

United States Senate  
WASHINGTON, DC 20510

June 16, 2020

Gene L. Dodaro  
U.S. Comptroller General  
Government Accountability Office  
441 G St. NW  
Washington, D.C. 20548

Dear Mr. Dodaro:

We write to request a Government Accountability Office (GAO) investigation of the operation of commercial Institutional Review Boards (IRBs), the private, for-profit entities that approve drug research and other studies involving human subjects. As clinical trials related to the coronavirus disease 2019 (COVID-19) pandemic accelerate, ensuring that IRBs are providing adequate patient protection is more important than ever. Our preliminary investigation, opened in November 2019, raises questions about whether the commercial IRBs' reviews of these studies have significant vulnerabilities that may leave patients exposed to unnecessary risks during their participation in clinical trials.

In 2009, GAO released a study that exposed alarming vulnerabilities in human subject research reviews.<sup>1</sup> In an undercover investigation, GAO was able to obtain IRB approval for a fictitious test of a medical device that met the Food and Drug Administration's (FDA) guidelines for "significant risk." The for-profit IRB that approved the fictitious device, Coast IRB, closed after the GAO investigation was made public.<sup>2</sup> The report concluded that "the IRB system is vulnerable to unethical manipulation, particularly by companies or individuals who intend to abuse the system or to commit fraud, or who lack the aptitude or qualifications to conduct and oversee clinical trials. This vulnerability elevates the risk that experimental products are approved for human subjects testing with little or no substantive due diligence."<sup>3</sup>

In the decade since this GAO investigation, the IRB landscape has shifted in several significant ways. First, while the 2009 GAO study noted "IRBs were historically located at academic institutions," it found that commercial IRBs "are playing an increasingly prominent role in the protection of human research subjects."<sup>4</sup> That trend has continued in the intervening decade, and commercial, for-profit IRBs now oversee approximately 70% of all drug and medical device

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<sup>1</sup> Government Accountability Office, "Human Subjects Research: Undercover Tests Show the Institutional Review Board System is Vulnerable to Unethical Manipulation," March 26, 2009, <https://www.gao.gov/assets/130/122142.pdf>.

<sup>2</sup> *Wall Street Journal*, "Coast IRB, Caught in Sting, to Close," Alicia Mundy, April 22, 2009, <https://www.wsj.com/articles/SB124042341694744375>.

<sup>3</sup> Government Accountability Office, "Human Subjects Research: Undercover Tests Show the Institutional Review Board System is Vulnerable to Unethical Manipulation," March 26, 2009, <https://www.gao.gov/assets/130/122142.pdf>.

<sup>4</sup> *Id.*

trials in the United States.<sup>5</sup> This is a particular concern because this private, for-profit model creates an inherent conflict of interest for IRBs, which may incentivize them to approve as many studies as they can as rapidly as possible.<sup>6</sup> The urgency of the COVID-19 pandemic may further increase pressure for IRBs to provide rapid approvals that may be inadequate or incomplete. Though conflicts of interest are common among individual IRB reviewers, including at academic IRBs,<sup>7</sup> the profit motive and lack of transparency at commercial IRBs make potential conflicts especially worrisome.

Furthermore, over the last decade, more than a dozen independent IRBs of all sizes have merged or been acquired to form two major firms, WCG Clinical and Advarra.<sup>8</sup> Both IRBs are owned by private equity investors, raising questions about whether they are under pressure to reduce costs and ramp up profits, trends that often accompany private equity's entry into a market.<sup>9</sup>

In addition, recent reports have identified a growing trend of “pay to participate” trials, in which patients are asked to pay fees of thousands of dollars in order to participate in clinical research.<sup>10</sup> In one particularly egregious example, a Florida physician proposed patient fees as high as \$285,000 for participants in a study of plasma infusions to prevent aging.<sup>11</sup> Another trial asked parents of autistic children to pay over \$20,000 in enrollment, travel, and other expenses to participate in a trial of stem cell therapy.<sup>12</sup> These practices, by definition, restrict access to clinical trials and risk taking advantage of vulnerable patients and their families. In addition, they create strong incentives for sponsors to oversell the potential benefits of the research, despite the high failure rate of early-stage trials.<sup>13</sup> Furthermore, these studies' scientific validity is

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<sup>5</sup> Stat News, “In clinical trials, for-profit review boards are taking over for hospitals. Should they?” Sheila Kaplan, July 6, 2016, <https://www.statnews.com/2016/07/06/institutional-review-boards-commercial-irbs/>.

<sup>6</sup> Letter from Senators Elizabeth Warren, Bernard Sanders, and Sherrod Brown to WCG Clinical and Advarra, November 19, 2019, <https://www.warren.senate.gov/oversight/letters/senators-warren-brown-and-sanders-investigate-inherent-conflicts-of-interest-of-private-equity-owned-institutional-review-boards>.

<sup>7</sup> *JAMA Internal Medicine*, “Industry Relationships Among Academic Institutional Review Board Members: Changes from 2005 Through 2014,” September 2015, E.G. Campbell, C. Vogeli, S.R. Rao, M. Abraham, R. Pierson, and S. Applebaum, <https://www.ncbi.nlm.nih.gov/pubmed/26168043>.

<sup>8</sup> Melissa Fassbender, “IRB Consolidation: Advarra acquires Quorum Review and Kinetiq,” March 5, 2019, <https://www.outsourcing-pharma.com/Article/2019/03/05/IRB-consolidation-Advarra-acquires-Quorum-Review-and-Kinetiq>; Center Watch Compilation Report Series, “IRB market consolidating rapidly,” <https://www.centerwatch.com/products/270-july-2014-the-centerwatch-monthly-print>.

<sup>9</sup> Melissa Fassbender, “Advarra finds new owner in Genstar Capital,” June 6, 2019, <https://www.outsourcing-pharma.com/Article/2019/06/06/Advarra-finds-new-owner-in-Genstar-Capital>; Center for Economic and Policy Research, “Private Equity Partners Get Rich at Taxpayer Expense,” Eileen Applebaum and Rosemary Batt, July 2017, <https://populardemocracy.org/pirateequity>.

<sup>10</sup> Stat News, “Amid rising concern, pay-to-play clinical trials are drawing federal scrutiny,” Rebecca Robbins, August 6, 2019, <https://www.statnews.com/2019/08/06/amid-rising-concern-pay-to-play-clinical-trials-are-drawing-federal-scrutiny/>.

<sup>11</sup> Stat News, “How a society gala was used to sell young-blood transfusions to baby boomers desperate to cheat death,” Rebecca Robbins, March 2, 2018, <https://www.statnews.com/2018/03/02/young-blood-anti-aging-study/>.

<sup>12</sup> Spectrum News, “Experts question rationale for stem cell trial for autism,” Hannah Furfaro, July 25, 2019, <https://www.spectrumnews.org/news/experts-question-rationale-for-stem-cell-trial-for-autism/>.

<sup>13</sup> *Medicine, Health Care, and Philosophy*, “Permitting patients to pay for participation in clinical trials: the advent of the P4 trial,” David Shaw, Guido de Wert, Wybo Dondorp, David Townend, Gerard Bos, and Michel van Gelder, October 18, 2016, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5487744/>.

potentially compromised because in many cases, they forego a control group, since participants are unlikely to be willing to pay if they are not actually receiving a treatment.<sup>14</sup>

In response to these troubling trends, in November 2019 we asked the two largest for-profit IRBs, WCG Clinical and Advarra, for information on their policies and procedures for reviewing human subjects research, including information about how they ensure that reviews are thorough and high-quality, how and whether they prevent and disclose panel members' conflicts of interest, and how they identify and review "pay to participate" clinical trial proposals.<sup>15</sup> We also asked for data to substantiate each of these procedures and to understand the scope of each IRB's responsibility.

WCG Clinical and Advarra responded in generalities, assuring us that their review process is thorough and high-quality, but provided little data to corroborate these claims. But their responses – which we have attached to this request - failed to address many of our key concerns or questions with appropriate detail and specificity. Concerns that were not appropriately addressed in these responses included:

- **Conflicts of interest.** Advarra provided helpful guidance, indicating that the company's policies require disclosures of conflicts, examples of relationships that would constitute a conflict, and a requirement that individuals with conflicts "recuse themselves from participation in the review of any project for which they have a conflict of interest."<sup>16</sup> But the company provided no further details on the number of panel members who have recused themselves over conflicts in the past. WCG Clinical provided no details whatsoever on how they identify, address, and prevent undue influence from panel members' conflicts of interest.
- **"Pay for participation" trials.** We asked a series of questions about how the two largest IRBs protect patients and scientific integrity in "pay for participation" trials. Again, WCG ignored these questions, raising concerns about the company's approach to review of these ethically questionable studies. Advarra provided more helpful information, indicating that "these types of research proposals are still relatively rare."<sup>17</sup> They reported that they have reviewed nine such proposals to date, of which four were disapproved, three were withdrawn or tabled permanently, and two were approved.
- **Quality Metrics.** Neither IRB provided the specific metrics we sought in order to evaluate the quality, efficiency, and effectiveness of the review process and determine whether these for-profit IRBs had appropriate processes and procedures in place to protect patients and ensure the scientific integrity of human-subject studies. Advarra

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<sup>14</sup> Wharton Public Policy Initiative, "Pay to Play: Should Patients Have to Pay to Be Part of Experimental Trials?" Danielle Martinez-McCormack, November 7, 2016, [https://publicpolicy.wharton.upenn.edu/live/news/1514-pay-to-play-should-patients-have-to-pay-to-be-part#\\_edn2](https://publicpolicy.wharton.upenn.edu/live/news/1514-pay-to-play-should-patients-have-to-pay-to-be-part#_edn2).

<sup>15</sup> Letters from Senators Warren, Brown, and Sanders to WCG Clinical and Advarra, November 19, 2019, <https://www.warren.senate.gov/oversight/letters/senators-warren-brown-and-sanders-investigate-inherent-conflicts-of-interest-of-private-equity-owned-institutional-review-boards>.

<sup>16</sup> Letter from Scott E. Uebele, CEO of Advarra, to Sen. Warren, April 8, 2020. See attached.

<sup>17</sup> *Id.*

reported only that 80% of their proposals are approved with modifications and “a small percentage” are approved with no modifications.

To address these unanswered questions, we request a GAO investigation of the operation of commercial IRBs. We ask that this investigation address the following questions:

1. What is the current market structure for IRBs? To what extent has the use of commercial IRBs increased relative to the use of academic or other non-profit IRBs? What has driven the market consolidation of for-profit IRBs, what role does private equity play in this process, and how does it affect the ability of IRBs to appropriately review research proposals and protect patients and scientific integrity?
2. Do commercial IRBs have appropriate protections in place to address the inherent conflicts of interest posed by their profit-seeking mission? Do they have appropriate procedures in place to address and ensure transparency regarding conflicts of interest among panel members that may have industry ties?
3. Do commercial IRBs have appropriate processes and procedures in place to protect patients and ensure the scientific integrity of “pay for participation” studies?
4. Do existing standards of quality, efficiency, and effectiveness provide adequate protection for participants in IRB-approved clinical trials? How can IRBs, the FDA, and the Department of Health and Human Services address any shortcomings in the current system to improve quality and patient outcomes?
5. How do procedures and outcomes differ between academic and commercial IRBs?

Thank you for your attention to this matter. We are happy to provide additional details regarding our concerns about commercial IRBs and about this request.

Sincerely,

Elizabeth Warren  
United States Senator

Bernard Sanders  
United States Senator

Sherrod Brown  
United States Senator