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Client Alert

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A Pandemic Silver Lining: FDA's New Guidance on Using Digital Health Technologies for Clinical Investigations

With spring timidly approaching, it's hard not to dwell on the fact that we are almost two full years into the COVID-19 pandemic. The pandemic has placed into clear relief many of the access issues faced by patients and treatment developers alike. About one in two healthcare consumers surveyed say they have postponed or canceled healthcare services since the beginning of the pandemic. Race, gender, and socioeconomic disparities have increased as well.[1]

These trends have impacted clinical investigations, making data collection more challenging. It can be challenging for patients in remote locations to access clinical investigations and for sponsors to collect data from remote locations. Enter digital health technologies, or "DHTs," which can facilitate clinical investigations being conducted to evaluate medical products. The last few years have seen great strides in technologies that can be used to remotely collect and analyze data from a broad array of trial participants.

Signaling potential openness toward the use of DHTs in the regulatory approval process and, by extension, the collection of more data and from more diverse populations, the U.S. Food and Drug Administration ("FDA" or the "Agency") published a draft guidance in December 2021 entitled, "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations" ("*Draft DHTs Guidance*").[2] The draft guidance describes FDA's thinking about how sponsors, study investigators, and others can use DHTs to gather health-related information from study participants to evaluate the safety and effectiveness of investigational medical products.[3]

The December 2021 Draft DHTs Guidance

In the *Draft DHTs Guidance*, FDA recognizes the growing use of DHTs to collect relevant data for clinical research and the benefits of using them. Per the draft guidance, a DHT is "a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses."[4] For example, a DHT may consist of sensor hardware that allows for continuous or intermittent data collection (*e.g.*, glucose levels) and an algorithm to translate that data in a way that may be relevant to a clinical investigation (*e.g.*, to identify incidents of hypoglycemia).[5] Or a DHT may be a software application that runs on a general-purpose computing

platform (*e.g.*, a mobile phone, tablet, or smart watch) to administer electronic outcome assessments (*e.g.*, memory tests).[6]

The *Draft DHTs Guidance* notes that many DHTs potentially used in clinical investigations will "meet the definition of a device under the Federal Food, Drug, and Cosmetic Act (FD&C Act)."[7] The draft guidance makes clear that this fundamental question is "outside the scope" of the draft guidance, while also noting that devices intended for use in clinical investigations are generally exempt from premarket clearance or approval requirements (as long as the clinical investigation is compliant with 21 C.F.R. Part 812).[8] Instead, the draft guidance focuses on the utility of DHTs—if selected, validated, and managed appropriately—to facilitate remote collection of data that can then be used in support of medical product evaluation.[9] Specifically, given their technological capabilities (*e.g.*, their ability to remotely gather data directly from participants at any time and wherever they are geographically located), DHTs can offer opportunities to gather clinical data that can be elusive in centralized trials.[10] For example, DHTs can acquire data from study participants who may otherwise be unable to report their experiences, such as infants or persons with cognitive impairments.[11] DHTs can also collect a broad range of data, including clinical, physiological, psychological, behavioral, or functional information.[12] Accordingly, DHTs can help sponsors expand their clinical research to include more information from a more diverse group of participants and transcend barriers inherent to centralized trials.

To fully harness the potential of DHTs, the *Draft DHTs Guidance* provides recommendations on the information that sponsors should include in an investigational new drug ("IND") or investigational device exemption ("IDE") application for a clinical investigation in which the sponsor plans to use a DHT or in a marketing application that includes such a clinical investigation.[13] Those recommendations relate to:

- The selection of DHTs that are suitable for use in a clinical investigation;
- The description of DHTs in regulatory submissions;
- Verification and validation of DHTs for use in a clinical investigation;
- The definition and evaluation of clinical endpoints from data collected using DHTs;
- Risk management considerations when using DHTs;
- The protection and retention of records; and
- Additional sponsor and investigator considerations for using DHTs in a clinical investigation.[14]

Each of these topics is briefly summarized in the following sections.

Fit-for-Purpose

FDA encourages sponsors to perform a self-assessment to ensure that a proposed DHT is "fit-for-purpose" or suitable for use in the specific clinical investigation—and that the data collected ultimately will be reliable for regulatory decision-making.[15] This inquiry should consider the clinical event or the characteristic of the disease/condition to be measured, the proposed clinical investigation population, the design of the clinical investigation, characteristics of the DHT that may influence trial participant use, and whether the participant's own DHT and/or general-purpose computing platform may be appropriate for data collection.[16] For example, the sponsor may factor in: (1) a trial population's education, language, and age; (2) the design (*e.g.*, material, size, weight, appearance, portability) and ease of use of the DHT; (3) battery life and charging needs; (4) operational specifications (*e.g.*, data storage, capacity, frequency of data transmission); (5) the availability and capacity of participants' and the sponsor's network systems; and (6) the advantages and disadvantages of allowing participants to use their own DHTs or general-purpose computing platforms during the clinical investigation.[17]

Description

FDA instructs sponsors to include in their regulatory submissions an explanation on why the DHT is fit-for-purpose for use in the clinical investigation.[18] This explanation should also include basic information about the DHT (*e.g.*, what it is, how it is used, what data will be collected, how the data will be maintained, etc.).[19]

Verification, Validation, and Usability

FDA expects sponsors to confirm, through verification and validation activities, that their proposed DHTs are fit-for-purpose. FDA requests sponsors to submit relevant verification and validation data with respect to the DHT(s) used, as

well as any general-computing platform used and any DHT modifications made as a result of verification and validation testing (*e.g.*, benchtop studies, studies in healthy volunteers, studies in individuals representing the clinical investigation population, and usability testing).[20] FDA defines "verification" as "confirmation by examination and provision of objective evidence that the physical parameter that the DHT measures . . . is measured accurately and precisely over time."[21] By comparison, FDA defines "validation" as "confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population."[22] Of particular note, in addition to various testing and assessments of the DHT (including, for example, interoperability of the DHT and the impact of any utilized computing platforms on DHT software functionality), the *Draft DHTs Guidance* announces FDA's expectation that sponsors will conduct their own usability studies as part of the validation process to ensure that participants can use the DHT as directed in the trial protocol.[23] "Usability studies are a critical component in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation," the draft guidance notes, though it also leaves open the option for sponsors to leverage verification and validation data from DHT manufacturers or other third parties, as appropriate.[24]

Clinical Endpoints

FDA asks sponsors to include in their submissions a description and justification of any clinical endpoint(s) measured from data collected by a DHT.[25] The *Draft DHTs Guidance* explains that the methods used to evaluate the endpoint should be well-defined and reliable.[26] If the sponsor selects a novel clinical endpoint, FDA recommends seeking input from the relevant review division as well as other stakeholders.[27]

Statistical Analysis

FDA looks for submissions that discuss the analyses of data collected from DHTs in their statistical analysis plans.[28] These plans should pre-specify the definition of the endpoint(s), the source data, and intercurrent events (*i.e.*, events that contribute to missing or erroneous data) and how the sponsor will account for them.[29]

Risk Considerations

FDA recommends that sponsors, investigators, and institutional review boards ("IRBs") evaluate any risks, including clinical and privacy-related risks, that may be associated with the use of DHTs for remotely gathering data.[30] FDA indicates that some risks may need to be assessed by the IRB, relayed to study participants in the informed consent document, and addressed by the sponsor in the submission.[31] These risks could include, among others: (1) the risk of injury to the participant; (2) when measurements are used in the administration of the investigational product or treatment of a participant, the risk of erroneous measurements; (3) the risk of cybersecurity attacks targeting the proper functionality of the DHT; (4) the risk of cybersecurity breaches and unauthorized access to patient data; (5) the risk of potential disclosure of participant identifiable information; and (6) risks relevant to obtaining a participant's informed consent.[32]

Record Protection and Retention

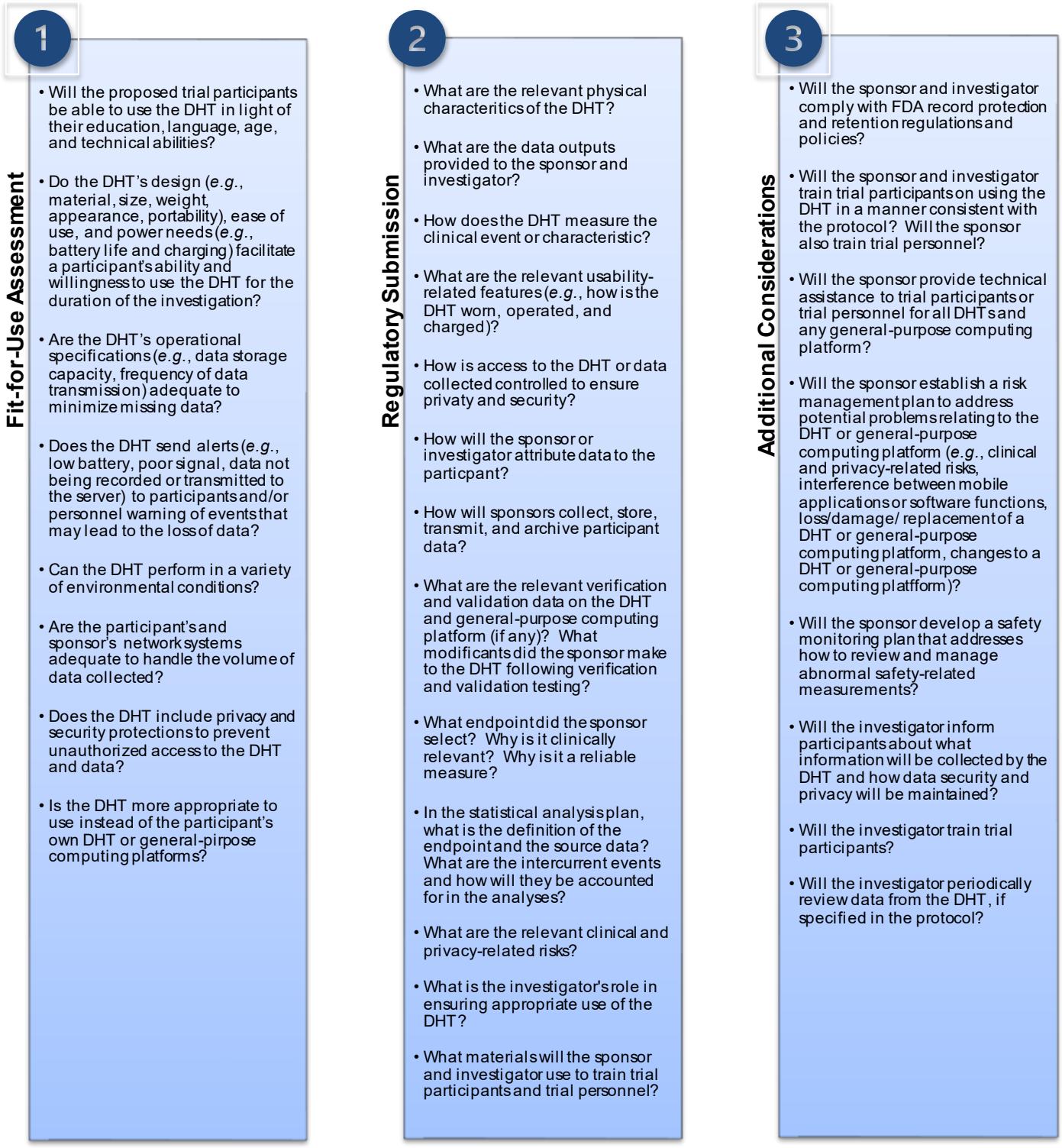
FDA requires sponsors and investigators to record and retain data captured by the DHT in accordance with FDA's record retention regulations for sponsors and investigators.[33] FDA also recommends that sponsors and investigators refer to FDA's draft guidance for industry entitled, "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11—Questions and Answers"; discuss with the appropriate review division the type of DHT data being recorded and submitted to FDA; transmit DHT data to a durable electronic data repository; and maintain the source data as part of adequate and accurate case histories.[34]

Other Considerations

Finally, FDA summarizes the specific responsibilities for sponsors and investigators when using DHTs to remotely collect data during a clinical investigation.[35]

Figure 1 below summarizes FDA's recommendations for the fit-for-use assessment, regulatory submission, and additional considerations.

Figure 1. Considerations for Use of DHTs in Clinical Investigations



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King & Spalding LLP regularly counsels manufacturers and other life sciences companies on FDA's regulation of drugs and devices, including applicability of FDA regulations to diagnostic and digital health technologies and clinical

investigations for and development and submission of marketing applications, where applicable. Comments on the *Draft DHTs Guidance* are due on March 23, 2022. Please let us know if you have any questions regarding this draft guidance, or if you would like to consider submitting a comment.

[1] Teva Pharm. Indus. Ltd., Press Release, *Research Finds COVID Pandemic Worsened Health Equity Gap*, BUSINESS WIRE (Feb. 1, 2022), https://www.tevausa.com/news-and-media/press-releases/research-finds-covid-pandemic-worsened-health-equity-gap/.
[2] U.S. Food & Drug Admin., DIGITAL HEALTH TECHNOLOGIES FOR REMOTE DATA ACQUISITION IN CLINICAL INVESTIGATIONS: GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND OTHER STAKEHOLDERS ("Draft DHTs Guidance") (Dec. 2021).
[3] *Id.* at 1.
[4] *Id.*
[5] *Id.* at 3.
[6] *Id.*
[7] *Id.* at 1–2.
[8] *Id.* at 2 n.6, 4. For a clinical investigation of a drug or biologic involving a DHT that is an uncleared or unapproved device, FDA expects sponsors to comply with both Parts 812 (for the device DHT) and 312 (for the drug/biologic). This includes submission of an IDE application under Part 812 if the DHT is a "significant risk" device. In these cases, FDA encourages sponsors to consult CDRH to streamline the information needed to support an IDE application. *Id.* at 4 n.14.
[9] *Id.* at 2.
[10] *Id.* at 3–4.
[11] *Id.* at 3.
[12] *Id.*
[13] *Id.* at 2.
[14] *Id.* at 6–22.
[15] *Id.* at 6.
[16] *Id.*
[17] *Id.* at 7–8.
[18] *Id.* at 8.
[19] *Id.* at 8–9.
[20] *Id.* at 9–10.
[21] *Id.* at 9.
[22] *Id.*
[23] *Id.* at 10, 12.
[24] *Id.* at 9–10, 12.
[25] *Id.* at 12.
[26] *Id.*
[27] *Id.* at 13.
[28] *Id.* at 14.
[29] *Id.* at 14–15.
[30] *Id.* at 15.
[31] *Id.*
[32] *Id.* at 15–18

[33] *Id*. at 18.
[34] *Id*. at 18–19; *see also* U.S. Food & Drug Admin., USE OF ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES IN CLINICAL INVESTIGATIONS UNDER 21 CFR PART 11 – QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY (June 2017).
[35] Draft DHTs Guidance at 19–22.