, part A, 88 Stat. at 348.

<sup>30</sup>The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, (Washington, D.C.: DHEW Publication, April 1979).

<sup>31</sup>45 C.F.R. § 46.107; 21 C.F.R. § 56.107.

<sup>32</sup>45 C.F.R. §§ 46.108, 46.115; 21 C.F.R. §§ 56.108, 56.115.

that risks are minimized, subject selection is fair, and data confidentiality is maintained.<sup>33</sup>

- **Informed consent.** IRBs must ensure that information provided to research subjects or their legal representatives includes a reasonable and understandable description of the research study and the risks and benefits of participation.<sup>34</sup>

OHRP's IRB oversight is focused on ensuring that HHS-supported research is consistent with the Common Rule—regulations that outline basic provisions for IRBs influenced by the Belmont Report.<sup>35</sup> In addition to HHS, 19 other federal departments or agencies follow either the original or the revised version of the Common Rule.<sup>36</sup> HHS and the other Common Rule agencies issued a substantial revision to the Common Rule in 2017, with all revisions in effect by 2020.<sup>37</sup> These revisions aimed to reduce administrative burden for IRBs and investigators, and increase the protection of human research participants. Examples of revisions that affect IRBs include, expanding the types of research that are exempt from IRB review, removing the requirement that IRBs conduct periodic reviews for certain minimal risk studies, and requiring key information about research procedures and risks and benefits be described early in the consent document.<sup>38</sup>

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<sup>33</sup>45 C.F.R. §§ 46.109–12; 21 C.F.R. §§ 56.109–11.

<sup>34</sup>There are circumstances in which the IRB may determine that informed consent or documentation of informed consent can be waived. 45 C.F.R. §§ 46.116–17; 21 C.F.R. §§ 50.20, 50.25, 50.27, 56.109, 56.111.

<sup>35</sup>OHRP's oversight activities are limited to HHS-supported studies and studies conducted by institutions that voluntarily apply the Common Rule, regardless of the source of support.

<sup>36</sup>Federal Policy for the Protection Human Subjects, 82 Fed. Reg. 7,149 (Jan. 19, 2017).

<sup>37</sup>Federal Policy for the Protection Human Subjects, 82 Fed. Reg. 7,149 (Jan. 19, 2017). Most revisions to the Common Rule went into effect on January 21, 2019; however, the requirement that institutions engaged in cooperative research use a single IRB went into effect on January 20, 2020.

<sup>38</sup>While the Common Rule specifies the types of research that are exempt from IRB review, such as anonymous surveys, OHRP guidance states that institutions should have a person who is well-acquainted with the regulations determine if a research study is exempt and that this determination should not be made by the investigator. See Department of Health and Human Services, Office for Protection from Research Risks, *Exempt Research and Research that May Undergo Expedited Review* (May 1995).

FDA's IRB oversight activities are directed to ensuring the protection of the rights and welfare of human subjects enrolled in clinical trials involving the products FDA regulates regardless of the source of the research funding. For example, medical research involving FDA-regulated products may be funded by NIH or another federal agency, private individuals, research organizations, or pharmaceutical or medical device companies.<sup>39</sup> FDA has adopted a separate set of regulations for IRBs for the protection of human subjects. These regulations apply to the research on products FDA regulates and are similar, but not identical, to the Common Rule. FDA is working to harmonize its regulations with the revised Common Rule to the extent practicable and consistent with other statutes, as required by the 21st Century Cures Act of 2016.<sup>40</sup>

Organizations that operate IRBs involved in research that is either HHS-supported or involves an FDA-regulated product must submit certain information to an internet-based registration system maintained by HHS (the OHRP IRB Registry).<sup>41</sup> Specifically, they must submit basic information about their organization and IRBs they operate, such as the name and contact information for the organization operating the IRB; the name of its head official, and information on the approximate number of research protocols the IRB has reviewed in the 12 months prior to the registration application.<sup>42</sup>

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Additional changes to the Common Rule include providing participants with greater control over their biospecimens and personal information, and requiring research institutions to publicly post informed consent forms on a publicly available federal website.

<sup>39</sup>OHRP and FDA have joint oversight over IRBs involved in research that is both HHS-supported and involves an FDA-regulated product.

<sup>40</sup>In September 2022, FDA issued two proposed rules to harmonize its regulations with the revised Common Rule. See 87 Fed. Reg. 58,733 (Sep. 28, 2022) and 87 Fed. Reg. 58,752 (Sep. 28, 2022). Pub. L. No. 114-255, § 3023, 130 Stat. 1033, 1098 (2016).

<sup>41</sup>See 45 C.F.R. §§ 46.501–05 and 21 C.F.R. § 56.106.

<sup>42</sup>The number of IRBs an organization registers does not indicate how frequently the IRB organization convenes meetings to review research. For example, some IRB organizations may register one IRB that convenes several meetings with board members weekly or daily, whereas other IRB organizations may register multiple IRBs that meet less often.

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## Other Entities Involved in the Protection of Human Research Participants

IRBs are just one of the entities charged with ensuring the protection of human research subjects. Research subjects are protected by a system of interdependent elements that involve a number of other entities, including federal agencies, research institutions, research sponsors, and investigators. For example, research institutions establish broad institutional research oversight systems called human research protection programs, which include, but are not limited to, institutional review boards.<sup>43</sup> In addition to IRBs, FDA and OHRP have direct oversight over other entities with responsibilities for the protection of human subjects, such as researchers. (See fig. 2).

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Additionally, entities conducting HHS-supported research must file a Federalwide Assurance. This assurance is a declaration by an entity engaged in human subjects research that it will comply with federal regulations on the protection of human subjects. As part of this assurance, entities report basic information about their institution, such as institution name and key contacts, and must designate one or more IRBs to review their applicable research. See 42 C.F.R. § 46.103. Entities that conduct only FDA-regulated research are not required to file a Federalwide Assurance.

<sup>43</sup>In addition to ethical review of research protocols, human research protection programs are responsible for reviewing protocols for scientific merit and potential conflicts of interest, ensuring ethically sound participant-investigator interactions, ensuring ongoing safety monitoring, and conducting quality improvement and compliance activities. See Institute of Medicine, Committee on Assessing the System for Protecting Human Research Participants, *Responsible Research: A Systems Approach to Protecting Research Participants* (Washington, D.C.: National Academies Press, 2003).

**Figure 2: Examples of Other Entities Involved in the Protection of Human Subjects for HHS-supported or FDA-regulated Research**



Source: Information from the Department of Health and Human Services (HHS); HHS Office of Inspector General; the National Academy of Medicine; and the World Health Organization. | GAO-23-104721

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<sup>a</sup>Research institution generally refers to institutions that conduct research studies supported by HHS or another funding source. Other HHS agencies, in addition to NIH, fund research involving human subjects.

<sup>b</sup>Research sponsor refers to the entity that initiates the research, such as a pharmaceutical or biotechnology company. Sponsors may delegate certain responsibilities to contract research organizations or data monitoring committees.

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## Most IRBs Are University-Based; Use of Independent IRBs Has Increased

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### University-Based IRBs Are Most Prevalent and Reviewed the Majority of Clinical Research Protocols Involving Regulated Drugs through 2020

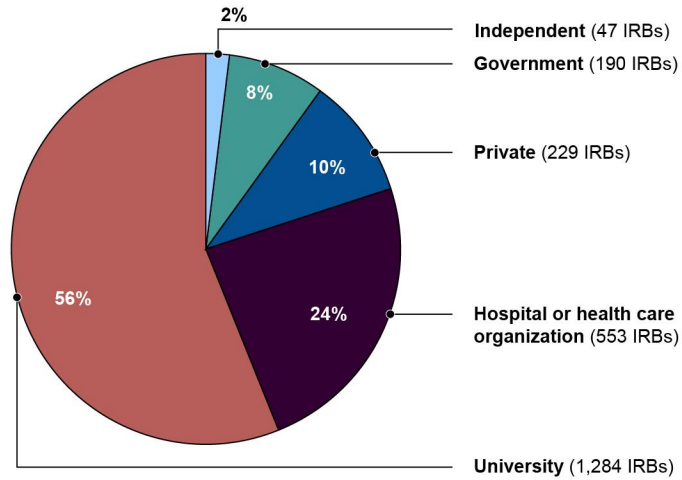
According to our analysis of OHRP and FDA data, university-based IRBs are the most prevalent type of IRB that reviewed federally regulated research studies.<sup>44</sup> OHRP registration data indicate that, of the about 2,300 IRBs operating in the United States with active registrations as of April 2021, the highest percentage (56 percent) were based at universities.<sup>45</sup> (See fig. 3) The majority of these IRBs (58 percent) reported to OHRP that they reviewed both HHS-supported and FDA-regulated product protocols.

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<sup>44</sup>We categorized educational institutions, such as universities and colleges, and academic medical centers as university IRBs.

<sup>45</sup>This analysis is limited to IRBs in the 50 United States and the District of Columbia with active registrations as of April 2021 that reported reviewing at least one HHS-supported or one FDA-regulated protocol in the year prior to the date of their registration or registration renewal. Another 1,130 IRBs in the 50 United States and the District of Columbia had active registrations, but reported that they had not reviewed any HHS-supported or FDA-regulated protocols. An additional 1,701 IRBs had active registrations but were located outside of the United States.

**Figure 3: Registered Institutional Review Boards (IRB) by IRB Type, as of April 2021**



Source: GAO analysis of Office of Human Research Protections (OHRP) data. | GAO-23-104721

**Accessible Data for Figure 3: Registered Institutional Review Boards (IRB) by IRB Type, as of April 2021**

	Independent	Government	Private	Hospital	University	Total
<b>Active IRBs</b>	47	190	229	553	1,284	2303
<b>(Percent)</b>	2%	8%	10%	24%	56%	100%

Notes: These 2,303 IRBs were operated by 1,780 organizations. We analyzed data on active IRBs registered with OHRP as of April 2021. An IRB registration is active for 3 years. This analysis is also limited to IRBs in the 50 United States and the District of Columbia that reported reviewing at least one protocol involving research supported by the Department of Health and Human Services or regulated by the Food and Drug Administration. We categorized IRBs by IRB type using a multi-step process that involved assigning an IRB to a category based upon the IRB name or address, and by conducting additional research, such as identifying the mission of an organization from its website.

OHRP data show independent IRBs make up a small portion of the review boards in the United States (2 percent), even as the number of such IRBs has varied over time. Two sources we reviewed report that the first independent IRB began in 1968.<sup>46</sup> One IRB trade publication reported that the number of independent IRBs increased steadily until around 2007, when independent IRBs began to consolidate.<sup>47</sup> According to our

<sup>46</sup>See Department of Health and Human Services Office of Inspector General, OEI-01-97-00192; and Frederick P. Ognibene and John I. Gallin, *Principles and Practice of Clinical Research*, 3<sup>rd</sup> edition (Cambridge, M.A.: Academic Press, 2012).

<sup>47</sup>Korieth, "IRB market consolidating rapidly," *The CenterWatch Monthly*, vol. 21, no. 7 (2014): p. 1.

analysis of OHRP registration data for IRBs registered as of April 2021, 31 IRB organizations operated 47 independent IRBs. As noted earlier, an IRB organization may register and operate more than one IRB. However, several of these IRB organizations have ceased operating or consolidated with other IRBs since that time. We estimate that 19 of these 31 IRB organizations were operating independent IRBs at the time of our review, based on a review of IRB and industry documents.<sup>48</sup>

FDA data show the university-based IRBs reviewed the largest share of studies involving FDA-regulated drugs each calendar year from 2012 through 2020.<sup>49</sup> Specifically, in 2020, university-based IRBs reviewed protocols for 48 percent of clinical research conducted under investigational new drug application regulations. In comparison, independent IRBs reviewed research for 41 percent in 2020. (See fig. 4) Our analysis of FDA data shows that in 2021, independent IRBs reviewed the largest share of FDA-regulated research (48 percent) compared with other IRB types, with university IRBs reviewing the second-highest share (42 percent).<sup>50</sup> This reflects a trend of independent IRBs reviewing an increasing share of research protocols involving FDA-regulated drugs during the period of our review, from 25 percent in 2012 to 48 percent in 2021.

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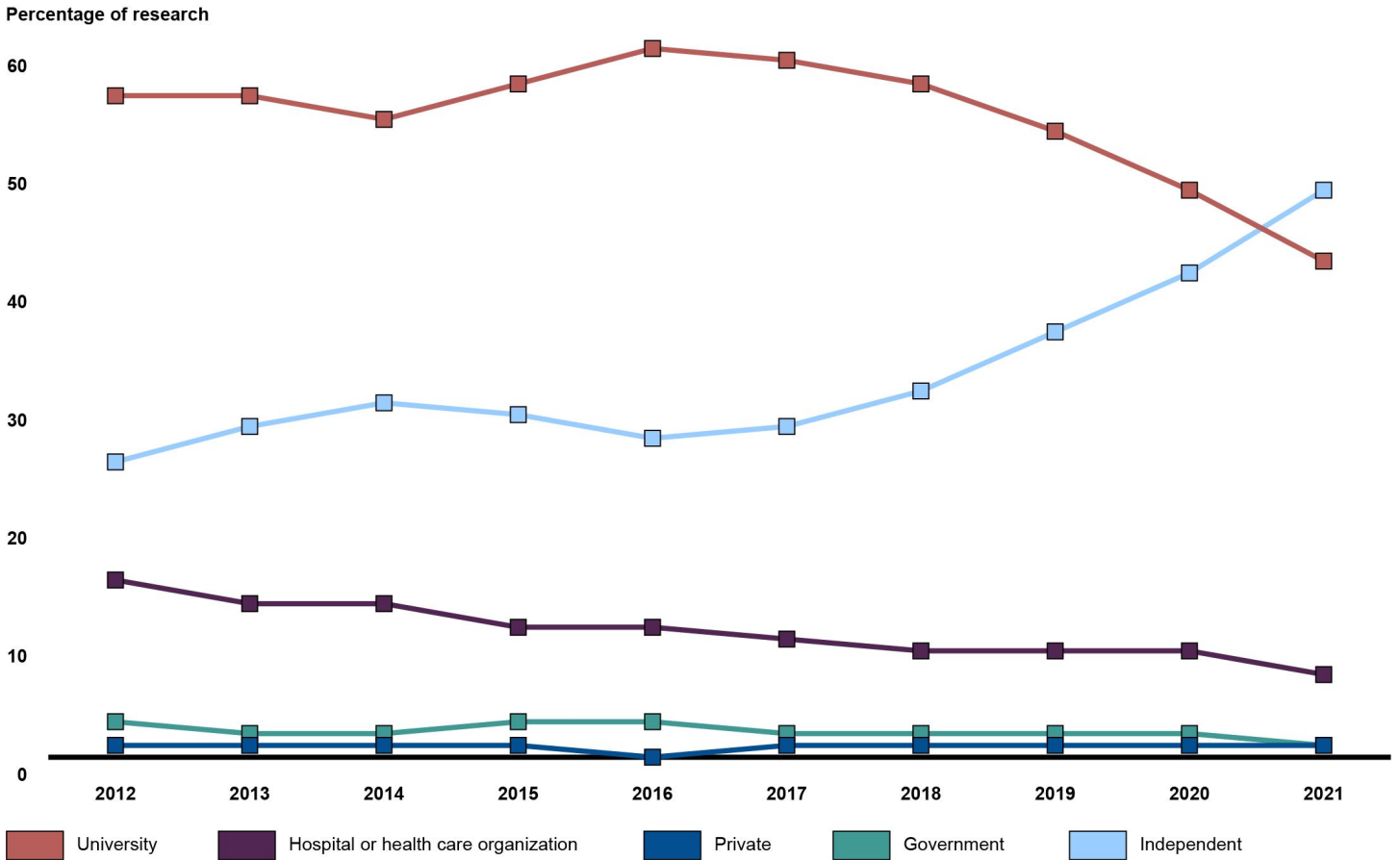
<sup>48</sup>Although the IRB registry indicated these IRBs were active as of April 2021, we found that four of these organizations have ceased operating and seven consolidated with other organizations.

<sup>49</sup>FDA's BMIS dataset captures information on the IRB associated with research involving regulated drugs and biologics under an investigational new drug application, enabling an examination of trends in the types of IRBs associated with such research. These data do have limitations. Namely, the data only capture certain FDA-regulated research. For example, BMIS captures research involving regulated drugs and biologics conducted under an investigational new drug application regulated by FDA's Center for Drug Evaluation and Research, but does not capture other FDA-regulated products. Additionally, BMIS data are voluntarily submitted to FDA by clinical trial investigators.

<sup>50</sup>Our analysis of these FDA data from 2012 through 2021 also show that the majority (68 percent) of clinical research reviewed by all IRB types are for commercial use, with independent IRBs reviewing a higher share in comparison with other IRB types for all of these years. According to FDA, an investigational new drug application is generally considered commercial when the product under investigation is intended to be commercialized at a later date. In comparison, an investigational new drug application is generally considered research if the product under investigation is not intended to be commercialized at a later date.



**Figure 4: Institutional Review Board (IRB) Review of Clinical Research Conducted under Food and Drug Administration (FDA) Investigational New Drug Applications, by Type of IRB for Calendar Years 2012 through 2021**



Source: GAO analysis of FDA Bioresearch Monitoring Information System (BMIS) data. | GAO-23-104721

**Accessible Data for Figure 4: Institutional Review Board (IRB) Review of Clinical Research Conducted under Food and Drug Administration (FDA) Investigational New Drug Applications, by Type of IRB for Calendar Years 2012 through 2021**

IRB Type	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
University	56%	56%	54%	57%	60%	59%	57%	53%	48%	42%	54%
Hospital	15%	13%	13%	11%	11%	10%	9%	9%	9%	7%	11%
Private	1%	1%	1%	1%	0%	1%	1%	1%	1%	1%	1%
Government	3%	2%	2%	3%	3%	2%	2%	2%	2%	1%	2%
Independent	25%	28%	30%	29%	27%	28%	31%	36%	41%	48%	33%

Notes: Before beginning a clinical investigation conducted under an investigational new drug application, FDA requires research sponsors to collect information from the investigator in Form FDA 1572 (the Statement of Investigator), which includes the name of the IRB that reviewed and approved

of the investigation. This information is voluntarily submitted to FDA and only collected in BMIS for investigations regulated by the Center for Drug Evaluation and Research. We categorized IRBs located in the United States using a multi-step process that involved assigning an IRB to a category based upon the IRB name or address, and by conducting additional research, such as identifying the mission of an organization from its website. FDA officials noted that universities and hospitals were operating under restrictions due to the COVID-19 pandemic, which may have limited the number of clinical trials their IRBs reviewed by hospitals and universities for 2020 and 2021.

This trend is similarly supported by a weighted average analysis we conducted of these data. Specifically, among the almost 25,000 unique investigational new drug applications received by FDA and captured in BMIS from 2012 through 2021, this analysis found an increasingly higher proportion of applications were associated with independent IRBs.<sup>51</sup> Specifically, 28 percent of applications were associated with independent IRBs in 2012 and this proportion grew to 53 percent of applications in 2021. Conversely, the proportion of applications associated with other IRB types (university, hospital or health care organization, private, and government) decreased during this period, from 72 percent to 47 percent.

In commenting on the finding that independent IRBs reviewed the largest share of FDA-regulated research involving drugs in 2021, FDA officials noted that universities and hospitals were operating under restrictions due to the COVID-19 pandemic, which may have limited the number of clinical trials their IRBs reviewed. Specifically, FDA officials noted that hospital and university research activities grounded to a halt, which may have led to a decrease in the volume of non-COVID-19 research and IRB activities. This may affect the trends we observed for 2020 and 2021.

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### Private Investment in Clinical Research and Other Factors Contributed to Increased Use and Consolidation of Independent IRBs

Based on documents reviewed and interviews conducted, we found that the use of independent IRBs can largely be attributed to (1) increases in clinical research funding—particularly, increases due to private industry-

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<sup>51</sup>According to our analysis of data from 2012 to 2021, the total number of unique investigational new drug applications captured in BMIS ranged from 3,623 in 2012 to 1,582 in 2021, with an average of about 2,500 per year.

Each investigational new drug application was associated with one or more clinical investigations, and each investigation was subject to review by a particular type of IRB. By weighting each application (determined on an annual basis) by the proportion of clinical investigations within each type of IRB, we derived a weighted average of investigational new drug applications for each year.

sponsored clinical research, (2) federal actions, and (3) private investment in independent IRBs.

**Clinical research funding.** Increases in private industry-sponsored clinical trials led to greater demand for IRB review and for quicker IRB review, which presented an opportunity for independent IRBs to increase their reach, according to experts, stakeholders, and IRB officials we interviewed and documents we reviewed. Historically, private industry and the federal government have together accounted for the majority of U.S. research funding, and in the past, federal research funding outpaced industry-funded research, according to two reports we reviewed.<sup>52</sup> However, according to these reports, in the 1980s, industry-sponsored trials began to grow at a faster rate than federal funding. Around 1989, clinical trial research funding from pharmaceutical companies outpaced NIH's total budget. Since the early 1990s, the number of industry-funded clinical trials has increased at a greater rate than NIH-funded trials.<sup>53</sup>

Independent IRBs were able to respond to the increased demand for reviews and for quicker reviews, according to most experts and some stakeholders we interviewed.<sup>54</sup> Affiliated IRBs have generally been slower in reviewing research protocols compared to independent IRBs, according to some stakeholders and published articles, as well as trade documents. For example, a study published in 2019 examined IRB review times for 263 government, hospital, and university IRBs between 2017 and 2018.<sup>55</sup> The study reported that the average time from protocol submission to final approval for studies requiring the full IRB panel varied from about 25 days for government IRBs to about 44 days for university IRBs.<sup>56</sup> This pattern was also reflected in our non-generalizable sample of IRBs:

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<sup>52</sup>Sarah Babb, *Regulating Human Research: IRBs from Peer Review to Compliance Bureaucracy*, First edition (Stanford, C.A.: Stanford University Press, 2020); and Congressional Research Service, *U.S. Research and Development Funding and Performance: Fact Sheet*, R44307 (Washington, D.C.: October 4, 2021).

<sup>53</sup>Babb, *Regulating Human Research*, pgs. 23 and 65.

<sup>54</sup>Babb, *Regulating Human Research*, pg. 56.

<sup>55</sup>S. Berry, D. Khodyakov, D. M. Grant, A. Mendoza-Graf, E. Bromley, G. Karimi, B. Levitan, K. Liu, and S. Newberry, *Profile of Institutional Review Board Characteristics Prior to the 2019 Implementation of the Revised Common Rule* (Santa Monica, C.A.: RAND Corporation, 2019).

<sup>56</sup>The study did not report an average time for independent IRBs.

- Regarding the time between protocol submission and initial IRB review, four independent IRBs reported this process took approximately 1 week, whereas three affiliated IRBs reported average times ranging from about 3 to 8 weeks.
- Regarding the time between protocol submission and final IRB approval, two independent IRBs reported this process took approximately 3 weeks, whereas two affiliated IRBs reported this process took approximately 18 weeks.

Some experts and two stakeholders we interviewed attributed slower turnaround times among affiliated IRBs to perceived structural and other differences between IRB types. Specifically, they noted that affiliated IRBs

- generally meet less regularly than independent IRBs;
- are largely composed of volunteer, uncompensated faculty members, physicians, or hospital employees that have other work priorities that may limit their time for reviewing protocols; and
- may have fewer financial, technological, or other resources to hire IRB staff or members to help facilitate review.

Conversely, they said independent IRBs often have boards that meet more frequently (e.g., weekly or several times a week). They also have access to more resources, which can be used to compensate board members, reach a larger pool of potential IRB members, and hire staff to facilitate faster IRB review, according to some experts.

Further, some articles we reviewed suggest other reasons why university IRBs, in particular, have longer turnaround times. For example, university IRBs may also become focused on improving the design of a study protocol, rather than focusing only on whether the study, as written, will harm research participants. Universities may also require that research protocols be reviewed by a research and development committee, or by a scientific committee to ensure the protocol reflects the highest scientific standards and can withstand professional critiques.<sup>57</sup>

**Federal actions.** A number of federal actions, including changes in federal oversight, also facilitated initial increases in, as well as an increased use of, independent IRBs, according to some experts and

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<sup>57</sup>See Robert Klitzman. "The Ethics Police?: IRBs' Views Concerning Their Power," *PLOS ONE*, vol. 6, no. 12 (2011): e28773.

stakeholders interviewed and documents we reviewed. These actions had the effect of making independent IRBs more attractive to research sponsors as well as research institutions, according to some experts and a stakeholder we interviewed. For example

- FDA regulations require IRB review for certain research. Prior to 1981, FDA required IRB review of research on FDA-regulated products conducted at institutions that (1) accepted responsibility for the research study or (2) involved subjects institutionalized in a mental health facility. This process changed when FDA issued regulations in 1981 that required IRB review for research conducted outside of an institution, such as by doctors in private offices and others. To address this requirement, FDA said that researchers not affiliated with an institution could have their research reviewed by an existing IRB, by an IRB created by the sponsor, or by an IRB created under the auspices of another entity, such as a community hospital or independent nonprofit group. In commenting on a 1998 HHS-OIG report, FDA suggested independent IRBs were created, and the number of them increased, in response to this regulation.<sup>58</sup>
- FDA develops guidance on use of a single IRB. To curb delays, duplication, and inefficiencies resulting from separate reviews of the same study in a multi-site clinical trial, FDA issued guidance in 2006 recommending sponsors and institutions select one IRB—known as a single IRB—to review the research protocol for all study sites.<sup>59</sup> Independent IRBs were often selected as the single IRB for these multi-site studies because they have more staff to facilitate such reviews, according to some experts and stakeholders we interviewed.

<b>Single Institutional Review Board (IRB) Model</b>
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<sup>58</sup>See Department of Health and Human Services Office of Inspector General, *Institutional Review Boards: A Time For Reform*, OEI-01-97-00193 (Washington, D.C., June 1998).

<sup>59</sup>See Department of Health and Human Services, Food and Drug Administration, *Using a Centralized IRB Review Process in Multicenter Clinical Trials Guidance for Industry* (March 2006).

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As clinical trials became more complex, involving multiple research sites—known as multi-center trials—the single IRB model emerged. Traditionally, each research site in a multi-center study obtained approval from its own affiliated IRB. Under the single IRB model, one IRB serves as the IRB of record of the multi-site trial or cooperative research and has the responsibility for reviewing and approving the research conducted across multiple research sites. Both affiliated and independent IRBs can serve as the single IRB. Even when the research is not multi-site, institutions with affiliated IRBs may cede their review of research to another affiliated or independent IRB, for example, at the request of the sponsor. Generally, when a research institution relies on a single IRB to review a study, the single IRB and the research institution enter into a reliance agreement, which spells out the human subjects related protection responsibilities of each party.

Source: GAO analysis of interviews with selected IRBs and document review. | GAO-23-104721

- OHRP clarifies liability for institutions using independent IRBs. Through a series of actions, OHRP made it clear that a research institution that uses an IRB with which it is not affiliated would not be liable for violations to the Common Rule resulting from that IRB's review. For example, in 2009, OHRP sought public comment on whether it should make IRBs, and not just institutions conducting research, accountable for meeting regulations for protecting human subjects.<sup>60</sup> OHRP suggested this change to encourage institutions to rely on IRBs operated by another institution or organization where appropriate, such as in multi-site clinical trials, and to be in agreement with FDA guidance on using single IRBs.<sup>61</sup> Through these actions, more sponsors and institutions could cede IRB review to an independent IRB without the fear of liability, according to two experts and three IRBs.
- HHS introduces requirements for single IRB review. In 2016, NIH established a policy stating its expectation that NIH-funded multi-site studies would use a single IRB for review beginning in 2018.<sup>62</sup> Prior to this policy, NIH was already ceding review of some intramural

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<sup>60</sup>See 74 Fed. Reg. 9,578 (Mar. 5, 2009). OHRP echoed its position in a letter to Carolinas Medical Center in May 2010 where it stated that when research institutions use IRBs unaffiliated with their institutions for protocol review, the institution would not be considered liable for the IRB's noncompliance with Common Rule regulations; liability would be attributed to the IRB instead. The letter also outlined other steps OHRP was taking to address research institutions' concerns about using these IRBs.

<sup>61</sup>In March 2006, FDA issued guidance titled *Using a Centralized IRB Review Process in Multicenter Clinical Trials* to outline to industry how it could use a central IRB (also known as a single IRB) to review protocols for multi-site studies.

<sup>62</sup>Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, 81 Fed. Reg. 40,325 (June 21, 2016). In 2016, NIH also clarified that research institutions could receive federal funding to pay an IRB serving as a single IRB for research protocol review, such as an independent IRB, as part of their direct costs.

research to IRBs outside of NIH. The revised Common Rule, issued in 2017, requires single IRB review for certain HHS-supported or conducted cooperative research; this requirement went into effect in 2020.<sup>63</sup> Two experts and two stakeholders said independent IRBs are more likely to be selected as the single IRB because they generally have more experience working with multiple research study sites. An article we reviewed and some experts and IRBs noted that it is unclear how the change to the use of single IRBs will affect how human subjects are protected.<sup>64</sup>

**Private investment in IRBs.** In addition to the federal actions that led to increased use of independent IRBs, private investment in independent IRBs also led to IRB consolidation, according to some experts and stakeholders.<sup>65</sup> Thus, while independent IRBs have conducted an increasing share of reviews since 2012, these reviews have been increasingly concentrated among a smaller number of independent IRBs, some experts and stakeholders told us. According to some experts and one stakeholder we interviewed, as well as trade documents we reviewed, as independent IRBs became profitable, private equity companies began to add independent IRBs to their portfolios. Private equity firms generally increase their assets through mergers and acquisitions and then eventually sell their assets for a profit. As a result, larger IRBs with private equity backing began to acquire multiple smaller independent IRBs, which led to consolidation and a decrease in the number of active independent IRBs, according to an expert and some stakeholders we interviewed, published trade articles and a research document we reviewed, and our analysis of OHRP IRB Registry data.<sup>66</sup>

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<sup>63</sup>See Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7,149 (Jan. 19, 2017); HHS Policy for the Protection of Human Research Subjects, 84 Fed. Reg. 64,432 (Nov. 22, 2019). In September 2022, FDA issued a proposed rule that, if finalized, would require any institution located in the United States participating in FDA-regulated cooperative research to rely on review and approval by a single IRB. See 87 Fed. Reg. 58,752 (Sep. 28, 2022).

<sup>64</sup>A. Ervin, H. A. Taylor, and S. Ehrhardt, "NIH Policy on Single-IRB Review — A New Era in Multicenter Studies," *New England Journal of Medicine*, vol. 375, no. 24 (2016): 2315-2317.

<sup>65</sup>Our categorization of independent IRBs is without regard for the for-profit or not-for-profit status of an organization. According to this categorization, independent IRBs may operate as a for-profit or a not-for-profit enterprise.

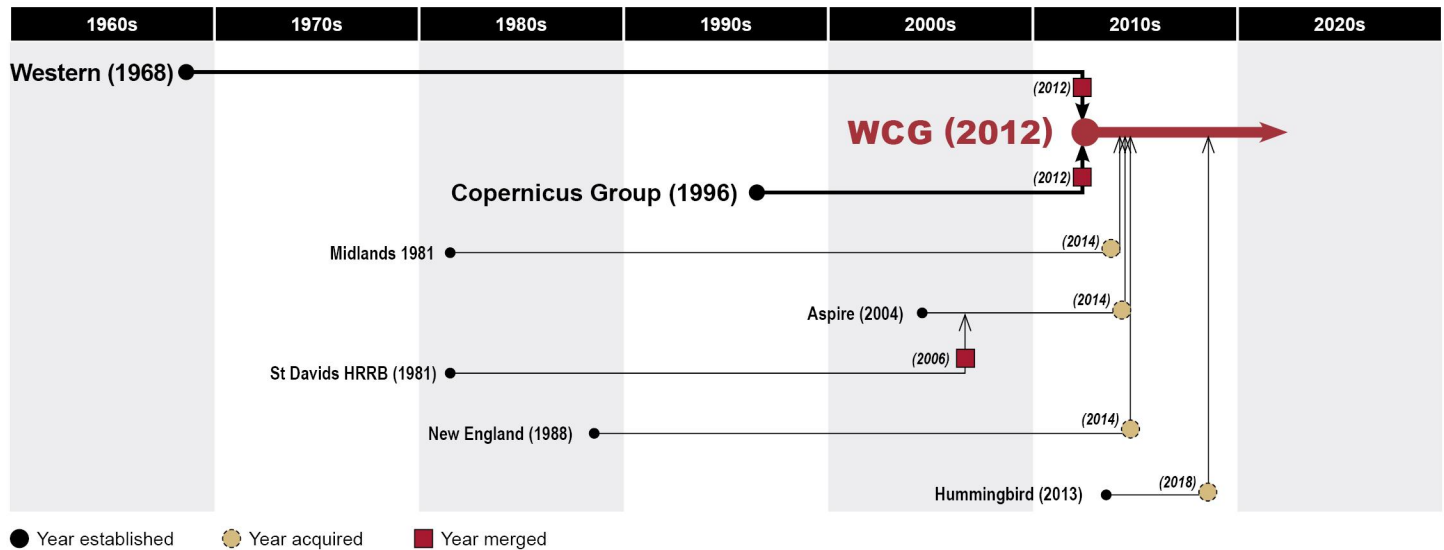
<sup>66</sup>Korieth, "IRB market consolidating rapidly."

Two independent IRBs with private equity backing—WCG and Advarra—illustrate the trend in IRB market consolidation.<sup>67</sup> Both developed through the consolidation of existing independent IRBs and accounted for about 92 percent of the clinical research conducted under investigational new drug applications involving regulated drugs and biologics in 2021 and reviewed by independent IRBs, according to our analysis of FDA data.

WCG was formed from the merger of Western IRB and Copernicus IRB Group in 2012. Since 2012, WCG has acquired another four independent IRBs. (See fig. 5.)

**Figure 5: Independent Institutional Review Board Consolidations in the Formation of WCG**

WCG formed in 2012 from the merger of two independent IRBs—Western and Copernicus Group—and has since acquired four additional IRBs.



Source: GAO analysis of WCG information. | GAO-23-104721

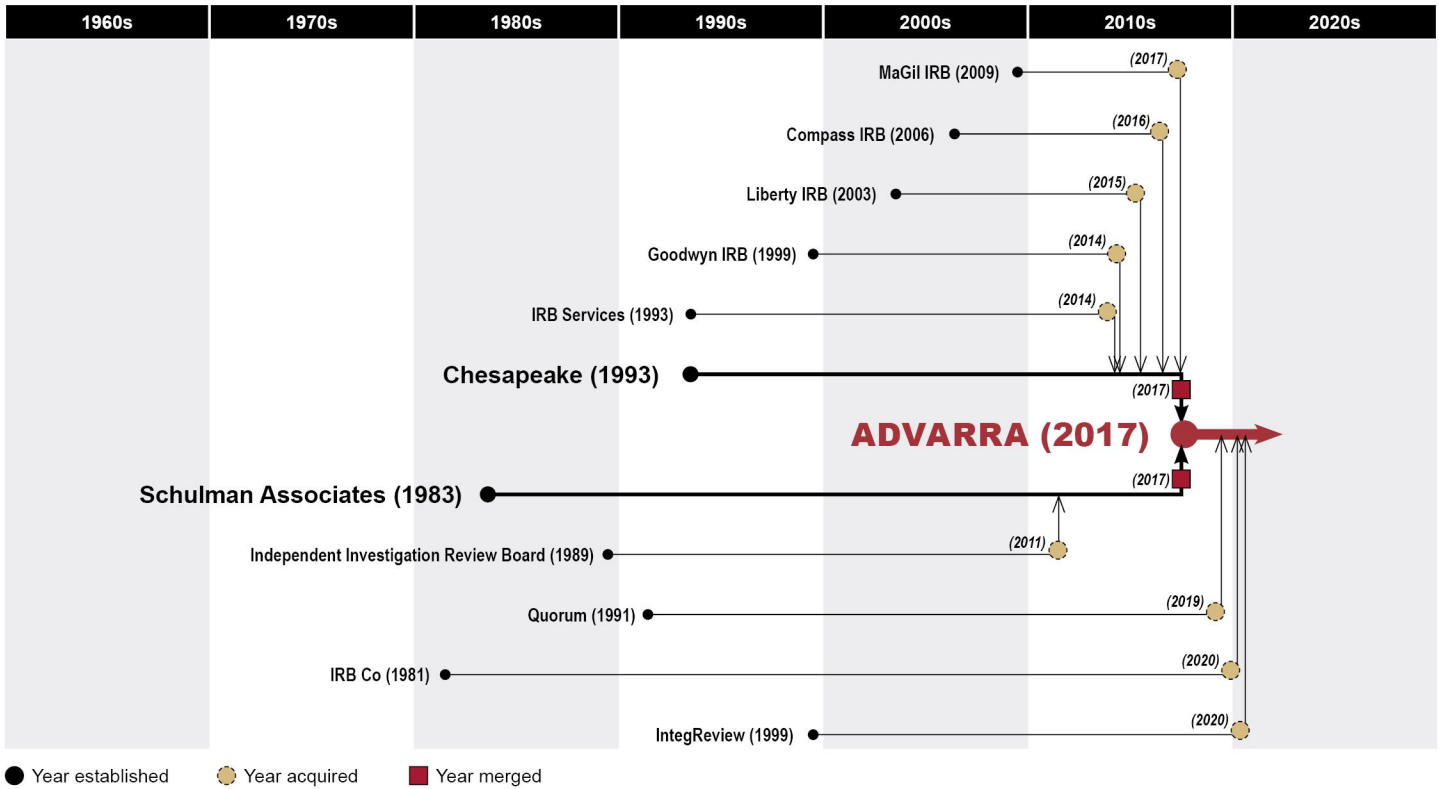
<sup>67</sup>The ownership of Advarra and WCG may change again in new ways, according to industry publications. The private equity firms that own both companies have indicated that they may offer shares in the ownership of these companies to the public through an initial public offering. An initial public offering is the sale of a private company's ownership shares to the public for the first time and is done to raise capital for the company. See Pitchbook, "Genstar explores sale, IPO of Advarra" (Seattle, W.A.: Feb. 11, 2022), accessed September 18, 2022, <https://pitchbook.com/newsletter/genstar-explores-sale-ipo-of-advarra>; and Reuters, "UPDATE 1-GIC-backed clinical trial firm WCG withdraws U.S. IPO plans" (New York, N.Y.: Oct 13, 2021), accessed September 18, 2022, <https://www.reuters.com/article/wcg-clinical-ipo/update-1-gic-backed-clinical-trial-firm-wcg-withdraws-u-s-ipo-plans-idUSL4N2R938M>.



Similarly, Advarra was formed from the merger of two independent IRBs—Chesapeake and Schulman Associates—in 2017. Prior to the creation of Advarra, both Chesapeake and Schulman Associates had acquired independent IRBs—six in total. Since 2017, Advarra has acquired another three independent IRBs. (See fig. 6.)

**Figure 6: Independent Institutional Review Board Consolidations in the Formation of Advarra**

Advarra formed in 2017 from the merger of two independent IRBs—Chesapeake and Schulman Associates—and has since acquired three additional IRBs.



Source: GAO analysis of Advarra information. | GAO-23-104721

In addition to the consolidation of independent IRBs, most experts, some stakeholders, and officials from two IRBs described other effects of investment in IRBs on the IRB market and its operations. They noted private investment in IRBs has led to several positive changes to the IRB industry. For example, an expert we interviewed noted that staff at private-equity backed IRBs were well trained and resourced, which leads to a high-level of trust in their reviews. Additionally, private equity backed

IRBs have the resources to provide training and educational opportunities to staff across the industry, which has led to increased professionalization of, and educational opportunities for, IRB staff at both independent and other types of IRBs, according to interviews we conducted with two IRBs that do not have private equity backing.

The growth in independent IRBs has led to specialization, according to two experts, two stakeholders, and two IRB officials. For example, officials with one hospital IRB we spoke to said they 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.<sup>68</sup>

According to data collected by AAHRPP from the institutions they accredit, about 46 percent of non-independent IRBs relied on an IRB not affiliated with their institutions in 2021 to review more than 10 percent of research protocols.<sup>69</sup>

Although independent IRBs were described by most experts and some stakeholders as efficient in conducting their reviews, an expert and two IRBs we interviewed indirectly attributed private equity investment in independent IRBs with a greater emphasis on IRB efficiency and speed across the industry. The expert credited private equity investment for other types of IRBs adopting approaches more common to independent IRBs, such as hiring IRB staff with experience and certifications that demonstrate their knowledge of the regulatory requirements to conduct and administer ethical research.

However, most experts and some stakeholders described potential negative effects of private investment in IRBs. For example, most experts and one stakeholder noted concerns that the emphasis on profit or faster IRB protocol review may have resulted in independent IRBs with private equity investment being less focused on potential harms of research to

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<sup>68</sup>According to FDA and NIH, clinical trials are conducted in sequenced steps called “phases”. Phase 1 trials test a drug or treatment for the first time to learn about safety and identify side effects, and may involve under 100 human subjects. In Phase 2 trials, the drug or treatment is given to a larger group of people (under 300) to determine effectiveness and further study safety. Phase 3 trials involve larger groups of people (under 3,000) to confirm effectiveness, monitor side effects, compare to standard or similar treatments, and collect information to enable safe use. Phase 4 trials track drug safety in the general population, after FDA approval.

<sup>69</sup>Association for the Accreditation of Human Research Protections Programs, Inc., “2021 Metrics for AAHRPP-Accredited Human Research Protection Programs,” (June 2022), accessed September 28, 2022, <https://www.aahrpp.org/resources/for-accreditation/metric/all-organizations-2021>.

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human subjects. According to some experts, a stakeholder, and an IRB we interviewed, private equity backed IRBs are beholden to their clients or equity holders. Three experts noted for-profit IRBs, in particular, may be more inclined to approve a protocol and do so expediently in order to satisfy a client. Officials with one IRB noted the importance of monitoring any changes to IRB quality to determine the effect of independent IRBs relative to other IRB types.

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## Selected IRBs Reported Implementing Recommended Practices to Strengthen the Quality of Their Reviews

Selected IRBs reported implementing practices for promoting the quality of IRB reviews, such as procedures for managing member conflicts of interest. IRB officials also reported implementing practices for assuring the quality of IRB reviews, such as audits of internal processes. We found variation in the extent to which the 11 IRBs in our sample implemented these practices.

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### Practices for Promoting Quality

IRB officials from our 11 selected IRBs reported implementing various practices for helping promote quality reviews. These practices were identified in expert interviews and in the literature we reviewed, and are consistent with federal regulations. Specifically, IRBs reported having procedures for managing member conflicts of interest, managing organizational conflicts of interest, and monitoring the conduct of research. Although recommended, 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.

**Examples of Member Conflicts of Interest**

**Definition:** Financial and non-financial interests of an institutional review board member that competes with their obligation to protect participants or compromises the credibility of the review process.

**Financial conflicts of interest example:** Board member reviews a protocol sponsored by ABC Pharmaceutical Company. Board member or board member’s family is employed by or a paid consultant to ABC Pharmaceutical Company.

**Non-financial conflicts of interest example:** Board member reviews a protocol submitted by an investigator with whom they have a close or professional relationship.

Source: GAO review of expert and stakeholder interviews, published literature, FDA regulations, and the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), *Evaluation Instrument For Accreditation* (2018). | GAO-23-104721

**Managing IRB member conflicts of interest.** Published literature and one expert recommend that IRBs implement practices that mitigate the risk of IRB members reviewing protocols for which they have a conflicting interest. This can include instances when the IRB member has a financial or non-financial interest in a study that the IRB is reviewing (see sidebar). While the Common Rule and FDA regulations stipulate that IRB members cannot participate in the review of research in which they have a conflicting interest, research has found that IRB members have participated in discussions of, and voted on protocols, with which they have conflicts.<sup>70</sup>

All of the 11 selected IRBs in our sample reported having processes in place to mitigate the risk of members reviewing protocols for which they have a conflict, although there was variation in the types of practices used.

To help ensure potential conflicts are identified, nine IRBs reported requiring members to disclose potential conflicts at time of appointment, and six IRBs reported having processes for members to update their disclosures on an ongoing basis. One IRB reported that it checks Open Payments—a publicly available register of payments made by drug and device companies to physicians—to determine if physician members have any undisclosed conflicts.<sup>71</sup> To help prevent members from reviewing protocols for which they have a conflict, 10 IRBs reported reminding board members at the beginning of meetings to recuse themselves, six IRBs reported having processes in place for members to alert IRB staff about conflicts with agenda items prior to meeting, and

<sup>70</sup>See 45 CFR § 46.107(d); 21 CFR § 56.107(e). Members with conflicts can participate to the extent the IRB requests information from them.

A 2015 study of conflicts of interest based on a survey of IRB members at academic institutions found that IRB members had conflicts, although there were some improvements compared to a 2005 study. Specifically, among those members who reported they had conflicts, 20 percent did not always disclose these conflicts to the IRB, 32 percent did not always leave the room when protocols for which they had a conflict were being considered, and 25 percent voted on protocols for which they had a conflict. In comparison, for example, the 2005 study showed that 45 percent of IRB members reported they did not always disclose these relationships. See Eric G. Campbell et al., “Industry Relationships Among Academic Institutional Review Board Members: Changes From 2005 Through 2014,” *JAMA Intern Med* 175, no 9 (2015):1500–1506.

<sup>71</sup>See Centers for Medicare & Medicaid Services, “What is Open Payments?,” (last modified June 30, 2022), accessed August 29, 2022, <https://www.cms.gov/openpayments>.

seven IRBs reported having processes for ensuring members are not assigned to studies with potential conflicts based on prior disclosures.

**Managing organizational conflicts of interest.** Published literature and two experts recommend that IRBs mitigate organizational conflicts of interest that may unduly influence the decision-making of the board. In contrast to member conflicts of interest, organizational conflicts of interest can occur when the organization to which the IRB reports has a business interest in the study or studies the IRB is reviewing. There are no requirements under the Common Rule or FDA regulations for IRBs to manage organizational conflicts of interest, although, according to OHRP and FDA officials, IRBs can set their own requirements.<sup>72</sup> Some experts and one stakeholder have suggested that while both affiliated IRBs—such as IRBs affiliated with hospitals or universities—and independent IRBs are at risk for organizational conflicts of interest, the sources of organizational conflicts of interest differ by IRB type. Previous reports have suggested that unless properly managed, these conflicts put organizations at risk of placing undue pressure on the IRB to rush through reviews or approve inadequate protocols.<sup>73</sup>

Ten of the 11 selected IRBs reported having procedures related to mitigating organizational conflicts of interest. For example, five of the independent IRBs in our review prohibit individuals involved in company business operations from serving on the review board, and four affiliated IRBs prohibit individuals involved in attracting and securing research funding at the affiliated institution from serving on the board. Examples of the types of strategies used by selected IRBs to manage organizational conflicts of interest are described in Table 1.

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<sup>72</sup>In 2004, HHS issued guidance on financial conflicts of interest, which directs research institutions engaged in HHS conducted or supported human subjects to consider certain institutional conflict management strategies. FDA has also recommended that institutions and IRBs should determine what constitutes a conflicting interest. According to FDA officials, this extends to IRBs in considering organizational conflicts of interest. See Department of Health and Human Services, *Guidance for Human Subject Protection: Financial Relationships and Interests in Research Involving Human Subjects* (May 2004); Department of Health and Human Services, Office for Human Research Protections and Food and Drug Administration, *Guidance for Institutions and IRBs: Institutional Review Board (IRB) Written Procedures* (May 2018); and Protection of Human Subjects: Informed Consent, 46 Fed. Reg. 8,942, 8,966 (Jan. 27, 1981).

<sup>73</sup>See Department of Health and Human Services Office of Inspector General, OEI-01-97-00193; National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants* (Bethesda, M.D., 2001); and Institute of Medicine, *Responsible Research*.

**Table 1: Examples of Sources of and Practices Used to Manage Organizational Conflicts of Interest, According to Selected Institutional Review Boards (IRB)**

IRB Type	Source of Conflict	Conflict Mitigation Strategy <sup>a</sup>
<b>Independent IRBs</b>	Companies that provide independent IRB services may profit from IRB review of research protocols.	<ul style="list-style-type: none"> <li>• IRB members are prohibited from holding equity in the company.</li> <li>• Individuals responsible for the company's business development are prohibited from serving on the board, participating in day-to-day operations of the IRB, and from attending board meetings.</li> <li>• Board members are separated from individuals responsible for business development, such as through prohibitions on discussing specific board deliberations or determinations; and restricting board members' access to information regarding the company's business development or finances.</li> </ul>
<b>Independent IRBs</b>	Companies that provide independent IRB services may offer non-IRB services to the entities sponsoring or conducting the study, such as consulting on the design of the clinical trial.	<ul style="list-style-type: none"> <li>• Board members and IRB staff are separated from staff who provide other company services, including through restrictions on contact.</li> </ul>
<b>Independent IRBs</b>	Companies that provide independent IRB services may have investors who also invest in companies that sponsor research, such as biomedical device companies.	<ul style="list-style-type: none"> <li>• Investors do not have access or visibility into IRB operations, including the protocols that the IRB reviews.</li> </ul>
<b>Affiliated IRBs<sup>b</sup></b>	IRBs may be affiliated with universities, hospitals, or other institutions that obtain financial support from the conduct of research involving human subjects.	<ul style="list-style-type: none"> <li>• Individuals responsible for attracting and securing research funding for the affiliated institution (e.g., the Vice President for Research) are prohibited from serving on board or being involved in its daily operations.</li> <li>• A board member who is unaffiliated with institution—that is, not an employee or contractor, or an immediate family member of an employee or contractor—is required to be present at all board meetings.<sup>c</sup></li> </ul>
<b>Affiliated IRBs<sup>b</sup></b>	IRBs may be affiliated with universities, hospitals, or other institutions that have investments in, or receive payments or gifts from, study sponsors.	<ul style="list-style-type: none"> <li>• Affiliated institutions have systems to track their financial ties and identify studies submitted to IRB that present an organizational conflict.</li> <li>• Affiliated institutions have conflicts of interest offices or committees that review potential study-specific conflicts of interest and develop conflict management plans, which may include ceding the IRB review of the study to an external IRB.</li> </ul>
<b>All IRBs</b>	Senior company or institutional officials may have ties to a study sponsor.	<ul style="list-style-type: none"> <li>• Organizational conflicts of interest policies address conflicts of senior officials, such as presidents, vice presidents, and members of the company's board of directors.</li> <li>• Senior officials are required to complete regular disclosure forms and conflict management plans are developed when the board reviews a protocol for which an official has a conflict.</li> <li>• Senior officials are prohibited from directly holding stock in any company sponsoring research that is reviewed by the board.</li> </ul>

Source: GAO analysis of published literature, reports, and a quality assessment tool, as well as interviews, written responses, and documents from affiliated and independent IRBs, and one expert interview. | GAO-23-104721

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Note: The source of the conflict may be more applicable to certain types of IRBs than others, as the source of organizational conflicts of interest depends on the circumstances of the IRB.

<sup>a</sup>Practices were reported by a non-generalizable sample of six independent IRBs and five affiliated IRBs.

<sup>b</sup>We use the term affiliated IRB to refer to an IRB affiliated with a university, hospital, private, or government institution.

<sup>c</sup>Federal regulations require IRBs to have a member who is unaffiliated with the institution on the board, however, this member does not need to be present for the IRB to vote on protocols. 45 CFR §§ 46.107(c), 46.108(b); 21 CFR §§ 56.107(c), 56.108(c).

**Monitoring the conduct of research.** Published literature and two experts recommend that IRBs monitor the conduct of research—activities that include visiting research sites and evaluating investigators to narrow the gap between the IRB review process and real-world situations that may place research participants at risk for harm. The Common Rule and FDA regulations require that IRBs follow written procedures for ensuring changes in research activity are being reported to the IRB before they are initiated.<sup>74</sup> OHRP and FDA’s 2018 joint guidance on written procedures for IRBs recommends that IRBs undertake certain activities, such as random audits of research records, to ensure this is occurring.<sup>75</sup>

Most IRBs in our sample reported conducting site visits to observe the conduct of research, but with the type of visit and process varying. These visits may include review of regulatory information regarding the trial, the files of enrolled subjects and signed consent forms, as well as interviews with investigators and research staff, according to IRB officials. After these visits, IRB board members review any findings of noncompliance and may take actions when indicated. Affiliated IRBs collaborate with others within their institutions’ human research protection program to conduct such visits.

- Officials representing 10 of the 11 selected IRBs reported that they conduct (or, in the case of affiliated IRBs, request that the research compliance program at their institution conduct) a site visit if there is cause, such as the IRB received complaints or concerns of noncompliance or misconduct at a research site.
- Officials from two of the six independent IRBs and four of the five affiliated IRBs in our sample said they incorporated routine, not-for-

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<sup>74</sup>45 C.F.R. § 46.108(a)(3); 21 C.F.R. § 56.108(a)(3)-(4).

<sup>75</sup>See Department of Health and Human Services, Office for Human Research Protections and Food and Drug Administration, *Guidance for Institutions and IRBs: Institutional Review Board (IRB) Written Procedures* (May 2018).

cause site visits into their review processes.<sup>76</sup> Conversely, officials from two independent IRBs that do not conduct routine site visits reported they expect study sponsors to oversee research sites and report noncompliance to them.<sup>77</sup>

Officials with the four affiliated IRBs also reported providing IRB review on behalf of one or more institutions they are not affiliated with, also known as serving as the single IRB. However, when serving as a single IRB for another institution, none of these IRBs reported conducting routine site visits of those research studies. Officials with two of these IRBs explained that they expect research institutions to be overseen by their local research compliance program, and to be notified of any findings of noncompliance.

See app. II for information on additional practices that officials at a non-generalizable sample of eleven IRBs reported using to protect human research subjects.

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## Practices for Assuring Quality

Experts that we interviewed and published literature recommend that IRBs engage in a number of quality assurance activities to assess their performance and thereby identify opportunities for improvement, even though the Common Rule and FDA regulations do not have quality assurance requirements. Additionally, while OHRP and FDA have developed tools that any IRB can use to perform operational assessments, use of these tools by IRBs is optional and neither OHRP

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<sup>76</sup>Officials representing these four affiliated IRBs reported that they or their institution's research compliance program regularly conduct routine, not-for-cause site visits of research conducted at their institution.

Officials reported using different considerations when selecting studies for not-for-cause site visits, such as the probability of risks to the subjects, whether the study included vulnerable subjects or subjects with complex medical conditions, a high number of changes to the protocol, the rapid enrollment of subjects, and inexperienced investigators or research team members.

<sup>77</sup>Under FDA regulations, sponsors are required to monitor the progress of all clinical investigations being conducted under investigational drug applications, including ensuring that the investigator is complying with the protocol. See 21 C.F.R. § 312.56.



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nor FDA review the results of these assessments as part of their oversight activities.<sup>78</sup>

Selected IRBs reported conducting a number of quality assurance activities, including assessing their operations and auditing their processes, seeking accreditation or staff certifications, and conducting quality measurement. These approaches are voluntary and not validated or standardized, and it is unclear how widely some of these practices are used by IRBs that we did not interview.

**Operational assessments and process audits.** Officials from nine of our 11 selected IRBs reported conducting some type of annual assessment to examine their operations, such as policies, staffing, number and composition of boards, and the education that they provide members.

Additionally, IRB officials from 10 of our 11 selected IRBs reported conducting some form of regular auditing of their internal processes; however, there was variation in the approaches used. These internal auditing programs ranged from audits focused on areas identified as deficient during previous external audits—including audits by FDA or sponsors—to more comprehensive audits focused on both procedural compliance and the quality of board decision-making. (See Table 2.) For example, IRBs reported assessing meeting minutes to ensure that conflicted members recused themselves from voting on conflicted items and IRB-approved informed consent forms to ensure that forms contain all elements required by federal regulations. Most selected IRBs reported auditing IRB documents, such as protocol files and meeting minutes (nine IRBs), while fewer reported they observed board meetings (four IRBs). Seven selected IRBs reported conducting audits on a scheduled basis, and five set standards for the number of audits that they will conduct each year. There are no requirements under the Common Rule or FDA regulations for IRBs to conduct operational assessments or quality audits.

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<sup>78</sup>For example, according to OHRP officials, the *Quality Assurance Self-Assessment Tool* can be used by IRBs to identify gaps in the performance of their IRB. The tool helps IRBs assess workload and staffing resources of the IRB, educational training for IRB staff and members, the IRB review process, and IRB meeting minutes, among other things. Additionally, according to OHRP and FDA, *Guidance for Institutions and IRBs: Institutional Review Board (IRB) Written Procedures* (May 2018) helps institutions prepare and maintain written procedures that address regulatory requirements as well as additional topics that institutions should consider, such as what constitutes a conflicting interest.

**Table 2: Examples of Practices Selected Institutional Review Boards (IRB) Reported Using to Audit Internal Processes**

Category	Category information
<b>Protocol files</b>	Quality assurance staff review protocol files to ensure that there are no missing documents, the appropriate level of review was performed (exempt, expedited, full board), staff and reviewers used checklists, informed consent forms contain all required elements of consent, and decisions were appropriate.
<b>Meeting minutes</b>	Quality assurance staff review meeting minutes to ensure votes were captured, quorum was present, conflicted members recused themselves from the discussion and vote for the conflicted item, members knowledgeable about a particular vulnerable population were present if a protocol involving a vulnerable population was reviewed, and discussions of controverted issues and their resolution, reasons for modifications, and determinations were documented.
<b>Meeting observations</b>	Quality assurance staff observe meetings to assess whether board members received the appropriate materials in advance of the meeting, the chair’s role in leading the meeting, the primary reviewer’s presentation, and whether board members spent an adequate amount of time reviewing each submission. IRB chairs observe other board meetings to assess the decision-making or the performance of chairs, vice chairs, and members.

Source: GAO analysis of interviews, written responses, and policies of selected affiliated and independent IRBs. | GAO-23-104721

Note: Practices were reported by a non-generalizable sample of six independent IRBs and five affiliated IRBs.

**Accreditation.** Eight IRBs in our sample and a total of about 200 organizations in the United States are accredited by AAHRPP. An IRB, either as an independent entity, or as part of an institution’s human research protection program, can obtain accreditation through AAHRPP.<sup>79</sup> AAHRPP accreditation involves a self-examination process whereby the entity ensures that its policies and procedures align with AAHRPP standards—which are based, in part, on the Common Rule and FDA regulations—followed by a site visit that is performed by peers. According to AAHRPP officials, site visits involve a review of the organization’s policies and interviews with personnel to assess whether they have an understanding of those policies and other expectations.

AAHRPP-accredited IRBs in our sample reported that accreditation assists them in meeting regulatory requirements and filling in gaps in the regulatory framework, aligning practices with peers, and identifying opportunities for improvement. However, two selected non-accredited IRBs noted they were able to meet federal requirements without incurring

<sup>79</sup>AAHRPP is the only active accreditor of human research protection programs in the United States. Note that we selected IRBs for our sample, in part, with consideration of whether they were AAHRPP accredited. According to AAHRPP, the majority of organizations they accredit are academic organizations, and all major independent IRBs are accredited.

the extra cost of accreditation.<sup>80</sup> Two stakeholders and two experts indicated that AAHRPP accreditation is recognized as the hallmark of quality in the field. Some experts as well as an OHRP official and an NIH official also noted limitations with the AAHRPP accreditation process, including that the process focuses on policies and paperwork and does not include auditing IRB meetings or decisions or interacting with research participants. OHRP and FDA officials also noted that there is no evidence that indicates that accreditation leads to improvement in IRB quality and neither the Common Rule nor FDA regulations require IRBs to obtain accreditation.

**Certification.** Officials from nine of the 11 selected IRBs reported employing some staff who have passed certification exams regarding the rules and regulations governing IRBs in the United States and IRB administrative practices, such as from the Public Responsibility in Medicine and Research (PRIM&R).<sup>81</sup> According to a 2019 RAND study, 52 percent of IRB administrators were certified.<sup>82</sup> Officials from five of our selected IRBs reported requiring certification for certain positions; certification ensures that IRB staff members have a thorough understanding of IRB regulations and the review process, according to officials with three selected IRBs. However, officials from one IRB reported that they do not consider such certification a necessary marker of proficiency, and FDA officials noted that there is no evidence indicating that certification of IRB staff improves an IRB's review.<sup>83</sup> As with accreditation, the Common Rule and FDA regulations do not require IRBs to have certified administrative staff.

**Quality measurement.** Nine of 11 selected IRBs reported collecting performance measurement data. The Common Rule and FDA regulations

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<sup>80</sup>The cost of AAHRPP accreditation varies based on the number of active protocols overseen by the IRB. For initial accreditation, this cost can range from about \$13,000 to about \$91,000, with annual fees ranging from about \$6,000 to about \$28,000 thereafter. FDA and OHRP officials noted that these costs may be prohibitive for some organizations.

<sup>81</sup>In addition to PRIM&R, Professional Certification Services Testing also offers certification exams for IRB professionals. Among selected IRBs we interviewed, most noted their staff were certified by PRIM&R.

<sup>82</sup>Sandra H. Berry et al., *Profile of Institutional Review Board Characteristics*.

<sup>83</sup>FDA officials noted that these costs may be prohibitive for some IRB staff. The cost of PRIM&R certification is at least \$350 and the cost of Professional Certification Services Testing is \$300, with additional renewal costs.

do not require IRBs to collect performance measures that IRBs can use to evaluate their quality.<sup>84</sup>

- Most measures these IRBs reported collecting pertain to operational performance (e.g., volume of reviews, review turnaround time, customer satisfaction) or regulatory compliance.
- Three IRBs reported tracking unanticipated problems involving risk to subjects, investigator noncompliance, or research participant complaints. As officials with one IRB explained, while these measures are not direct indicators of IRB performance because the IRB review process may have no bearing on whether such events occurred, they may highlight systemic issues in the IRB review process or in the system designed to support the conduct of research.
- Two IRBs reported surveying IRB members to assess the quality of the IRB review process.<sup>85</sup>
- One affiliated IRB reported surveying research participants about their experience (see text box). However, this IRB reported it does not survey subjects who participate in research at sites not affiliated with its institution when the IRB is serving as a single IRB for other institutions. Officials from three selected IRBs noted there are challenges to surveying subjects if an IRB is not affiliated with the site of research, as IRBs do not have the contact information of research participants in the studies that they oversee.

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<sup>84</sup>In commenting on a draft of this report, OHRP noted its *Quality Assurance Self-Assessment Tool*—while it does not assess effectiveness—is intended to help institutions understand the strengths and potential gaps in their IRB operations and human research protection programs.

<sup>85</sup>Although these IRBs did not indicate what tool they use to conduct these surveys, the IRB Researcher Assessment Tool (IRB-RAT) has been used to measure IRB quality from the perspective of IRB members, IRB staff, and investigators whose protocols are reviewed by the IRB. For example, survey questions ask respondents to assess whether the IRB recognizes when it lacks sufficient expertise, conducts a “conscientious informed analysis” of potential risks and benefits, and views the protection of human participants as its primary function. See Patricia Keith-Spiegel, Gerald P. Koocher, and Barbara Tabachnick, “What Scientists Want from Their Research Ethics Committee,” *Journal of Empirical Research on Human Research Ethics*, vol. 1, no. 1 (2006): 67-82.; Jonathan C. Reeser et al., “Investigating Perceived Institutional Review Board Quality and Function Using the IRB Researcher Assessment Tool,” *Journal of Empirical Research on Human Research Ethics*, vol. 3, no. 1 (2008): 25-34.

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**Research Participant Perception Survey**

The Research Participant Perception Survey was developed to assess the perspectives of research participants regarding their research experience. This survey contains the following questions that pertain to the effectiveness of IRB review of informed consent forms:

- Were the risks of joining the study included on the informed-consent form?
- Were the details of the study included on the informed-consent form?
- Was the informed-consent form written in a way that you could understand?
- Did the informed-consent form prepare you for what to expect in the research study?

Source: GAO review of Rhonda G. Kost et al., "Assessing Participant-Centered Outcomes to Improve Clinical Research." *New England Journal of Medicine*, vol. 369, no. 23 (2013): 2179–2181. | GAO-23-104721

Some experts, officials from two selected IRBs, and agency officials reported that the available measures do not directly examine the IRB's ability to make ethical decisions or protect human subjects. Officials at one IRB acknowledged the need to develop such measures, and officials at a second noted they were considering actions they could take to help foster the development of such measures in response to recommendations made by an external review of their operations.

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## FDA and OHRP Inspect IRBs, but Inspections Are Limited and Agencies Have Not Examined IRB Effectiveness

FDA and OHRP rely on inspections to oversee IRBs. However, these inspections are limited by inaccuracies in the data used to inform them, and the agencies have not conducted a risk-based assessment of their IRB inspection program. Further, while OHRP and FDA use inspections to assess whether IRBs are following regulations, the agencies have not examined the effectiveness of IRBs in protecting human subjects.

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## FDA and OHRP Use Annual Inspections to Oversee IRBs

Based on our review of agency documentation and interviews with officials, we found that FDA and OHRP conduct two types of compliance inspections as a key mechanism for ensuring IRBs adhere to human subject protection regulations: routine inspections and for-cause

inspections, which are conducted in response to allegations of noncompliance.<sup>86</sup>

In some ways, FDA and OHRP use similar inspection approaches, and some IRBs fall under both FDA and OHRP jurisdiction. When selecting entities to inspect annually, both agencies consider specific factors, such as the volume of research reviewed and available resources, and both use those inspections to determine if noncompliance exists.<sup>87</sup> However, the agencies also differ in their approaches. For example, OHRP has historically inspected research institutions. As such, OHRP inspections evaluate an institution's human research protections program and are not limited to the activities of the IRB.<sup>88</sup> Other differences include the information used to select IRBs to inspect, and the categorizations used to classify inspection findings. (See Table 3.)

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<sup>86</sup>The agencies also issue guidance and provide education and outreach to assist all types of IRBs and research institutions in adhering to federal regulations on the protection of human research subjects. For more information on these activities, see App. IV. In addition, OHRP reviews incident reports, which are submitted when reportable events occur, such as unanticipated problems involving risks to subjects or others. In commenting on a draft of this report, HHS officials said that monitoring incident reporting is important because it provides information on the types of noncompliance that occurs in human subjects research.

<sup>87</sup>OHRP officials told us that OHRP and FDA officials meet regularly to discuss allegations of IRB non-compliance that fall under both agencies' jurisdiction to determine which agency is the most appropriate to lead an investigation, but do not consult with each other when selecting IRBs for inspections.

<sup>88</sup>Within research institutions, human research protection programs establish and enforce appropriate policies and procedures for the protection of human subjects and ensure investigators conduct research activities in accordance with the terms of the IRB approval. IRBs are generally one component of an institution's human research protection program.

**Table 3: FDA and OHRP Inspections of Institutional Review Boards (IRB)**

	<b>Food and Drug Administration (FDA)</b>	<b>Office for Human Research Protections (OHRP)</b>
<b>IRBs subject to oversight<sup>a</sup></b>	1,481 IRBs within 1,042 organizations	2,149 IRBs within 1,641 organizations
<b>Approach for selecting IRBs to inspect</b>	<p>Routine: FDA uses a site selection tool to consider several factors, such as the last inspection date, last inspection finding, and the number of FDA and total protocols reviewed.</p> <p>For cause: FDA initiates inspection in response to an allegation of noncompliance. A for-cause inspection may be limited to the topic of the allegation or cover all aspects of compliance.</p>	<p>Routine: OHRP considers several factors, including the volume of HHS-supported research the institution conducts, whether the institution submits any incident reports to OHRP, and whether an inspection is needed to evaluate implementation of corrective actions following a previous for-cause inspection. OHRP refers to this type of inspection as an evaluation.</p> <p>For cause: OHRP initiates inspection in response to an allegation of noncompliance. OHRP's inspection is generally limited to the topic of the allegation; however, OHRP officials said they evaluate other issues of noncompliance that arise during the inspection. OHRP refers to this type of inspection as an investigation.</p>
<b>Inspection approach</b>	<p>Inspections consist of an in-person review of the following by one or more inspectors: a sample of up to 3 research protocols reviewed; IRB documentation, including written procedures, IRB membership rosters, and up to 12 months of IRB minutes; and interviews with various IRB administrative staff and members.</p>	<p>Inspections evaluate an institution's human research protections program, and those inspections are not limited to the activities of the IRB.<sup>b</sup> Inspections involve a team of 8 to 10 inspectors.</p> <p>Inspections are in person or virtual. With respect to IRBs, OHRP staff review similar documentation and conduct similar interviews as FDA.<sup>c</sup> OHRP officials told us they review documentation for 30-50 studies and at least 6 months of IRB meeting minutes. In addition, OHRP observes 1-2 IRB meetings.</p> <p>For cause investigations may involve more than one organization operating an IRB if, for example, a multi-site trial is under review.</p>
<b>Findings classifications</b>	<p>Three classification levels.</p> <p><u>No action indicated:</u> Objectionable conditions or practices were not found.</p> <p><u>Voluntary action indicated:</u> Objectionable conditions or practices were found, but the agency is not taking or recommending any administrative or regulatory action because it does not meet threshold for regulatory action.</p> <p><u>Official action indicated:</u> Objectionable conditions or practices were found and the agency is taking administrative or regulatory action.<sup>d</sup> These actions may include withholding the approval of new studies conducted at the institution or reviewed by the IRB.<sup>e</sup></p>	<p>Eight outcomes that fall into three classification levels.</p> <p><u>No findings:</u> Noncompliance with regulations were not found.</p> <p><u>Recommendations:</u> OHRP may suggest improvements to IRB's or institution's human subject protection program or procedures.</p> <p><u>Findings of noncompliance:</u> Noncompliance with one or more requirements was found, or IRB review or conduct was determined to be noncompliant with regulations. In response OHRP may take one of the following actions: require that the institution develop and implement corrective actions; place restrictions or conditions on the institution's Federalwide Assurance (FWA), such as requiring special reporting to OHRP or that OHRP review of some or all research projects to be conducted under the FWA; or suspend the institution's FWA.<sup>f</sup></p>

Source: GAO analysis of Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) information. | GAO-23-104721

<sup>a</sup>These totals represent active IRBs located in the United States that were registered with OHRP as of April 2021 and reported that they reviewed research subject to FDA, OHRP, or joint jurisdiction. Of the 2,303 active IRBs in the United States as of April 2021, we found that 1,327 IRBs (58 percent)

reported that they reviewed at least one FDA-regulated and at least one HHS-sponsored protocol, subjecting them to both FDA and OHRP jurisdiction.

<sup>b</sup>According to OHRP officials, the approach for inspecting independent IRBs will vary somewhat. As of June 2022, OHRP officials told us they were in the process of updating their compliance oversight procedures for routine inspections of independent IRBs.

<sup>c</sup>According to OHRP officials, because OHRP inspections evaluate an institution's human research protections program, OHRP inspections also include a review of institutional policies and procedures for investigators, and interviews with researchers who received HHS funding.

<sup>d</sup>In response to a finding of official action indicated, FDA issues a letter to the IRB. According to FDA, Restrictions Imposed Letters identify noncompliance and impose restrictions that, if not corrected, may result in FDA disqualifying the IRB. FDA issues Warning Letters to achieve voluntary compliance, and may include restrictions for the IRB until it or the research institution take appropriate corrective action. FDA issues Untitled Letters when violations cited do not meet the threshold for regulatory significance for a Warning Letter.

<sup>e</sup>Other actions FDA could take include directing the institution to add no new subjects to ongoing studies; terminating ongoing studies when doing so would not endanger the subjects; and notifying relevant state and federal regulatory agencies and other parties with direct interest in FDA's action of the deficiencies in the IRB in instances when the apparent noncompliance creates a significant threat to the rights and welfare of human subjects.

<sup>f</sup>Other actions OHRP could take include: recommending to appropriate HHS officials that an institution or investigator be temporarily suspended or permanently removed, recommending that the institutions or investigators be debarred in accordance with the procedures specified at 2 C.F.R. Part 376, or referring the matter to another federal department or agency for further review and action.

As noted in Table 3, FDA and OHRP consider several factors when selecting IRBs to inspect. For example, FDA uses a selection tool to consider various information including the date of FDA's last inspection, prior inspection findings, and the number of FDA protocols under review that were reported in the OHRP IRB Registry. OHRP considers the volume of HHS-supported research and whether the research institution regularly submits incident reports, which are reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance, among other factors. The type of IRB—information that officials from both agencies said they do not collect—has not been a factor considered when selecting IRBs to inspect. FDA officials noted that although their risk-based site selection tool does not directly consider IRB type in determining which IRBs to inspect, IRBs that oversee a large number of protocols (such as independent IRBs) may be prioritized for FDA inspections since the number of protocols reviewed by the IRB is a data point weighted heavily by the FDA selection tool.

**Volume of inspections.** Our analysis of FDA and OHRP inspection data for fiscal years 2010 through 2021 shows that FDA completed more inspections than OHRP. From fiscal years 2010 through 2021, FDA completed 1,599 inspections of 1,054 IRBs, an average of about 133 inspections per year, inspecting roughly 13 percent of IRB organizations a



year.<sup>89</sup> According to FDA, the lower number of inspections conducted in fiscal years 2020 and 2021—52 and 20, respectively—was due to COVID-19 travel restrictions. During the same 12-year period, OHRP completed 88 inspections, or an average of about seven inspections per year.<sup>90</sup> This equates to OHRP inspecting annually less than 1 percent of IRBs it oversees, and roughly 5 percent of IRBs in total over the 12-year period. OHRP officials noted that they consider their inspections to be more comprehensive than FDA’s, including because they inspect an organization’s entire human research protections program and not solely the IRB, observe the conduct of the board by attending an IRB meeting, and review more research protocols, among other differences. (See Table 4.)

**Table 4: Number of Completed Inspections by Inspection Type and Fiscal Year**

Category	Inspection type	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
Food and Drug Administration (FDA)	Routine	175	183	136	149	140	118	132	137	131	98	52	18	1,469
	For-cause <sup>a</sup>	20	15	20	16	18	12	8	7	11	2	0	2	130
Food and Drug Administration (FDA)	<b>Total<sup>b</sup></b>	<b>195</b>	<b>198</b>	<b>156</b>	<b>165</b>	<b>158</b>	<b>130</b>	<b>140</b>	<b>144</b>	<b>141</b>	<b>100</b>	<b>52</b>	<b>20</b>	<b>1,599</b>
Office for Human Research Protections (OHRP)	Routine	3	4	4	3	4	2	4	3	1	1	0	0	29

<sup>89</sup>Over this time period, FDA inspected over 1,000 unique IRBs, as FDA inspected some IRBs multiple times.

According to FDA officials, the agency consolidated and streamlined its inspection approach in 2019, which will result in fewer inspections than in prior years. Specifically, inspections will now cover a broader range of studies on FDA-regulated research, according to FDA officials. Previously, one center (e.g., the Center for Biologics Evaluation and Research) led an inspection and focused its review largely on studies regulated by the center.

<sup>90</sup>In addition to the completed inspections during this time period, OHRP began but had not completed another eight inspections, as of September 2022. According to OHRP officials, some of these inspections have not been completed due to resource constraints, including reduced staff resources; however, all findings from these inspections have been addressed.

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Category	Inspection type	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
Office for Human Research Protections (OHRP)	For-cause	12	12	9	5	2	3	8	3	0	2	3	0	59
	<b>Total</b>	<b>15</b>	<b>16</b>	<b>13</b>	<b>8</b>	<b>6</b>	<b>5</b>	<b>12</b>	<b>6</b>	<b>1</b>	<b>3</b>	<b>3</b>	<b>0</b>	<b>88</b>

Source: GAO analysis of FDA Field Accomplishments and Compliance Tracking System and OHRP inspection data. | GAO-23-104721

Note: Analysis is of FDA institutional review board (IRB) inspections and of all OHRP inspections in the 50 U.S. states and the District of Columbia, and is based on the year the inspection was completed. FDA inspections excludes inspections of Radioactive Drug Research Committees. OHRP inspections includes for-cause inspections in which allegations or findings were not directed to the IRB, but to the research team, investigator, or the institution at large, and separately counts inspections that involved multiple institutions. For example, if an OHRP inspection involved three different institutions, we counted it as three inspections. Five OHRP inspections were closed in 2022, and eight OHRP inspections remained open as of September 2022. FDA and OHRP inspection counts include re-inspections of the same IRB that occurred during the time period.

<sup>a</sup>For-cause inspections were conducted as a result of allegations, to follow-up on Warning Letters issued by FDA, to address consumer complaints, or as follow-up to prior inspections classified as “official action indicated.”

<sup>b</sup>According to FDA officials, the agency’s ability to conduct inspections in fiscal years 2020 and 2021 was significantly affected by COVID-19.

Our analysis of FDA and OHRP inspection data also shows that from fiscal years 2010 through 2021, the vast majority of inspections FDA conducted were routine (92 percent), whereas more of OHRP’s inspections (67 percent) were for cause. In addition, OHRP’s for-cause inspections decreased from 2000 to 2015, according to a 2017 HHS-OIG report. OHRP officials said the decrease in inspections was partially the result of the agency prioritizing other methods to resolve allegations of noncompliance.<sup>91</sup> For example, instead of initiating a for-cause inspection, the HHS-OIG reported that OHRP may contact a research institution directly to address allegations of noncompliance or to follow-up on the corrective actions initiated in response to noncompliance identified from incident reports.<sup>92</sup> OHRP officials told us that most allegations of noncompliance do not raise concerns about the conduct of the IRB, or can be resolved without an inspection. However, when a for-cause

<sup>91</sup>Department of Health and Human Services Office of Inspector General, *OHRP Generally Conducted Its Compliance Activities Independently, but Changes Would Strengthen Its Independence*, OEI-01-15-00350 (Washington, D.C.: July 2017).

<sup>92</sup>In response to a recommendation from that report, OHRP officials told us they post information about the agency’s compliance actions on OHRP’s website. For example, the website contains data on the number of complaints received.

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**Letter**

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inspection is warranted, it has the potential to uncover systemic issues, result in educational gain for the research community, or lead to the development of new policy, according to OHRP officials.

**Example of Office for Human Research Protections (OHRP) For-Cause Inspection and Result**

Between 2004 and 2009, 22 sites across the United States participated in a clinical trial known as the Surfactant, Positive Pressure, and Oxygenation Randomized Trial or “SUPPORT.” The trial aimed to determine what oxygen-saturation level would minimize the risk of retinopathy of prematurity, a potentially blinding eye disorder in premature infants. The study randomized infants into two groups: one group that maintained a lower oxygen-saturation rate and another group that maintained a higher saturation rate, where both groups maintained oxygen-saturation rates that were within the guidelines of the American Academy of Pediatrics.

Through the trial, investigators found lower rates of the disorder in the lower oxygen-saturation group; however, this group also had a significantly higher death rate. (As the result of the trial, the American Academy of Pediatrics amended its guidelines in support of providing premature infants higher oxygen-saturation rates due to the lower risk of death, despite the potentially higher risk of the blinding eye disorder.)

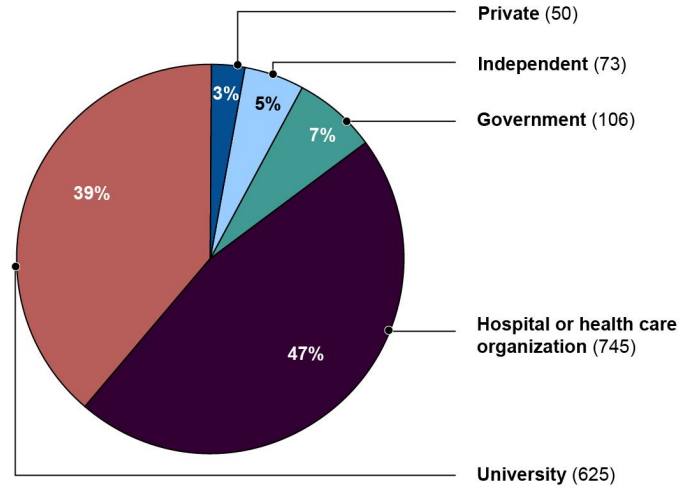
In 2011, OHRP began a for-cause inspection of the University of Alabama, Birmingham (UAB), the lead study site. In its findings, issued in 2013, OHRP noted it determined that the informed consent documents approved by the UAB institutional review board failed to include a description of all “reasonably foreseeable risks,” including the potentially higher risk of the disorder in the higher oxygen-saturation group and the higher risk of death in the lower oxygen-saturation group. OHRP also initiated compliance actions, but put them on hold pending the development of guidance to IRBs and the research community on how to define “reasonably foreseeable risks.” OHRP also released draft guidance in 2014 related to disclosing reasonably foreseeable risks in research evaluating standards of care. As of January 2023, OHRP was in the process of finalizing this guidance.

Sources: GAO analysis of a published article and OHRP documents. | GAO-23-104721

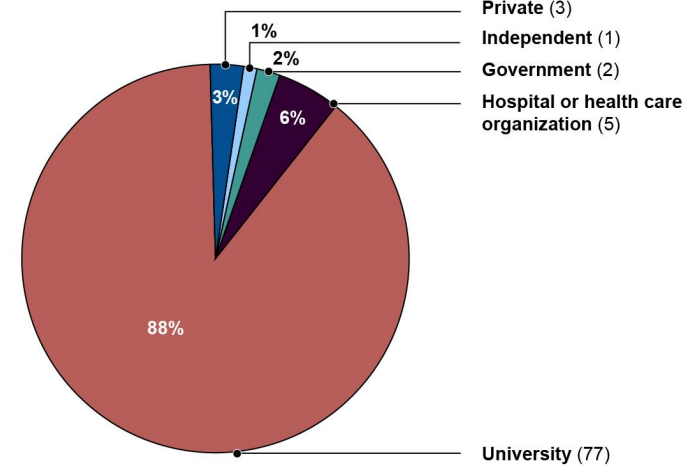
**Types of IRBs inspected.** The FDA and OHRP inspection data show that from fiscal years 2010 through 2021, 47 percent of FDA inspections were of IRBs based at hospitals or health care organizations, and 88 percent of OHRP inspections involved university-based IRBs. (See fig. 7).

**Figure 7: Completed Inspections by Type of IRB, Fiscal Years 2010 through 2021**

**Food and Drug Administration (FDA) inspections  
(Total: 1,599 inspections)**



**Office of Human Research Protections (OHRP) inspections  
(Total: 88 inspections)**



Source: GAO analysis of Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) data. | GAO-23-104721

**Accessible Data for Figure 7: Completed Inspections by Type of IRB, Fiscal Years 2010 through 2021**

IRB Type	Food and Drug Administration (FDA) Inspections	FDA Inspections	Office for Human Research Protections (OHRP) Inspections	OHRP Inspections
Private	50	3%	3	3%
Independent	73	5%	1	1%
Government	106	7%	2	2%
Hospital or healthcare organization	745	47%	5	6%
University	625	39%	77	88%
Total	1599	100%	88	100%

Notes: Analysis is of FDA institutional review board (IRB) inspections and of all OHRP inspections in the 50 U.S. states and the District of Columbia, and is based on the year the inspection was completed. OHRP inspections includes for-cause inspections in which allegations or findings were not directed to the IRB, but to the research team, investigator, or the institution at large, and separately counts inspections that involved multiple institutions. For example, if an OHRP inspection involved three different institutions, we counted it as three inspections. We categorized IRBs using a multi-step process that involved assigning an IRB to a category based upon the IRB name or address, and by conducting additional research, such as identifying the mission of an organization from its website. Percentages may not add up to 100 percent due to rounding.

As illustrated earlier, university-based IRBs were associated with between 56 and 42 percent, respectively, of clinical research conducted under

investigational new drug applications between 2012 and 2021, and IRBs based at hospitals or health care organizations were associated with between 15 and 7 percent, respectively, during the same time period.

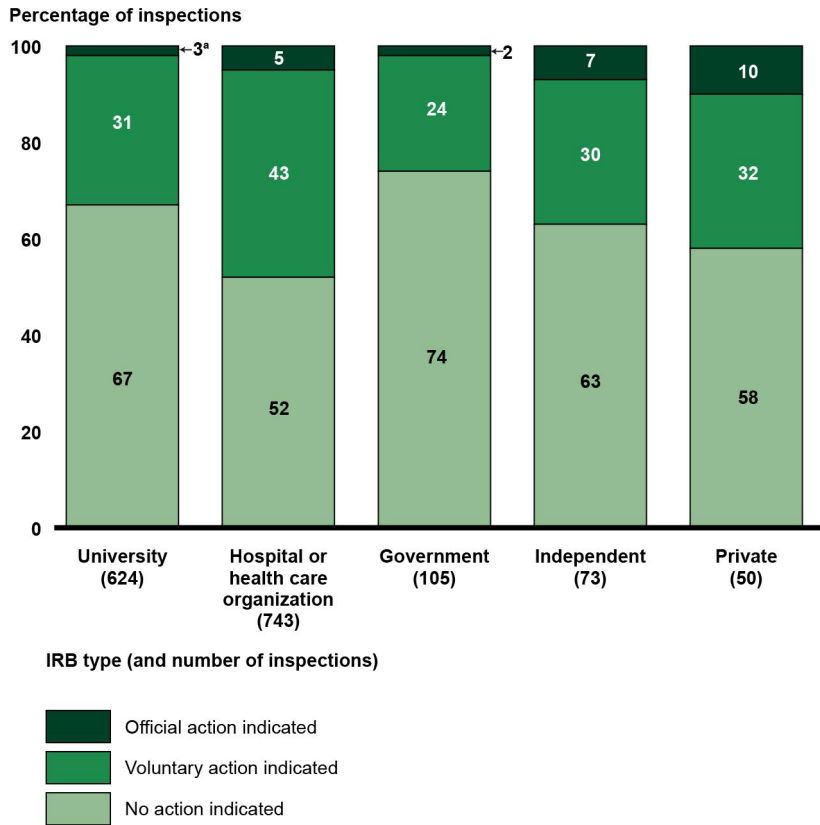
OHRP did not historically conduct routine inspections of independent IRBs because, until 2018, OHRP officials said their oversight authority over independent IRBs was unclear.<sup>93</sup> Revisions to the Common Rule finalized in 2018 gave OHRP the authority to conduct routine inspections of independent IRBs, and the agency completed its first such inspection in 2022. OHRP officials told us, as of June 2022, they were in the process of updating their compliance oversight procedures to begin conducting routine inspections of independent IRBs, though it is unclear how frequently they may inspect independent IRBs in the future.

**Results of inspections.** Our analysis of FDA IRB inspections shows that the majority did not identify noncompliance with federal regulations. Specifically, 96 percent of FDA inspections from fiscal years 2010 through 2021, resulted in determinations of no action indicated (i.e., objectionable conditions or practices were not found) or voluntary action indicated (i.e., objectionable conditions or practices found, but observations did not meet the threshold for regulatory action). FDA identified the most serious classification of noncompliance—referred to as official action indicated—in just 4 percent of inspections (68 inspections). The greatest percentage of inspections resulting in determinations of official action indicated were among private and independent IRBs. Specifically, 10 percent of private IRB inspections and 7 percent of independent IRB inspections resulted in official action indicated. (See fig. 8.)

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<sup>93</sup>According to OHRP officials, OHRP did occasionally conduct for-cause inspections that involved independent IRBs prior to 2018.

**Figure 8: Analysis of Food and Drug Administration (FDA) Institutional Review Board Inspection Findings, Fiscal Years 2010 through 2021**



Source: GAO analysis of FDA data. | GAO-23-104721

**Accessible Data for Figure 8: Analysis of Food and Drug Administration (FDA) Institutional Review Board Inspection Findings, Fiscal Years 2010 through 2021**

IRB Type (and number of inspections)	No action indicated	Voluntary action indicated	Official Action indicated	Total
<b>University (624)</b>	<b>66.8%</b>	<b>30.6%</b>	<b>2.6%</b>	<b>100.0%</b>
<b>Hospital or healthcare organization (743)</b>	<b>52.1%</b>	<b>42.5%</b>	<b>5.4%</b>	<b>100.0%</b>
<b>Government (105)</b>	<b>74.3%</b>	<b>23.8%</b>	<b>1.9%</b>	<b>100.0%</b>
<b>Independent (73)</b>	<b>63.0%</b>	<b>30.1%</b>	<b>6.8%</b>	<b>100.0%</b>

IRB Type (and number of inspections)	No action indicated	Voluntary action indicated	Official Action indicated	Total
<b>Private (50)</b>	<b>58.0%</b>	<b>32.0%</b>	<b>10.0%</b>	<b>100.0%</b>

Notes: We categorized IRBs using a multi-step process that involved assigning an IRB to a category based upon the IRB name or address, and by conducting additional research, such as identifying the mission of an organization from its website. FDA has three inspection classifications: no action indicated means that objectionable conditions or practices were not found; voluntary action indicated means that objectionable conditions or practices were found, but they do not meet the threshold for regulatory action; and official action indicated means objectionable conditions or practices were found and the agency is taking administrative or regulatory action in response. This figure excludes four inspections pending a final classification. Percentages may not add up to 100 percent due to rounding.

<sup>a</sup>Sum of percentages for university exceeds 100 percent due to rounding.

Our analysis of OHRP inspections from fiscal years 2010 through 2021 shows that 52 percent of not-for-cause inspections resulted in noncompliance determinations involving the conduct of the IRB.<sup>94</sup> When including for-cause inspections, the percentage of total inspections that resulted in noncompliance determinations decreased. Specifically, 42 percent of not-for-cause and for-cause inspections conducted during the same period resulted in noncompliance determinations involving the conduct of the IRB. During this period, OHRP did not complete any not-for-cause inspections involving independent IRBs.<sup>95</sup> However, in 2022, OHRP completed one such inspection and it resulted in noncompliance determinations.

Our analysis of FDA Restrictions Imposed and Warning Letters issued to IRBs for inspections conducted from fiscal years 2010 through 2021 found that the most common theme of noncompliance was related to failure to maintain adequate board meeting minutes and failure to create

<sup>94</sup>We analyzed determinations of noncompliance OHRP made in its compliance oversight determination letters, issued to the inspected entities. However, in some inspections, OHRP raised concerns about human subject protections—including concerns related to the conduct of the IRB—but did not ultimately make any determinations of noncompliance. For example, in two inspections completed in 2022, OHRP officials noted that the institutions adequately resolved concerns before OHRP issued the final determination letter, which occurred about 5 years after the agency opened each investigation. As a result, OHRP officials stated that the agency did not make any determinations of noncompliance.

<sup>95</sup>As noted above, OHRP officials said their oversight authority over independent IRBs was unclear until 2018.



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written procedures.<sup>96</sup> Examples of IRB-related findings of noncompliance from OHRP include approving inadequate informed consent documents, such as because the document did not sufficiently explain risks to the subject; and approving research without having sufficient information to grant the approval, such as related to participant risk.<sup>97</sup>

The noncompliance FDA and OHRP found from fiscal years 2010 through 2021 rarely resulted in administrative actions taken against IRBs. Specifically, based upon inspection findings, FDA required eight IRBs to take one or more of the following actions: stop using the expedited review process, stop approving new studies, suspend enrollment of new subjects in studies approved by the IRB, or terminate existing studies. For example, FDA imposed restrictions on one private IRB after finding it failed to register as an IRB before reviewing research studies and had not prepared or maintained any written procedures. Noncompliance that OHRP found during this time period did not result in OHRP imposing restrictions or conditions on IRBs or institutions, according to OHRP officials. FDA and OHRP also noted that two organizations chose to dissolve their IRBs after inspections.

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### Data Used to Select IRBs for Inspection Contain Inaccuracies; Agencies Have Not Conducted a Risk-Based Assessment to Inform Inspection Program

While IRB compliance inspections are key to OHRP and FDA's oversight of IRBs, two issues may limit their effectiveness. First, while both agencies consider specific factors to determine which organizations to inspect, we found inaccuracies in the data FDA and OHRP use to select

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<sup>96</sup>In response to a finding of official action indicated, FDA issues a letter to the IRB. According to FDA, Restrictions Imposed Letters identify noncompliance and impose restrictions that, if not corrected, may result in FDA disqualifying the IRB. FDA issues Warning Letters to achieve voluntary compliance, and may include restrictions for the IRB until it or the research institution take appropriate corrective action. FDA issues Untitled Letters when violations cited do not meet the threshold for regulatory significance for a Warning Letter.

<sup>97</sup>During the course of our work, we identified several discrepancies between the findings described in OHRP determination letters and determination codes, which OHRP officials stated they have used to identify the type of noncompliance determinations cited since 2013. These discrepancies made it difficult to assess the most commonly cited noncompliance findings. We made OHRP aware of these discrepancies, and HHS officials reported in December 2022 that they had reviewed all letters and associated codes and corrected inaccuracies.

organizations, which affects their ability to ensure they are using a risk-based approach in their oversight of IRBs. The agencies consider the volume of protocols IRBs and the organizations that operate them report reviewing, in addition to other information, to help determine which IRBs to select for inspection.<sup>98</sup> Information on the number of active protocols an IRB reviews provides insight into an IRB's activity level, according to OHRP. Further, an IRB's activity level provides an indication of the volume of human subjects whose welfare is affected by the IRB's review. For example, in 2021, FDA reported that over 38,000 individuals participated in clinical trials supporting 50 novel therapies approved by its Center for Drug Evaluation and Research.<sup>99</sup> Given FDA and OHRP's charges to protect human subjects, accurate information on the number of protocols an IRB reviews is essential to identify IRBs that may have responsibilities affecting a larger share of individuals.

However, our examination of the protocol data both agencies use to select IRBs for routine inspections, along with interviews with some IRB officials from our 11 selected IRBs, identified several inaccuracies that raise questions about the reliability of the data for such a purpose. These inaccuracies are inconsistent with federal internal control standards, which state that an agency should use quality information to achieve its objectives.

Specifically, an analysis of OHRP registration data identified 96 organizations that submitted duplicative protocol data for the 301 IRBs that they operate. That is, OHRP data indicate that each IRB had reviewed the same number of protocols as other IRBs operated by the same organization. OHRP officials told us that they did not consider this analysis to indicate data inaccuracies in protocol submissions; they consider such submissions to mean that each IRB within the organization had reviewed the same number of protocols. However, that was not the case with two IRBs in our sample, which submitted duplicative protocol data. For example, officials with one IRB said that instead of reporting the

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<sup>98</sup>IRBs conducting HHS-sponsored or FDA-regulated research are required to update their registration at least every 3 years. When they update their registration, they are required to submit to the OHRP IRB registry the approximate number of (a) all active protocols, (b) active protocols supported by HHS, and (c) active protocols involving FDA-regulated research. Active protocols are defined as any protocol or study for which an IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure in the last 12 months.

<sup>99</sup>See FDA, Center for Drug Evaluation and Research, *Drug Trials Snapshots, Summary Report 2021*.

specific number of protocols reviewed by each of the eight registered IRBs, their organization reported that each of its IRBs reviewed the exact same number of protocols—that is, they summed the number of protocols reviewed across their eight registered IRBs, and reported that number for each of their IRBs. Thus, based on the inaccurate data reported, OHRP would consider the IRB to have reviewed eight times as many protocols.

Our interviews with officials from some of our selected IRBs pointed to other inaccuracies in the protocol data they submitted to the registry. Specifically, when we asked them to confirm the accuracy of the data they submitted to OHRP, some acknowledged they had submitted inaccurate data. For example

- One IRB counted protocols it did not review but relied on another IRB to review. This is inconsistent with OHRP guidance. According to OHRP guidance, IRBs should count any protocol for which the IRB conducted (1) an initial or continuing review at a convened meeting, or (2) an expedited review. After reviewing their data, officials at this IRB organization said their protocol totals across its eight IRBs were about 50 percent lower than what they submitted to OHRP for one board.
- Officials with two other selected IRBs acknowledged that their protocol counts were inaccurate. For example, officials representing both of these IRBs said that when they update other registration information—such as to register a new IRB or to change the name of a head official—they are not prompted to also update their protocol counts. Thus, one IRB’s official acknowledged that the data they had submitted were old and inaccurate. According to OHRP officials, existing guidance to IRBs makes it clear that when submitting any updates to the registry, the entire IRB registration form should be accurate and complete, including updates to protocol estimates.<sup>100</sup>

Consistent with our findings, officials with one organization that conducted research on the effects of the Common Rule revisions on IRBs for the NIH told us of inaccuracies in the protocol data they observed in their work. They noted that those inaccuracies made it difficult to understand the extent to which protocol review was occurring at any institution.

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<sup>100</sup>According to OHRP guidance, any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period. See “IRB Registration Process FAQs”, accessed September 10, 2022, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/irb-registration-process/index.html>.

In addition, it is unclear whether IRBs are submitting protocol data consistent with changes made by the revised Common Rule that affect HHS-supported research. Those revisions changed the requirements for the types of studies that are subject to IRB review. Specifically, more types of studies are exempt from IRB review under the revised Common Rule and, thus, need no longer be included in the counts of active protocols reported.<sup>101</sup> One IRB we interviewed said its organization had already excluded exempt studies from the protocol data it reported to OHRP while officials with another IRB we interviewed said their organization had not done so.

The extent of these inaccuracies and the effect of them on the IRBs that OHRP and FDA select to inspect is unknown because OHRP officials said they do not verify the accuracy of the protocol data IRBs submit. OHRP officials indicated that they do not need to take additional steps to verify the protocol data reported to the IRB registry, because the data are comparable to the data they obtain directly from IRBs during inspections. However, as noted earlier, OHRP has inspected an average of seven IRBs annually since 2010 and fewer in recent years, so the agency has limited opportunities to make such a comparison. In June 2022, in response to a summary of our findings, OHRP officials stated that they would look for opportunities to clarify guidance to IRBs regarding protocol data submissions.

Ensuring the accuracy of the protocol data that inform IRB inspections would be consistent with federal internal control standards, which state that an agency should use quality information to achieve its objectives. This includes processing data the agency's management obtains into quality information, and making revisions to ensure the data are appropriate, current, complete, and accurate.<sup>102</sup> OHRP could, for example, update its instructions to IRBs regarding its expectations for reporting accurate, updated protocol data at each time a registry is modified; excluding from protocol data research that is exempt from review; and excluding from protocol data research that was reviewed by an external IRB (i.e., by another IRB serving as the single IRB under a

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<sup>101</sup>Prior to the Common Rule revisions, additional exempted protocols would have been reviewed by the IRB and should have been reported to OHRP as part of the approximate number of protocols the IRB reviewed. Subsequent to these revisions, these protocols should not be reported to OHRP.

<sup>102</sup>See [GAO-14-704G](#).

reliance agreement).<sup>103</sup> Additionally, OHRP could examine data accuracy for a sample of IRBs. OHRP and FDA are responsible for ensuring the protection of individuals participating in clinical research, and both agencies rely on OHRP registry data to achieve this mission and conduct IRB oversight. Without accurate registry data, the ability of these agencies to ensure they are using a risk-based approach in their oversight of IRBs and adequately achieve these agency goals is limited. In commenting on a draft of this report, HHS noted that protocol data are only one source of information that could inform a risk-based approach in the oversight of IRBs. Specifically, HHS noted that the number of subjects associated with a research protocol and variation in the level of risk associated with a research protocol are important factors. However, OHRP does not systematically collect that type of information by IRB.

The second issue that may limit the effectiveness of inspections is the risk presented by the relatively few number of inspections that OHRP and FDA conduct. In the case of OHRP, our review of IRB inspections found that OHRP inspects a small number of IRBs conducting human subjects' research annually. Since fiscal year 2010, OHRP has annually inspected less than 1 percent of IRBs it oversees. As previously noted, OHRP conducted an average of seven inspections per year (routine and for-cause) from fiscal years 2010 through 2021, and completed only one routine inspection in each of the 2 years prior to the COVID-19 pandemic. In comparison, over 1,600 organizations in the United States reported operating IRBs reviewing HHS-supported research, according to our analysis of OHRP's registry for IRBs registered as of April 2021. Three experts and one stakeholder we interviewed remarked that OHRP was not inspecting as many IRBs as in the past.

There may be a risk to inspecting less than 1 percent of organizations operating IRBs on an annual basis. OHRP does not know the extent to which this risk affects its oversight goals, because it has not assessed the risk. OHRP officials said that they have not discovered major systemic problems in recent routine inspections of institutions and view the inspections of both OHRP and FDA as complementary in the oversight of IRBs under their joint oversight. As a result, OHRP officials said the agency has not shifted its limited resources in order to conduct more

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<sup>103</sup>Generally, when an institution relies on a single IRB to review a study, the institution and the single IRB enter into a reliance agreement, which is a written agreement used to document the delegation of IRB review responsibilities between the IRB of record and the relying institution.

inspections. However, it is unclear whether few inspection findings is due to OHRP conducting so few inspections.

Although one of OHRP's main objectives is to conduct regulatory oversight of IRBs, OHRP has not independently examined how many routine IRB inspections it should conduct, or conducted a risk-based assessment to determine whether the agency is conducting an adequate number of routine IRB inspections.<sup>104</sup> OHRP officials acknowledge that resources contribute to the number of inspections they conduct. According to our analysis of the President's budget and information collected from OHRP, OHRP had a nearly flat budget over the last 8 years, with about 21 staff total, including 3 to 4 staff in the division responsible for compliance. According to OHRP officials, based on resources available to the office, the agency tries to conduct three to four not-for-cause inspections per year.<sup>105</sup>

In the case of FDA, although it conducts more inspections than OHRP, FDA has also not independently examined how many routine IRB inspections it should conduct, or conducted a risk-based assessment to determine whether the agency is conducting an adequate number of routine IRB inspections. While FDA guidance calls for the re-inspection of IRBs following a prior inspection finding within 1 year or 5 years, depending on the severity of the findings, FDA officials told us that they do not track whether they are meeting this standard.<sup>106</sup> Similar to OHRP, FDA officials said that the number of routine annual IRB inspections FDA conducts is driven by resources available to FDA's Bioresearch Monitoring program, which has responsibility for inspecting many other

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<sup>104</sup>According to OHRP officials, for-cause inspections are driven by the number of allegations that OHRP receives.

<sup>105</sup>In most of the last 8 years, appropriations for OHRP were less than what the administration requested. In 2017, OIG recommended that HHS evaluate the sufficiency of OHRP's resources and consider ways to elevate the prominence of its budget, such as by including OHRP's budget as a line item in the President's budget. In response, OHRP officials said the Office of the Assistant Secretary for Health annually evaluates resources as a part of the budget formulation and would continue to evaluate the sufficiency of OHRP's resources. See Department of Health and Human Services Office of Inspector General, OEI-01-15-00350.

<sup>106</sup>Specifically, FDA documentation states the agency will conduct routine inspections every 5 years for IRBs with a previous classification of no action indicated or voluntary action indicated, and a follow-up inspection within 1 year for any IRB previously cited for official action indicated.

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entities that fall within FDA's oversight responsibilities, such as clinical investigators, sponsors, and contract research organizations.

While it may be challenging for OHRP and FDA to inspect a large volume of IRBs annually, conducting a risk-based assessment would be consistent with the Office of Management and Budget's Circular A-123. This circular requires federal agencies to integrate risk management activities into their program management and regularly re-examine risks to help ensure they are effectively managing risks that could affect achieving agency goals.<sup>107</sup> Similarly, federal internal control standards state an agency should define risk tolerances and identify, analyze, and respond to risks related to achieving the defined objectives.<sup>108</sup> Annually assessing the risk posed by their current approach to inspections and determining whether they are inspecting an adequate number of IRBs and if there are other ways to optimize inspections to further mitigate risks to research participants, will provide the agencies with greater assurance that they are meeting their goals of ensuring the protection of individuals participating in clinical trials. For example, the risk assessment could consider 1) the number of IRBs registered in OHRP's IRB registry that review research protocols under each agency's purview; 2) the number of studies IRBs review, including that some organizations operate multiple IRBs; 3) resources, including annual appropriations and inspection staff; and 4) other agency activities that help ensure the protection of human research participants. This annual assessment could also help ensure that federal resources are allocated to address identified risks.

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## OHRP and FDA Have Not Examined IRB Effectiveness

While OHRP and FDA use inspections to assess whether IRBs are following regulations, the agencies have not examined the effectiveness of IRBs in protecting human subjects. Doing so would be consistent with the responsibilities of OHRP and FDA in protecting human research subjects. Specifically, OHRP's Statement of Organization and Functions—which outlines the office's responsibilities—states that the office is responsible for evaluating the effectiveness of HHS policies and programs for the protection of human subjects, and for promoting the

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<sup>107</sup>Office of Management and Budget, Circular No. A-123.

<sup>108</sup>See [GAO-14-704G](#).

development of approaches to enhance such protections.<sup>109</sup> Similarly, FDA officials have said the agency is charged with promulgating and enforcing regulations that help ensure the protection of human subjects who participate in clinical investigations involving FDA-regulated products.<sup>110</sup> Further, a 2018 memorandum of understanding between FDA and OHRP describes how the two agencies collaborate, including to protect and improve the public health through regulation of IRBs.<sup>111</sup>

Our review shows that OHRP and FDA have not assessed IRB effectiveness in large part because the agencies have not overcome the challenge of determining the best approach or approaches for doing so. Since the late 1990s, numerous federal bodies and other entities have recommended that HHS or other federal agencies involved in research with human subjects identify approaches for evaluating the effectiveness of IRBs in protecting human subjects. The HHS Office of the Inspector General suggested in its 1998 report on IRBs and federal oversight of them that in the absence of such approaches, regulatory bodies have limited mechanisms to foster accountability among IRBs.<sup>112</sup> Examples of these recommendations include,

- In 1998, the HHS Office of the Inspector General recommended that NIH, FDA, and OHRP's predecessor convene symposia with IRBs to

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<sup>109</sup>Department of Health and Human Services, Office of the Assistant Secretary for Health, *Statement of Organization and Functions for the Office for Human Research Protections (OHRP): Part L* (March 6, 2002).

<sup>110</sup>See also Standards for Institutional Review Boards for Clinical Investigations, 43 Fed. Reg. 35,186, 35,197 (Aug. 8, 1978) ("The Commissioner has therefore concluded that legal authority to promulgate these regulations regarding clinical investigators exists under sections 505(i), 520(g), and 701(a) or the Act, as essential to protection of the public health and safety and to enforcement of the agency's responsibilities[.]")

<sup>111</sup>Food and Drug Administration and Office for Human Research Protections, "Memorandum of Understanding between the Food and Drug Administration and Office for Human Research Protections," accessed January 10, 2022, <https://www.fda.gov/about-fda/domestic-mous/mou-225-18-014>.

<sup>112</sup>Department of Health and Human Services Office of Inspector General, OEI-01-97-00193.



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discuss the type of performance measures and evaluations that would foster a system of accountability.<sup>113</sup>

- In 2011, the Presidential Commission for the Study of Bioethical Issues recommended that OHRP, in conjunction with other federal agencies that support research involving human subjects, support the development of systematic approaches to assess the effectiveness of protections for those subjects.<sup>114</sup>

However, we found that the agencies did not identify and implement an approach or approaches for such an evaluation. (See app. III.) In 2000, HHS contracted with the Institute of Medicine (now known as the National Academy of Medicine) to address the protection of human research subjects, including requesting recommendations for steps that institutions conducting research and the federal government should take to monitor and evaluate the system for protecting human subjects. The resulting work recommended that research sponsors initiate research programs and funding support to develop evaluation criteria. The reports did not provide specific criteria for evaluating the performance of IRBs, but did discuss related concepts, according to OHRP officials.<sup>115</sup> Both OHRP and FDA reported that they have not contracted with any other group to develop criteria or measures for examining the effectiveness IRBs in protecting human subjects since that time.

According to OHRP officials, HHS and other Common Rule agencies discussed implementing various approaches for measuring IRB effectiveness during the Common Rule revision process, including requiring investigators to report adverse events to a centralized federal

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<sup>113</sup>Department of Health and Human Services Office of Inspector General, OEI-01-97-00193. HHS-OIG's recommendations were to the Office for Protection from Research Risks (OPRR), within NIH, which at the time was responsible for leading the HHS's efforts to protect human subjects. In June 2000, HHS established OHRP within the Office of the Assistant Secretary for Health to replace OPRR in an effort to elevate the office's stature and effectiveness.

<sup>114</sup>Presidential Commission for the Study of Bioethical Issues, *Moral Science: Protecting Participants in Human Subjects Research* (Washington, D.C., December 2011).

<sup>115</sup>The Institute of Medicine completed two reports under this contract, which aimed to examine the structure and functioning of human research protection programs. See Institute of Medicine, Committee on Assessing the System for Protecting Human Research Participants, *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs* (Washington, DC: National Academies Press, 2001) and Institute of Medicine, *Responsible Research*.

database.<sup>116</sup> However, that provision was not included in the final rule, as many commenters expressed, among other things, concerns about the validity of this measure.<sup>117</sup> Other approaches that might have helped examine IRB effectiveness were similarly not adopted in the revised Common Rule, according to OHRP officials.<sup>118</sup>

We recognize that assessing the effectiveness of IRBs in protecting human subjects is challenging, for several reasons. First, there is an absence of validated performance measures that pertain to how well IRBs protect human subjects, according to four articles that systematically reviewed published literature or quality assessment instruments, some experts, OHRP, FDA, and NIH officials, and two selected IRBs.<sup>119</sup> Second, there are various challenges in developing measures that directly assess an IRB's ability to protect human subjects, according to published literature, as well as some experts, a selected IRB, and agency officials. These challenges include

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<sup>116</sup>Adverse events are untoward or unfavorable medical occurrences in human research subjects, including any abnormal sign, symptom, or disease, temporally associated with participation in the research, whether or not considered related to participation in the research. OHRP officials reported that they believed that this database could have been used to compare performance across IRBs (e.g., an adverse event rate) and assess the performance of the human research protection system.

<sup>117</sup>Many commenters expressed concerns that the database would not yield generalizable conclusions as the data would come from varied sources and context. See 80 Fed. Reg. 54,038 (Sept. 8, 2015).

<sup>118</sup>According to OHRP officials, accreditation, certification, and quality measurement were considered as part of the Common Rule revision process, but these were not adopted. The revised Common Rule did adopt one new requirement that, according to OHRP officials, could be used to examine IRB quality. Specifically, the revised Common Rule requires that awardees of federal research funding or federal agencies conducting research must post one IRB-approved consent form used to enroll subjects on a publicly available federal website. See 45 C.F.R. §46.116(h). According to the final rule, this requirement aims to increase transparency and accountability as well as enhance confidence and identify concerns with the IRB review process. See 82 Fed. Reg. 7,228 (Jan. 19, 2017).

<sup>119</sup>Lura Abbot and Christine Grady, "A Systematic Review of the Empirical Literature Evaluating IRBs: What We Know and What We Still Need to Learn." *Journal of Empirical Research on Human Research Ethics*, vol. 6, no. 1 (2011): 3–19; Stuart G. Nicholls et al., "A Scoping Review of Empirical Research Relating to Quality and Effectiveness of Research Ethics Review." *PLOS ONE*, vol. 10, no. 7 (2015); Holly Fernandez Lynch et al., "Evaluating the Quality of Research Ethics Review and Oversight: A Systematic Analysis of Quality Assessment Instruments," *American Journal of Empirical Bioethics*, vol. 11, no. 4 (2020): 208–222; and Sandra H. Berry et al., *Profile of Institutional Review Board Characteristics*.

- An IRB is only one component of a larger framework charged with protecting human subjects, thus it is difficult to isolate its specific contribution relative to the actions of the sponsor, the institution, the investigator, or the research staff.
- There is lack of clarity about how IRBs and IRB reviews contribute to protecting human subjects.

Third, one expert and an NIH official noted that there is a lack of funding available to support research related to evaluating the effectiveness of IRBs. Additionally, FDA officials reported that the agency would need additional funding to engage in such research.

In lieu of direct measures of how well IRBs protect human subjects, some experts have also proposed surrogate methods for examining how well IRBs protect human subjects, including assessments of an IRB's ability to make ethical decisions.<sup>120</sup> However, these approaches have yet to be widely studied or adopted. Approaches suggested include the following:

- Peer audits of IRB meetings to assess IRB decision-making and the deliberative process,
- IRB reviews of mock protocols to determine if the IRB is able to identify key ethical issues,
- Surveys of IRB members, staff, and investigators to assess the quality of the IRB review process, and
- Surveys of research participants to assess if they feel protected.

Due to the aforementioned complexities and limited evidence supporting surrogate methods for examining how well IRBs protect human subjects, OHRP and FDA are likely to need input from a wide range of stakeholders involved in human subjects research to identify promising approaches for measuring IRB effectiveness. These stakeholders include IRBs, ethicists, sponsors, investigators, research participants, and other government agencies. Obtaining such input would be consistent with change management practices identified in our prior work that can help ensure the success of agency reforms or transitions, such as improving the effectiveness of government operations.<sup>121</sup> For example, as we have

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<sup>120</sup>According to a 2003 report from the Institute of Medicine, the chief function of IRBs is to conduct comprehensive ethical reviews of research protocols. See Institute of Medicine, *Responsible Research*.

<sup>121</sup>GAO, [GAO-18-427](#).

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previously reported, successful reforms require an integrated approach that involves key stakeholders.

There is interest in identifying approaches for evaluating the effectiveness of IRBs in protecting human subjects, according to OHRP and FDA officials.<sup>122</sup> As noted by some experts, the need for measures of IRB effectiveness is more pressing than it has been in the past. Under the single IRB requirement, institutions may now be required to rely on IRBs that are not affiliated with their institution—that is, either independent IRBs or other affiliated IRBs—and do not have any mechanisms for assessing the effectiveness of those IRBs.<sup>123</sup>

By convening stakeholders to identify approaches for evaluating the effectiveness of IRBs in protecting human subjects and implementing approaches, as appropriate, the agencies will have taken a critical first step in helping assure that IRBs are successful in protecting the health and safety of human research subjects. Moreover, taking such actions could identify mechanisms for assessing the effect of changes to the IRB system, such as the implementation of the single IRB requirement or the increased use and consolidation of independent IRBs, on the protection of human subjects. Further, such actions could reassure the public and policy makers about aspects of the IRB system that are functioning well and foster greater accountability among IRBs.

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## Conclusions

The ability of OHRP and FDA to fulfill their charge of protecting human research subjects is dependent on their success in monitoring which entities are reviewing and conducting research studies, particularly those reviewing high volumes of research, and identifying and evaluating how these entities address pertinent federal regulations and conduct research

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<sup>122</sup>There is at least one group of individuals working to develop IRB quality measures, known as the Consortium to Advance Effective Research Ethics Oversight. According to its website, this group, formed in 2018, consists of leaders in human subjects research oversight, research ethics, and empirical methods and is working to improve and evaluate the effectiveness of IRBs and human research protection programs, including through the development of IRB effectiveness measures.

<sup>123</sup>Under the single IRB requirement, which went into effect in January 2020, all domestic, federally funded cooperative research studies must be reviewed by a single IRB. Under this requirement, institutions, which may have previously relied on their own IRB to review research conducted by their investigators must rely instead on external IRBs (either those affiliated with other institutions or independent IRBs).

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review. Over time, independent IRBs have grown in prominence, and available data indicate they are reviewing a larger share of federally conducted or supported drug clinical trials involving human subjects.

While inspections are a key mechanism through which OHRP and FDA help ensure that IRBs are following federal regulations for protecting human subjects, our review shows this oversight needs to be strengthened. First, to the extent that OHRP and FDA rely on inaccurate data on the number of protocols that IRBs review, they are limited in their ability to appropriately select IRBs and to prioritize for selection the IRBs that are reviewing large volumes of research involving human subjects. Second, both OHRP and FDA determine the number of IRBs to inspect each year based on available resources and not on whether the number of annual inspections is sufficient to help achieve the agencies' oversight objectives—protecting human subjects. Until OHRP and FDA conduct an annual risk-based assessment—which could take into account the inspections conducted by each agency, resources, and the agencies' other activities that help ensure the protection of human research participants—HHS will lack assurance that these agencies are optimizing IRB inspections and fulfilling their requirements to effectively oversee IRBs in their activities to protect human research subjects.

Finally, neither agency has examined whether or to what extent IRB reviews themselves are effective in protecting human subjects, despite longstanding recommendations that the agencies do so. Such an approach is challenging for a variety of reasons, including an absence of validated performance measures that pertain to how well IRBs protect human subjects. However, identifying approaches for evaluating the effectiveness of IRBs in protecting human subjects—with input from a wide range of stakeholders—and implementing approaches, as appropriate, are critical steps. Such steps could help OHRP and FDA assure the public and policymakers that IRBs are successfully protecting human subjects and assess the effect of changes to the IRB system on the protection of human subjects, such as the increased use and consolidation of independent IRBs.

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## Recommendations for Executive Action

We are making a total of four recommendations, including three recommendations to HHS and one recommendation to FDA. Specifically:

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The Assistant Secretary for Health 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 1.)

The Assistant Secretary for Health 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 2)

The Commissioner of the Food and Drug Administration 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 3)

The Secretary of Health and Human Services 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. (Recommendation 4)

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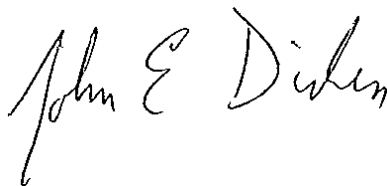
## Agency Comments and Our Evaluation

We provided a draft of this report to HHS for review and comment. The department's comments are reprinted in appendix V. In its written comments, HHS concurred with our recommendations, two of which we modified while HHS was reviewing the draft report. Specifically, we made changes to the two recommendations calling for OHRP and FDA, respectively, to conduct a risk assessment of the adequacy of the number of routine IRB inspections and to optimize the use of inspections. Initially, we were recommending that OHRP and FDA develop a standard defining the minimum number of routine IRB inspections each agency should annually conduct based on a risk assessment. While HHS was reviewing our draft report, FDA officials expressed concerns about the practicality and feasibility of implementing such a recommendation. FDA officials were concerned that establishing a mandated number of IRB inspections each year would pull resources away from the agency's ability to inspect other entities with responsibilities for ensuring protection of research

participants that also fall under FDA's oversight responsibilities, such as clinical investigators. We acknowledged those concerns and modified our recommendations accordingly, as reflected in our final report. HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, the Secretary of Health and Human Services, the Assistant Secretary for Health, the Commissioner of the Food and Drug Administration, and other interested parties. In addition, the report will be available at no charge on the GAO website at <https://www.gao.gov>.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or [DickenJ@gao.gov](mailto:DickenJ@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix VI.



John E. Dicken  
Director, Health Care

## Appendix I: Scope and Methodologies

The following appendix provides a more detailed description of the scope and methodologies used to (1) select experts, stakeholder organizations, and organizations that operate IRBs, (2) describe the composition of the Institutional Review Board (IRB) market, (3) identify relevant literature, (4) describe the practices selected IRBs have implemented to help strengthen the quality of their reviews, (5) examine the Office for Human Research Subject Protections' (OHRP) and the Food and Drug Administration's (FDA) oversight of IRBs, and (6) categorize IRBs into one of five IRB types.

**Experts, stakeholder organizations, and organizations that operate IRBs.** As part of our review, we interviewed or collected information from 11 experts, seven stakeholder organizations, and 11 organizations that operate IRBs.

- Of the 11 experts we contacted, nine were researchers or ethicists who have published books, studies, or reports on IRB review and assessing human research subject protections programs, and 10 have experience as an IRB chair or member.<sup>1</sup> Four of the 11 experts were former Department of Health and Human Services (HHS) officials from agencies or offices that inspect institutions and private entities that conduct clinical trials. We selected these individuals based on our review of articles and materials identified through our background search.
- The seven stakeholder organizations we contacted represent entities or individuals who sponsor, administer, or have developed measurement tools for clinical trials, or accredit institutions or credential staff who operate IRBs or clinical trials.<sup>2</sup> We selected these

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<sup>1</sup>The expert categories are not mutually exclusive; therefore, there is some overlap with experts that act as researchers or bioethicists and experts with experience as an IRB chair or member.

<sup>2</sup>Clinical trials are a type of clinical study in which participants are prospectively assigned an intervention based on the research plan or protocol.



organizations based on a review of background materials and recommendations from entities we interviewed.

- The 11 organizations that operate IRBs we contacted consisted of six organizations that operate independent IRBs and five that operate affiliated IRBs (e.g., IRBs affiliated with universities and hospitals).<sup>3</sup> An organization may operate one or more IRBs, and nine of the 11 organizations we selected operated multiple IRBs. Throughout this report, we refer to these 11 organizations as “selected IRBs.” We selected these IRBs to provide variation across several factors, including type of IRB, geography, accreditation status, and experience with OHRP or FDA inspections, and in consideration of the volume of research reviewed. Although we selected these IRBs to represent a wide range of characteristics, our interviews are not generalizable to all IRBs we did not select and interview.

**Composition of the IRB market.** To determine the number of active IRBs, we analyzed OHRP’s IRB Registry for IRBs registered as of April 2021, the most recent information at the time we began our review.<sup>4</sup> IRBs involved in research that is either HHS-supported or involves an FDA-regulated product must submit certain information to the registry. An IRB registration and any subsequent updates or renewals are active for 3 years from the date of acceptance by OHRP. If an IRB does not renew its registration with OHRP after 3 years, OHRP may deactivate it. Research institutions cannot use IRBs with a deactivated OHRP IRB registration for HHS-supported or FDA-regulated research.

For our analysis, we defined active IRBs as those IRBs whose registrations were not deactivated by OHRP as of April 2021, and limited our analysis to IRBs located in the 50 United States or the District of Columbia. Another 1,130 IRBs in the 50 United States and the District of

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We contacted the following organizations: the Association of Clinical Research Organizations, the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), the Biotechnology Innovation Organization, the Clinical Trials Transformation Initiative, the Pharmaceutical Research and Manufacturers of America, Public Responsibility in Medicine and Research, and the World Health Organization.

<sup>3</sup>Throughout this report, we use the term affiliated to refer to IRBs that we categorized as university, hospital or health care organization, private, or government, in contrast to an independent IRB.

<sup>4</sup>Apart from OHRP IRB registration data and FDA’s Bioresearch Monitoring Information System (BMIS) data, we were unable to find other data that captures the proportion of federally funded or regulated clinical research protocols that are under review at different types of IRBs, including over time.

Columbia had active registrations, but reported that they had not reviewed any HHS-supported or FDA-regulated protocols. In addition, 1,701 IRBs had active registrations but were located outside of the United States.

The registry also captures the approximate number of active protocols involving HHS-supported and FDA-regulated products the IRB reviewed in the 12 months preceding their registration submission. Using this information, we limited our analysis to IRBs that reported reviewing at least one HHS-supported or FDA-regulated protocol in their registration, and determined the percentage of active IRBs that reported having reviewed at least one of each type of protocol. We also considered the number of protocols that IRBs reported reviewing in our selection of IRBs. Specifically, among all active IRBs in the United States, all 11 IRBs we selected were at or above the median in terms of the approximate number of FDA-regulated protocols, and nine of the 11 IRBs selected were at or above the median in terms of the approximate number of HHS-supported protocols IRBs reported.

To determine IRB organizations that submitted duplicative protocol data to OHRP, we reviewed OHRP data to identify IRBs within an IRB organization with the same value for the approximate number of active protocols involving both HHS-supported and FDA-regulated products. For example, if an IRB organization registered four IRBs and reported that each of them reviewed the exact same amount of HHS and FDA protocols, we considered this IRB organization to have reported duplicative protocol data to OHRP.

We determined the protocol data to be reliable for the purpose of selecting the judgmental sample of IRBs for the purpose of our interviews; however, we determined the protocol data were not reliable for the purpose of understanding the share of protocols reviewed by different types of IRBs. Specifically, the protocol information is not reviewed by OHRP for accuracy or redundancies.

To report on active IRBs by type of IRB, we used the name and address of the IRB as collected in the OHRP registry to categorize IRBs into one of five types of IRBs as described below.

To determine trends in the type of IRBs reviewing FDA-regulated research over time—that is, from calendar years 2012 through 2021, the most recent calendar year data available at the time of our review—we analyzed data from FDA’s Bioresearch Monitoring Information System

(BMIS). BMIS captures information on research involving drugs and biologics conducted under an investigational new drug application regulated by FDA's Center for Drug Evaluation and Research, including the name and address of the IRB associated with the research. This information is derived from Form FDA 1572 (the Statement of Investigator), which clinical trial sponsors are required to collect from each clinical investigator participating in a trial conducted under FDA's investigational new drug regulations. When the form is submitted to FDA, the information is manually entered into BMIS.

While FDA makes some BMIS data publicly available, we obtained and analyzed data we obtained directly from FDA, which contained the following information for each Form FDA 1572: a unique identifier representing the investigational new drug application number, the date the Form FDA 1572 was received by FDA, and the name and address of the IRB identified on the Form FDA 1572. Any one investigational new drug application may have multiple Form FDA 1572s—that is, multiple clinical investigators with different dates as each form was received by FDA, for example, as clinical investigators were added to an ongoing study. Additionally, any one investigational new drug application may indicate that multiple IRBs reviewed the research, for example, if multiple clinical investigators from separate research institutions were involved in the research, and each used a different IRB to review the protocol before initiating the research.

To determine the share of FDA-regulated research reviewed by IRB type, we used the name and address of IRBs located in the United States as collected in the BMIS extract to categorize IRBs into one of five types of IRBs as explained below. We then analyzed the information in two ways, both of which used the date the Form FDA 1572 was received by FDA to determine the year. First, we counted the number of Form FDA 1572s submitted by IRB type and year. This approach does not adjust for the number of Form FDA 1572s (i.e., clinical investigators and IRBs) associated with a unique investigational new drug application. Second, since each investigational new drug application is associated with one or more clinical investigation, and each clinical investigation may have had the research protocol reviewed by a different type of IRB, we conducted a weighted-average analysis by investigational new drug application number. To conduct this analysis, we determined the unique number of applications each year and weighted each application by the proportion of Form FDA 1572s associated with each type of IRB and year. For example, an application that was associated with five IRBs in 2019—one independent and four universities—would be distributed 20 percent to the

independent IRB category and 80 percent to the university IRB category for 2019. We also determined the number and proportion of applications on which the IRB was identified as either WCG or Advarra.

BMIS has notable limitations and does not provide a complete picture of IRBs associated with FDA-regulated research. BMIS does not capture clinical trial information for other relevant FDA centers, such as the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health. Those two centers told us that they do not have a database that captures the IRB associated with FDA-regulated research they review. Additionally, the Form FDA 1572 is voluntarily submitted to FDA by clinical trial sponsors. According to FDA, while not required, many sponsors submit the form to FDA. We found that the BMIS data extract captured information on almost 25,000 unique investigational new drug applications involving about 170,000 clinical investigations (i.e., Form FDA 1572s) in the United States and submitted to FDA from 2012 through 2021.<sup>5</sup>

**Literature review.** To help inform all three of our objectives, we conducted a literature review. We searched news and scholarly articles published from 2010 to June 2021 in ProQuest, EBSCO, Scopus, Dialog, and CQ, using search terms such as “institutional review board,” “independent ethics committee,” “ethical review board,” “research ethics committees,” and “research ethics board.” The team included additional trade documents, research articles, and reports published from 2010 to 2021 that were identified by searching ProQuest, PubMed, internet searches using Google, or provided to GAO by stakeholders and experts. We excluded articles that did not focus on IRBs or human research protection or were focused on one type of research or a previous GAO report. This process yielded a total of 126 articles for review.

**Practices implemented to help strengthen the quality of their reviews.** To describe the practices selected IRBs have implemented to help strengthen the quality of their reviews, we reviewed articles identified from the literature search and conducted expert interviews to identify recommended practices, and collected information from our non-generalizable sample of 11 IRBs to understand the extent to which they were using those recommended practices. The literature review process yielded 46 articles that contained recommended practices for IRBs. We

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<sup>5</sup>For the purpose of our weighted average analysis, we determined the number of unique investigational new drug applications on an annual basis (approximately 45,000).

narrowed those to 35 articles after excluding articles that met one of the following three criteria: the article was limited to one organization's approach to complying with federal guidance or obtaining accreditation; the article was a commentary piece from outside the United States; or the article entirely focused on best practices associated with a specific type of research or subject population (e.g., community-based participatory research, mental health research with prisoners, etc.). Through our review of the 35 articles, we identified 142 practices recommended for IRBs, which we grouped into 40 practice categories.

We used a similar process to identify and group practices identified among the 11 experts we interviewed. Among those interviews, 10 included a discussion of recommended practices for IRBs. Through review of those 10 interviews, we identified 61 practices recommended for IRBs, which we grouped into 21 practice categories. In total, we identified 203 recommended practices, which we consolidated into 43 practice categories.

To determine recommended practice categories to include in the report, we prioritized practice categories that were feasible to assess and were not specific to one item that the IRB should review or require as part of its review process. We also categorized OHRP and FDA regulatory requirements into four categories and aligned recommended practice categories with the four broad regulatory requirement categories. A number of the practice categories relate to quality assurance activities, and there are no requirements for IRBs to engage in quality assurance activities under Common Rule or FDA regulations. As a result, we organized these practice categories into a fifth broad category. This report focuses on 23 of the 43 practice categories. To determine how the selected IRBs implemented each of the recommended practice categories, we collected information from IRB officials through interviews and a questionnaire and reviewed policies and procedures, when provided to us.

**Oversight of IRBs.** To describe OHRP's and FDA's oversight of IRBs, we analyzed FDA and OHRP IRB inspection data for fiscal years 2010 through 2021—the most recent complete year of data at the time of our review—to describe federal oversight of IRBs. This analysis was based on the year the inspection was completed, and was limited to entities in the 50 U.S. states and the District of Columbia. In analyzing FDA inspection data, we excluded inspections of Radioactive Drug Research Committees—which review basic science research protocols using radioactive drugs in humans—because the only IRB-specific requirement

for a Radioactive Drug Research Committee is to ensure research is reviewed and approved by an IRB. The team considered a Radioactive Drug Research Committee failing to seek IRB approval to be related to the conduct of those committees and not an IRB deficiency. We also categorized FDA inspections conducted as a result of allegations, to follow-up on Warning Letters issued by FDA, to address consumer complaints, or as follow-up to prior inspections classified as “official action indicated,” as “for-cause” inspections. In categorizing FDA inspection findings, we excluded inspections without a final classification as of May 2022. In analyzing OHRP inspection data to determine the percentage of noncompliance found, we reviewed OHRP Determination Letters to identify inspections in which at least one noncompliance determination was related to the conduct of the IRB. We also separately counted inspections that involved multiple institutions. For example, if an OHRP inspection involved three different institutions, we counted it as three inspections. For both FDA and OHRP inspection data, we used the name of the IRB to categorize IRBs into one of five types of IRBs as explained in more detail below.

To further analyze IRB oversight, we obtained and analyzed FDA Restrictions Imposed and Warning Letters from inspections conducted from fiscal years 2010 through 2021 that resulted in a classification of official action indicated. According to FDA, Warning Letters provide IRBs an opportunity to take voluntary action to achieve prompt compliance, and Restrictions Imposed Letters require an IRB to institute corrective actions to achieve compliance with the regulations. We also reviewed Determination Letters OHRP issued to IRBs following inspections conducted and the associated determination codes. We also reviewed reports issued by federal bodies and other entities that describe human subjects research protection, including mechanisms for assessing IRB performance and ensuing IRB quality.

**Categorization of IRBs.** As noted above, to describe the composition of the IRB market and to describe mechanisms used by HHS’s OHRP and FDA for ensuring the protection of human research subjects, we developed an approach that involved assigning an IRB to one of the following five categories based upon the IRB name, address, or both as captured by the associated data. We also conducted additional research, such as identifying the mission of an organization from its website.

- University: IRBs at a specific educational settings (e.g., university or college), or a hospital that has a major affiliation with a medical school. For example, we assigned IRBs to this category if the name

included “university,” “college,” or “graduate school,” including text variations of those terms. In addition, to capture academic medical centers, we assigned hospitals to this category if we found that they had a major affiliation with a medical school, according to the 2021 Centers for Medicare & Medicaid Services’ Provider of Services data file, a publicly available data source that contains information on hospitals.

- Hospital or health care organization: IRBs at a hospital or other health care organization (e.g., clinic, doctor’s office, or managed care organizations) that provides direct, medical care to patients, excluding hospitals with a major affiliation with a medical school. For example, we assigned IRBs to this category if the IRB name included “hospital,” or “medical”. As noted above, we also checked hospitals against the 2021 Centers for Medicare & Medicaid Services’ Provider of Services data file.
- Private: IRBs at private organizations, such as a research foundation, a professional organization, trade, or business that does not provide medical care. We also categorized the following as private IRBs: contract research organizations; laboratories; and imaging centers.<sup>6</sup>
- Government: IRBs at a federal, state, or local government agency and includes health care facilities operated by the Departments of Veterans Affairs and Defense; the National Cancer Institute Central IRB, known as CIRB, which was established by the National Institutes of Health’s National Cancer Institute to review research sponsored by the National Cancer Institute; and IRBs associated with the National Cancer Institute’s Community Oncology Research Program, which are sites that bring together researchers, hospitals, physician practices, and others within communities for the conduct of National Cancer Institute-sponsored clinical trials.
- Independent: IRBs that are not affiliated with organizations that conduct or sponsor research, and do not meet one of the above categories. Our designation of independent IRBs is without regard to the for-profit or not-for-profit status of the IRB.

We recognize that others attempting such a process might develop different categories and that our approach has limitations. For example, we made no distinctions in our categorizations based on the for-profit or

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<sup>6</sup>FDA defines a contract research organization as an independent contractor that assumes one or more of the obligations of a sponsor, including the design of a protocol, the selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to FDA. See 21 C.F.R. § 312.3.

not-for-profit status of an organization (i.e., the independent IRB category includes both for-profit and not-for-profit independent IRBs). Additionally, we may not have appropriately categorized some hospitals affiliated with an academic medical center if the data source we used did not indicate the hospital had a major affiliation with a medical school.



## Appendix II: Practices Used by Selected Institutional Review Boards

The following appendix provides information on the practices that officials at a non-generalizable sample of 11 institutional review boards (IRB) reported using to improve the quality of reviews. Some practices align with federal regulations or guidance, while others are consistent with recommended practices for helping ensure quality IRB review, which were identified by experts we interviewed and the literature we reviewed. IRBs may adopt different practices to comply with federal regulations and guidance, and to help ensure their quality. For example, regulations require an IRB to “be sufficiently qualified through the experience and expertise of its members,” but those regulations do not set minimum requirements for such a determination.<sup>1</sup> As a result, IRBs are left to make their own judgment on “sufficiently qualified,” which could entail conducting annual performance evaluations, or perhaps, examining IRB member performance on an ongoing basis.

The practices described in this appendix are organized into four sections: IRB membership; IRB functions, operations, and records; IRB research review; and informed consent.

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### IRB Membership

**Federal regulations:** IRBs must have at least five members from professionally varying and diverse backgrounds who are qualified to review research protocols and are not permitted to review protocols for which they have a conflicting interest. 45 C.F.R. § 46.107; 21 C.F.R. § 56.107

**Examples of recommended practices:** Members are committed, knowledgeable about human research participant protections, diverse, and reflective of the perspective of research participants and the community. Members are free from personal conflicts of interest and undue influence from the organization.<sup>a</sup>

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Source: GAO review of the Common Rule and FDA regulations, expert interviews, and published literature | GAO-23-104721

<sup>a</sup>Information on practices that IRBs use to identify and mitigate member and organization conflicts of interest are detailed earlier in this report.

**Committed members.** Ten of the 11 selected IRBs reported having formal processes for evaluating board member performance. According to IRB officials, these evaluations are performed by IRB chairs, institutional

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<sup>1</sup>See 45 C.F.R. § 46.107; 21 C.F.R. § 56.107.

officials, or other quality or regulatory leaders and occur annually, biennially, or on an ongoing basis. Performance evaluations may include assessing meeting attendance, completion of training requirements, preparation for and engagement in meetings, and knowledge of and ability to consistently apply regulatory criteria, and may involve observation of member performance at IRB meetings.

**Knowledgeable members.** Ten of the 11 IRBs reported providing orientation and all 11 IRBs reported providing or requiring continuing education for their members. According to IRB officials, board member orientation may include trainings, observation of meetings prior to participation, and mentorship programs. Continuing education may occur as part of the board meeting and may focus on new regulations or guidance, changes to internal processes, and new types of research. Officials at two IRBs reported using case studies to help IRB members apply federal regulations to ethically difficult protocols.

**Diverse board.** Officials from four IRBs reported that the composition of their panels or their voting requirements exceed federal regulations. For example, one IRB noted that its board includes a bioethicist, a nurse, and a pharmaceutical expert on drug studies, while another reported filling half its board with non-scientist members. Four IRBs reported evaluating the diversity of their boards on a regular or frequent basis, and one IRB reported surveying its members to understand the unique perspectives that they contribute to the board. Two IRBs reported that they consider how new members will contribute to the diversity of the board as part of their recruitment processes.

**Board reflects perspectives of participants and community.** IRBs described taking different approaches when serving as an IRB for affiliated versus external institutions. For example, one affiliated IRB reported seeking community leaders, such as pastors and former patients of their institution, to serve on the board. That affiliated IRB also reported scheduling regular meetings between IRB leaders and the patient and community members of the IRB to obtain feedback regarding IRB review processes and consulting the institution's community-based research advisory council regarding certain protocols.

Independent IRBs and affiliated IRBs, when serving as a single IRB for an external research institution (10 of the selected IRBs), are not always located in the same communities as the research sites and thus may not be aware of the specific participant or community perspectives they should consider during their review. In response, officials with four of

these IRBs reported asking the sponsor or the investigator if the proposed population of research participants has any pertinent community or cultural norms with respect to research. If the IRB does not have an appropriate member knowledgeable about the patient population, one IRB reported that it would obtain a consultation from an individual who reflects the perspective of that community.

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**IRB Functions, Operations, and Records**

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**Federal regulations:** IRBs must have sufficient staff to support IRB review and recordkeeping duties; follow written procedures conducting review and reporting unanticipated problems or noncompliance; and prepare and maintain documentation of IRB activities, such as meeting minutes. 45 C.F.R. §§ 46.108, 46.115, 21 C.F.R. §§ 56.108, 56.115.

**Examples of recommended practices:** IRB staff are knowledgeable, pre-review investigator submissions prior to review by the board, and provide regulatory support at meetings. IRB uses compliance tools and electronic IRB management systems.<sup>a</sup>

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Source: GAO review of the Common Rule and FDA regulations, expert interviews, and published literature | GAO-23-104721

<sup>a</sup>Information on IRB staff member knowledge is detailed in the quality assurance practice section of this report.

**Submission pre-review.** Officials from 10 of the 11 IRBs reported having pre-review processes, whereby administrative staff members may review investigator submissions for IRB approval, which include submission forms, protocols, informed consent documents, and accompanying materials, for completeness and regulatory issues before sending the submission to the board. For example, this review may include determining if the research requires an investigational drug or device application to be submitted to the Food and Drug Administration (FDA), or if the study involves a vulnerable population and will require additional review procedures.

**Regulatory support.** Five of 11 IRBs reported having regulatory support staff or lawyers present at board meetings to, for example, help members correctly apply regulatory criteria and ensure consent forms contain required language. Additionally, one IRB reported that the legal consultant who was present for the meeting reviews the meeting minutes prior to distribution to the members for approval.

**Compliance tools.** Ten of 11 IRBs reported using compliance tools to ensure that protocols and informed consent forms contain required elements, including policies and procedures, checklists, worksheets,

guidance documents, and submission forms.<sup>2</sup> Three IRBs reported having designed informed consent form templates to align with regulatory requirements for informed consent, and three reported having specialist staff dedicated to reviewing consent forms.

**Electronic IRB management systems.** Nine of the 11 IRBs reported using electronic IRB management systems. An additional IRB reported recently contracting with a vendor to implement an electronic system. IRB officials reported that these systems may be used to support investigator submissions, correspondence between the investigator and IRB staff, completion of reviews and checklists, documentation of meeting minutes, and retention of IRB documents. According to the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), most IRBs they accredit used electronic IRB management systems in 2020.<sup>3</sup>

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**IRB Research Review**

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**Federal regulations:** In order to approve research, IRBs must determine the research is consistent with specific criteria, which include ensuring that risks are minimized, subject selection is fair, and data confidentiality is maintained. 45 C.F.R. §§46.109–12; 21 C.F.R. §§ 56.109–11

**Examples of recommended practices:** IRB conducts thorough reviews of research and uses experts to explain complex protocols; IRB reviews investigator qualifications; and IRB monitors the conduct of research.<sup>a</sup>

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Source: GAO review of the Common Rule and FDA regulations, expert interviews, and published literature | GAO-23-104721

<sup>a</sup>Information on IRB monitoring of the conduct of research are detailed earlier in this report.

**Thorough reviews.** Nine IRBs reported they assign one or two board members to act as primary reviewers of the protocol.<sup>4</sup> Most IRBs that use this approach reported assigning board members with appropriate scientific experience or expertise to serve as primary reviewers.

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<sup>2</sup>IRBs may require investigators to complete submission forms to accompany research proposals, consent forms, and other materials. For example, one IRB’s submission form asks questions that target different regulatory requirements, such as the investigational new drug application number, qualifications of research staff, cultural norms in the setting where the research will be conducted, and storage of study documents.

<sup>3</sup>See Association for the Accreditation of Human Research Protection Programs, Inc., “2020 Metrics for AAHRPP-Accredited Human Research Protection Programs,” accessed August 30, 2022, <https://www.aahrpp.org/resources/for-accreditation/metric/all-organizations>.

<sup>4</sup>One IRB in our sample reported using a system in which all board members are responsible for the review.

According to IRB officials, the functions of the primary reviewers may include:

- obtaining sufficient background on the research, sponsor, and the product;
- reaching out to the investigator to ask questions in anticipation of the meeting;
- completing checklists that guide the reviewer through the regulatory criteria for approval;
- presenting a summary of the information during the board meeting, highlighting potential issues for discussion and consideration, making a recommendation for action by the board, and leading the discussion; and
- ensuring that the board makes determinations consistent with related research previously reviewed.

Six of the nine IRBs reported also assigning a second reviewer to conduct a comprehensive review, and some IRBs assign the second review to a member with a different perspective, such as a nurse or a layperson.

A 10th IRB reported using a similar approach but referred to its approach as a primary presenter system. Officials from this IRB emphasized that all members are responsible for reviewing the protocol and associated materials in enough depth to independently determine whether the regulatory criteria for approval were satisfied. That is, members should not rely on the primary presenter's determination. Most IRBs that reported using the primary reviewer approach also reported expecting the rest of the members of the board to review the study materials in enough detail to determine the appropriateness of the study or to contribute to the IRB discussion.

**Expert review.** Officials representing all of the IRBs we spoke to reported they maintain processes for ensuring that protocols receive review from members with the appropriate expertise. Four IRBs reported regularly reviewing the expertise of their panels, and six reported recruiting new members with expertise that matches the protocols reviewed by the IRB. Additionally, all IRBs reported using expert consultants to supplement the IRB's expertise, when needed, although most IRBs reported relying

primarily on the expertise of their members.<sup>5</sup> Two IRBs reported tracking their use of consultants to identify the types of expertise that they need to add to their board. When presented with a protocol outside of the board's expertise, officials representing one independent IRB reported that they may choose to decline to review the protocol, and two affiliated IRBs reported that they may choose to cede review to an IRB not affiliated with their institution. For example, one IRB reported that it does not review research on prisoners, but relies on another research institution's IRB to conduct such reviews.

**Investigator qualifications.** Officials representing four of the five affiliated IRBs reported requiring institutional leaders to sign off that the investigator—who is a member of the affiliated institution—has sufficient qualifications to conduct the study. Independent IRBs, which may not know the investigator, reported using different processes, which may include:

- reviewing the investigator's curriculum vitae to ensure that the investigator has sufficient expertise to conduct the research study (four of six independent IRBs),
- checking one or more administrative databases to confirm the investigator's licensure or identify any disciplinary actions against the investigator (six of six independent IRBs),
- contacting a study sponsor or representatives of the investigator's institution to learn more about the investigator's qualifications or experience (two of six independent IRBs), or
- maintaining a list of investigators that they will not work with or will closely watch in the future (four of six independent IRBs).

Officials representing three of the four affiliated IRBs that serve as single IRBs described the process they use to review the investigators' qualifications at institutions that rely on, but are not affiliated with, the IRB.<sup>6</sup> Specifically, officials representing two affiliated IRBs reported

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<sup>5</sup>Federal regulations permit IRBs to include non-board members in deliberations and for these individuals to assist in IRB review for issues that require additional expertise beyond that available on the IRB, though they these experts may not vote with the IRB.

<sup>6</sup>Under a single IRB model, a reliance agreement is a written agreement between two or more institutions that is used to document the delegation of IRB review responsibilities between the IRB of record (that is, the IRB performing review on behalf of one or more institutions, also referred to as the single IRB or central IRB) and the institution that agrees to rely upon the reviewing IRB (also referred to as the relying institution).

establishing reliance agreements that make it clear that the relying institutions are responsible for ensuring that investigators are qualified to conduct the research described in the protocol. Officials representing another affiliated IRB that serves as a single IRB reported requiring the relying institution's designated human research protection program official to confirm that all study personnel at their site are appropriately qualified.

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**Informed Consent**

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**Federal regulations:** IRBs must ensure that information provided to research subjects or their legal representatives includes a reasonable and understandable description of the research study and the risks and benefits of participation and that subjects document their informed consent. 45 C.F.R. §§ 46.116–17; 21 C.F.R. §§ 50.20, 50.25, 50.27, 56.109, 56.111

**Examples of recommended practices:** IRB ensures that informed consent forms are comprehensible; uses alternative methods to enhance informed consent comprehension, when merited; and observes the informed consent process.

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Source: GAO review of the Common Rule and FDA regulations, expert interviews, and published literature | GAO-23-104721

**Comprehensible informed consent forms.** Officials from six of the 11 IRBs reported checking the reading level of consent forms, and one IRB reported providing consent readability statistics back to study teams. Four IRBs reported assigning non-scientific members of the board to evaluate whether the informed consent form appears to be comprehensible to study participants.

**Alternative methods to enhance informed consent.** While three selected IRBs reported encouraging investigators to submit protocols that include alternative methods to augment comprehension—such as interactive computer modules, videos, and quizzes—as part of the informed consent process, only one IRB reported requiring investigators to include these strategies when appropriate. Officials with one IRB reported asking investigators in the application how they will determine that the subject understands the information explained during the informed consent process and will review the answer as part of board deliberations. This IRB makes available an informed consent quiz that investigators can use to assess comprehension. One IRB reported providing its members with education regarding the research supporting the use of enhanced comprehension strategies, which IRB officials reported has assisted the board in both evaluating these strategies when

proposed by investigators and in recommending such options to investigators when thought to be appropriate.<sup>7</sup>

**Observe informed consent process.** Federal regulations provide IRBs the authority to directly observe or have a third party observe the informed consent process and research.<sup>8</sup> Officials representing eight of the 11 IRBs reported that they, or another research oversight office at their institution, may observe the consent process. However, four of these IRBs specified only observing informed consent in rare situations, such as when they have concerns that informed consent is not occurring in accordance with federal regulations. Officials with one IRB reported that although they do not routinely observe the informed consent process, they regularly review documentation of the informed consent process by requiring investigators to provide copies of the last two consent forms signed by subjects as part of their application for continuing approval. When investigators do not submit consent forms with their continuing approval application, this IRB may decide to have an auditor observe the consent process. Officials with one affiliated IRB that serves as a single IRB reported that it includes a provision in its reliance agreements that the relying institution must have the capability to observe the informed consent process if requested by the single IRB.

Officials representing an independent IRB reported that there is little value in observing the informed consent process. These officials stated that when both the investigator and the research participant are aware that the informed consent process is being observed, it is unlikely that either party will act in a way that allows the observer to obtain any useful information about a typical consent discussion.

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<sup>7</sup>The following studies have found that research participants exposed to alternative informed consent methods, such as quizzes and videos, had better understanding of the information shared during the informed consent process. See Holly Taylor et al., "Randomized Comparison of Two Interventions to Enhance Understanding during the Informed Consent Process for Research," *Clinical Trials*, vol. 18, no. 4 (2021): 466-476.; and Nancy Kass et al. "A Pilot Study of Simple Interventions to Improve Informed Consent in Clinical Research: Feasibility, Approach, and Results," *Clinical Trials*, vol. 12, no. 1 (2015): 54-66.

<sup>8</sup>45 CFR § 46.109(g); 21 CFR § 56.109(f)



## Appendix III: Performance and Quality Assessment Mechanisms

Since the late 1990s, numerous federal bodies and other entities have recommended that the Department of Health and Human Services (HHS) or other federal agencies involved in research with human subjects evaluate mechanisms for assessing institutional review board (IRB) performance and ensuring IRB quality. Below are examples of the recommendations made and the associated outcomes. (See Table 5.)

**Table 5: Examples of Recommendations Related to Institutional Review Board (IRB) Performance and Quality Assessment Mechanisms**

Topic of recommendation	Year	Federal or other entity issuing the recommendation	Recommendation	Outcome
Performance measurement	1998	Department of Health and Human Services Office of Inspector General	The National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Office for Protection from Research Risks (OPRR)—the Office for Human Research Protections’ predecessor—should convene symposia with institutional review boards (IRB) to discuss the type of performance measures and evaluations that would foster a system of accountability.	The Office for Human Research Protections (OHRP) and FDA have not conducted or sponsored any research or projects that have yielded measures of IRB effectiveness, according to agency officials. <sup>a</sup>
Performance measurement	2006	National Conference on Alternative IRB Models	The Department of Health and Human Services (HHS) should give OHRP the authority to issue grants to support research on identifying metrics for assessing IRB performance.	
Performance measurement	2011	Presidential Commission for the Study of Bioethical Issues	OHRP, in conjunction with other federal human subjects’ research agencies, should support the development of systematic approaches to assess the effectiveness of protections for human subjects.	
Accreditation	2001	Institute of Medicine	HHS should evaluate the effect that accreditation of human research protection programs has on the rights and interests of participants.	OHRP and FDA have not conducted or sponsored an evaluation of accreditation, according to agency officials.
Accreditation	2001	National Bioethics Advisory Commission	The federal government should approve accreditation programs that are premised upon demonstrated competency in core areas.	
Accreditation	2004	Secretary’s Advisory Committee on Human Research Protections	HHS should organize a systematic evaluation of accreditation to determine whether it can serve as an assurance of quality research and protections for human subjects.	

**Appendix III: Performance and Quality  
Assessment Mechanisms**

<b>Topic of recommendation</b>	<b>Year</b>	<b>Federal or other entity issuing the recommendation</b>	<b>Recommendation</b>	<b>Outcome</b>
Certification	2001	National Bioethics Advisory Commission	The federal government should encourage the development of certification programs and mechanisms to evaluate their effectiveness.	OHRP and FDA have not conducted or sponsored an evaluation of certification, according to agency officials.
Certification	2004	Secretary's Advisory Committee on Human Research Protections	HHS, with involvement of FDA, OHRP, and others, should organize a conference to examine certification, as well as other self-regulatory activities.	

Sources: Department of Health and Human Service Office of Inspector General, *Institutional Review Boards: A Time For Reform* (Washington, D.C., June 1998); Office for Human Research Protections (OHRP) et al. *National Conference on Alternative IRB Models: Optimizing Human Subject Protection*, November 19-21, 2006; Presidential Commission for the Study of Bioethical Issues, *Moral Science: Protecting Participants in Human Subjects Research* (Washington, D.C., December 2011); Institute of Medicine Committee on Assessing the System for Protecting Human Research Participants, *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs* (Washington, D.C.: National Academies Press, 2001); National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants* (Bethesda MD, 2001); Secretary's Advisory Committee on Human Research Protections, *SACHRP Letter to HHS Secretary on Children's Research* (Rockville, MD, July 8, 2004); and interviews with OHRP and FDA officials | GAO-23-104721

Note: Some entities recommended that HHS implement related oversight mechanisms—either after a successful evaluation or without an evaluation—but we have not listed those recommendations in this table. For example, the 2001 National Bioethics Advisory Commission recommended that sponsors, institutions, and independent IRBs be accredited in order to conduct or review research involving human participants.

<sup>a</sup>In 2000, HHS contracted with the Institute of Medicine (now known as the National Academy of Medicine) to address the protection of human research subjects, including requesting recommendations for steps that institutions conducting research and the federal government should take to monitor and evaluate the system for protecting human subjects. The reports did not provide specific criteria for evaluating the performance of IRBs, but did discuss related concepts, according to OHRP officials.

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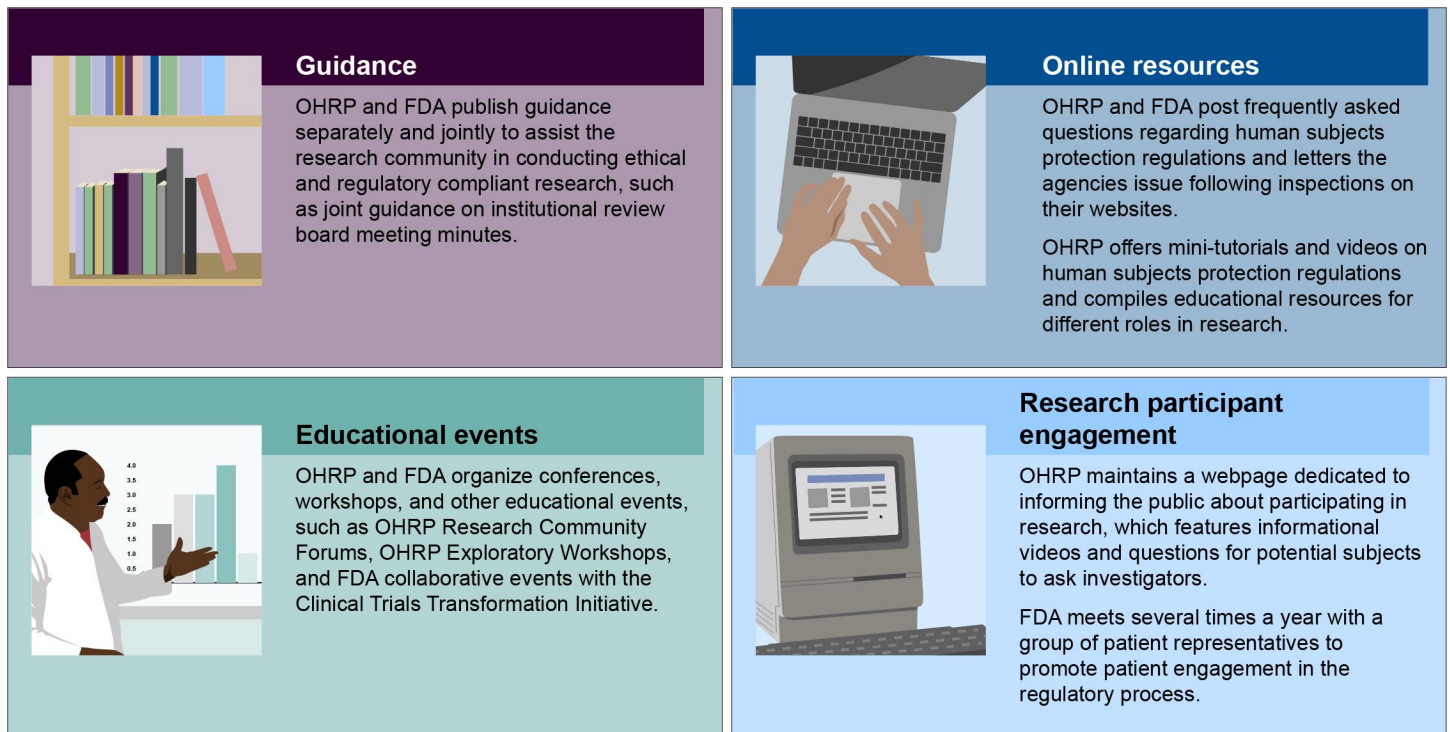
## Appendix IV: Guidance and Educational Materials

The Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) issue guidance and provide education and outreach to assist all types of institutional review boards (IRB) and research institutions adhere to federal regulations on the protection of human research subjects. For example, OHRP's website contains education and training materials for the research community on the Common Rule and research involving human subjects, and FDA engages with a variety of stakeholders in the IRB industry through the Clinical Trials Transformation Initiative.<sup>1</sup> (See fig. 9.)

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<sup>1</sup>The Clinical Trials Transformation Initiative was co-founded by Duke University and FDA and is a group of individuals and organizations that want to improve the quality and efficiency of clinical trials; identify and address challenges to well-designed, properly executed clinical trials; and offer recommendations to improve and modernize research.

Figure 9: Guidance, Educational Materials, and Outreach Provided by the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA)



Source: GAO analysis of OHRP, FDA, and Clinical Trials Transformation Initiative information. | GAO-23-104721

According to agency officials, OHRP and FDA may incorporate recommendations made by the Secretary’s Advisory Committee on Human Research Protections (SACHRP), a federal advisory committee that provides expert advice and recommendations to the Secretary of Health and Human Services on the protection of human research subjects, in developing guidance documents.<sup>2</sup> SACHRP also provides recommendations to IRBs. For example, while the Common Rule does not address pay-to-participate research—that is, research in which study participants are charged for research interventions and associated care—SACHRP has developed information to help IRBs, investigators, and research subjects, among others, navigate this topic. Officials

<sup>2</sup>SACHRP advises the Secretary on how to improve the quality of human research protection programs, including the responsibilities of investigators, IRBs, administrators, institutional officials, and the role of OHRP and other offices within the Department of Health and Human Services (HHS). SACHRP’s membership includes representatives of federal agencies, private industry, and academic centers.

representing one selected IRB we interviewed noted they would review pay-to-participate research consistent with SACHRP's recommendations.<sup>3</sup> Officials representing two selected IRBs and one expert indicated that they or the IRB community treat SACHRP recommendations as guidance.

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<sup>3</sup>Under FDA regulations, with prior written authorization from the FDA, sponsors may charge participants for investigational drugs and biologics under an investigational new drug application under limited circumstances where the sponsor can show the following: the drug has a potential benefit that could provide a significant advantage over available products; the data from the clinical trial is essential to establishing effectiveness or safety; and the trial could not be conducted without charging participants because of extraordinary cost to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed, or some combination of these or other extraordinary circumstances. See 21 C.F.R. § 312.8.

### Pay-to-Participate Research

According to the Secretary's Advisory Committee on Human Research Protections (SACHRP) in 2019, Institutional Review Boards (IRB), are increasingly being asked to review pay-to-participate research, though such research is still unusual. Pay-to-participate research is research in which the study participants are charged for research interventions and associated care. SACHRP guidance recommends a careful review of each pay-to-participate trial, based on consideration of a list of questions it provides and the satisfaction of all regulatory criteria for approval.

Among our sample of 11 IRBs, officials with six IRBs reported that they have never reviewed pay-to-participate research and would likely disapprove or would follow an internal policy or SACHRP guidance if they received one. Officials with five IRBs (all independent) reported having reviewed pay-to-participate studies, although two of them noted that they rarely review such studies. Four of these IRBs reported that they only approve these studies under certain circumstances (e.g., the Food and Drug Administration authorized a sponsor to charge for an investigational product) or that they typically disapprove of these studies.

Source: SACHRP recommendation on charging subjects for clinical trial participation (2019) and GAO analysis of interviews with a non-representative sample of 11 IRBs. | GAO-23-104721

In June 2022, OHRP officials told us the agency has been working to develop guidance documents for IRBs related to the Common Rule revisions. It issued draft guidance for public comment related to the use of a single IRB for cooperative research in July 2022, as well as two other Common Rule-related guidance documents earlier in the year.<sup>4</sup> Officials also said OHRP is in the process of developing approximately 20 additional policy and guidance documents for IRBs, including related to secondary research, broad consent, and limited IRB review. Officials representing two stakeholders and three IRBs we interviewed noted that such guidance was needed. For example,

- Regarding the single IRB review requirement, one expert said it is unclear what qualifies one IRB over another to have the responsibility of being the single IRB, and there is confusion around who has liability when a participant is harmed in one of these trials; and

<sup>4</sup>See OHRP, "Use of a Single Institutional Review Board for Cooperative Research", 87 Fed. Reg. 39,534 (Jul. 1, 2022); OHRP, "Informed Consent Posting Instructions: General Instructions on the Informed Consent Posting Requirement (45 CFR 46.116(h))" (Mar. 29, 2022), accessed July 1, 2022, <https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/informed-consent-posting-guidance/index.html>; and OHRP, "Posting Requirement for the Exemption at 45 CFR 46.104(d)(5) of the 2018 Requirements (2022)" (April 20, 2022), accessed July 1, 2022, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/posting-requirement-for-the-exemption-at-45-cfr-46-104-d-5-of-2018-requirements/index.html>.

- Regarding the informed consent requirement, one IRB said they have questions about the applicability of the new requirements and what the key information section should contain.

FDA is working to address differences between its regulations regarding human subjects and the revised Common Rule, consistent with the 21st Century Cures Act, which required the Secretary of Health and Human Services to harmonize differences between Department of Health and Human Services and FDA regulations.<sup>5</sup> According to FDA officials, FDA is working to harmonize FDA regulations with the revised Common Rule to the extent practicable and consistent with other statutory guidance.<sup>6</sup> OHRP and FDA officials said they have long engaged in efforts to harmonize the two agencies' requirements. According to FDA and OHRP officials, these efforts include regular meetings to discuss harmonization and emerging issues, issuing joint guidance, and issuing separate guidance that is harmonious.<sup>7</sup>

Officials representing three selected IRBs noted the need for such harmonization, in particular, because of differences in how IRBs should review certain protocols subject to the revised Common Rule as compared to protocols subject to FDA regulations. For example, under the revised Common Rule, IRBs are no longer required to conduct periodic review of ongoing research in certain circumstances; however, all

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<sup>5</sup>Pub. L. No. 114-255, § 3023, 130 Stat. 1033, 1098 (2016).

<sup>6</sup>In September 2022, FDA issued two additional proposed rules to harmonize its regulations with the revised Common Rule. These proposed changes, if finalized, would require the use of a single IRB for FDA-regulated cooperative research, make changes to informed consent documents to aid participant comprehension, and allow for the elimination of continuing reviews for certain studies. See 87 Fed. Reg. 58,733 (Sep. 28, 2022) and 87 Fed. Reg. 58,752 (Sep. 28, 2022). Additionally, in June 2022, FDA officials told us that the agency anticipates finalizing a 2018 proposed rule to allow for waivers or alterations of informed consent for studies that pose no more than minimal risk to the human subjects in 2022. See 83 Fed. Reg. 57,378 (Nov. 15, 2018).

<sup>7</sup>An example of joint guidance includes the following: HHS, OHRP and FDA, *Guidance for Institutions and IRBs: Minutes of Institutional Review Board (IRB) Meetings* (September 2017). According to OHRP officials, OHRP and FDA issued separate guidance during the COVID-19 pandemic, but worked together to ensure the guidance was harmonious. See HHS, FDA, *Guidance for Industry, Investigators, and Institutional Review Boards: Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency* (updated August 2021); and OHRP, "Research Guidance on Coronavirus," accessed July 1, 2022, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html#:~:text=OHRP%20has%20received%20questions%20regarding,prioritize%20public%20health%20and%20safety>.

FDA-regulated studies must still be periodically re-reviewed.<sup>8</sup> Officials from one selected IRB said that this difference means they must maintain two sets of standard operating procedures to ensure they are consistent with both the Common Rule and FDA regulations.

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<sup>8</sup>Before it was revised, the Common Rule required an IRB to conduct periodic reviews of ongoing research at intervals appropriate to the degree of risk, not less than once per year. Under the 2018 revision, IRBs are not required to conduct periodic reviews for 1) exempt research conditioned on limited IRB review, 2) research that is eligible for expedited review, or 3) research that has progressed to the point that the only remaining activities are data analysis or accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care, unless the IRB determines otherwise. 45 C.F.R. §§ 46.109(f), 46.110, 46.115(a)(8)). Certain exempt research must be reviewed by limited IRB review, whereby an experienced IRB member must determine that certain conditions, which are specified in the regulations, are met, but does not need to consider all of the IRB approval criteria (45 C.F.R. § 46.109(a)). See 21 CFR § 56.109(f) for FDA regulations regarding periodic reviews.



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# Appendix V: Comments from the Department of Health and Human Services

**Appendix V: Comments from the Department  
of Health and Human Services**



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation  
Washington, DC 20201

December 7, 2022

John Dicken  
Director, Health Care  
U.S. Government Accountability Office  
441 G Street NW  
Washington, DC 20548

Dear Mr. Dicken:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, **"INSTITUTIONAL REVIEW BOARDS: Actions Needed to Improve Federal Oversight and Examine Effectiveness"** (GAO-23-104721).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

*Melanie Anne Egorin*

Melanie Anne Egorin, PhD  
Assistant Secretary for Legislation

Attachment

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**Appendix V: Comments from the Department  
of Health and Human Services**

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**GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED — INSTITUTIONAL REVIEW BOARDS: ACTIONS NEEDED TO IMPROVE FEDERAL OVERSIGHT AND EXAMINE EFFECTIVENESS (GAO-23-104721)**

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

**Recommendation 1**

The Assistant Secretary for Health 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.

**HHS Response**

HHS concurs with the recommendation and thanks GAO for identifying potential inaccuracies in the information some institutions have provided about their approximate portfolio sizes when registering IRBs with our office. OHRP has begun to explore ways to improve the accuracy of the information that institutions submit during the initial and renewal registration process for IRBs.

**Recommendation 2**

The Assistant Secretary for Health 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.

**HHS Response**

HHS concurs with this recommendation. OHRP will 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 research participant protections.

**Recommendation 3**

The Commissioner of the Food and Drug Administration 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.

**HHS Response**

HHS concurs with this recommendation. FDA will 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 research participant protections. FDA envisions the annual risk assessment would review the number of IRB inspections, inspection coverage across different types of IRBs, sizes of IRBs, and the prioritization of IRB inspections relative to other inspection programs designed to protect the rights, safety, and welfare of research participants.

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**Appendix V: Comments from the Department  
of Health and Human Services**

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**Recommendation 4**

The Secretary of Health and Human Services 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.

**HHS Response**

HHS concurs with this recommendation. FDA and OHRP will identify opportunities to convene relevant stakeholders to explore additional measures of the effectiveness of IRBs' oversight in protecting research participants. FDA and OHRP will evaluate which, if any, of these approaches may benefit from appropriate action to support implementation.

# Accessible Text for Appendix V: Comments from the Department of Health and Human Services

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John Dicken  
Director, Health Care  
U.S. Government Accountability Office  
441 G Street NW  
Washington, DC 20548

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Sincerely,

Melanie Anne Egorin, PhD  
Assistant Secretary for Legislation

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HHS Response

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approximate portfolio sizes when registering IRBs with our office. OHRP has begun to explore ways to improve the accuracy of the information that institutions submit during the initial and renewal registration process for IRBs.

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#### HHS Response

HHS concurs with this recommendation. OHRP will 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 research participant protections.

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The Commissioner of the Food and Drug Administration 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.

#### HHS Response

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#### HHS Response

HHS concurs with this recommendation. FDA and OHRP will identify opportunities to convene relevant stakeholders to explore additional measures of the effectiveness of

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IRBs' oversight in protecting research participants. FDA and OHRP will evaluate which, if any, of these approaches may benefit from appropriate action to support implementation.

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## Appendix VI: GAO Contact and Staff Acknowledgments

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### GAO Contact

John E. Dicken, (202) 512-7114 or [DickenJ@gao.gov](mailto:DickenJ@gao.gov)

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### Staff Acknowledgment

In addition to the individual named above, Shannon Legeer (Assistant Director), Toni Harrison (Analyst-in-Charge), Ivy Benjenk, and Grace Kwon made key contributions to this report. Also contributing were Giselle Hicks, Sonia Chakrabarty, Sam Amrhein, Brandon Nakawaki, Vikki Porter, Lisa Rogers, Shana Deitch, Robert Marek, Abigail Loxton, and Pam Snedden.