March 23, 2022

Via Docket Submission

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability

Docket No. FDA-2021-D-1128

Dear Dockets Management Staff,

On behalf of the Digital Therapeutics Alliance (DTA), we are pleased to submit the below comments related to the Food and Drug Administration's "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations," published on December 23, 2021.

DTA is a global non-profit trade association of industry leaders and stakeholders with the mission of broadening the understanding and adoption of digital therapeutics (DTx) into healthcare. We work across numerous geographic regions to enable expanded access to high quality, clinically evaluated digital therapeutics for patients, clinicians, and payors to improve clinical and health economic outcomes.

Defining Digital Therapeutics in Context of DHTs

We are encouraged by the Agency's effort in compiling a guidance that outlines recommendations to facilitate the use of digital health technologies (DHT) in clinical investigations for the evaluation of medical products. By defining DHTs as systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses, this guidance addresses a wide spectrum of products.

Per the draft guidance, "There is a large spectrum of DHTs available for potential use in a clinical investigation, some of which meet the definition of a device under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and some of which do not." It is important for the FDA to further distinguish between the types of products that are both subject to this guidance and qualify as a medical device.

For example, digital therapeutics (DTx) – a subcategory of digital health technologies – primarily deliver clinical interventions to patients, in addition to having the ability to generate and deliver insights to end users and decision makers for the purpose of real-world patient care and/or clinical trials.

We concur with the Digital Medicine Society (DiMe), that:

> "Lines 110-112 describe devices used in clinical investigations as "exempt from most requirements applicable to devices." We request additional clarification on this terminology, [including] who is able to make this distinction, and through what mechanism this distinction should be pursued. Specifically,

whether a medical device clearance is preferred or irrelevant to the Agency would assist our community.

"There is an opportunity to define the boundaries between exempt DHTs, DDT/MDDT, SaMD, and other qualification programs, including specifics across different centers. Clarifying these boundaries could allow for harmony across guidances and centers to produce a guidance library that supports digital health innovation through a shared unifying language and understanding of processes."

Since such a diverse representation of products exists across the clinical trial to real-world use spectrum – all of which fit under the "digital health technology" umbrella term – significant ambiguity exists in terms of relevant requirements and use cases. It is crucial for the Agency to provide greater context related to how key constructs relate to each other (i.e., DHT, DTx, medical device, software as a medical device (SaMD), software in a medical device (SiMD), drug development tool (DDT), medical device development tool (MDDT)).

As part of this effort, we also encourage the FDA to officially recognize and define digital therapeutics in formal guidance. Although the Agency reviews and clears DTx products through various medical device regulatory pathways, by formally defining and recognizing digital therapeutics in this capacity, the Agency will provide clarity for *patients* (i.e., transparency regarding DTx product attributes, quality standards, and claims), *clinicians* (i.e., evidence, safety, and prescription requirements to provide patient access), and *government agencies* (i.e., Federal Communications Commission and Federal Trade Commission enforcement of product claims).

Additionally, the following comments are provided following broader consultation with DTA members:

General Comments

1. Throughout this draft guidance FDA provides information regarding content that should be included in the submission supporting the use of a DHT in a clinical investigation. However, it is unclear where in the submission this information should be provided. We ask that the Agency clarify if the DHT information should be included in the Module 5. This clarity will drive consistency in submissions and reduce inefficiency resulting from improper placement of information which can lead to delays in review timelines.

2. We ask the Agency to describe how a DHT that has been evaluated in the context of an IND can be repurposed in a similar context of use without requiring repetitive validation studies, even if the data is included in a proprietary IND application.

3. We ask that the FDA provide more information on how Sponsors or DHT developers can engage with the Agency outside of the IND or IDE pathway on the verification and validation of DHTs for use as data collection tools in drug or device development. While we appreciate the section on regulatory engagement, we note that it seems to confuse qualification of DHTs with qualification of DHT-derived measures (e.g., biomarkers and COAs). We also acknowledge that CDER and CDRH have several potentially relevant pathways, such as the CDRH's pre-submission program and CDER's ISTAND pilot, but we note that the former is specific to medical devices while the latter is currently unfunded and limited to a small number of submissions. Therefore, we request

that FDA consider creating DHT-specific qualification pathways within CDER and CDRH.

4. While we recognize that clinical validation of DHT-derived measures is beyond the scope of this guidance, we note that the use of DHTs to measure biomarkers and clinical outcome assessments (COAs) introduces unique considerations beyond those currently outlined in FDA's Biomarker Qualification Guidance[1] and the Patient-Focused Drug Development (PFDD) Methodological Guidance Series.[2] For example, DHTs enable quantification of functionally relevant characteristics of behavior such as gait parameters and the acoustic features of speech. It is unclear how such measures will be categorized and what evidence can be provided to establish their clinical relevance. We encourage FDA to address these considerations in future biomarker- and COA-specific guidances.

Specific Comments

I. INTRODUCTION

Lines 16-18: *"This guidance provides recommendations for sponsors, investigators, and other interested parties on the use of DHTs for remote data acquisition from participants in clinical investigations evaluating medical products"*

While the use of DHTs provides the potential for remote data acquisition, DHTs may also be used to collect data within traditional locations (e.g., clinical trial site). To ensure that the scope of the guidance is not limited to remote data acquisition scenarios only, we recommend revising the text as follows: "This guidance provides recommendations for sponsors, investigators, and other interested parties on the use of DHTs for remote data acquisition from participants in clinical investigations evaluating medical products including remote data acquisition."

Lines 44 – 47: *"The following topic is beyond the scope of this guidance: Whether a DHT meets the definition of a device under section 201(h) of the FD&C Act."*

We suggest that FDA also indicate here that evidentiary requirements to validate the clinical relevance of the DHT-derived measure are also beyond the scope of this guidance and refer to existing guidances for biomarkers and clinical outcome assessments (COAs) that address these topics.

II. BACKGROUND

Lines 68-70*: "DHTs provide opportunities to record data directly from trial participants (e.g., performance of activities of daily living, sleep) wherever the participants may be (e.g., home, school, work, outdoors)."*

In order to be consistent with FDA's Patient-Focused Drug Development (PFDD) framework, we recommend that FDA clearly indicate in this draft guidance that DHTs can collect data through passive

[1] FDA CBER and CDER. Biomarker Qualification: Evidentiary Framework Draft Guidance for Industry and FDA Staff. December 2018. https://www.fda.gov/media/119271/download. Accessed Feb. 14, 2022

[2] FDA CDER. Patient Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. Accessed Feb. 14, 2022

monitoring or through active test, and that the measures assessed by DHTs can be COAs or biomarkers. Providing examples of each type here or in Appendix A would be helpful.

Line 75: "DHTs often consist of sensor hardware that allows for continuous or intermittent recording of physiological and/or behavioral data"

We note that "behavioral" data is not defined in FDA's BEST glossary or in FDA's PFDD glossary. We ask FDA to clearly indicate how measures of behavioral data will be categorized (e.g., as biomarkers or clinical outcome assessments).

Line 83: "These DHTs may be used to administer electronic clinical outcome assessments (eCOAs) including electronic patient-reported outcome (ePRO) instruments and electronic performance outcome (ePerfO) instruments."

We note that while eCOAs, ePROs, and ePerfOs are recognized in the literature, they are not defined in FDA's BEST glossary or in FDA's PFDD glossary and there may be different interpretations of what these terms refer to. We recommend that FDA update these glossaries to include definitions for ePRO, ePerfO, and eCOA. The eCOA definition should be clear if it includes only those COAs that are administered electronically, or if it also includes sensor-derived clinical outcome assessments such as those that are captured through continuous or intermittent measurement (e.g., passive monitoring of physical function).

III. REGULATORY CONSIDERATIONS AND ENGAGEMENT WITH THE AGENCY

Footnote 14: "It is possible that a DHT, as proposed for use in a clinical investigation of a drug or biological product under an IND, may meet the definition of a significant risk device under 21 CFR 812.3(m) and require submission of an IDE application to FDA under part 812 for the same clinical investigation. In these cases, when information required under 21 CFR 812.20 is also contained in the IND, sponsors should consult with CDRH regarding ways to streamline the IDE application submission process for the particular clinical investigation. See, e.g., 21 CFR 812.20(d)."

In situations where sponsors have to submit an IND and an IDE in parallel, we ask that CDER/CBER and CDRH collaborate in order to streamline both reviews to ensure the tool development and/or the trial is not delayed. We also ask that CDRH applies its "The Least Burdensome Provisions: Concept and Principles" (February 2019) guidance to the review of a DHT needing an IDE.

Lines 124-144: "FDA also has qualification programs that are intended to support the development of tools for use in assessing medical products and that provide another avenue for sponsors and other stakeholders to engage with the Agency…."

In certain cases, a concept of interest may measure disease impacts that are relevant to patients' experience across a range of disease areas. In these cases, it would be useful for the Agency to describe how a single DHT can be qualified to measure the same concept of interest across multiple diseases with overlapping signs and symptoms, and what evidence should be submitted to support this.

Line 121: "Sponsors should engage early with the appropriate Center responsible for the medical product under investigation to discuss use of DHTs in a specific clinical investigation."

We request that FDA elaborate on the process to engage with multiple Centers for the regulatory review of the DHTs and DHT-derived measures to ensure an aligned review and avoid a delay in verification and validation of the DHT and clinical validation of the DHT-derived measure. We suggest that the new Type D meeting described in the PDUFA VII commitment letter could provide an opportunity for such discussions.

Lines 133-134: "Developers of DHTs may choose to submit qualification proposals to the appropriate CDER/CBER DDT Qualification Programs."

We note that FDA has previously deemed review of the DHT to be out of scope in COA qualification submissions.[3] Clarification would be helpful as to whether verification (of hardware/ firmware) and analytic validation of DHTs will become part of the CDER COA and Biomarker Qualification Programs (i.e., for digital measures that are COAs or biomarkers, respectively). Alternatively, FDA should specify if these qualification programs will continue to be specific for review of COA or biomarker measures, with verification and validation of the DHT reviewed separately (e.g., through the ISTAND pilot or another pathway).

IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS

A. Selection of a Digital Health Technology and Rationale for Use in a Clinical Investigation

Lines 197-198: "Operational specifications (e.g., data storage capacity, frequency of data transmission) should be adequate to minimize missing data."

We suggest that FDA edit this bullet as follows: "Operational specifications (e.g., data storage capacity, frequency of data capture/sampling and transmission) should be adequate to minimize missing data."

Lines 211-212: "The functioning of the DHT should ensure privacy and security to prevent unauthorized access to the DHT and the data it collects."

We suggest that this bullet be updated to reflect that the DHT system also needs to consider security, so that data transmission from device to servers is secure, and that there is an audit trail for data. We also recommend that FDA include an additional bullet on user verification to prevent fraudulent/ mis-labeled submissions.

Lines 224-226: "This approach may not be appropriate for clinical investigations that require highly specialized or customized measurements."

We ask the Agency to clarify what measurements are considered to be highly specialized or customized. If the outlined approach in the draft guidance would not apply to such measurements, we ask FDA to elaborate on what approach would be appropriate.

Lines 241-248: "Sponsor-provided DHTs and, as applicable, general-purpose computing platforms should be available as an option to ensure that participants who do not have their own protocol specified DHT or general-purpose computing platform are not excluded from the clinical investigation for that reason."

[3] DDT COA #000103: ActiMyo®, August 30, 2018. FDA Response to LOI Submission: https://www.fda.gov/media/119253/download. Accessed Feb. 14, 2022

We ask the Agency to clarify that providing a DHT or general-purpose computing platform to a trial participant will not impact our compliance with the Anti-Kickback statute.

Line 246: "Sponsor-provided telecommunications technologies…"

Suggested Revision: "Sponsor-provided telecommunications technologies (i.e., portable Wi-Fi router, mobile phone, etc.) ..."

B. Digital Health Technology Description in a Submission
Lines 268-270: "To help show how integrity of the data collected with DHTs will be or is maintained, sponsors should include information about data management, including collection, storage, transmission, and archiving in the submission."

We suggest revising as follows: "To help show how integrity of the data collected with DHTs will be or is maintained, sponsors should include information about collected metadata and data management, including collection, storage, transmission, and archiving in the submission."

C. Verification, Validation, and Usability of Digital Health Technologies
Lines 283 -284: "Verification and validation may begin with benchtop studies, progress to testing in healthy volunteers, and continue in individuals representing the population to be studied in the clinical investigation."

We request that FDA consider including recommendations that validation of software components, especially in the event of an upgrade, could be carried out on retrospective data sets when appropriate. For example, if an algorithm is used to detect cough, it may be appropriate to validate newer versions of the algorithm on previously captured audio files rather than in a prospective new study.

Lines 345 -348: "DHT software may gather data remotely from trial participants and may be run on a variety of general-purpose computing platforms. There are specific verification and validation considerations for DHT software that may be used to administer eCOAs, such as interactive assessments of participant functionality…"

We note that DHT software can be used for measuring more than just eCOAs. For example, it has been used to provide a user interface to enable behavioral and physiological measurements. We recommend making this explicit by adding the following sentence: "DHT software can be used for different purposes, such as to administer an eCOA."

Lines 301-341: Sensor-based DHTs

We urge FDA to more clearly differentiate evidentiary requirements for different aspects of validation, including:

- Validation of the sensor output, (e.g., accelerometer units), often called verification in the literature
- Validation of the algorithm used to convert sensor outputs to a physiologic, behavioral, or functional metric, (e.g., steps), often called analytic validation in the literature

- Validation of the outcome measure calculated from the physiologic, behavioral, or functional metric, (e.g., moderate to vigorous physical activity or daily step count), often called clinical validation or psychometric validation in the literature. Rather than listing examples of what validation may include, we ask FDA to define the required level of evidence for each type of validation to support endpoints derived from data collected using DHTs.

Lines 312-313: *"As part of the validation process, sponsors should consider involving DHT manufacturers, patients, caregivers, and other technical and clinical experts as appropriate."*

We note that it would be helpful for FDA to clearly define in its forthcoming PFDD guidances the evidence requirements to establish patient- relevance of digital measures, particularly given that DHT-derived passive monitoring outcome measures have been rejected from the COA Qualification program for lack of evidence of patient-relevance.[4]

For example, we request the FDA to describe if evidence of patient relevance is required for the meaningful aspect of health, the concept of interest, or the outcome measure? We also ask FDA to outline when patient-relevance should be established through qualitative research with patients, and when other means may be acceptable, including quantitative analyses and clinical expert input?

We also recommend that this guidance, when finalized, references considerations for COA development described in the PDUFA VI PFDD guidance series.

Lines 333-334, and 373-375: *"Validation studies, including usability studies, can be conducted in healthy volunteers and/or individuals with varying degrees of disease severity"..."These [usability] studies are considered part of the validation process and should enroll a cohort that is similar to intended trial participants."*

We note that these statements seem to conflict with each other. Clarification on whether usability studies (and verification studies and other validation studies) must be conducted in the population of interest would be helpful.

Lines 349-350: *"Among others, content validation, construct validation, and normative testing may be appropriate…"*

We note that this statement may lead to confusion. For a COA, measurement properties such as content validity and construct validity apply to the measure (e.g., the questions and responses), rather than the software (e.g., the app used to collect the measure). We recommend deleting this statement or, at a minimum, clarifying that it only applies only to a novel COA captured with DHT software, not to the DHT software itself, and not to an existing COA captured with new DHT software.

Line 372: *"...confirming the suitability of the DHT…"*

Suggested Revision: "...confirming the suitability and scalability of the DHT…"

[4] DDT COA #000129: Advanced Gait Analysis. June 5, 2020. FDA Response to LOI Submission: https://www.fda.gov/media/139872/download. Accessed Feb. 14, 2022

D. Evaluation of Clinical Endpoints From Data Collected Using Digital Health Technologies
Line 426: "However, this may also lead to challenges in establishing an optimal and clinically relevant endpoint."

We suggest that it would be helpful if this point could be elaborated on by describing what challenges are being referred to (e.g., DHTs are able to detect more aspects but some of these may not be relevant to the individual, etc.).

E. Statistical Analysis
Lines 473 -486: "In a clinical investigation using DHTs, missing or erroneous data may occur as a result of intercurrent events, such as: …"

It is unclear under what evidence Sponsors should provide to account for missing data. We suggest that FDA provide considerations for reporting and addressing missing data, including what evidence is sufficient to support a conclusion that data are intermittently missing at random.

Lines 481 -482: "Trial participant error or non-compliance with study procedures using the DHT or general-purpose computing platform"

When participants do not complete a task according to instructions, it is unclear if and when it would be appropriate to exclude the data from analysis and what evidence should be provided to support doing so. We request that FDA describe considerations for how sponsors can minimize the need to exclude data from analysis (e.g., through training), and expectations for documentation of any excluded data. For example, evidence to justify excluding such data from analysis could include a description of the potential problematic behavior, the expected resulting data pattern, the rules or mechanism by which this data pattern is identified and evidence that such occurrences are not associated with plausible disease-related factors.

F. Record Protection and Retention
Lines 622-625: "For data collected directly from study participants through DHTs, FDA would generally consider the data in the durable electronic data repository to constitute the source data. Review of these data may be necessary to reconstruct and evaluate the clinical investigation, and the data should be available for inspection."

We would appreciate clarification in the guidance what level of data is in scope for inspection and should be retained. For example, should raw (unprocessed data) directly from the sensor be retained or is FDA referring to feature (processed) time series data, or aggregate feature (further processed). It would also be helpful to understand if FDA requires data described above to be retained in any particular format to allow it to be inspection ready.

G. Other Considerations When Using Digital Health Technologies During a Clinical Investigation
Line 716: "Setting up, activating, and operating DHTs and, as applicable, general purpose computing platforms"

We suggest expanding this bullet to include considerations for software updates and/or procedures for malfunctions/deficiencies and hardware upgrades.

Line 732: "Connecting to wireless networks"

We suggest revising as follows: "Connecting to wireless networks as well as how the data is handled in cases of intermittent connectivity."

Line 734: "Handling known adverse events associated with the DHT (e.g., rash from actigraphy bands)"

We suggest revising as follows: "Handling known adverse events associated with the DHT (e.g., rash from actigraphy bands) and clearly delineating the adverse events associated with the DHT vs the study drug, when possible."

APPENDIX B: EXAMPLE OF SELECTING A DIGITAL HEALTH TECHNOLOGY (DHT) FOR A CLINICAL INVESTIGATION
Line 894: Table 1

We suggest that this table be revised to also include the digital measure (e.g., sleep latency)

Thank you for the opportunity to provide commentary on this process. We look forward to ongoing conversations regarding this and other related efforts.

Sincerely,
Megan Coder, PharmD, MBA
Chief Policy Officer