Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

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Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

December 2021
Clinical/Medical

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TABLE OF CONTENTS

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations Guidance for Industry, Investigators, and Other Stakeholders[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

A **digital health technology**[2] (DHT) is a system that uses computing platforms, connectivity, software, and/or **sensors,** for healthcare and related uses. 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.[3,4,5]

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

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH) and the Oncology Center of Excellence (OCE) at the Food and Drug Administration (FDA).

[2] Words and phrases in **bold** are defined, for the purposes of this guidance, in the Glossary.

[3] For the purposes of this guidance, the terms *participant* and *subject* are used interchangeably.

[4] For FDA's regulatory definitions of *clinical investigation* or *investigation*, see 21 CFR 50.3(c), 56.102(c), 312.3(b), and 812.3(h). For the purposes of this guidance, the terms *clinical trial* and *clinical investigation* are used interchangeably.

[5] For the purposes of this guidance, all references to medical products mean human drugs and biological products, medical devices, and combination products that are regulated by CDER, CBER, or CDRH.

Act) and some of which do not.[6] DHTs may take the form of hardware and/or software.[7] In many instances, DHT software may run on **general-purpose computing platforms** (e.g., mobile phone, tablet, or smart watch). A clinical investigation can use multiple DHTs to collect a range of information that may include clinical, physiological, psychological, behavioral, or functional data.

This guidance outlines recommendations intended to facilitate the use of DHTs in a clinical investigation as appropriate for the evaluation of medical products. These recommendations address some of the information that should be contained in an investigational new drug application (IND) or an investigational device exemption (IDE) application for a clinical investigation in which the sponsor plans to use one or more DHTs or in a marketing application that includes such a clinical investigation.[8]

These recommendations address the following topics:

- Selection of DHTs that are suitable for use in the clinical investigation
- **Verification** and **validation** of DHTs for use in the clinical investigation
- Use of DHTs to collect data for trial endpoints
- Identification of risks associated with the use of DHTs during the clinical investigation
- Management of risks related to the use of DHTs in clinical investigations

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.[9]

Some of the considerations in this guidance may also be helpful for uses of DHTs other than remote collection of data to evaluate endpoints in a clinical investigation (e.g., enrichment strategies[10]).

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[6] See section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the definition of a device. How to determine whether a DHT proposed for use in a clinical investigation meets the definition of a device under the FD&C Act is outside the scope of this guidance. For further information about FDA digital health regulatory policies, see https://www.fda.gov/medical-devices/digital-health-center-excellence/ask-question-about-digital-health-regulatory-policies.

[7] For the purposes of this guidance, the term *hardware* includes its firmware (i.e., software that is embedded within the hardware and that is essential to the core operation of the hardware). The term *software* refers to other software (e.g., a mobile application) that is not part of the hardware.

[8] For the purposes of this guidance, FDA uses the term *submission* to refer to an IND, an IDE application, and/or a marketing application.

[9] See footnote 6.

[10] Enrichment is the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population. See the guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs*

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II. BACKGROUND

Advances in sensor technology, general-purpose computing platforms, and methods for data transmission and storage have revolutionized the ability to remotely obtain and analyze clinically relevant information from individuals. DHTs used for remote data acquisition are playing a growing role in health care and offer important opportunities in clinical research. Compared to intermittent trial visits, the use of DHTs to remotely collect data from trial participants may allow for continuous or more frequent data collection. This may provide a broader picture of how participants feel or function in their daily lives. 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). Some DHTs also may facilitate the direct collection of information from participants who are unable to report their experiences (e.g., infants, cognitively impaired individuals).

DHTs often consist of sensor hardware that allows for continuous or intermittent recording of physiological and/or behavioral data (e.g., blood pressure, physical activity, glucose levels). Some of these DHTs use algorithms to translate these data into clinical events or characteristics that may be of interest in a clinical investigation (e.g., hypertensive event, tremors, acute hypoglycemia). Table 1 in Appendix A provides an example of sensor-based DHT hardware used in a clinical investigation.

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.[11] 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. Table 2 in Appendix A provides an example of DHT software used in a clinical investigation.

Some DHTs consist of hardware and software (e.g., a continuous glucose monitoring device that includes a sensor and a mobile application), both of which are necessary to achieve the DHT's

and Biological Products (March 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] Examples of DHT software include tests of visual acuity, memory, and auditory acuity in which participant responses to stimuli are analyzed to provide a clinical assessment.

intended function or functions.[12] Table 3 in Appendix A provides an example of a DHT that consists of sensor-based hardware and software used in a clinical investigation.

Some clinical investigations can use multiple DHTs to measure one or more clinical characteristics or events. Table 4 in Appendix A provides an example of a system that includes multiple DHTs in a clinical investigation.

Data captured by DHTs can often be transmitted directly to investigators, sponsors, and/or other authorized parties, with the capability to maintain blinding or masking when appropriate. The ability to transmit data remotely increases opportunities for patients to participate in clinical investigations at locations remote from the investigator's site (**decentralized clinical trials)**. Remote data acquisition may also address challenges associated with centralized trials, such as the burden of traveling to the trial site for participants, especially for participants with physical or cognitive limitations, time constraints, or for those who may be geographically dispersed.

III. REGULATORY CONSIDERATIONS AND ENGAGEMENT WITH THE AGENCY

Some DHTs that may be appropriate for use in a clinical investigation may meet the definition of a device under section 201(h) of the FD&C Act.[13] Devices intended for use in clinical investigations are exempt from most requirements applicable to devices, including premarket clearance or approval, as long as the investigation complies with applicable requirements under 21 CFR part 812.[14] Therefore, DHTs used in clinical investigations of medical products typically would be exempt from applicable requirements to obtain marketing authorization[15] and other device requirements, as long as the clinical investigation is compliant with part 812. The CDRH Digital Health Center of Excellence, which was established to empower stakeholders to advance health care by fostering responsible and high-quality digital health innovation, can also

[12] For the purposes of this guidance, for any given product, the term *function* is a distinct purpose of the product, which could be the intended use or a subset of the intended use of the product. For example, a product with an intended use to analyze data has one function: analysis. A product with an intended use to store, transfer, and analyze data has three functions: (1) storage, (2) transfer, and (3) analysis. As this example illustrates, a product may contain multiple functions.

[13] See footnote 6.

[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).

[15] Namely, clearance of a premarket notification (510(k)) submission (see 21 CFR part 807, subpart E), granting of a De Novo classification request (see section 513(f)(2) of the FD&C Act), approval of a premarket approval application (PMA) (see 21 CFR part 814) or humanitarian device exemption application (see part 814, subpart H).

serve as a resource on DHTs, including their regulatory status, for sponsors, DHT manufacturers, and other stakeholders.[16]

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.[17]

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. Developers of DHTs may choose to pursue qualification of DHTs as a Drug Development Tool (DDT) or a Medical Device Development Tool (MDDT) for a specific **context of use.** A qualified DHT may be relied upon in multiple clinical investigations to support premarket submissions for drugs or biological products (if qualified as a DDT) or devices (if qualified as an MDDT) where the context of use is the same (e.g., measurement of a specific outcome in a specific disease population), without having to repeat studies that supported the qualification, provided that the qualification has not been rescinded or modified.[18] Developers of DHTs may choose to submit qualification proposals to the appropriate CDER/CBER **DDT Qualification Programs**[19,20] (e.g., the Animal Model Qualification Program for animal models used for product development under the Animal Rule,[21] the Clinical Outcome Assessment (COA) Qualification Program, and the Biomarker Qualification Program) and/or CDRH's **MDDT Qualification Program**.[22,23] Of note, sponsors

[16] For further information about the CDRH Digital Health Center of Excellence, see https://www.fda.gov/medical-devices/digital-health-center-excellence.

[17] Sponsors should follow each FDA center's procedures for engaging with the Agency in the context of a development program. For drugs and biological products, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018). When final, these guidances will represent FDA's current thinking on these topics. For medical devices, see the guidance for industry and FDA Staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (January 2021). For further information about FDA digital health regulatory policies, see https://www.fda.gov/medical-devices/digital-health/ask-question-about-digital-health-regulatory-policies.

[18] The draft guidance for industry and FDA staff *Biomarker Qualification: Evidentiary Framework* (December 2018) may also be a helpful resource. When final, this guidance will represent FDA's current thinking on this topic.

[19] See CDER's web page Drug Development Tools (DDT) Qualification Programs, available at https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs.

[20] See the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020).

[21] The regulations that set forth the pathway for approval of certain products under 21 CFR 314.600 through 314.650 (drugs) or 21 CFR 601.90 through 601.95 (biological products) when human efficacy studies are not ethical or feasible are commonly referred to as the Animal Rule.

[22] See CDRH's web page Medical Device Development Tools (MDDT), available at https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt.

[23] See the guidance for industry, tool developers, and FDA staff *Qualification of Medical Device Development Tools* (August 2017).

and other stakeholders may also wish to consider submitting DHT-related proposals to the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which is designed to expand DDT types by encouraging development of DDTs that are out of scope for other DDT qualification programs but may still be beneficial for drug development.[24] These are voluntary qualification programs that are independent of an individual marketing submission for a DHT that is a device or a marketing submission for a medical product that uses a DHT to collect data in a clinical investigation.

IV. CONSIDERATIONS WHEN USING DIGITAL HEALTH TECHNOLOGIES IN CLINICAL INVESTIGATIONS

Sponsors should ensure that a DHT is **fit-for-purpose** (i.e., that the level of validation[25] associated with the DHT is sufficient to support its use and interpretability in the clinical investigation). This section outlines some considerations for using DHTs in a clinical investigation and what information regarding a DHT's use in a clinical investigation should be included in a submission.[26] Sponsors are encouraged to engage with the DHT manufacturer or other parties in order to leverage any existing information, as appropriate, to support the DHT's suitability for use in the specific clinical investigation.

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

In choosing an appropriate DHT, sponsors should consider the clinical event or characteristic of the disease or condition of interest that is to be measured, the proposed trial population, the design of the clinical investigation, and the characteristics of the DHT that may influence trial participant use. Sponsors should also consider whether the participant's own DHT (e.g., continuous glucose monitor, commercial activity tracker) and/or general-purpose computing platform (e.g., mobile phone, tablet, or smart watch) may be appropriate to reliably collect or facilitate the collection of data during the clinical investigation. The following are some specific issues that should be considered:

[24] See Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program Submission Process, available on FDA's web page at https://www.fda.gov/drugs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program-submission-process.

[25] Validation may also encompass much of the process required for verification. See section IV.C of this guidance for further discussion of verification and validation.

[26] FDA takes a *least burdensome* approach to regulatory questions or issues that arise throughout the total product lifecycle for medical devices, including evaluation of premarket submissions. *Least burdensome* is defined to be the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time. For medical device submissions, the proposed recommendations in this guidance will be implemented consistent with the least burdensome principles outlined in the guidance for industry and FDA staff *The Least Burdensome Provisions: Concept and Principles* (February 2019).

1. Clinical Investigation Population

Education, language, age, and technical aptitude of trial populations should be considered to ensure that trial participants will be able to use the DHT and, as applicable, the general-purpose computing platform as intended for the purposes of the trial. For example, certain trial participants may need DHTs with large text, buttons, or screens, and translated versions may be needed to allow inclusion of diverse populations. Section IV.C.5 of this guidance discusses **usability studies** to gather feedback on the proposed DHT from individuals similar to the intended trial population.

2. Design and Operation of DHTs

The design and operation of the DHT hardware, the DHT software, and as applicable, the general-purpose computing platform should be considered to determine if the DHT is fit-for-purpose.

- Design (e.g., material, size, weight, appearance, portability) and ease of use may influence whether trial participants will use the DHTs for the duration of the clinical investigation and in the manner described in the protocol. These factors may be particularly important for wearable DHTs, where comfort and convenience, may influence a trial participant's ability and willingness to use the DHTs for the duration specified in the protocol.

- Power needs, such as battery life and charging recommendations, may influence the feasibility of the DHT for data capture and a trial participant's ability and willingness to use the DHT for the duration specified in the protocol.

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

- DHT alerts (e.g., low battery, poor signal, data not being recorded or transmitted to the server) are recommended to help trial participants and/or trial personnel prevent loss of data or missing data. Trial participants should be informed about how to respond to these alerts.

- Environmental factors (e.g., temperature) that may affect the performance of DHTs in a clinical investigation should be considered.

- Availability and capacity of participant and sponsor network systems should be adequate to handle the volume of data obtained from frequent or continuous recordings.

- The functioning of the DHT should ensure privacy and security to prevent unauthorized access to the DHT and the data it collects.

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

Sponsors should evaluate the advantages and disadvantages of allowing trial participants to use their own DHTs or general-purpose computing platforms in a clinical investigation. Such an approach allows participants to use DHTs or general-purpose computing platforms with which they are already familiar, and it reduces the burden of carrying additional DHTs or general-purpose computing platforms provided by the sponsor. When allowing participants to use their own DHTs or general-purpose computing platforms, sponsors should ensure that the measurements are consistent across all protocol-specified DHTs. This approach may not be appropriate for clinical investigations that require highly specialized or customized measurements.

In the submission, the sponsor should describe the minimum technical specifications (e.g., operating system, storage capacity, sensors) and performance specifications (e.g., **accuracy** and **precision** for measuring specified clinical events or characteristics) that would allow use of the participant's own DHT in the clinical trial. The sponsor should identify specific DHTs or general-purpose computing platforms (brand, model, and/or version) that meet the minimum technical and performance specifications. The sponsor should also specify if successful functioning of the DHT requires availability of telecommunications technologies, such as broadband or cellular networks.

- The sponsor should ensure consistent precision and accuracy across all brands, models, and/or versions of DHTs or general-purpose computing platforms specified for use in a clinical investigation protocol. See section IV.C of this guidance.

- 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.

- Sponsor-provided telecommunications technologies should also be made available as needed so that participants who have no or limited access to these technologies are not excluded from the clinical investigation.

B. Digital Health Technology Description in a Submission

In the submission, the sponsor should explain why the DHT is fit-for-purpose for use in the clinical investigation. A description of the DHT should be provided and should contain basic information about the DHT (e.g., the relevant physical characteristics of the DHT, data output provided to the sponsor and investigator, and information on how the DHT measures the clinical event or characteristic of interest, such as use of accelerometry to measure steps or use of photoplethysmography to count heartbeats). For many commercially available DHTs, the technical specifications and descriptions provided by the DHT manufacturer may be sufficient.

To assist the Agency in understanding the sponsor's plans for consistent data collection during the clinical investigation, sponsors should describe usability-related features such as how the DHT is worn, operated, and charged. Sponsors should describe how access to the DHT or the data collected from it is controlled to ensure privacy and security. 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.

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.

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

This guidance uses the terms verification and validation to describe steps that help ensure the DHT is fit-for-purpose for remote data collection use in a clinical investigation.[27] For the purposes of this guidance, verification[28] is confirmation by examination and provision of objective evidence that the physical parameter that the DHT measures (e.g., acceleration, temperature, pressure) is measured accurately and precisely over time. Validation[29] 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. Verification is often viewed as part of the validation process.

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.[30] These studies should include demonstration that the clinical event or characteristic to be assessed (e.g., step count or heart rate) is consistently and appropriately measured in the population of interest. For example, the algorithm the DHT uses to capture steps in a healthy participant may not be applicable for participants with Parkinson's disease with a

[27] Verification and validation are steps for ensuring any DHT used for remote data collection in a clinical investigation is fit-for-purpose, regardless of whether the DHT meets the definition of a device under section 201(h) of the FD&C Act. Therefore, the terms verification and validation as used in this guidance are not intended to be synonymous with the terms defined in 21 CFR 820.3(aa) and 820.3(z) under the Quality System Regulation for devices (21 CFR part 820) or the terms device software function verification and validation as described in the guidance for industry and FDA staff *General Principles of Software Validation* (January 2002).

[28] FDA uses the term *verification* in this guidance where others may use the term *analytical validation* as described in BEST (Biomarkers, EndpointS, and other Tools) Resource Glossary, 2016, available at https://www.ncbi.nlm.nih.gov/books/NBK338448.

[29] FDA uses the term *validation* in this guidance where others may use the terms *analytical validation* and *clinical validation* as described in BEST (Biomarkers, EndpointS, and other Tools) Resource Glossary, 2016, available at https://www.ncbi.nlm.nih.gov/books/NBK338448.

[30] Where a DHT to be used for remote data collection in a clinical investigation meets the definition of a device under section 201(h) of the FD&C Act, clinical verification or validation testing of the DHT may meet the definition of a clinical investigation subject to applicable requirements under 21 CFR parts 50, 56, and/or 812.

shuffling gait. Additionally, usability testing should identify and address any potential errors or problems trial participants may experience when using the DHT.

Sponsors can leverage verification and validation data made available by DHT manufacturers or other third parties, when appropriate. The following subsections of this guidance present some considerations for the validation and verification of DHT hardware (section IV.C.1), DHT software (section IV.C.2), and general-purpose computing platforms (section IV.C.3), as well as **interoperability** of connected systems with the DHT (section IV.C.4) and usability studies on the DHT (section IV.C.5). The submission should include relevant verification and validation data on the DHT and, if applicable, the general-purpose computing platform, as well as a discussion of any DHT modifications made as a result of testing.

1. Sensor-Based DHTs

Verification confirms that the DHT meets performance specifications. Verification can include testing according to consensus performance standards, when applicable (e.g., International Electrotechnical Commission 60601-1) and/or an analysis to identify potential failure modes of a DHT and their causes and effects (e.g., *failure modes and effects analysis*). For some DHTs and investigations, it may be appropriate to identify the conditions (e.g., temperature range) under which the DHT functions reliably. When the protocol permits use of more than one brand or model of DHT to collect the same data in a clinical investigation, sponsors should verify that measurements across protocol-specified DHTs are consistent. (See section IV.A.3.)

As part of the DHT validation process, sponsors should consider involving DHT manufacturers, patients, caregivers, and other technical and clinical experts as appropriate. Depending on the particular DHT and clinical investigation, the validation process may include:

- Comparisons of measurements made by the DHT with reference measurements of the clinical event or characteristic (e.g., step count by actigraphy versus step count by observation).

- Evaluation of factors that might affect the precision and accuracy of the measurement, such as placement of a wearable DHT (e.g., wrist versus hip), and physical interference with the measurement, such as participant activities that may be misinterpreted as the clinical event or characteristic of interest (e.g., a bumpy car ride misinterpreted as a tremor).

- Evaluation of the calibration process, when applicable. Certain DHTs may require calibration by the user, with or without assistance by trial personnel (e.g., calibrating a mobile app or smart watch for individual stride length to allow computation of the distance covered in a specific time interval). The calibration process should be validated to ensure accurate and precise measurements of the clinical characteristic or event of interest, and the appropriate frequency of calibration should be determined.

Validation studies, including usability studies, can be conducted in healthy volunteers and/or individuals with varying degrees of disease severity. These studies can be conducted in a

controlled laboratory setting, in a simulated living environment, and/or in a natural living environment. The appropriate population to consider for these studies may depend on whether the parameter being measured would be similarly obtained from a healthy trial participant and the target patient population for the medical product being studied. For example, measurement of heart rate may be similar in age-matched healthy trial participants and patients with Parkinson's disease, while assessment of step count may not, given the gait disturbances in patients with this disease.

2. DHT Software

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 (e.g., tests of auditory or visual acuity, tests of cognitive function). Among others, content validation, construct validation, and normative testing may be appropriate, and additional information on these topics is provided in other FDA guidance documents and FDA references.[31,32] DHT software should be verified and validated for its intended purpose.

3. General-Purpose Computing Platforms

If DHT software is run on general-purpose computing platforms, the sponsor should assess whether the computing platforms used might impact the DHT software function in the trial. The general-purpose computing platform should be appropriate to ensure the reliable collection of data during the clinical investigation.

4. Interoperability

Sponsors should ensure the ability of connected systems in the clinical investigation to effectively and securely exchange information. FDA encourages the use of public data exchange standards, including those related to identification of the data source, as appropriate. Interoperability of DHTs should be evaluated to demonstrate that the interactions on the

[31] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

[32] See FDA's web page COA Educational Resources and Publications of Interest, available at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/coa-educational-resources-and-publications-interest.

electronic interface perform as intended and the resulting DHT measurements are interpreted appropriately.[33,34]

5. Usability Studies

Usability studies are a critical component in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation.[35] 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.

- Usability testing should assess whether users are able to enter all data before being logged out of a DHT.

- When appropriate, sponsors can refer to published studies in similar populations or on early use of the DHT in exploratory studies to evaluate whether trial participants can appropriately use the DHT.

- Findings from the usability studies can be used to improve the design and functionality of the DHT, to improve user satisfaction, to inform the instructions for use provided to trial participants, and to improve ease of learning and training for trial participants and trial personnel.

D. Evaluation of Clinical Endpoints From Data Collected Using Digital Health Technologies

The submission should include a description of the clinical endpoint or endpoints measured from data collected through a DHT. If the endpoint is novel, sponsors should justify use of the endpoint in the clinical investigation. Methods of assessing a trial participant's response to a medical product (e.g., increase in activity as measured by actigraphy, change in blood pressure) in a clinical investigation should be well-defined and reliable.[36]

[33] The guidance for industry and FDA Staff *Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices* (September 2017) discusses important considerations regarding interoperability of medical devices. The principles addressed in that guidance may be helpful for addressing interoperability of DHTs used in clinical investigations of medical products.

[34] The FDA-recognized series of standards "IEEE ISO 11073 Health informatics—Point-of-care medical device communication" address interoperability of personal health devices. The principles addressed in these standards may be helpful for addressing interoperability of DHTs used in clinical investigations of medical products.

[35] The guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* (February 2016) discusses important considerations for human factors validation testing. The principles addressed in that guidance may be helpful for designing appropriate usability studies for DHTs proposed for use in clinical investigations of medical products.

[36] See 21 CFR 314.126 and 860.7.

This section outlines general considerations for justifying clinical endpoints measured using data collected from DHTs but does not address any disease-specific endpoints.[37]

1. Defining the Clinical Endpoint

A precise definition of an endpoint typically specifies the type of assessments made (e.g., activity level, average heart rate, sleep quantity and quality), the timing of those assessments, the tools used for the assessments, and other details, as applicable, such as if (and if so, how) multiple assessments for a trial participant will be combined.

2. Established Clinical Endpoints

DHTs may serve as new ways to measure clinical characteristics or events that were previously measured in a clinical setting (e.g., video-based pulse measurement). When DHT measurements replicate existing measurements (e.g., weight measurements at home versus in the clinic) for the same clinical endpoint, FDA generally would not expect sponsors to provide a new justification for the endpoint. However, validation of the new way to measure the endpoint should be provided to support its reliability. See section IV.C of this guidance regarding verification and validation of the DHT.

3. Novel Clinical Endpoints

Novel endpoints based on data captured by DHTs may provide opportunities for additional insight into participant function or performance that was previously not easily measurable (e.g., tremors). While it is possible to measure some aspects of function or performance during a participant's visit to the clinic at a point in time, the use of DHTs potentially provides for their measurement over a greater time period and in different settings. However, this may also lead to challenges in establishing an optimal and clinically relevant endpoint.

The principles that should guide development of novel endpoints based on data captured by DHTs are the same as the principles for developing novel endpoints captured by other means. Sponsors should obtain input from stakeholders (such as patients, disease experts, caregivers, clinicians, engineers, and regulators) to ensure that the novel endpoint is both clinically relevant and the data is adequately captured by the DHT. Discussions with the relevant review division are also important in these situations.

When justifying a novel endpoint using data captured by the DHT, sponsors should address the following:

- Whether the endpoint is a clinically meaningful reflection of how a participant feels, functions, or survives.

[37] FDA has issued many disease-specific guidance documents that may address considerations for using particular endpoints in clinical trials of medical products for a given disease. Sponsors should discuss disease-specific endpoints with the relevant review divisions. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- How the endpoint relates to other endpoints of effectiveness that have been used to support a marketing authorization for a similar indication (e.g., clinical scales, patient-reported outcomes, hospitalization, mortality). In the absence of related endpoints, evidence from other sources of information (e.g., literature or input from stakeholders and experts) may support use of the endpoint.

- Whether the novel endpoint is a sufficiently reliable measure of disease severity or health status (e.g., mild, moderate, or severe) to allow assessment of disease modification or progression.

- When an existing medical product has already received marketing authorization based on evidence from a study using an established endpoint for the disease or condition of interest, it may be useful to determine whether the effect of that existing medical product (positive control) can be detected using the novel endpoint.

See Appendix B for an example of justifying a novel endpoint using a DHT.

E. Statistical Analysis

Analyses of data collected from DHTs should be discussed in a statistical analysis plan.

- 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 DHTs, making it difficult or impossible to define the non-inferiority margin.[38,39]

- The definition of the endpoints and the source data[40] from which the endpoints are derived for each trial participant (e.g., average daily number of steps across the treatment period) should be prespecified in the statistical analysis plan.[41]

- 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, such as:

[38] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

[39] See the International Council for Harmonisation (ICH) guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001).

[40] See section IV.G Record Protection and Retention.

[41] See the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

476 – Software updates that change how the data are collected or that change the
477 algorithms used to process data
478
479 – Software incompatibility caused by operating system upgrades
480
481 – Trial participant error or non-compliance with study procedures using the DHT or
482 general-purpose computing platform
483
484 – DHT or general-purpose computing platform failure
485
486 – Data transmission failure
487
488 **F. Risk Considerations When Using Digital Health Technologies**
489
490 Sponsors, investigators, and institutional review boards (IRBs) should consider any risks to trial
491 participants associated with use of the DHTs for data collection.[42] The risks of using a DHT in a
492 clinical investigation can generally be broadly categorized as clinical risks and privacy-related
493 risks, although there is some overlap between these two areas. The following sections describe
494 some of the risks pertaining to the use of DHTs that, depending on the specific design of the
495 clinical investigation and DHTs used, may need to be assessed by the IRB, communicated in the
496 informed consent document, and addressed by the sponsor in the submission.[43]
497
498 *1. Clinical Risks*
499
500 • The physical features of the DHT should be evaluated for risk of injury (e.g., wrist band
501 occluding blood supply, skin contacting components and skin irritation). Evidence from
502 safety testing conducted by the DHT manufacturer, if available, or the sponsor of the
503 clinical investigation may be helpful to show that risks associated with use of a DHT by
504 trial participants are minimized.
505
506 – If applicable, instructions for re-use, such as processes for cleaning the DHT (e.g.,
507 electrode sensors) before and after use, should be provided to trial participants to
508 prevent infection or other adverse events.[44]

[42] See 21 CFR parts 50 and 56 for requirements pertaining to the protection of human subjects participating in and IRB review of clinical investigations.

[43] For example, to approve a clinical investigation, an IRB must determine that, among other things, risks to subjects are minimized in accordance with 21 CFR 56.111(a)(1), and the informed consent process must describe reasonably foreseeable risks or discomforts to the subject under 21 CFR 50.25(a)(2). In addition, sponsors must provide certain information in an IND or IDE application regarding risks to subjects and the safety of proposed clinical investigations. See, e.g., 21 CFR 312.23(a)(6)(iii)(g), 312.23(a)(10)(iv), 812.20(b)(2), and 812.25(c).

[44] Manufacturers of reusable DHTs that are devices are responsible for having labeling that bears adequate directions for use, including instructions on preparing a device for use. See 21 CFR 801.5(g). For more information on the formulation and scientific validation of reprocessing instructions for reusable devices, see the guidance for industry *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling* (March 2015).

- When measurements made by DHTs (e.g., glucometers) are used to modify the administration of the investigational product or the treatment of the participant, it is critical to evaluate the risk of erroneous measurements resulting in excessive, deficient, or inappropriate treatment.

- Sponsors should consider cybersecurity risks that could potentially impact the functionality of the DHT and/or compromise patient privacy. Accordingly, sponsors should consider FDA information on cybersecurity[45] to ensure that data can be securely stored and transmitted.

2. Privacy-Related Risks

Sponsors, investigators, and IRBs should be aware that unique privacy risks may arise when DHTs and, as applicable, the general-purpose computing platforms they run on are used in a clinical investigation. The following should be considered, as applicable:

- Sponsors should address the risk of potential disclosure of identifiable information via a breach of the DHT, general-purpose computing platform, or **durable electronic data repository**.

- DHTs or general-purpose computing platforms may have end-user licensing agreements or terms of service that allow sharing of data with the DHT or general-purpose computing platform manufacturer and potentially other parties. See section IV.F.3 of this guidance for considerations related to informing potential trial participants about who will have access to their trial data if they decide to participate.

  – To protect data privacy for trial participants, it may be appropriate for sponsors to work with DHT or general-purpose computing platform manufacturers to modify the end-user license agreement or terms of service for the purposes of the study, as applicable.

- Sponsors should ensure security safeguards are in place to secure data at rest and in transit to prevent access by intervening or malicious parties.

3. Informed Consent

FDA regulations under 21 CFR part 50 set forth the requirements for obtaining the informed consent of human subjects participating in clinical investigations. Some considerations for what information to include in the informed consent process regarding the DHT being used in a clinical investigation include the following:

[45] Additional information on cybersecurity, including managing cybersecurity risk, is provided by the CDRH Digital Health Center of Excellence at https://www.fda.gov/medical-devices/digital-health-center-excellence/cybersecurity

- The informed consent process must describe any reasonably foreseeable risks or discomforts to the subject (see sections IV.F.1 and IV.F.2 of this guidance), including reasonably foreseeable risks or discomforts related to the use of the DHT in the clinical investigation.[46] Information regarding what may be done to mitigate the risks most likely to occur should also be considered for inclusion.

- When appropriate, a statement must be included indicating that use of the DHT during the clinical investigation may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) that are currently unforeseeable.[47]

- The informed consent process should explain the type of information that will be collected by the DHT and how that information will be used and monitored. Where relevant, subjects should be informed of what action to take in case of any concerning sign, symptom, or abnormal clinical event (e.g., hypoglycemia or abnormal cardiac rhythm) detected by a DHT, such as seeking emergency medical attention if appropriate.

- The informed consent process should specify who may have access to data collected through the DHT during or after the clinical investigation (e.g., sponsor, investigator, subject, DHT manufacturer, other third parties) and during what time frame.[48]

- An explanation of measures to protect a subject's privacy and data, and limitations to those measures, when DHTs are used should be included.

- If subjects may incur additional expense because they are taking part in the clinical investigation, the consent process must explain the added costs,[49] which could include costs for the trial subject that may result from using the DHT or general-purpose computing platform during the clinical investigation (e.g., data use charges).

- DHTs and, as applicable, general-purpose computing platforms may include end-user license agreements or terms of service as a condition of use, which may, among other things, allow DHT manufacturers and other parties to gain access to personal information and data collected by the DHT. Where applicable, sponsors and investigators should ensure that the informed consent process explains to subjects that their data may be shared by the DHT or general-purpose computing platform manufacturer or third parties outside of the clinical investigation, according to the end-user license agreement or terms of service. End-user license agreements and terms of service typically are lengthy and use complex terminology. Sponsors and investigators proposing use of DHTs for data

[46] See 21 CFR 50.25(a)(2).

[47] See 21 CFR 50.25(b)(1).

[48] In addition, the informed consent process must note the possibility that FDA will inspect records identifying the subject (21 CFR 50.25(a)(5)).

[49] 21 CFR 50.25(b)(3).

collection should understand how such agreements or terms of service may affect trial participants and consider this information when developing informed consent documents.

G. Record Protection and Retention

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.[50,51]

The draft guidance for industry *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers* (June 2017) provides proposed recommendations on the use of electronic records in clinical investigations of medical products.[52] The draft guidance addresses mobile technologies[53] that allow for remote data capture directly from study participants during a clinical investigation, as well as related issues pertaining to access controls, data sources, inspections, and audit trails of the records created for data obtained directly from study participants.

Consistent with the proposed recommendations in that draft guidance, in planning for record retention in a clinical investigation using DHTs, FDA recommends the following:

- 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.

[50] See 21 CFR 312.57, 312.58, 312.62, and 312.68.

[51] See 21 CFR 812.2(b)(1)(v), 812.140, 812.145, and 812.150.

[52] When final, this guidance will represent FDA's current thinking on this topic.

[53] The recommendations regarding *mobile technologies* in the draft guidance for industry *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers* are also applicable to DHTs.

Review of these data may be necessary to reconstruct and evaluate the clinical investigation, and the data should be available for inspection.

- When the protocol specifies review of the source data by the clinical investigator, the investigator must retain these source data as part of the adequate and accurate case histories required under 21 CFR 312.62(b) and 812.140(a)(3). The investigator must also permit FDA to access and copy these case history records in accordance with 21 CFR 312.68 and 812.145(b).

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

To help ensure the quality and integrity of data, adequate protection of participants, and satisfaction of regulatory requirements applicable to clinical investigations, sponsors and investigators should consider the following recommendations with respect to clinical investigations that involve use of a DHT to remotely acquire data.[54]

1. Sponsor's Role

The sponsor should:

- Ensure training of trial participants and trial personnel (see section IV.H.4 of this guidance) on using DHTs and, as applicable, the general-purpose computing platforms, according to the protocol (e.g., wearing the DHT for the specified time period).

- Develop a plan for technical assistance to trial participants or study personnel for all protocol-specified DHTs and, as applicable, the general-purpose computing platform, which may involve collaboration with DHT or platform vendors or other parties.

- Develop a risk management plan to address potential problems trial participants may experience when using a protocol-specified DHT or general-purpose computing platform, including, but not limited to:

  – Clinical (see section IV.F.1) and privacy-related (section IV.F.2) risks.

  – Interference between mobile applications or software functions used in a clinical investigation and the other potential functions of a DHT. This may be of particular importance if a participant is using their own DHT or general-purpose computing platform during the clinical investigation (see section IV.H.3).

  – Loss, damage, and replacement of a DHT or general-purpose computing platform, including a corrective action plan to prevent compromising participant privacy or data integrity.

[54] See generally, e.g., 21 CFR part 11, part 50, part 312, and part 812.

- Trial participants upgrading or updating a DHT or general-purpose computing platform (hardware or software; models or versions) during the clinical investigation.

- Develop a safety monitoring plan that addresses how abnormal measurements related to participants' safety (e.g., hypoglycemia, arrhythmia, apnea) measured by DHTs will be reviewed and managed.

- Ensure that data has been downloaded from the DHT into a durable electronic data repository (see section IV.G of this guidance).

2. Investigator's Role

Investigators should:

- Ensure that participants understand what information will be collected by the DHT and how the security and privacy of data collected by the DHT will be maintained. The relevant submission should describe the investigator's role in ensuring appropriate use of DHTs.

- Ensure training of participants on using the DHT according to the protocol (e.g., wearing the DHT for the specified time period).

- Review data from DHTs periodically, if specified in the protocol.

3. Training

Training trial participants and trial personnel on the appropriate use of DHTs and, as applicable, general-purpose computing platforms, including training on responsibilities for data collection in a clinical investigation, is critical for appropriate use of the DHT and to maintain data integrity and data quality throughout the investigation.[55] Any training materials should be included as part of the submission.

Training should:

- Occur before participants begin using the DHT to collect data for the purposes of the clinical investigation

- Be scheduled, provided, and documented during the investigation, as appropriate (e.g., if changes or updates to the DHT and, as applicable, the general-purpose computing platform alter the way sponsors, clinical investigators, other trial personnel, or trial participants interact with the DHT)

- Be available to trial personnel and trial participants having difficulty using DHTs or, as applicable, general-purpose computing platforms during the investigation

[55] See 21 CFR 11.10(i).

Sponsors should consider addressing the following as part of the training for trial participants and trial personnel, as appropriate:

- Setting up, activating, and operating DHTs and, as applicable, general-purpose computing platforms
- Collecting data at appropriate time intervals
- Uploading or syncing data
- Ensuring the security and privacy of data collected by the DHT
- Wearing DHTs appropriately (e.g., location and duration), if applicable
- Properly cleaning the DHTs before or after use, if applicable
- Sharing of the same DHT and, as applicable, general-purpose computing platform with other individuals
- Connecting to wireless networks
- Handling known adverse events associated with the DHT (e.g., rash from actigraphy bands)
- Responding to DHT signals, notifications, and errors, including procedures for troubleshooting and elevating unresolved issues
- Verifying that DHTs are being used appropriately and that data are being collected, uploaded, or synchronized as planned

4. DHT Updates and Other Changes

Contingency plans should be made for changes to the DHT and, as applicable, the general-purpose computing platform during the clinical investigation (e.g., when a manufacturer discontinues a specific model or releases a new model).

Sponsors should keep a record of the timing and nature of any updates for each DHT and, as applicable, the general-purpose computing platform used for remote data collection in a clinical investigation.

- Sponsors should assess all updates to a DHT to ensure that verification and validation studies (see section IV.C of this guidance) are still relevant and that there is no significant impact on measuring the clinical events or characteristics using the DHT.

- When feasible, sponsors should consider locking software algorithms for the duration of the clinical investigation to avoid variability that can make results difficult to interpret. When software algorithms are not locked, sponsors should make plans to demonstrate that the data are not meaningfully different.

- When feasible, planned software updates or operating system updates that may modify how DHT signals are processed/interpreted should be delayed until the completion of the clinical investigation unless there is a security concern.

  - If updates cannot be delayed, sponsors should consider the implications of the update (e.g., through comparison of data from before and after the update) to show they are not meaningfully different.

  - If meaningful differences are observed, the sponsor should specify how these differences have been addressed in the analysis of trial results and how the differences impact interpretability of those results.

5. DHT Error or Loss

- Procedures should be in place to identify and address DHT and, as applicable, general-purpose computing platform errors (such as those involving batteries, sensors, software, etc.) and to replace lost or damaged DHTs or general-purpose computing platforms, as applicable. Contingency plans may provide for alternate data collection and recording mechanisms, if possible, during these times.

If malware is detected on a DHT or on a general-purpose computing platform (as applicable) during a clinical investigation, sponsors should pursue any appropriate corrective action.

GLOSSARY

The following terms are defined for the purposes of this guidance:

accuracy: The level of agreement between the measured value and the true value of the clinical event or characteristic.

clinical outcome assessment (COA): Assessment of a clinical outcome that can be made through report by a clinician, a patient, or a non-clinician observer or through a performance-based assessment. Types of COAs include clinician-reported outcomes, observer-reported outcomes, patient-reported outcomes, and performance outcomes. A COA can be administered on a general-purpose computing platform (e.g., mobile phone, tablet, or smart watch) and is then referred to as an *electronic* COA or **eCOA**.

context of use: A statement that fully and clearly describes the way the medical product development tool is to be used and the regulated product development and review-related purpose of the use.

DDT (Drug Development Tool) **Qualification Program:** An FDA program that manages the DDT qualification process under section 507 of the FD&C Act. Under the qualification process, FDA guides stakeholders in the development and refinement of DDTs (e.g., biomarkers, clinical outcome assessments, and animal models used for product development under the Animal Rule[56]) determined to aid drug development and regulatory review for the purposes of section 507.[57]

decentralized clinical trial: A clinical investigation where some or all of the trial-related activities occur at a location separate from the investigator's location.

digital health technology (DHT): A system that uses computing platforms, connectivity, software, and/or sensors for healthcare and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products.

durable electronic data repository: An enduring database that is electronically protected from alterations and is maintained until the end of the record retention period.

fit-for-purpose: In the context of use of a DHT in a clinical investigation, a conclusion that the level of validation associated with a DHT is sufficient to support its context of use.

general-purpose computing platform: A commercial off-the-shelf computing platform, with or without wireless connectivity, that may be handheld or otherwise portable in nature (e.g., mobile

phone, tablet, or smart watch). A portable general-purpose computing platform may also be described as a *mobile platform*.

intercurrent events: Events that occur after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

interoperability: The ability of two or more products, technologies, or systems to exchange information and to use the information that has been exchanged.

MDDT (Medical Device Development Tool) **Qualification Program:** A CDRH program to identify, facilitate, and qualify tools to assess the effectiveness, safety, or performance of a medical device. An MDDT is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making. Examples of MDDTs are clinical outcome assessments, assessments of biomarkers, and nonclinical assessment methods or models.

patient-reported outcomes (PROs): A type of clinical outcome assessment (COA). A measurement based on a report that comes directly from the patient (i.e., when used in a clinical trial, a trial participant) of the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. A PRO may be administered on a general-purpose computing platform (e.g., mobile phone, tablet, or smart watch) and is then referred to as an *electronic* PRO or **ePRO**.

Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. Examples of PRO measures include:

- Rating scales (e.g., numeric rating scale of pain intensity)
- Questionnaires (e.g., Minnesota Living with Heart Failure Questionnaire for assessing heart failure)
- Counts of events (e.g., patient-completed log of emesis episodes or micturition episodes)

performance outcome (PerfO): A type of clinical outcome assessment (COA). A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions. A PerfO assessment may be administered by an appropriately trained individual or completed by the patient independently. A PerfO may be administered on a general-purpose computing platform (e.g., mobile phone, tablet, or smart watch) and is then referred to as an electronic PerfO or ePerfO. Examples of PerfO assessments include:

- Measures of gait speed (e.g., timed 25-foot walk test using a stopwatch or using sensors on ankles)
- Measures of memory (e.g., word recall test)

precision: The level of agreement between measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions.

remote data acquisition: Collection of data from locations that are distant from the investigator or trial personnel.

sensor: A transducer that converts a physical, biological, or chemical parameter into an electrical signal; for example, temperature, pressure, flow, or vibration sensor. A sensor is typically hardware.

usability studies: Studies conducted to demonstrate that the DHT can be used as intended by the intended trial population, without serious errors or problems.

validation: Confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population.

verification: Confirmation by examination and provision of objective evidence that the physical parameter that the DHT measures (e.g., acceleration, temperature, pressure) is measured accurately and precisely over time.

APPENDIX A: EXAMPLES OF POTENTIAL DIGITAL HEALTH TECHNOLOGY (DHT) USE IN CLINICAL INVESTIGATIONS

Table 1: Sensor-based hardware example

Evaluation of a novel orthotic device to treat knee osteoarthritis. The clinical investigation uses a general-purpose consumer activity tracker to measure step count.	
DHT	**General-purpose consumer activity tracker bracelet**
DHT hardware*	General-purpose consumer activity tracker bracelet with sensors
DHT software	None
General-purpose computing platform	None
Purpose of using DHT	Measure a participant's steps during the clinical investigation as part of the endpoint of interest

Table 2: Software example

Evaluation of a drug to treat symptoms of Alzheimer's disease. Participants perform a clinical outcome assessment (COA) memory task on their smartphone during the clinical investigation.	
DHT	**Memory task mobile application**
DHT hardware*	None
DHT software	Memory task mobile application
General-purpose computing platform	Smartphone
Purpose of using DHT	Measure a participant's active performance on a memory task during the clinical investigation as part of the endpoint of interest. Send a participant a reminder to complete the memory task.

Table 3: Sensor-based hardware and software example

Evaluation of a drug for the management of Type 2 Diabetes. The clinical investigation uses an FDA-cleared continuous glucose monitor device, including a sensor and a mobile application, to track hypoglycemic episodes in participants remotely 24/7.

DHT	**FDA-cleared continuous glucose monitor device with a mobile application serving as the interface and providing analysis and alarm functions**
DHT hardware*	FDA-cleared continuous glucose monitor sensor that uses a mobile application to function
DHT software	Mobile application that serves as the interface and provides analysis and alarm functions
General-purpose computing platform	Smartphone or tablet (the mobile application is compatible with multiple platforms)
Purpose of using DHT	Continuously measure glucose levels in the body during the clinical investigation as part of the endpoint of interest

902
903 **Table 4: Multiple DHTs example**
904

Evaluation of a medical product to treat a pulmonary disease. Multiple DHTs are used during the clinical investigation to measure different aspects of participants' functioning while at home.	
DHTs	**1. FDA-cleared spirometer with smart connectivity** **2. General-purpose consumer activity tracker bracelet** **3. Mobile application where participants rate their perceived functioning each day**
DHT hardware*	1. FDA-cleared spirometer with smart connectivity 2. General-purpose consumer activity tracker bracelet with sensors
DHT software	3. Mobile application where a participant rates their perceived functioning each day
General-purpose computing platform	Smartphone or tablet (the mobile application is compatible with multiple platforms)
Purpose of using DHTs	Measure participant's daily functioning and related metrics longitudinally in the participant's home environment during the clinical investigation as part of the endpoint of interest

905
906 *For the purposes of this guidance, the term *hardware* includes its firmware (i.e., software that is embedded within
907 the hardware and that is essential to the core operation of the hardware). The term *software* refers to other software
908 (e.g., a mobile application) that is not part of the hardware.

APPENDIX B: EXAMPLE OF SELECTING A DIGITAL HEALTH TECHNOLOGY (DHT) FOR A CLINICAL INVESTIGATION[1]

A portable wearable device to assess sleep parameters in the home setting in trial participants with insomnia disorder

A sponsor is developing a new drug for the treatment of insomnia disorder and is considering the use of a portable wearable device that has received FDA marketing authorization to remotely measure sleep parameters (e.g., latency to persistent sleep, wake after sleep onset, and total sleep time (TST)) in the home setting. Existing methods to assess these sleep parameters in clinical investigations are based on diary-recorded participant estimates or on polysomnography (PSG) conducted in a sleep laboratory. The sponsor believes that this digital health technology (DHT) will be able to measure sleep parameters with greater accuracy than diary-recorded estimates. The sponsor also believes that measuring a participant's sleep parameters in a home environment through a DHT will allow measurements over longer periods of time than PSG and is more generalizable than laboratory-based PSG measurements.

Table 1: DHT Summary

Evaluation of a medical product to treat insomnia. A DHT is used during the clinical investigation to measure multiple sleep parameters while participants sleep at home.	
DHT	**Portable wearable device that has received FDA marketing authorization**
DHT hardware*	Portable wearable device that has received FDA marketing authorization
DHT software	None
General-purpose computing platform	None
Purpose of using DHTs	Remotely measure a participant's sleep parameters during the clinical investigation as part of the endpoint of interest

*For the purposes of this guidance, the term *hardware* includes its firmware (i.e., software that is embedded within the hardware and that is essential to the core operation of the hardware). The term *software* refers to other software (e.g., a mobile application) that is not part of the hardware.

[1] This appendix provides a hypothetical, simplified example intended to illustrate considerations related to selecting an appropriate DHT to use for remote data collection in a clinical investigation. It is not intended to suggest that any particular DHT will be suitable to use for remote data collection in a clinical investigation or that data collected from such a DHT will be sufficient to support a regulatory submission to FDA.

Important issues for the sponsor to consider in its development plan are as follows:

DHT Selection, Verification, and Validation:

FDA marketing authorization of the DHT can support verification and validation of the DHT for use in the clinical investigation. Additional questions sponsors should consider when selecting a DHT include:

1. How does the DHT's analysis of sleep parameters compare with PSG in terms of accurately determining whether patients are awake or asleep at a given point in time?

2. Are the DHT's measurements reproducible over a range of environmental conditions (e.g., temperature, nearby electronics)?

3. Are the DHT's measurements consistent across a range of factors (e.g., body morphology, skin color, variation in sensor placement, movements during sleep, other neurologic or psychiatric conditions, other medications or psychoactive substances) that may introduce variability into measurements?

Usability Testing:

The sponsor may consider conducting usability studies to assess whether the intended population for the clinical investigation will be able to use the DHT as directed in the protocol. In designing these studies, sponsors should consider the following:

1. Is the DHT appropriately designed for use by the intended population for the clinical investigation of the drug, including older adult patients and/or their caregivers (if applicable)?

2. Is the planned clinical investigation using the DHT feasible? For example:

    a. Will trial participants wear the DHT correctly?

    b. How frequently should the DHT be charged and are there any expected challenges with the participant's charging practices?

    c. How will participants transmit data from the DHT to the investigator or sponsor?

Endpoint Justification:

This hypothetical DHT would provide data similar to sleep data collected during laboratory-based PSG. This DHT would, however, allow for nightly monitoring of sleep activity, whereas PSG data are typically collected at only select times relative to the entire duration of the clinical investigation (e.g., 2 successive days at baseline and 2 successive days at end of treatment). The increased monitoring frequency presents opportunities to construct novel endpoints that rely on multiple data points (e.g., extended observation period averages and temporal trends).

The sponsor should consider the following when developing an endpoint based on measurements using the portable wearable device:

- The sponsor can solicit input from subject matter experts, clinicians, regulators, patients, and/or caregivers to support a proposed novel endpoint.

- An established TST endpoint using PSG is the change in TST from baseline to end of treatment. Using a DHT for remote data acquisition can permit longitudinal measurement, and the primary endpoint could potentially make use of the entire time series of TST values over the duration of the clinical investigation.

- Because an endpoint might involve high-volume, high-frequency data (e.g., the entire time series of nightly assessments over the duration of the clinical investigation), the sponsor should:

  - Prespecify the population-level summary measure that compares the investigational product to a control and the statistical analysis methodology.

  - Describe the potential scenarios for missing data and the methods for assessing the impact of the missing data on trial results. Types of missing data may include missing a group of observations within a day, missing an entire day, or missing an entire week.

- Describe how the DHT measurements compare to traditional PSG measurements and how a difference may impact the assessment of a drug effect.

The sponsor may want to consider incorporating clinical outcome assessments (COAs) such as patient-reported outcome measures to understand how a trial participant feels and functions during the clinical investigation. Associations between COAs and wearable device data may provide for a broader assessment of sleep parameters and their impact on a participant's daily activities.