ROPES & GRAY

ALERT

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Congress Enacts Legislation Requiring Guidance on Clinical Research Diversity and Modernization

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On December 29, 2022, President Biden signed into law the Consolidated Appropriations Act, 2023 (H.R. 2617), an omnibus appropriations bill to fund the U.S. government through fiscal year 2023. Included in the omnibus bill is the Food and Drug Omnibus Reform Act of 2022 ("FDORA"), which includes several provisions intended to promote diversity in clinical trial enrollment, encourage the growth of decentralized clinical trials, and streamline clinical trials. This alert analyzes the provisions of FDORA addressing clinical trials and their importance for the clinical research enterprise. For an overview of FDORA's other provisions, please see Ropes & Gray's alert entitled New FDA Reform Legislation: Congress Gifts a "FDORA" for the Holidays.

Clinical Trial Diversity

Summary of FDORA Requirements

Under FDORA, clinical trial sponsors must submit to the Secretary of the U.S. Department of Health and Human Services (the "Secretary") "diversity action plans" for certain late-stage drug trials, including all phase 3 trials, as well as most device studies. The diversity action plan must include the sponsor's goals for enrollment in the clinical study, the sponsor's rationale for those goals, and an explanation of how the sponsor intends to meet them. The Secretary is permitted to waive the requirement for a diversity action plan if the Secretary determines that a waiver is necessary based on what is known or can be determined about the prevalence or incidence of the disease or condition for which the product is under investigation, presumably to permit a waiver of the requirements for studies for which demographic limitations of the patient population affected by the relevant disease would preclude enrollment of a diverse population. The Secretary may also waive the diversity action plan requirement if conducting a clinical investigation in accordance with a diversity action plan would otherwise be impracticable or if a waiver is necessary to protect public health during a public health emergency. In addition, the statute excludes from the diversity action plan requirements the provision of products through the expanded access framework as well as device studies that are exempt under 21 C.F.R. § 812.2(c) from most investigational device exemption ("IDE") requirements. Because the provisions of FDORA governing "diversity action plans" amend the Federal Food, Drug, and Cosmetic Act, the processing and reviewing of such diversity action plans will likely be carried out by the Commissioner of Food and Drugs (the "Commissioner") under existing delegation by the Secretary to the Commissioner.[1]

Notably, FDORA builds upon earlier federal agency efforts to enhance diversity and inclusion in clinical research, including the National Institutes of Health's 2001 policy and guidelines on the inclusion of women and minorities in clinical research and FDA's 2020 guidance on enhancing the diversity of clinical trial populations and 2022 draft guidance on diversity plans for clinical trials participation.[2] FDORA directs the Secretary, again likely through the Commissioner, to update or issue guidance on the format and content of diversity action plans for clinical studies through issuing draft guidance not later than one year after the act's effective date and to finalize such guidance not later than nine months after the close of the comment period on the guidance. FDORA further directs the Secretary to convene in consultation with drug sponsors, medical device sponsors, clinical research organizations, academia, patients and other stakeholders one or more public workshops to solicit stakeholder input regarding enhancing enrollment in clinical studies of historically underrepresented populations and encouraging clinical study participation that reflects the prevalence of the disease or condition among demographic subgroups. The act requires that such workshops be convened within one year of the act's effective date. FDORA additionally requires the Secretary to submit to Congress and publish on the U.S. Food and Drug Administration ("FDA") website an annual report summarizing the diversity action plans received and containing aggregate information on whether the enrollment goals set in diversity action plans were met.

Commentary

For investigators, clinical trials sites and institutional review boards ("IRBs"), FDORA's requirements will likely build on long-standing IRB considerations pertaining to equitable subject selection. The Belmont Report,[3] the Federal Policy for the Protection of Human Subjects (also known as the "Common Rule"),[4] and FDA's regulations on protection of human subjects and IRBs[5] each require that subject selection in clinical studies be equitable. Therefore, we expect that FDORA's emphasis on diversity and subsequent FDA guidance will likely enhance the opportunity for IRBs and institutions to encourage, and for investigators to plan, more equitable subject recruitment and enrollment in clinical trials. While the legislation appears directed at FDA, the Office for Human Research Protections ("OHRP"), which administers the Common Rule, might be expected ultimately to produce complementary guidance or issue joint guidance with FDA on these topics; such guidance would establish firm expectations pertaining to diverse and equitable subject selection for investigators, IRBs, and institutions in designing and conducting clinical studies in both FDA- and non-FDA-regulated research.

Decentralized Clinical Trial Studies

Summary of FDORA Requirements

FDORA requires the Secretary, within one year of the act's effective date, to issue or revise draft guidance providing recommendations clarifying and advancing use of "decentralized clinical studies" to support development of drugs and devices. The act defines a "decentralized clinical study" as a "clinical study in which some or all of the study-related activities occur at a location separate from the investigator's location." The act specifies that the guidance should address 14 topic areas, including the following:

- Recommendations related to digital health technology;
- Recommendations on subject recruitment;
- Recommendations to reduce burdens for clinical trial participants, including through use of telemedicine, local health care providers, home visits, and direct-to-participant shipping of investigational products;
- Recommendations for methods of remote data collection, including through digital technologies;
- Recommendations to encourage meaningful diversity in clinical trial participation with respect to race, ethnicity, age, sex and geographic location;
- Recommendations for review and oversight by sponsors and IRBs of remote trials; and
- Considerations for sponsors to validate digital technologies and establish appropriate clinical endpoints for use in decentralized trials.

FDORA contains a separate provision requiring the Secretary, within one year of the act's effective date, to issue or revise draft guidance clarifying the use of digital health technologies in clinical trials and providing recommendations on the use of seamless, concurrent, and other innovative clinical trial designs. The act requires that the guidance on these topics address several topic areas, including:

- Recommendations for incorporation of data collection methodologies using digital health technologies in clinical trials to collect data remotely;

- Considerations for privacy and security protection for clinical trial data, including compliance with the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), the Confidentiality of Substance Use Disorder Patient Records regulations codified at 42 C.F.R. Part 2 ("Part 2"), the FDA regulations on human subjects research, and the Common Rule;

- Recommendations regarding data and information needed to demonstrate that a digital health technology is fit-for-purpose for a clinical trial;

- Recommendations for increasing access to, and the use of, digital health technologies in clinical trials to facilitate inclusion of diverse and underrepresented populations;

- Recommendations on the use of clinical trial designs that involve concurrent conduct of different or multiple clinical trial phases;

- Recommendations for how to streamline trial logistics to facilities for efficient collection and analysis of data, including through interim analyses; and

- Recommendations for communications between sponsors and the FDA on the development of seamless, concurrent, or other adaptive clinical trial designs.

FDORA further directs the Secretary to work with foreign regulators to facilitate international harmonization of the regulation and use of decentralized trials, digital health technologies in clinical trials, and seamless, concurrent, and other adaptive or innovative clinical trial designs.

Commentary

The guidance documents required by FDORA are likely to provide helpful clarity in several key areas for clinical trial sponsors, investigators, sites and IRBs. Use of decentralized clinical studies started to gain prominence in the years preceding the COVID-19 pandemic, and the pandemic accelerated their growth and prominence due to the inability of subjects to travel to physical study sites. Currently, sponsors, investigators, IRBs, and institutions that review, design and conduct interventional trials must take into consideration various legal and regulatory requirements, including HIPAA, the Common Rule, FDA regulations, and state licensure and privacy requirements.

As a result, several questions have arisen regarding the application of FDA regulations and the Common Rule in the context of decentralized clinical studies. These include, for example, questions of whether certain health care providers performing procedures in the subject's home are sub-investigators who should be listed on Form FDA 1572,[6] whether companies performing in-home services in connection with a study are "engaged" in research within the meaning of the Common Rule,[7] and how an investigator at a central study site can provide adequate supervision of home health resources that are contracted by the sponsor as opposed to the study site/investigator. The guidance required by FDORA hopefully will provide a forum for FDA, and potentially OHRP, to clarify these ambiguities.

Additional questions have arisen regarding the use of digital technologies in a study, such as when a digital tool used in the study is being used as a device subject to FDA's IDE regulations[8] and when a digital tool is sufficiently validated for data collection purposes. FDA released draft guidance on remote data collection using digital health technology in 2022,[9] and the guidance called for by FDORA also should provide an opportunity for FDA to clarify further some of these issues. The requirement to issue guidance on innovative trial design may also build on existing FDA guidance on adaptive trial design.[10]

A key challenge presented by decentralized clinical studies and the use of digital health technologies in clinical trials has been that they are often subject to concurrent oversight under different regulatory schemes enforced by the U.S. Department of Health and Human Services ("HHS"), including the FDA regulations on human subjects research, the Common Rule, HIPAA, and Part 2, each of which is enforced by a different component of HHS. Historically, much of the guidance on clinical studies issued by HHS has not addressed these regulatory regimes holistically, instead leaving it to the regulated community to piece together how different regulations apply to clinical study activities. FDORA requires interaction between these different components of HHS by explicitly requiring the guidance on digital health technologies in clinical trials to address HIPAA, FDA regulations, the Common Rule and Part 2 concurrently. This continues a recent trend of Congress calling for harmonization of regulations governing clinical research and should be helpful to the regulated community.

One area that FDORA does not address is the application of fraud and abuse laws, such as the federal Anti-Kickback Statute and the beneficiary inducement provisions of the Civil Monetary Penalties Law, to the use of digital technologies in clinical studies.[11] The use of digital health technologies in clinical trials can implicate these laws because the provision by a study sponsor or site of valuable digital tools to study subjects can in some cases be seen as an inducement for the use by such subjects of products and services that are billable to federal health care programs. It appears Congress did not take account of these issues in enacting FDORA.

Notably, the federal government's ability to decrease the complexity of decentralized clinical trials is limited by the fact that many of the issues related to decentralized trials in the U.S. arise from state laws governing licensure and the practice of medicine. These include restrictions, typically enforced by state medical boards, on the practice of medicine by practitioners not licensed in the state in which the patient is located and differing state laws on the use of telemedicine.[12] Although FDORA requires the Secretary to issue guidance regarding use of telemedicine in clinical studies, such guidance is not likely to clarify how sponsors, IRBs and researchers should address issues pertaining to disparate state law.

Ropes & Gray will continue to monitor developments in these areas. If you have any questions regarding the topics addressed in this alert, please contact David Peloquin, Mark Barnes, or your usual Ropes & Gray advisor.

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1. See FDA Staff Manual Guides, Volume II – Delegations of Authority (Nov. 29, 2022), https://www.fda.gov/media/81983/download (delegating "Functions vested in the Secretary under the Federal Food, Drug & Cosmetic Act" to the FDA Commissioner).
2. National Institutes of Health, NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research, https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm. Food and Drug Administration, Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs: Guidance for Industry (Nov. 2020), https://www.fda.gov/media/127712/download, Food and Drug Administration, Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials: Draft Guidance for Industry (Apr. 2022), https://www.fda.gov/media/157635/download.
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report (Apr. 18, 1979), https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.
4. 45 C.F.R. pt. 46, subpt. A.

5. 21 C.F.R. pts. 50 & 56.

6. *See* Food and Drug Administration, Statement of Investigator (Form FDA 1572), https://www.fda.gov/media/71816/download; *see also* Food and Drug Administration, Instructions for Filling out Form FDA 1572 – Statement of Investigator, https://www.fda.gov/media/79326/download ("[I]f an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the Form FDA 1572 . . . Hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the clinical data, do not need to be listed individually").

7. *See* Office for Human Research Protections, Determining When Institutions are Engaged in Research (Jan. 13, 2009), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/determining-when-institutions-are-engaged-in-research/index.html; *see also* Secretary's Advisory Committee on Human Research Protections, A New Interpretation of the "Engaged in Research" Standard (July 20, 2022), https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-d-july-25-2022-letter/index.html#:~:text=The%20standard%20that%20SACHRP%20would,informed%20consent%20from%20human%20subjects.

8. *See* 21 C.F.R. pt. 812.

9. Food and Drug Administration, Digital Health Technologies for Remote Data Acquisition in Clinical Investigations: Draft Guidance for Industry, Investigators, and Other Stakeholders (Jan. 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations.

10. Food and Drug Administration, Adaptive Design for Clinical Trials of Drugs and Biologics: Guidance for Industry (Nov. 2019), https://www.fda.gov/media/78495/download.

11. *See* 42 U.S.C. §§ 1320a-7b(b), 1320a-7a(a)(5).

12. *See e.g.*, Medical Board of California, Practicing Medicine Through Telehealth Technology, https://www.mbc.ca.gov/Resources/Medical-Resources/telehealth.aspx ("Physicians using telehealth technologies to provide care to patients located in California must be licensed in California").