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Considerations When Using Digital Health Technologies in Clinical Investigations

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In a recently published draft guidance document, the U.S. Food and Drug Administration ("FDA") outlined important factors to facilitate the use of digital health technologies ("DHTs") for remote data acquisition in clinical investigations.[1] With the increasing interest and emphasis on decentralized trial designs, sponsors should continue to carefully assess opportunities to use DHTs, and legal and regulatory teams should prepare to help support and evaluate possible risks with using DHTs in clinical trials.

The COVID-19 pandemic has accelerated opportunities to use decentralized clinical trials and regulators continue to issue guidance about how sponsors can conduct such trials and how regulators will accept data from such trials for marketing authorization. DHTs offer the opportunity to capture data remotely and may expand opportunities for clinical trial participation. Sponsors must consider a number of significant legal and regulatory factors when using DHTs as outlined in FDA's draft guidance document.

DHTs as Medical Devices

Although devices intended for use in clinical investigations are often exempt from many device requirements, including premarket clearance or approval, the investigation itself must comply with federal device requirements (21 CFR part 812) and "significant risk" devices may necessitate the submission of an Investigational Device Exemption ("IDE"). Legal and regulatory teams at sponsors should carefully review DHTs, including third-party technology, to assess their regulatory status to avoid surprises or delays during the regulatory review process.

DHTs Need to Be "Fit for Purpose"

To be acceptable for use in clinical investigations supporting marketing authorizations, DHTs must be "fit for purpose." This means that the level of validation for the DHT is sufficient to support its use and interpretability in the clinical investigation. It will be important to evaluate the intended use, novelty, and risks associated with the DHTs to determine the level of verification, validation, and usability testing that will be needed to support their use. While technical and scientific data may form the basis of this testing, there are a number of important legal and regulatory factors to consider.

First, although DHTs often provide the opportunity to increase diversity in clinical trial enrollment, the technologies must also be compatible with such diversity. This means that software may need to be translated or available in multiple languages or that the software may need to have accessibility features such as larger text or buttons for elderly populations.

Second, sponsors need to consider the potential for missing data and how the DHT will help to manage or mitigate the associated risk. This may mean using alerts that signal a low battery, poor signal, or when data is not being recorded. Usability testing should also identify potential errors or problems.

Third, privacy and security concerns are critical in a clinical trial context where human subject protections are paramount. When using third-party DHTs or general computing platforms (e.g., smart phones or watches), end-user licensing agreements or terms of service may allow sharing of data with the DHT or computing platform manufacturer or others. In the context of a clinical investigation, it may be necessary to consider modification of the end-user license agreement or terms of service. These issues also need to be factored into informed consent documentation that should explain, among other things: the type of information that will be collected and how the information is be used and monitored, who will have access to the data collected, and measures taken to protect a subject's privacy and data.

FDA Expectations for Product Submissions

Product submissions will need to explain why the DHTs are fit for purpose for clinical investigation, including basic information and description of usability-related features such as how the DHTs are worn, operated, and charged. Perhaps most significantly, the submission should describe the clinical endpoints to be measured from data collected from the DHTs—any novel endpoints will need to be justified. Such novel endpoints will also need to be validated and shown to be clinically relevant and adequately captured by the DHTs. From a regulatory and legal perspective, it is important to understand how the proposed endpoint relates to other efficacy endpoints that have been used to support marketing authorization for a similar indication. If they do not, consider other opportunities to confirm the effect of the novel endpoint.

DHTs also raise important legal considerations about data management, including data collection, storage, transmission, and archiving. Data management remains an area of significant FDA compliance focus, and that scrutiny is likely to continue. Relevant metadata from the DHTs should be securely transferred and retained, and other data controls should be assessed and implemented.

Risk Management

ICH guidance continues to emphasize rigorous risk management as part of clinical trial oversight. FDA emphasizes that sponsors need to review DHT-related risks in conjunction with their formal risk management planning and, in some cases, these risks may need to be assessed by an Institutional Review Board ("IRB"). DHT-related risks may include, for example, risk of injury from the physical features of the DHT (e.g., skin contact components, instructions for re-use/cleaning), risk of erroneous measurements, and cybersecurity risks. Cybersecurity threats continue to grow, and sponsors will need to develop appropriate security controls, monitoring, and response plans should threats be identified.

Sponsors need to develop a risk management plan to address potential problems trial participants may experience when using DHTs. These issues are likely to include potential problems related to clinical aspects, privacy, interference between applications, loss or damage of DHT, and issues arising from software or firmware updates.

Consultation with the Appropriate Review Center

Given the early stage at which many DHTs are being developed and used, it is critical to consult with the appropriate FDA Center responsible for the medical product and discuss the use of DHTs in specific clinical investigations, particularly with novel endpoints. For example, non-inferiority trial designs may not be appropriate where there is a lack of historical evidence of effectiveness of the control treatment

when measured using the proposed DHTs. FDA notes in its guidance that DHTs may also be qualified as a Drug Development Tool or a Medical Device Development Tool for a specific context of use. This would enable the sponsor to rely on the DHT in multiple clinical investigations to support premarket submissions where the context of use is the same without having to repeat qualification studies.

As part of its discussion with the appropriate Center, the sponsor should also discuss the type of DHT data to be recorded and submitted for FDA review, including whether the submission will include the complete data set, summary data, sample data, or listings of abnormal data only.

FDA is accepting comments on the draft guidance document until March 22, 2022.

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If you have any questions concerning these developing issues, please do not hesitate to contact either of the following Paul Hastings Washington, D.C. lawyers:

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[1] FDA Draft Guidance for Industry, Investigators, and Other Stakeholders: *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (Dec. 2021).