U.S. FOOD & DRUG ADMINISTRATION

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

DHTs for Remote Data Acquisition
Draft Guidance Webinar

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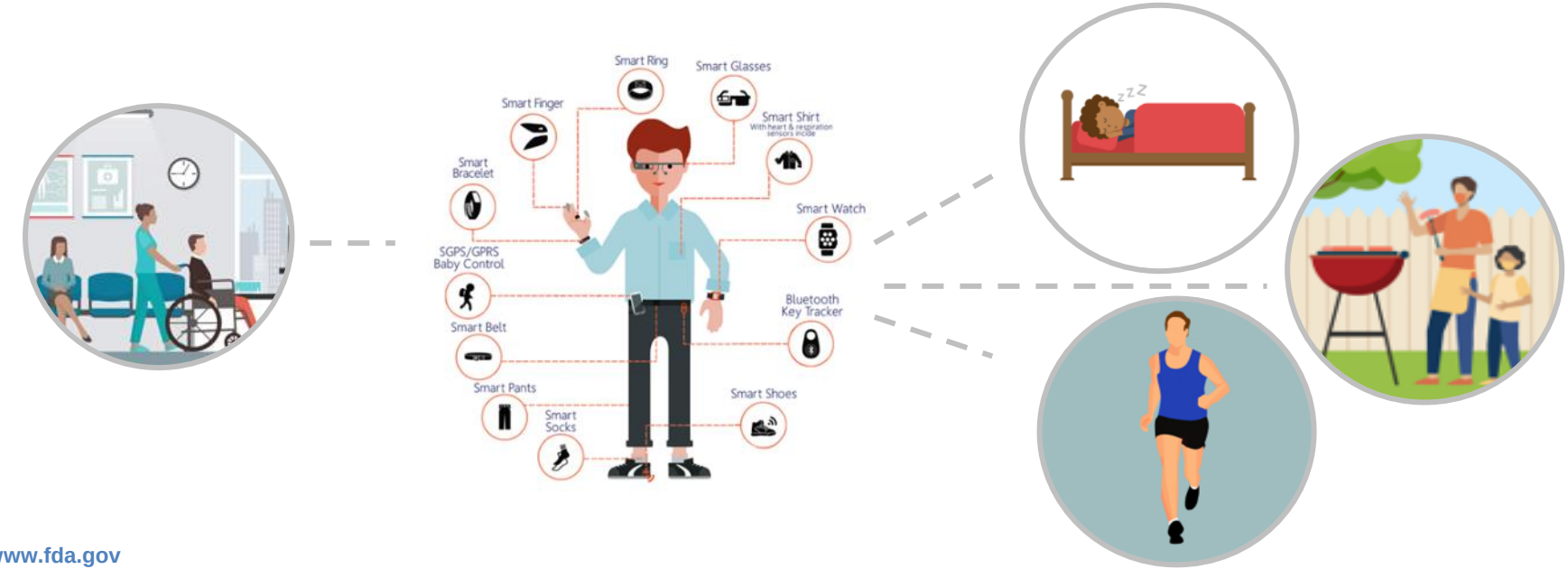
Digital Health: Part of a Patient's Lifestyle

Patient-generated health data (PGHD) collected from digital health technologies (DHTs) allows us to understand patient behavior in the context of their daily lives



Digital Health Technology

*Definition from FDA-NIH BEST Glossary. Available at https://www.ncbi.nlm.nih.gov/books/NBK338448/

DHTs can offer many unique benefits when used in a clinical investigation

- Continuous or frequent measurements
- Rare events
- Data from patients in their real-world environments
- Convenience for patients (Decentralized Clinical Trials)

Ensuring that DHT data are reliable, meaningful and confidential

- Correct measurements
- Suitable metrics
- Interpretation of continuous data
- Proper use by patients

Learning Objectives

- Identify digital health technologies (DHTs) and clarify regulatory considerations
- Identify factors for selecting a DHT for a clinical investigation
- Differentiate verification, validation, and usability studies of DHTs
- Construct endpoints from data collected using DHTs
- Design a clinical investigation using a DHT

Regulatory Considerations

Matthew Diamond, MD, PhD

Some DHTs meet the definition of a medical device* while others do not

*A device is defined by the Federal Food, Drug, & Cosmetic Act Section 201(h) as:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals…

Is marketing authorization (premarket clearance or approval) necessary to use a DHT in a clinical investigation?

Devices intended only for use in clinical investigations are typically exempt from many requirements applicable to Devices – including premarket clearance or approval – as long as the investigation complies with applicable requirements under 21 CFR part 812

Is marketing authorization (premarket clearance or approval) sufficient to show that a DHT is appropriate for use in a clinical investigation?

A DHT's marketing authorization does not necessarily mean that it is appropriate for use in a particular clinical investigation.
Sponsors are encouraged to leverage data that may be available from multiple sources, including marketing applications, to support that the DHT is fit-for-purpose* in a specific clinical investigation.

*The term "fit-for-purpose" will be discussed in subsequent slides.

Engage early with the appropriate Center to discuss the use of DHTs in a specific clinical investigation

Follow each FDA Center's procedures for engaging with the Agency in the context of a development program

For drugs and biological products

See these Draft Guidances for industry:

- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017);
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018).

For devices

See this Guidance for industry:

- FDA Staff Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (January 2021).

FDA has voluntary qualification programs to support the development of tools for use in assessing medical products

Drug Development Tool (DDT) Qualification Program

For drugs or biological products

Medical Device Development Tool (MDDT) Qualification Program

For devices

Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

For DDTs that are out of scope for other DDT qualification programs but may still be beneficial for drug development

These are voluntary qualification programs that are independent of individual marketing submissions

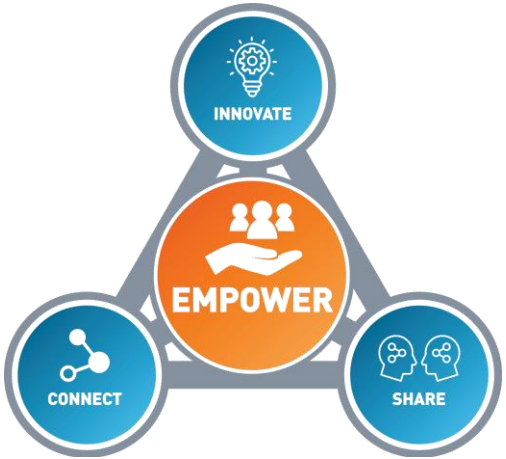
Developers of DHTs may choose to pursue qualification of DHTs for a specific context of use

A qualified DHT may be relied upon in multiple clinical investigations to support different premarket submissions…

for drugs or biological products (if qualified as a DDT) or for 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***.

CDRH Digital Health Center of Excellence

Digital Health Center of Excellence (DHCoE): Empower stakeholders to advance health care by fostering responsible and high-quality digital health innovation.



The DHCoE serves as a resource on DHTs, including their regulatory status, for sponsors, DHT manufacturers, and other stakeholders.

For more information see

Ask a Question about Digital Health Regulatory Policies

Email: *digitalhealth@fda.hhs.gov*

Website: *https://www.fda.gov/digitalhealth*

Selecting a DHT for a Clinical Investigation

Beth Kunkoski, MS

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DHTs used in clinical investigations should be fit-for-purpose

DHTs used in clinical investigations should be ***fit-for-purpose****

Fit-for-purpose: A conclusion that the level of validation associated with a biomarker, COA or DHT is sufficient to support its proposed use.

Clinical investigation ***endpoints**** should reflect an outcome of interest

Endpoint: *A precisely defined variable intended to reflect an outcome of interest* that is statistically analyzed to address a particular research question…

*Definitions from FDA-NIH BEST Glossary. Available at https://www.ncbi.nlm.nih.gov/books/NBK338448/

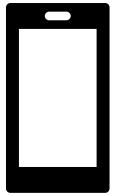
Considerations for selecting a DHT for a clinical investigation

- Measure the clinical event or characteristic of interest
- Usable for the patient population of interest
  - Education, language, age, and technical aptitude of trial populations

- DHT design and operation
  - Physical characteristics of DHT
  - Power needs
  - Operational specifications
  - Alerts
  - Availability and capacity of network systems

Use of a participant's own DHT or general-purpose computing platform and telecommunications

- Performance specifications for measuring specified clinical events or characteristics
- Minimum technical specifications of DHT
- Availability of telecommunications technologies
- Sponsor-provided DHTs, general-purpose computing platforms and telecommunication technologies should be available to ensure participants are not excluded



Verification, Validation, and Usability Studies of DHTs

Christina Webber, PhD

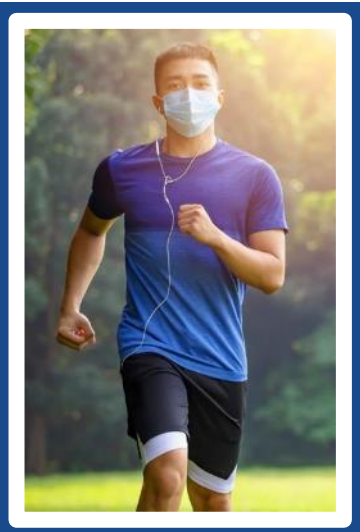
Verification and validation are important steps to help ensure a DHT is fit-for-purpose

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.* Verification is often viewed as part of the validation process

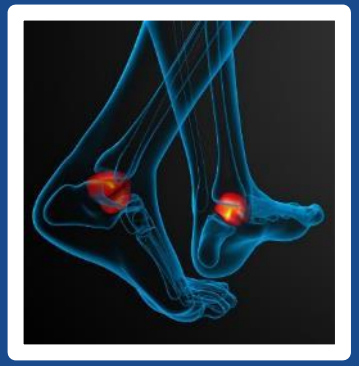
Validation: confirmation by examination and provision of objective evidence that the DHT appropriately assesses the clinical event or characteristic *in the proposed participant population*

Third party verification and validation data may be leveraged, when appropriate

Benchtop studies



Studies with healthy volunteers



Studies with individuals representing the clinical population of interest

Verification

- Testing according to consensus performance standards
- Identifying potential failure modes and their causes and effects
- Identifying appropriate operating conditions
- Confirming consistent measurements across protocol-specified DHTs

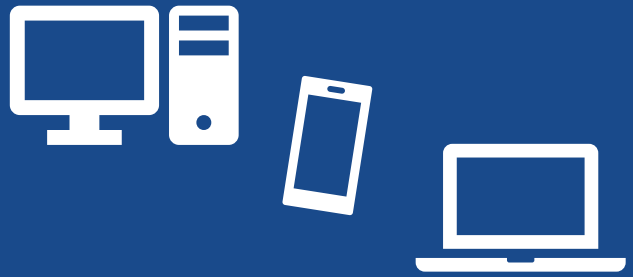
Validation

- Comparing DHT measures to reference measures
- Evaluating factors that might affect the precision and accuracy of the measurement
- Evaluating calibration, when needed, to ensure accurate and precise measurements

DHT software may be run on a variety of general-purpose computing platforms

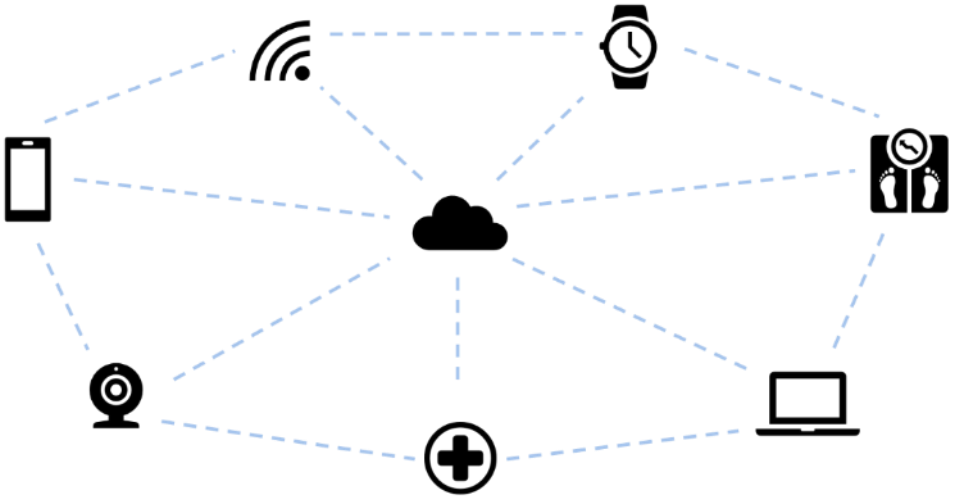
When using a general-purpose computing platform to administer electronic clinical outcome assessments (COAs), consider specific verification and validation steps including:

- Content validation
- Construct validation
- Normative testing



The general-purpose computing platform should be appropriate to ensure the reliable collection of data during the clinical investigation

Connected systems in the clinical investigation should effectively and securely exchange information



Interoperability of DHTs should be evaluated to demonstrate that the interactions on the electronic interface *perform as intended* and the resulting DHT *measurements are interpreted appropriately*

Usability studies can help confirm the DHT's suitability for use in the proposed clinical investigation

Donning/doffing the DHT or general-purpose computing platform

Logging on

Beginning data collection or completing data entry

Evaluation of Clinical Endpoints from Data Collected Using DHTs and Other Considerations

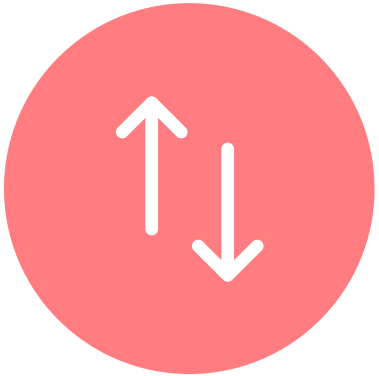
Beth Kunkoski, MS

Endpoint Development

Definition

Justification

Type
(Safety, Effectiveness)



Positioning
(Primary, Secondary, etc.)

When using data from a DHT to inform an endpoint, begin by treating the endpoint like you would any other endpoint

Novel Endpoints

- Is the endpoint a clinically meaningful reflection of how a participant feels, functions, or survives?
- Does the endpoint relate to other endpoints of effectiveness?
- Is the endpoint a reliable measure of disease severity or health status?
- Can you assess whether the effect of an existing medical product (positive control) can be detected using the novel endpoint?

Examples of risks to participants when using DHTs

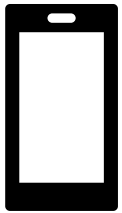
- Clinical risks
  - Physical features of DHTs
  - Measurements made by DHTs that affect treatment
  - Cybersecurity risks that may impact DHT operation

- Privacy-related risks
  - Disclosure of identifiable information
  - End-user licensing agreements/terms of service
  - Security safeguards to protect data

Further considerations when using a DHT for remote data acquisition in a clinical investigation

Participant and staff training

Technical support



DHT updates and changes

Record protection and retention

- Sponsor should discuss with review divisions the type of data recorded from each participant to be submitted to the FDA for review
- Data output of DHT to support an endpoint, and associated metadata, should generally be transmitted to a durable electronic data repository
- Source data is generally considered the data in the durable electronic data repository collected directly from participants

Further information: Draft guidance for industry *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers* (June 2017)

Example and Conclusions

Anindita Saha

Scenario: evaluation of a medical product to treat a pulmonary disease

A clinical investigation remotely measures different aspects of a participant's function using multiple DHTs, including an FDA-cleared spirometer with smart connectivity, a consumer activity tracker, and a mobile application administered on a smartphone or tablet where participants rate their perceived functioning daily

Purpose of Using DHTs: measure a participant's daily function, including their lung capacity, step count, and perceived functioning, longitudinally in the real world during the clinical investigation as part of the endpoint(s) of interest

Scenario: evaluation of a medical product to treat a pulmonary disease

A clinical investigation remotely measures different aspects of a participant's function using multiple DHTs, including an FDA-cleared spirometer with smart connectivity, a consumer activity tracker, and a mobile application administered on a smartphone or tablet where participants rate their perceived functioning daily

Note:

- Verification, validation, and usability studies should consider DHTs and general-purpose computing platforms, as appropriate
- Clinical outcome assessments may be captured using DHTs

Resources

- CDRH Digital Health Center of Excellence
  - FDA Digital Health Regulatory Policies
- CDER's Drug Development Tools (DDT) Qualification Programs
- Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program
- CDRH's Medical Device Development Tools (MDDT) Qualification Programs

Conclusions

- DHTs have revolutionized the ability to remotely obtain and analyze clinically relevant information from individuals
- 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
- 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)

Challenge Question #1

To select a DHT for a clinical investigation, the DHT should:

A. Automatically sync a participant's data daily

B. Never need to be charged

C. Be fit for purpose

D. Belong to the participant

Challenge Question #2

Which of the following statements is NOT true?

A. Verification is confirmation by examination and provision of objective evidence that the physical parameter that the DHT measures is measured accurately and precisely over time.

B. 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.

C. Usability studies are part of the verification process.

Submit comments to the Docket by March 22, 2022

https://www.regulations.gov/commenton/FDA-2021-D-1128-0002

Further Questions or Feedback

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