Critical Path Institute

Comments on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

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Submitted by: Scientific staff at the Critical Path Institute

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Description of the Critical Path Institute

The Critical Path Institute (C-Path) is an independent, nonprofit, public-private partnership with the U.S. Food and Drug Administration (FDA), created in 2005 under the auspices of the FDA's Critical Path Initiative program. C-Path's aim is to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies. These pre-competitive standards and approaches, also known as drug development tools (DDTs), are created through C-Path's collaborative consortia, and are put through rigorous regulatory review processes for confirmation of their validity for a given context of use.

C-Path's mission is to facilitate the development of new approaches to advance medical innovation and regulatory science by bringing together industry, academia, government agencies, patient groups, and non-government organizations in a pre-competitive and collaborative space to accelerate and de-risk important drug and other medical product development process (www.c-path.org). We achieve this by leading teams that share data, knowledge, and expertise, resulting in sound, consensus-based science, and actionable solutions to accelerate drug development and repurposing.

General Comments from Critical Path Institute:

C-Path thanks and commends FDA for inviting public comments as part of the creation of a guidance document for Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. C-Path believes the most effective and efficient means to bring life-saving therapies to patients requires meaningful collaboration between all stakeholders. These stakeholders include industry, regulatory agencies, patient groups, academic researchers and clinicians, disease foundations, and other organizations aiming to improve patients' lives.

Comments from C-Path Consortia and Programs

The individual consortia and programs have collaborated with their respective stakeholders to respond to the draft guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. Their responses are provided below and organized by consortium.

Clinical Outcomes Assessment (COA) Program

General comments

We appreciate having the opportunity to review and provide feedback on this draft guidance related to an important and rapidly evolving area of medical product development: remote data capture using digital health technologies (DHTs). We found the draft guidance to be thoughtful and well-written overall as it strikes a difficult balance of maintaining rigor with regard to expectations for medical product developers and electronic clinical outcome assessment (eCOA) and other DHT providers, while also indicating areas of flexibility. We offer the following suggestions for several areas where further clarification would improve the utility of the guidance for industry and other important stakeholders working to improve and standardize remote data capture using DHTs.

Specific comments

I. INTRODUCTION

Line 15-16: This definition of digital health technology is a very small portion of the full definition in the glossary. We suggest expanding the definition in the introduction to include the following: "which may be used as a medical product, in a medical product, or to develop a medical product." Without the connection to use in medical product development, the sentence leaves the reader wondering about the relevance to FDA.

Line 18: Please provide a rationale for limiting the scope of the guidance to use for remote data acquisition. By limiting the scope in this way, the guidance leaves readers wondering how use of DHTs in clinic settings during clinical investigations should be handled. This use case is being explored and may need to be addressed in the future. Note that in lines 29-30, the reference is to use of DHTs in clinical investigations without the limitation of remote data acquisition. The remaining sections all refer to clinical investigations more generally.

Lines 48-50: This sentence references use of DHTs for purposes other than remote collection of data. However, the example provided does not cover use in site-based data collection. We suggest adding "site-based data collection" as a second example to cover this potential use case.

II. BACKGROUND

Line 75: Please consider re-ordering the parenthetical examples to align with the prior text: "physiological and/or behavioral data (e.g., blood pressure, glucose levels, physical activity)."

Line 77: Suggest replacing "tremors" in the example with "sedentary behavior" as a more direct link to the prior concept of physical activity in line 75. While tremors can be detected with a DHT, if the intent is to link all examples listed in lines 77-78 to all concepts listed in line 75, as the other 2 examples do, then we propose replacing the second example with "sedentary behavior" as a more appropriate example to link to the concept of physical activity. Note that the ordering of the examples in this line should match line 75 if it is rearranged as suggested.

Line 84: We suggest amending this sentence fragment to "along with the platform on which it is intended to run," as this allows for the fact that software-based DHTs may be compatible with more than one platform.

Line 97: Given FDA's concern over the potential for source data to be under exclusive control of sponsors, it is inconsistent to imply that data "captured by DHTs can often be transmitted directly to…sponsors" as a standard assumption.

III. REGULATORY CONSIDERATIONS AND ENGAGEMENT WITH THE AGENCY

Line 115: Please include additional detail or a reference to illustrate what "other device requirements" would be.

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

Line 165: Whether an activity monitor is medical grade or consumer grade, it is a commercial product (i.e., it can be bought and sold). We propose deleting "commercial" in this sentence because it is unnecessary (and potentially confusing) since it is preceded by "the participant's own DHT." If it is necessary to qualify the activity monitor, then consider "consumer-grade activity monitor" to distinguish from medical-grade.

1. Clinical Investigation Population

Line 175: We suggest revising to: "participants may need DHTs and/or general-purpose computing platforms with large text, buttons, or screens, and translated versions may be…"

2. Design and Operation of DHTs

Line 180-212: Please consider these factors for inclusion: currentness or lifecycle stage of the DHT hardware; requirement for wireless linkage to a separate communications device or hub.

Line 211-212: We suggest adding examples of features that can ensure privacy and security to this bullet, such as biometrics or codes to access the device.

After line 212: The guidance needs to address whether DHTs and general-purpose computing platforms should blind the participant to their own data being collected on the device, meaning that the data would not be visible to the participant. This is usually advocated to prevent bias and the technology from serving as an intervention which could impact the signal of the treatment effect of the medical product under investigation. However, contextual flexibility may be needed in cases where the data collected and displayed by the device are an integral part of treatment/self-management decisions (e.g., continuous glucose monitors or CGMs).

3. Use of a Participant's Own DHT or General-Purpose Computing Platform and Telecommunications

Line 226: It would be helpful to address a recurring concern with allowing the use of the participant's own DHT or general-purpose computing platform, which is the inability to prevent the participant from seeing their own results and measurements. For example, if step count is the metric in question, then a

consumer device will display step count to the participant. There are concerns that seeing these results on a daily basis could lead the participant to change behavior to improve their metrics because they know they are being observed which could impact the true treatment effect of the medical product under investigation.

Lines 241-244: It is the case that some participants do not want to use their own technology, and that might be for a number of reasons; this fact should be reflected in this section of the guidance.

After line 248: It would be helpful to specify what level of data granularity should be requested when using the participant's own technology. Consumer devices may not provide the level of "raw" data that a medical-grade device provides, which may limit the types of analyses that can be performed with the data. Caution around this issue should be included in this section of the guidance.

B. Digital Health Technology Description in a Submission

Lines 254-255: The frequency of measurement or sampling is a key parameter that can vary significantly by DHT and, as a result, have an impact on output data. Please consider adding this expectation.

Lines 263-264: Please be clearer regarding what sponsors need to do to ensure that "DHT data should be attributable to the trial participant." In addition, the way "user annotations" would be operationalized on the DHT is unclear and this needs further detail as to when this would be necessary. Is this specific to it being used for a PerfO assessment or is it for when a device signals the participant to input specific information or answer questions regarding what they are doing when a specific event or physiologic parameter is recorded by the device?

C. Verification, Validation, and Usability of Digital Health Technologies

Line 294: Please consider reversing the order of "validation" and "verification" in this sentence for consistency.

Line 294: It would be very helpful if the section numbering was complete to make the document more user friendly; however, we recognize this is a long-standing style of FDA guidances. For instance, this line references "(section IV.C.1)" but that specific numbering doesn't appear anywhere in this document. It would be much more helpful if the next section heading was "IV.C.1. *Sensor-Based DHTs*" rather than just "1. *Sensor-Based DHTs."*

1. Sensor-Based DHTs

Line 306: We suggest removing the italicized formatting from the text within the parenthetical (unless the italicized formatting was intended for some reason).

2. DHT Software

Line 333: Usability studies should not be considered a type of validation study, and we propose to remove from this sentence.

Line 347: The sentence referencing the use of DHT software to administer eCOAs may be confusing to those who associate eCOAs with ePRO data collection. This sentence could imply that ePRO assessments require verification and validation, when verification has not historically been expected for

ePRO assessments in particular. As these are diaries or other measures, there is nothing against which they can be verified. This sentence should clarify that this statement may not apply to all eCOAs to avoid this potential misunderstanding.

5. Usability Studies

Line 370-388: It would be helpful in the section on usability studies to include additional detail on the level of testing needed. In cases where a DHT is using a totally new platform or device, more extensive testing may be required than for using a different device with similar functionality. While we agree that it is essential to include a thorough test of any trial system, including usability testing, the extent of testing required should vary with the novelty of the technology being used.

Lines 373-374: Although we agree that usability studies have a critical role in the determination of whether a device is fit-for-purpose in a specified context of use, we believe that stating they "are considered part of the validation process" reflects an overly broad and unhelpful definition of "validation." On lines 278-280, it is stated that "Validation is confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population." In addition, section IV.C is titled "Verification, Validation, and Usability of Digital Health Technologies," which correctly implies that these are three distinct steps. The term "validation" is overused in the literature leading to limited universal meaning or understanding; this should not be the case in this guidance document. Please consider deleting the unnecessary words so that this important sentence reads as follows: "These studies should enroll a cohort that is similar to intended trial participants."

Line 375: Another concern about the section on usability studies is that it conflates usability with feasibility studies. See the Clinical Trials Transformation Initiative tools supporting the use of DHTs in clinical trials, which specify the need for feasibility studies: https://ctti-clinicaltrials.org/our-work/digital-health-trials/testing-a-dht/. Feasibility studies are also described in Walton MK, Cappelleri JC, Byrom B, Goldsack JC, Eremenco S, Harris D, Potero E, Patel N, Flood E, Daumer M. Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials. *Contemp Clin Trials*. 2020 Apr; 91:105962. doi: 10.1016/j.cct.2020.105962. Epub 2020 Feb 20. PMID: 32087341. Walton and colleagues differentiate between usability and feasibility studies: "Usability testing is the assessment of the patient's ability to use the mobile sensor in question and may take place in a clinic or artificial setting. Feasibility research is the assessment of the use of a sensor in the context of a specific study design and assesses how well the patient is able to use the sensor in that context, particularly outside the clinic where he or she has to integrate it into daily life."

E. Statistical Analysis

Line 470-486: It may be worthwhile to add something about consideration for the time zone of data source versus time zone of the completion of data management and data analysis where the date format may change to align with a different time zone or assignment of correct assessment day.

F. Risk Considerations When Using Digital Health Technologies

After line 488: We recommend that consideration be given to potential safety issues that passive monitoring via a DHT might identify when DHTs are used in a remote setting. This is very use case-specific, but a monitoring plan must consider this. In the context of ePRO implementations, advice is

always given that any technology is never a substitute for normal clinical care, but in the passive measurement model another dimension is added.

1. Clinical Risks

Line 501: Please consider replacing "and" (between "components" and "skin") with "causing" to make it more consistent with the first example.

Lines 500-504: Usability testing might present evidence of the true passive nature of a technology (if applicable), and whether it impedes on normal participant function which would be clinical risk.

Lines 515-518: This bullet conflates cybersecurity, clinical risks, and privacy risks. We propose including an explanation of the clinical risk that may result from someone hacking into the system and altering/impairing the DHT's functionality. For a glucometer that may be used to modify treatment, this could cause significant clinical risk. Also, we suggest removing "and/or compromise patient privacy" on line 516 and addressing it in Section 2. Privacy-Related Risks. If there are additional security-related risks, consider a separate section to cover those.

3. Informed Consent

Lines 567-569: Location of how long and where data will be stored and accessed should be included in informed consent.

H. Other Considerations When Using Digital Health Technologies During a Clinical Investigation

1. Sponsor's Role

Line 657: If security-related risks become a separate section under IV.F., then this line should be updated to reference that section.

GLOSSARY

Lines 794-795: This sentence conflates what is being assessed (e.g., a patient-reported outcome) with the measurement tool that enables its assessment (e.g., a patient-reported outcome measure). Hence, please consider replacing the complete sentence on these two lines with: "Types of COAs include clinician-reported outcome measures, observer-reported outcome measures, patient-reported outcome measures, and performance outcome assessments."

Line 845: Please consider replacing "patient-reported outcomes (PROs)" with "patient-reported outcome (PRO) measure" since it is the PRO measure not the PRO that is a "type of clinical outcome assessment."

Line 850: "measure" should follow "PRO" in this sentence since it is the PRO measure that is being administered.

Line 854: "PROs" should be replaced with "PRO measures" since it is the PRO measure that is enabling the respondent to "assess."

Line 860: Please consider replacing “performance outcome (PerfO)” with “performance outcome (PerfO) assessment” since it is the PerfO assessment not the PerfO that is a “type of clinical outcome assessment.”

Line 863: “assessment” should follow “PerfO” in this sentence since it is the PerfO assessment that is being administered.

TYPOGRAPHICAL ERRORS

Line number	Incorrect word or phrase	Correction suggested
189	Please remove the comma after “convenience”	
432	the data is adequately captured by the DHT	the data are adequately captured by the DHT
675	Ensure that the data has been	Ensure that the data have been

Critical Path for Parkinson's (CPP)

Description of C-Path's Critical Path for Parkinson's Consortium

The Critical Path for Parkinson's Consortium (CPP) was launched on October 14, 2015 at C-Path. CPP launched a Digital Drug Development Tools (3DT) team in 2018 with the goal to leverage the unique role of CPP as a neutral convener to bring together stakeholders in a precompetitive space to facilitate and optimize the use of digital health technologies (DHTs) in clinical trials. This allows for collective engagement with regulatory agencies in an iterative process to optimize the effective use of DHTs in Parkinson's disease (PD) clinical trials.

General comments

We commend the FDA for drafting guidance documents on the use of DHT for remote data assessment and we appreciate the opportunity to provide comments and input into this comprehensive draft guidance. This draft guidance aligns well with the core competencies and accomplishments of CPP's 3DT team. The guidance provides useful recommendations and will enhance alignment in the community on the appropriate use of DHT in clinical trials.

The FDA has recommended that early and frequent feedback is key to advancing DHTs as tools for decision making in clinical trials. There are several pathways that have been proposed to consider in engaging with the agency. The biomarker and COA qualification pathways may not lend themselves particularly well to the rapidly evolving nature of DHTs. We appreciate FDA's consideration of new initiatives, such as the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program, to address gaps in traditional drug development tool qualification pathways. Yet, limited acceptance of qualification through the ISTAND initiative may further limit the vast growth and potential of DHTs and measures derived from DHTs (i.e., digital measures). We encourage the FDA to work with relevant stakeholders, such as CPP's 3DT, to ensure fit-for-purpose regulatory endorsement approaches for both DHTs and digital measures. One opportunity to consider would be CDER's Office of Clinical Pharmacology's Fit-for-Purpose pathway through Model Informed Drug Development. DHT's can be viewed as another tool to quantify disease progression and modeling strategies can enhance confidence in trial design and optimization for defined contexts of use.

As CPP represents a global audience, we also recommend that FDA identify how it can partner with other global regulators, specifically EMA, to promote convergence of evidentiary requirements necessary for qualification of DHTs and measures derived from DHTs.

We have identified several issues in the draft guidance that could use further clarification and provided the following recommendations.

Specific comments

Section: I. INTRODUCTION
Lines 15-16: "*A digital health technology (DHT) is a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses.*
Background: The FDA's proposed definition of a DHT is an overly broad definition that may also capture medical devices such as, for example, an MRI scanner which complies to all the

elements described in the DHT definition. We believe that this broad definition does not fully capture the intent of the common and current understanding of DHT, which generally is associated with a technology that can be worn or directly interacted with by trial participants.
Recommendation: We suggest refining the definition of DHT by highlighting the ability to use DHT in the natural environment and/or to be interacted with or worn by the trial participant.

Section: I. INTRODUCTION
Lines 16-19: *"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."*
Background: The draft guidance is very timely, as in this pandemic era it has become even more evident that there is a need for remote data acquisition with DHTs. However, while use of DHTs lends itself well for remote data acquisition, DHTs may also be used in the in-clinic setting as part of a clinical trial, for example for clinical validation purposes or to supplement clinical observation. It is unclear why this draft guidance is focused solely on remote data acquisition or if in-clinic use of DHTs is viewed differently than remote use.
Recommendation: We suggest that the FDA clarifies if the same considerations that are laid out in this draft guidance also apply to in-clinic use of DHTs as part of a clinical trial. If there is no difference, we suggest removing the word "remote" from the title of the draft guidance and update the scope of the draft guidance. Alternatively, if the FDA does perceive a difference, we recommend clarifying this as well in the scope of the draft guidance.

Section: II. BACKGROUND
Lines 80-86: "*DHTs can also be software applications that are run on general-purpose computing platforms. 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. It is important to consider the software application, along with the platform on which it runs, for the purpose of determining if it is appropriate for use in a clinical investigation."*
Background: The FDA defines different types of clinical outcome assessments (COAs) including patient-reported outcomes, and performance outcomes, that, when administered using a DHT, are referred to as an eCOA. These concepts are well-defined in the draft guidance, however, throughout the guidance the FDA also uses terminology such as 'novel endpoint' or 'clinical endpoint'. A clear definition of the concept of an endpoint in the context of DHT use in clinical trials is absent from the guidance. Additionally, the digital measures derived from the DHTs can also be viewed as a biomarker.
Recommendation: We recommend that the FDA provides a clear definition of 'endpoint'. We also recommend, within the context of DHT use in clinical trials, to clarify what type of digital measures are intended as an eCOA and what type of digital measures are intended as a biomarker. We recommend terminology used in the guidance to align with terminology used in other FDA guidance.

Section: III. REGULATORY CONSIDERATIONS AND ENGAGEMENT WITH THE AGENCY
Lines 121-122: *"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."*
Background: This guidance is an exemplar of multiple Centers at the FDA coming together to provide their expertise to provide comprehensive guidance. We appreciate the recommendation by the FDA to stakeholders to engage early with the Agency. Given the involvement of multiple Centers and the recommendation to engage with the Review Divisions as well, it may not always be clear to a Sponsor which Centers should be engaged or how the Centers communicate with each other.
Recommendation: We recommend that the guidance address the process of communication between Centers and how Sponsors should engage with FDA when multiple Centers are involved to avoid delays or duplicative requests or requirements. We also recommend that the FDA describes how DHTs, or measures derived from DHTs, can be qualified for multiple contexts of use and clarify the involvement of the different Centers in this process.

Section: IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS -- B. Digital Health Technology Description in a Submission
Lines 263-266: *"In addition, the DHT data should be attributable to the trial participant, and if applicable, user annotations (e.g., about their environment or activities) can be used to supplement data recordings to help in the interpretation of the recording."*
Background: Given the unique nature of remote assessments, attribution of DHT data to the trial participant may pose unique challenges.
Recommendation: We recommend that the FDA recognizes the unique challenges of data attribution in the context of remote assessments using DHT. We recommend that the FDA provides examples of appropriate attribution, e.g., could documentation of user training and consent be enough to assume trust on attributability?

Section: IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS -- C. Verification, Validation, and Usability of Digital Health Technologies
Line 370-376: *"Usability studies are a critical component in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation. These studies are considered part of the validation process and should enroll a cohort that is similar to intended trial participants. Usability studies should test the ability of future participants to use the DHT as directed in the trial protocol."*
Background: We appreciate the Agency's reference to guidance on appropriate usability study design. There are many existing approaches for usability testing along with various tools that can be used for usability testing, as laid out, for example, in the 2016 "Applying Human Factors and Usability Engineering to Medical Devices" guidance for Industry and FDA Staff (FDA-2011-D-0469).

Recommendation: We recommend that the FDA provides guidance as to which approaches or measures may be suitable or preferred by the Agency. In addition, the FDA could provide further guidance on alternative approaches (e.g., qualitative interviews) to assess usability.

Section: IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS -- E. Statistical Analysis

Lines 470-474: *"Statistical analysis plans should prespecify intercurrent events that may be related to the DHT and, as applicable, the general-purpose computing platform and how these events will be accounted for in the analyses to address the scientific questions of interest. In a clinical investigation using DHTs, missing or erroneous data may occur as a result of intercurrent events."*

Background: The draft guidance provides some examples of intercurrent events that may lead to missing data in a clinical trial (Lines 481-486). These intercurrent events should be pre-specified in the statistical analysis plan and it should be described how these events will be accounted for in the analyses to address the scientific questions of interest. Given the complexity of DHT data, such as continuous acquisition over prolonged periods of time, (undetected) hardware failures, or unsupervised remote use by patients, missing DHT data is unique compared to missing data in "traditional" clinical trials. It is unclear how current recommendations for treatment of missing data in clinical trials can apply to treatment of complex data in clinical trials using DHT [1].

Recommendation: We recommend that the FDA recognizes the uniqueness of missing data related to DHT use and clarifies in the draft guidance that addressing this may need innovative approaches. We also recommend that the FDA convenes an expert panel that provides evidentiary standards for handling of missing data in DHT clinical research.

Section: IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS -- G. Record Protection and Retention

Lines 593-598: *"When using DHTs to record and transmit data during a clinical investigation, the relevant data captured from the DHT, including all relevant associated metadata, should be securely transferred to and retained in a durable electronic data repository as part of the record of the clinical investigation. FDA regulations include record retention requirements for clinical investigators and sponsors and provide for FDA inspection of certain records relating to a clinical investigation."*

Background: Metadata has been defined as additional data to accompany and describe the primary data and is needed to interpret the data collected by a DHT [2]. Several frameworks and guidelines have been offered for the description of metadata in trials using DHT. The FDA draft guidance introduces the concept of metadata (Lines 594 and 614), however, there is no definition of metadata provided. Furthermore, there is limited guidance on the nature of metadata that needs to be documented.

Recommendation: We recommend including a definition of metadata both in the body of the text as well as in the Glossary. We also recommend adaptation of a metadata framework proposed by CPP's 3DT initiative that provides standards for capturing or storing DHT biosensor data applicable across modalities and disease areas, and which can also capture the clinical trial and environment-specific aspects [3].

Section: IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS -- G. Record Protection and Retention

Lines 611-623:

- *Sponsors should discuss with review divisions the type of DHT data recorded from each participant to be submitted for FDA review. This may involve complete data, summary data, sample data, and/or abnormal data obtained during continuous or frequent recording.*
- *The data output of the DHT to support an endpoint for the clinical investigation, and associated metadata, should generally be transmitted to a durable electronic data repository. These data can take the form of discrete clinical events measured using built-in analytics (e.g., heart beats, breaths, steps) or continuous recordings (e.g., electrocardiograms), among other things.*
- *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.*

Background: The use of DHT brings along unique challenges in terms of digital data acquisition, processing, and management. Some devices may capture and store digital "raw signal" data that is available for download and further processing while other devices only provide derived measures as output. The FDA recognizes the challenges that come along with DHT data, and we appreciate the recommendation to discuss this with the Review Divisions. Nonetheless, it would be helpful to have more detail on data requirements that could be helpful for Sponsors in the very early stages of designing a clinical study.

Recommendation: We recommend that the FDA provides definitions of concepts such as "complete data", "summary data", "sample data", and "source data". We also recommend that the FDA provides further detail on the format in which digital data needs to be submitted. For example, "raw digital data" from different DHT used in a study may come in different formats. The FDA should also be cognizant that some of the digital data collected generates large files and may consume significant computing resources. Transmission of these files may pose challenges. The Agency could clarify if these challenges are sufficiently addressed in the FDA's Technology Modernization Action Plan (TMAP) and Data Modernization Action Plan (DMAP).

Section: APPENDIX B: EXAMPLE OF SELECTING A DIGITAL HEALTH TECHNOLOGY (DHT) FOR A CLINICAL INVESTIGATION

Lines 912-913: "*A portable wearable device to assess sleep parameters in the home setting in trial participants with insomnia disorder"*

Background: The draft guidance provides an example of selecting a DHT for a clinical investigation (Appendix B). In this example, the use of a portable wearable device that has received FDA marketing authorization to remotely measure sleep parameters in the home setting is compared to the existing 'gold standard' in clinical investigations of diary-recorded participant estimates or polysomnography (PSG) conducted in a sleep laboratory. In this example, DHT measurements replicate existing measurements for the same clinical endpoint and a new justification for the endpoint is likely not expected from the Sponsors (Lines 411-417). This specific example provides clarity around the considerations for Sponsors to take

into account when developing a study. A common challenge in clinical trial design is that there are often no clear or gold standard clinical endpoint or COA to compare to. This provides an obvious challenge in selecting DHT.
Recommendation: We recommend providing an additional example of considerations for Sponsors to take into account, where a DHT is used with no reference clinical gold standard or traditional COA. We appreciate, however, that this may be outside the scope of this guidance. Therefore, we also recommend that the FDA holds public workshops to discuss these type of case studies and potential recommendations with interested stakeholders.

References

1. Little, R.J., et al., *The prevention and treatment of missing data in clinical trials.* N Engl J Med, 2012. **367**(14): p. 1355-60.
2. Badawy, R., et al., *Metadata Concepts for Advancing the Use of Digital Health Technologies in Clinical Research.* Digit Biomark, 2019. **3**(3): p. 116-132.
3. Hill, D.L., et al., *Metadata Framework to Support Deployment of Digital Health Technologies in Clinical Trials in Parkinson's Disease.* Sensors, 2022. **22**(6).

Type 1 Diabetes (T1D) Consortium

General comments

This guidance is overall clear, well-written, and provides product developers a broad overview of key considerations to incorporate digital health technologies (DHTs), like continuous glucose monitors (CGMs), into clinical trials.

The scientific staff from the C-Path's Type 1 Diabetes Consortium appreciate the opportunity to provide comments regarding this important draft guidance. CGMs have been used as an important component of diabetes care, especially for those living with type 1 diabetes (T1D), for over 20 years. As the performance of these devices has improved over time, their use has become increasingly frequent in the clinical setting, especially when considering the advent of high performance closed-loop systems. This guidance is timely and provides important information that will support the T1D community's goals of implementing the use of CGMs into clinical trials, thereby improving clinical trial design and ensuring new life saving therapies reach T1D patients.

We believe the following comments and considerations regarding the guidance document and use of DHTs in clinical trials will improve the ability of product developers to incorporate Agency recommendations into product development programs such that the overall product development ecosystem is improved. Critically, we believe the clinical review divisions must be engaged in the development of regulatory guidance and in conversations with sponsors. We encourage the Agency to continue to emphasize the role of Agency clinical reviewers in its guidance document development and implementation.

Specific comments

Use of a Participant's Own DHT or General-Purpose Computing Platform

In the context of T1D studies, allowing trial participants to use the CGM make and model used in their daily care can decrease the overall burden of trial participation, while potentially reducing the risk of adverse events due to use of an unfamiliar device.

However, in addition to these advantages, it is acknowledged that the use of a participant's own DHT in a clinical trial provides disadvantages when considering the interpretability of trial results, and variability is known to exist in the performance characteristics of different CGM devices, potentially compromising the ability to interpret data from multiple different devices in a single study.

The draft guidance states that sponsors should describe the minimum technical and performance specifications and identify which specific DHTs meet the minimum specifications. We believe these specifications should be standardized and consistent across clinical trials, for a specific DHT use case scenario, for example the use of CGMs to assess level 2 hypoglycemia (blood glucose measurements <54mg/dL). This construct can support broader research, data sharing, and learnings by more easily allowing for datasets from multiple trials to be harmonized and aggregated. As new device models/brands/versions are developed, consistent standards for use will maintain relevance of legacy efforts as future data is collected.

As specifications will vary depending on the therapeutic area and context in which a DHT is intended to be implemented, the relevant clinical review divisions across the Agency must be involved in

developing appropriate standards. The perspectives of other relevant stakeholders, including clinical trialists, product developers, and device manufacturers, in addition to the relevant regulatory divisions, should be considered establishing these standards.

In the absence of such technical and performance standards for a particular DHT use case, we encourage the agency, in collaboration with relevant stakeholders, to develop a consistent construct for how a sponsor should evaluate the use of a trial participants own DHT or general-purpose computing platform. We believe development of this framework can be taken on as a future effort that will complement the current guidance and should be geared toward ensuring more consistency in decision making across sponsors and trials when considering the same or similar uses of a DHT.

Data Standards Requirements

We firmly believe data standardization and data sharing are necessary components for meeting medical product development needs through the development and implementation of DHT-based-solutions in clinical trials. As technologies improve and the role of DHTs in clinical trials expand, the importance of data standardization for DHTs will increase. DHTs are being utilized in increasingly variable ways across trials, often with different versions or manufacturers being used, and differences in formatting and terminologies used for data collection, storage, and maintenance often exist (e.g., differences in whether raw data v. derived metrics are captured). The subsequent high variability can limit the overall utility and interpretability of the data beyond its primary use if the data cannot be integrated with other datasets because of missing or incompatible data components. It is critical to ensure that the minimum necessary data components for a specific use case of a DHT are defined and standardized. These should be considered in addition to the minimum technical and performance specifications mentioned in the previous comment.

We recommend development of a framework or workflow to identify the minimum standard DHT data requirements in specific use case scenarios, in close collaboration with the clinical review divisions, when clinical guidelines are being developed or revised. This information can guide the development of data collection standards such that they incorporate necessary characteristics to support future work.

A particular metric derived from a DHT could provide meaningful information regarding multiple concepts of interest, depending on how and when that metric is assessed. Thus, we also recommend development of data collection processes and standards for how a DHT is implemented into a trial protocol, whether being used as a new method to assess an existing clinical endpoint or to assess a novel endpoint. These standards should be therapeutic area and use case specific, will increase the likelihood that sufficient necessary data is collected, and will support standardization of DHT generated data, future secondary uses of that data, and improve overall data interpretability.

Standards for Reporting Performance Metrics

We support the Agency's recommendation to include existing consensus performance standards, when applicable, during the verification process. We believe the Agency should encourage the development of consensus standards for how performance of devices is assessed that specifically include considerations for the use of DHTs in clinical trials, as this will greatly facilitate consistent implementation of devices across trials. Key information regarding many devices is often considered proprietary or data used during the device clearance or approval process may not be adequate or suitable to verifying and validating a DHTs use in a clinical trial. We believe the development of standards for reporting device performance will encourage device manufactures to report or provide necessary

information to adequately undertake device verification and validation processes, thereby facilitating the use of DHTs in clinical trials. As with previous comments, the verification and validation process should be geared toward a specific context in which a DHT is intended to be used. For example, without raw performance data, given the nature and variability of commonly reported CGM performance metrics, it is difficult to verify the ability of a CGM to adequately assess very low blood glucose values, (i.e., level 2 hypoglycemic events defined as blood glucose concentrations <54 mg/dL).

Integration of data from multiple DHTs

DHTs have enabled observation of many types of clinical characteristics parameters and can provide information about metabolic, physical, cognitive, and other functions. Observations of multiple parameters simultaneously often provide a better and more comprehensive understanding of a therapeutic intervention's effects on a disease process. We appreciate agency's recognition of utilizing multiple DHTs for assessments as provided in line 93-95 and in Table 4. Such observations will become more prevalent and will support integrated assessments of disease, intervention, lifestyle, and other factors that will help better understand an investigational product's effects.

Frameworks for risk assessment

Risk assessment processes are well established for the assessment of devices for PMA and 510(k) submissions. However, the development of a risk assessment framework specifically for the use of a device as a DHT in a clinical trial would be helpful. This will ensure risks to trial participants when using a DHT in a specific trial context are adequately understood and appropriately managed. This is particularly important when considering a DHT that is used for guiding treatment administration (e.g., use of a CGM to guide insulin dose), in addition to use as a drug development tool. In addition to risk assessment for those using DHTs in a trial, consideration should also be given for how device characteristics (e.g., technical performance) may contribute uncertainty in regulatory decision making based on the device, which should also be considered in a risk assessment framework (for example, given a CGM's performance in hypoglycemic ranges, what are the risks of making erroneous conclusions regarding an investigational product's effects on hypoglycemia). We also encourage the DHT use in a clinical trial risk assessment framework to incorporate applicable components of exiting risk assessments from PMA or 510(k).