A Deep Dive into Clinical Trial Modernization and Decentralization through Digital Health Technologies and More (via FDORA)

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With the help of modern technology and a legislative push, clinical trials are leaping into the future. At the tail end of 2022, President Biden signed into law the Consolidated Appropriations Act, 2023, to fund the government through the 2023 fiscal year [1]. Tucked into this 4,000 page omnibus legislation is the Food and Drug Omnibus Reform Act of 2022, or "FDORA" (yes, sounds like the hat!) [2].

In this Alert, we drill down into the two sections of FDORA that focus on decentralized clinical trials (Section 3606) and modernizing clinical trials (Section 3607) [3]. In these two sections, FDORA directs FDA to issue or update three guidances: (1) decentralized clinical trials, (2) the use of digital health technologies (DHTs) in clinical trials, and (3) the use of innovative clinical trial designs. The three guidances will address recommendations, considerations and best practices on subject engagement, data collection and evaluation, clinical trial design, use of DHTs, data integrity and privacy, and the implementation of innovative clinical trial designs. We wrote about FDA's 2021 draft guidance DHTs here and note that FDA recently published a framework on DHTs as well. In addition, Section 3607(c) of FDORA calls on FDA to work with foreign regulators to facilitate international harmonization on the regulation and use of decentralized clinical trials, use of digital technology in clinical trials, and innovative clinical trial designs.

To a large degree, the concepts of "decentralized" and "modernizing" clinical trials go hand in hand, resulting in significant overlap of the mandates of Sections 3606 (decentralized) and 3607 (modernizing). This Alert consolidates these overlapping requirements into six categories. Section I defines key terms and provides a thumbnail overview of these two sections of FDORA. Section II dives into the six categories. For each category, we first discuss the points on which Sections 3606 and 3607 intersect, followed by reviewing certain noteworthy items that are section-specific.

Note that Sections 3606 and 3607 apply broadly to drug and device development, except that 3607(b)(1) is limited to drugs.

I. KEY TERMS AND OVERVIEW

Key Terms

Decentralized Clinical Trials or DCTs: means "a clinical study in which some or all of the study-related activities occur at a location separate from the investigator's location" (§3606(c)).

Digital Health Technologies or DHTs: means "systems that use computing platforms, connectivity, software, and/or sensors, for healthcare and related uses." FDORA does not define DHTs. This definition appears on FDA's website [4] and in the FDA draft guidance, Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

(December 2021) available here.

Overview

§3606 – Decentralized Clinical Trials: Section 3606 directs FDA to issue or update guidance aimed at clarifying and advancing the use of DCTs.

§3607 – Modernizing Clinical Trials:

Section 3607(a) directs FDA to issue or update a guidance aimed at clarifying the use of DHTs in clinical trials and in innovative, novel clinical trial designs.

Section 3607(b) directs FDA to issue or update a guidance aimed at the use of seamless, concurrent, and other innovative clinical trial designs in drug development. This subsection(b) applies only to drugs while the remainder of Sections 3606 and 3607 apply to both drugs and devices.

Section 3607(c) directs FDA to work with foreign regulators to facilitate international harmonization of the regulation and use of DCTs, DHTs in clinical trials, and seamless, concurrent, and other adaptative or innovative clinical trial designs.

II. FDORA DECONSTRUCTED: THE SIX CATEGORIES

Stepping back, the three guidances required by Sections 3606 and 3607 of FDORA fall into the six broad categories below. For each category, we first summarize where the two sections' requirements overlap, and then call to your attention to what we refer to as "Notable Specifics." These are noteworthy requirements of the specific section identified, not a comprehensive list of each item to be addressed in the guidances.

1. Subject recruitment, retention, and engagement through modern technologies

Intersection: Sections 3606 and 3607 each direct FDA to provide recommendations on methods of subject engagement, including diversity plans, minimization of burdens for participants, and increasing recruitment and participation.

Notable Specifics:

Section 3606 directs FDA to cover:

– Communication with study subjects, particularly underrepresented populations.

– Facilitation of meaningful diversity in DCTs, including with respect to race, ethnicity, age, sex, and geographic location.

– Considerations for sponsors to minimize burdens for participants, such as through the use of DHTs, telemedicine, local laboratories and health care providers, other assessment opportunities, home visits, direct-to-participant shipping of investigational drugs and devices, electronic informed consent, and other direct-to-participant engagement.

Section 3607(a) requires FDA to clarify the use of technology to modernize clinical trials, including:

– Use of electronic informed consent, taking into consideration Federal law, including the FDA informed

consent regulations (21 CFR 50), as well as State law.

– Increased access to and use of DHTs to facilitate the inclusion of diverse and underrepresented populations, including people with disabilities and pediatric populations.

In addition, we note that while Sections 3607 and 3607 address diversity plans for clinical trials, FDORA also includes specific sections dedicated to clinical trial diversity (§§3601-04). These sections are outside the scope of this Alert.

2. Data collection, evaluation, and communication in DCTs and studies using DHTs:

Intersection: Sections 3606 and 3607 both mandate recommendations on methods of remote data collection and on evaluation of data collected in DCTs and using DHTs or other remote collection methods.

Notable Specifics:

Section 3606 further instructs FDA to address:

– DHT or other assessment options like telehealth, local laboratories, local health care providers and other options for remote data collection including:

– Appropriate technology platforms and tools

– Data collection and use

– Data integrity and security

– Communication to participants through digital technology.

– Remote collection of participant experience data.

– Establishment of appropriate clinical endpoints.

Section 3607(a) requires that FDA include recommendations on:

– Data collection methods to improve recruitment, participation, burden reduction, and data quality optimization.

Section 3607(b) directs FDA to cover:

– Streamlining trial logistics to facilitate the efficient collection and analysis of trial data, including any planned interim analyses.

– Considerations to assist sponsors in ensuring reliability of clinical trial results.

– The manner in which FDA will assess or evaluate data collected through seamless, concurrent, or other adaptive clinical trial designs to support drug development.

Further, we note that FDORA includes multiple provisions to facilitate the use of real world data and real world evidence. A discussion of these is beyond the scope of this Alert.

3. Modernizing clinical trial design and evaluation:

Intersection: Sections 3606 and 3607 require recommendations regarding the design of DCTs, including protocols, and the use of DHTs and other remote assessment tools to facilitate effective DCTs.

Notable Specifics:

3606 requires FDA to describe:

– Considerations for oversight by sponsors and Institutional Review Boards (IRBs), as well as how FDA will assess and evaluate these trials.

– How it will assess or evaluate data collected in a DCT, if the manner it is collected is different from that used for a non-DCT.

Section 3607(b) directs FDA to address:

– Communication between sponsors and FDA on the development of seamless, concurrent, or other adaptive clinical trial designs, including review of, and feedback on, clinical trial protocols.

4. Use of appropriate DHTs and other digital technologies:

Intersection: Sections 3606 and 3607 require guidance on the appropriate use of DHTs and other digital technologies in the clinical trial environment.

Notable Specifics:

Section 3606 directs FDA to include:

– Considerations for sponsors to validate digital technologies for use in decentralized trials.

Section 3607(a) requires FDA to include:

– Recommendations regarding the data and information needed to demonstrate that a DHT is fit-for-purpose for a clinical trial.

Note that the FDA draft guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (December 2021), which we previously discussed here, contains detailed recommendations regarding the use of DHTs in clinical trials, including validation, fit-for-purpose assessments and more. We expect FDA to build upon this guidance as part of FDORA's legislative mandate.

5. Data privacy, security and integrity:

Intersection: While electronic technologies will modernize clinical trials, the legislation reflects the associated risks this creates for data privacy, security and integrity. Sections 3606 and 3607 require FDA to address these topics, including compliance with applicable laws and regulations.

Notable Specifics:

Section 3606 calls for FDA to address:

– Privacy and security of personally identifiable information of trial participants.

Section 3607(a) requires FDA to cover:

- The protection of participant data that are collected or used in clinical trials using DHTs, including:
  - Compliance with HIPAA regulations, the FDA informed consent and IRB regulations (21 CFR 50, 56), the Common Rule, and Substance Abuse Confidentiality Regulations (42 CFR 2).
  - Protection of participant data against cybersecurity threats.

Section 3607(b) directs FDA to include:

- Considerations to assist sponsors in minimizing risks to clinical trial data integrity and ensuring the reliability of study results.

6. Innovative clinical trial designs:

Intersection: Taken together, Sections 3607 and 3607 promote innovative clinical trial design.

Notable Specifics:

Section 3606 directs FDA to address:

- Considerations for conducting hybrid trials that would combine centralized and decentralized approaches.

Section 3607(b) calls for FDA to address:

- Use of expansion cohorts and other seamless clinical trial designs to assess different aspects of product candidates in one continuous trial, including how expansion cohorts and other seamless clinical trial designs can be used as part of meeting the substantial evidence standard under Section 505(d) of the FDCA (21 U.S.C. 355(d)).
- Use of clinical trial designs that involve concurrent conduct of different or multiple clinical trial phases, and the concurrent conduct of preclinical testing.
- Considerations to assist sponsors in ensuring the rights, safety, and welfare of clinical trial participants, and maintaining compliance with good clinical practice regulations.

III. CONCLUSION

FDORA Sections 3606 and 3607 direct FDA to issue or update three guidances with recommendations, considerations and best practices for decentralizing and modernizing clinical trials, and to undertake international harmonization efforts. These guidances will build on numerous pre-existing guidances that address a number of the topics covered by FDORA. Viewed as a whole, these FDORA initiatives will help boost the value, speed, efficiency and diversity of clinical trials by encouraging the use of modern tools, adoption of novel trial designs and by reaching a broader patient population. We will continue to monitor developments and encourage you to check our Insights for updates.

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[1] Pub. Law. No. 117-328 (2022).

[2] A copy of FDORA (H.R. 2617) is available at https://www.congress.gov/bill/117th-congress/house-bill/2617/text (accessed March 16, 2023). In this Alert, references to the Secretary of the Department of Health and Human Services will be referred to as FDA (to whom the duties will generally be delegated).

[3] Division FF, Title III, Subtitle F (Cross-Cutting Provisions), Chapter 1, §§3606 and 3607.

[4] https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-digital-health-technologies#:~:text=Digital%20health%20technologies%20(DHTs)%20are,applications%20as%20a%20medical%20device (accessed March 16, 2023).

If you have any questions or would like more information about these developing issues, please contact the following:

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