The Modernization of Clinical Trials through Digital Health Technologies (DHTs), Decentralized Clinical Trials (DCTs), and Point of Care Trials

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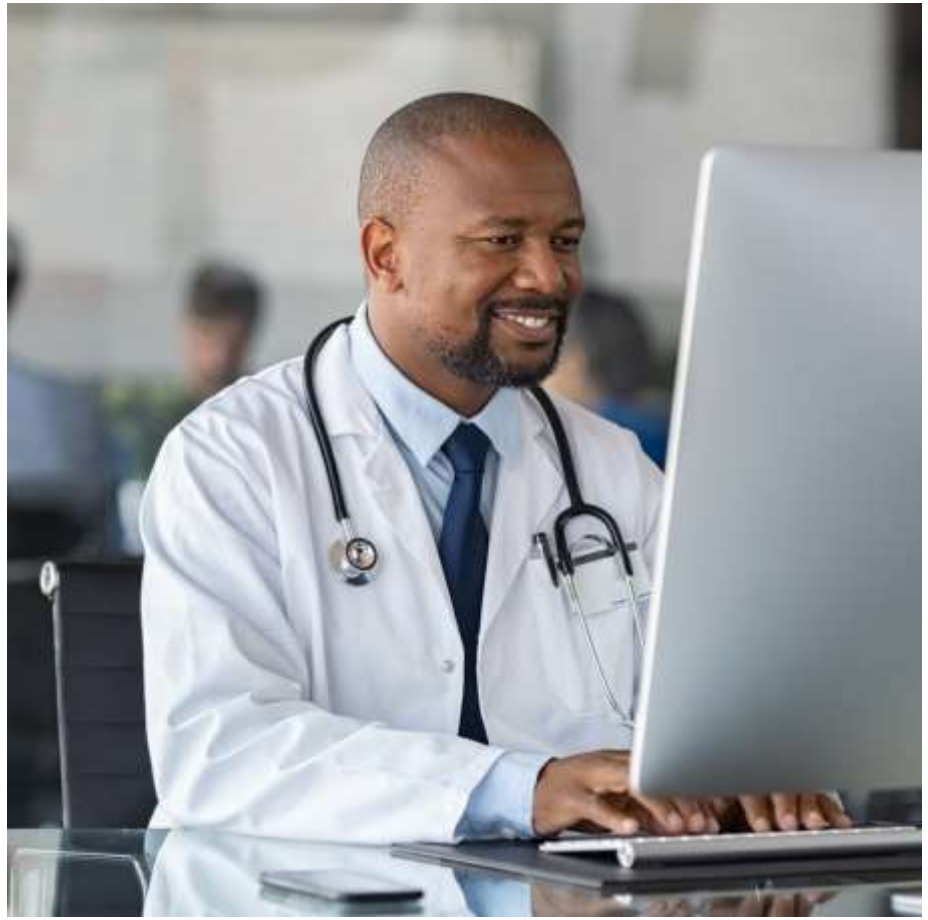
The Electronic Revolution



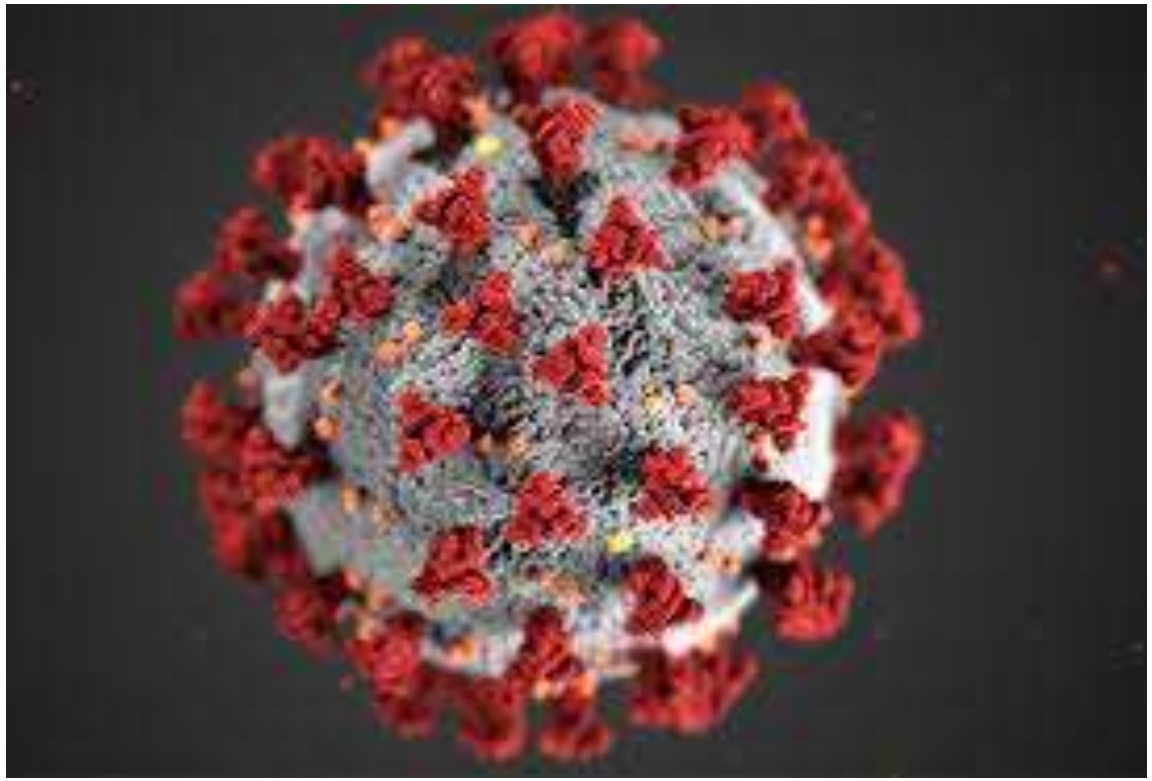
Information Technology Knows No Geographic Limits

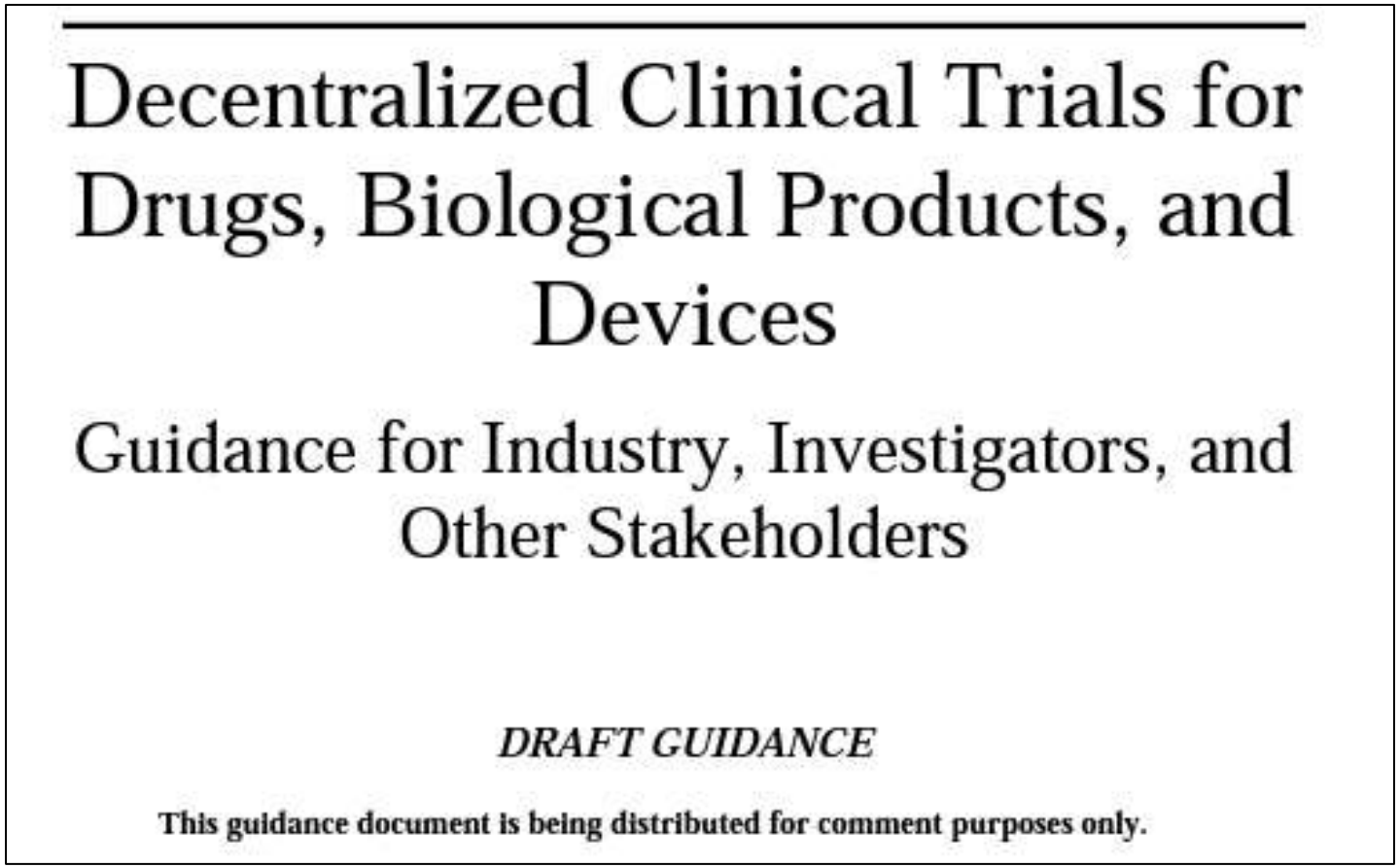
Decentralized Trial Procedures are Not New

- Patient diaries
- Interactive Voice Response Systems
- Telephone follow-up
- Web-based trials
- Electronic Informed Consent Guidance (2016)

COVID-19 was a Major Impetus to Avoid Traditional Site Visits

- Not having patients report to investigator sites for all trial-related activities was a critical tool to allow trials to continue during the COVID-19 health emergency
- Guidance on the *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency*





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Decentralized Clinical Trials
Strategies to Bring the Trial to the Patient

- A trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites
  - Use of telehealth visits
  - Use of digital health technologies
  - Direct distribution of product to participants
  - Use of electronic informed consent
  - Use of home visits to trial participants
  - Use of local healthcare providers and facilities

Why are Regulators Interested?

- Accessibility
  - Patients with rare diseases
  - Patients with mobility or cognitive challenges
  - Diversity of participants (socio-economic, cultural)
- Patient convenience
- Efficiencies
  - Travel
  - Physical facilities
  - Use of qualified community providers
- Experience with COVID-19
  - Contagious diseases

DCT Design

- Remote assessments may differ from on-site assessments
- Assessments performed by local HCPs may be more variable and less precise than assessments conducted by trial personnel
- Consideration of the statistical analysis to be performed
- For inspectional purposes, there should be a physical location where all clinical trial-related records for participants under the investigator's care are accessible and where trial personnel can be interviewed

Remote Trial Visits

Investigator can supervise remotely

Challenges

- Local regulations on telemedicine
- Physical examinations
- Photographs - may not fully capture the features of a lesion
- Patient engagement in absence of in-person contact
- Complex drug administration procedures
- Close medical supervision (e.g., infusion reaction)

Home Visits

- Novel approach
- Extend the physical reach of the trial
- Either dedicated or contracted trial staff
- Mobile trial units

Investigator's Role and Responsibilities

- Responsible for the conduct of the DCT and the oversight of individuals delegated to perform trial-related activities
- A key difference for DCTs is the extent to which the investigator uses telehealth, trial personnel working remotely, local HCPs, and/or DHTs in the conduct of the trial
- Decentralized features may necessitate additional training, coordination, and standard operating procedures to ensure consistent implementation

Direct Distribution of Investigational Product

- Investigator must control release of product to trial participants
- Local state laws differ on direct distribution to patients
  - May require locally licensed health care professionals such as pharmacists
- Packing, handling, and shipping of product
- Trial records tracking distribution
- Disposal of unused product

Use of Local Healthcare Providers

- Local HCPs, such as doctors or nurses, may be used by sponsors or investigators to perform certain trial-related activities
- The trial-related services they provide should not differ from those that they are qualified to perform in clinical practice
- These services should not require a detailed knowledge of the protocol or the investigational product
- Trial-related activities unique to research and/or require a detailed knowledge of the protocol or the IP should be performed by qualified trial personnel who have been appropriately trained

Investigator Delegation of Activities

- When permitted by the trial protocol, investigators may delegate trial-related activities to local HCPs to perform trial-related procedures that require in-person interactions with trial participants
- A critical consideration when delegating trial-related activities to local HCPs is the potential for variability in the approach across different practices
- Videoconferencing and other technologies may be useful to allow investigators to oversee trial personnel performing activities described in the trial protocol at participants' locations

Documentation: Investigators, Subinvestigators, Local HCPs

- Drug trials (Form 1572)
- When trial personnel contribute directly and significantly to the trial data, they should be included on Form FDA 1572 as subinvestigators
- Local HCPs (as defined in the draft guidance) should not be listed on Form FDA 1572 as subinvestigators. However, local HCPs should be included in a task log.
- For device trials, local HCPs are generally not considered investigators and should not be included in the IDE list of investigators. However, these local HCPs should be included in a task log

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions – Statement of Investigator (Form FDA 1572) (May 2010)

Task Log

- Investigators must maintain a task log of local HCPs who perform trial-related activities
- Task log should include:
  (1) The names and affiliations of the local HCPs
  (2) Description of their roles and assigned tasks
  (3) Dates these local HCPs are added to the log
  (4) Locations where these activities are conducted
- Should be dated and signed by the investigator when initially created and updated when a new local HCP is added
- Should be available to FDA during inspections

Electronic Informed Consent

- The regulatory requirements for obtaining informed consent and the IRB review process do not differ for DCTs
- Allows patients to review and sign at home
- May provide videos and graphics to make the process more informative and more easily understood
- FDA guidance *Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers* (December 2016)

CDER SMALL BUSINESS AND INDUSTRY ASSISTANCE (SBIA)

WEBINARS

www.fda.gov/CDERSBIALearn

Decentralized Clinical Trials (DCT) Draft Guidance

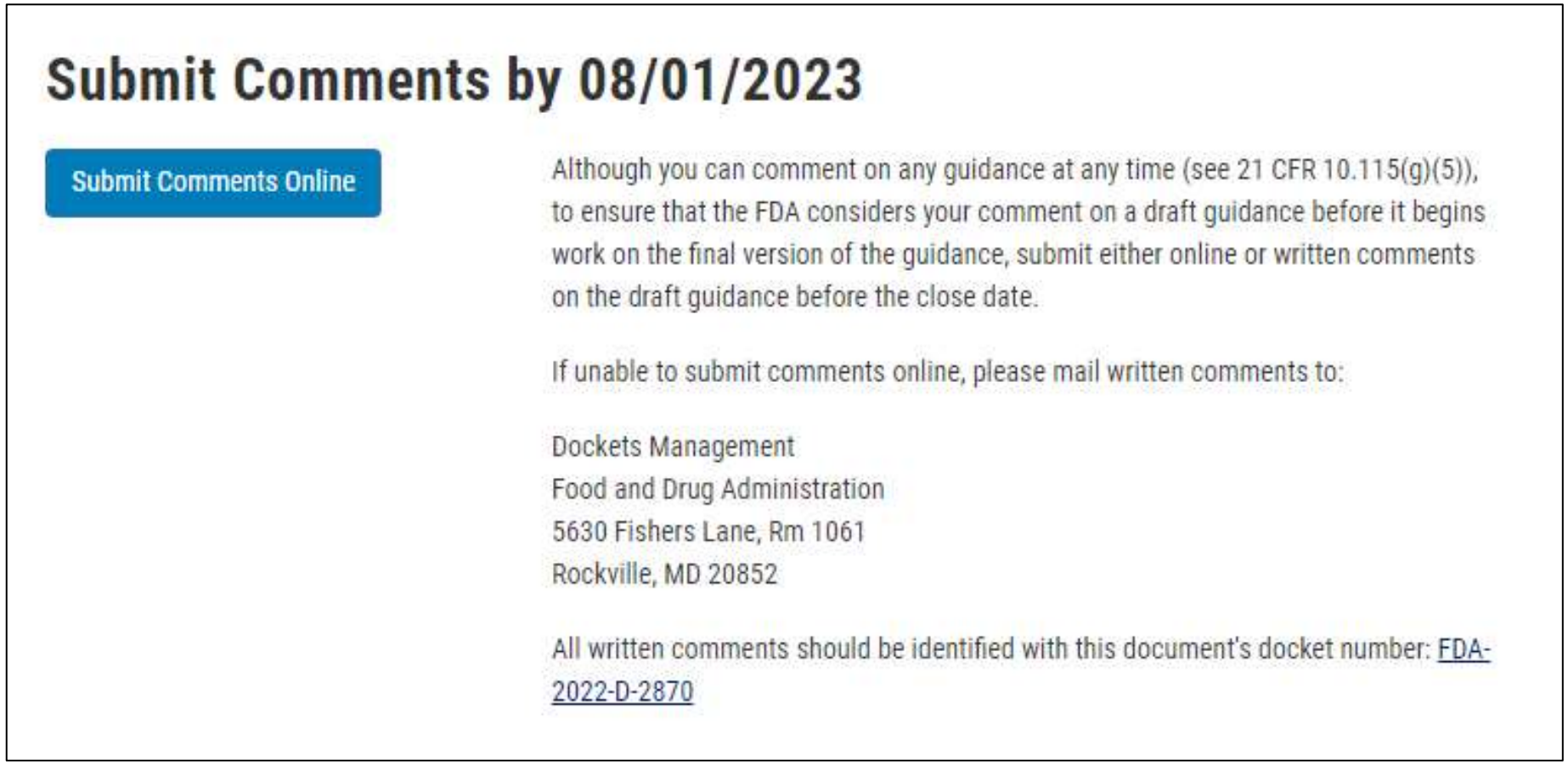
June 20, 2023
3:00 pm - 4:00 pm
(Eastern - UTC-4)

View Day One Start Time on World Clock

This workshop is FREE

Visit FDA CDER SBIA Webpage for Details

Submit Comments on the DCT Guidance



Submit Comments by 08/01/2023

Submit Comments Online

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the FDA considers your comment on a draft guidance before it begins work on the final version of the guidance, submit either online or written comments on the draft guidance before the close date.

If unable to submit comments online, please mail written comments to:

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

All written comments should be identified with this document's docket number: FDA-2022-D-2870

https://www.regulations.gov/docket/FDA-2022-D-2870

Challenge Question

All local health care providers participating in a clinical trial would need to be listed on Form FDA 1572 (Statement of investigator)

True or False

New Technologies, New Capabilities

- We all recognize the profound impact that new technologies have on our ability to gather clinical data
- Computers that formerly occupied entire buildings are now condensed into our cellphones with extraordinary capacities for data storage and analysis
- Digital health technologies (DHTs) can transmit data from patients wherever they are

What are DHTs?

A digital health technology (DHT) is a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses.

- Examples include, but are not limited to:
  - Portable sensors, such as activity trackers
  - Mobile applications (mobile apps)

Digital Health Technologies

- Access to more frequent or continuous data
- Ability to detect sporadic events (e.g., seizures, arrhythmias, falls)
- Collect patient reported outcomes (e.g., Ecological Momentary Assessments)
- Collect data in the real-world environment (e.g., work, exercise, sleep)
- Collect objective record of functionality

Digital Health Technologies

Biosensors	
Continuous Glucose Monitor	
Continuous ECG Monitor	
Continuous Blood Pressure Monitor	
Fall Detector	
Actigraphy	

Interactive Applications	
Patient Reported Outcome	
Cellphone Camera	
Coordination Test in Parkinson's Disease	

Published Dec 2021

Some DHTs Meet the Definition of a Medical Device, Others Do Not

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

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…

Question: Is premarket clearance or approval required to use a device in a clinical investigation?

Answer: 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 (IDE Regulations)

Other Good Clinical Practice (GCP) Regulations also apply, including those related to Institutional Review Boards and Protection of Human Subjects.

Question: When is an Investigational Device Exemption (IDE) application to FDA required?

Answer: For DHTs that are Devices,

- ***For a Non-Significant Risk Device,*** an IDE application to FDA is generally not required.
- ***For a Significant Risk Device,*** when all information required in an IDE application under 21 CFR 812.20 is also contained in an IND, FDA generally does not expect sponsors to submit a separate IDE for these clinical investigations.
- ***For a Device used in accordance with its authorized intended use,*** an IDE application to FDA is generally not required.

Other Good Clinical Practice (GCP) Regulations also apply, including those related to Institutional Review Boards and Protection of Human Subjects.

Challenge Question

All Digital Health Technologies need to be cleared or approved to be used in a clinical trial.

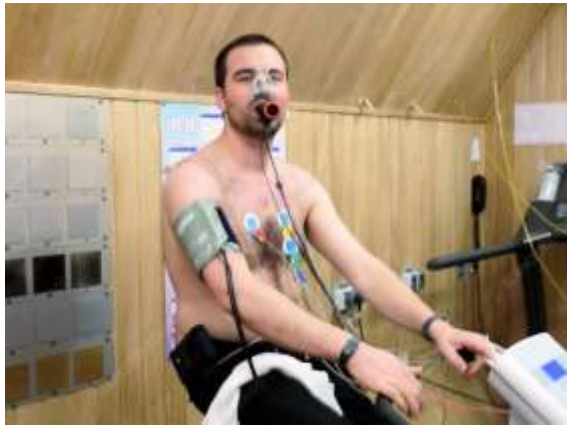
True or False

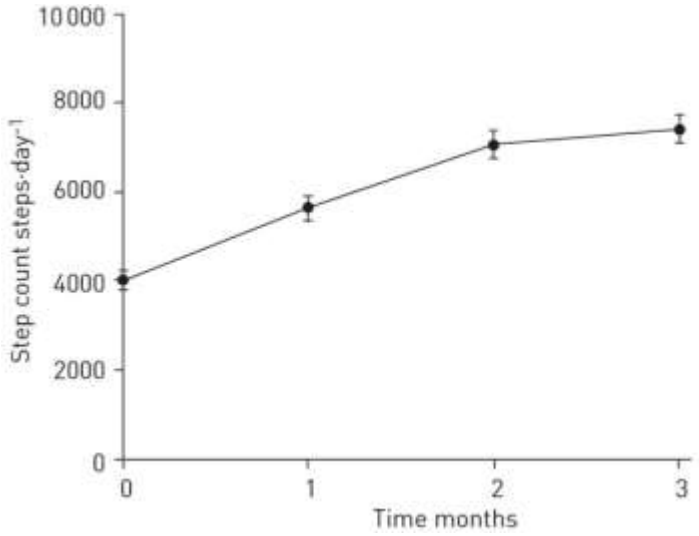
Is the DHT Suitable for Use in the Trial? *(Operational Issues)*

- Comfortable?
- Easy to put on?
- Easy to operate?
- Battery life?
- Syncing data?
- “Bring your own” approach?

Verification and (Analytic) Validation of the DHT Measurement

- This is a technology question to evaluate the DHT
- How accurate and precise is the DHT in measuring the targeted feature (e.g., temperature, steps, sleep)?
- Does the algorithm used to interpret the raw signal reliably represent the clinical characteristic or event we are trying to capture?
- Are the data recorded by the DHT in patients the same as the data we would report if we were looking at the patient? (e.g., steps in a patient with Duchenne's, Parkinson's disease)





Justification of the Endpoint as a Clinically Meaningful Measure of Drug Effect

- This is a clinical question about the feature being measured, regardless of the technology used to make the measurement
- Is the endpoint a clinically meaningful measurement of drug effect?
  - Comparison with existing benchmarks of performance - UPDRS, other patient reported outcomes, 6MWD
  - Input from patients, caregivers, professional societies, disease experts, regulators

Formulating a Meaningful Clinical Endpoint

What is being measured?	Steps
What is the time window of observation?	4 weeks
What is the formula for the response in each patient?	Change from week 1 to week 4 in average daily step count

Further Considerations When Using a DHT 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

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Draft Guidance for Industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* (March 2023)

Importance of DHTs in Drug Development

- DHTs may allow us to modernize the performance of trials, improve trial efficiencies
- Measurement in challenging populations such as neonates or patients with dementia
- They may allow measurement of rare events which were difficult to capture such as arrhythmias, seizures, apneic spells
- Measure new clinical characteristics such as stamina, gait stability, tremor
- They may provide more convenient and/or precise ways to measure existing features such as sleep, exercise, blood pressure

Challenge Question

Justification of an endpoint as clinically meaningful depends on the type of DHT used in a clinical investigation.

True or False

Trials in the Clinical Practice Setting

The opportunity to use existing clinical infrastructure, particularly when supported by interoperable data systems has become an area of increasing interest

Trials in the Clinical Practice Setting

- RECOVERY trial the UK for COVID -19
  - Reportedly recruited 40,000 COVID patients through the NHS in the UK within 6 weeks
  - Were able to show the mortality benefit of steroids in treating patients hospitalized with COVID.
- Practice settings allow engagement large numbers of patients in short periods of time
  - Reflect the effectiveness of treatment in real-world environments
  - Accessibility of clinical trials to patients who wouldn't normally participate

Working Towards a Common Goal

- FDA is committed to modernize clinical trials, incorporate technological and scientific advances and potentially address the enormous costs and burden of drug development
- Interest from Congress, Industry and others in the community to enhance efficiencies in drug development
- Interests of new stakeholders, engineers, and DHT manufacturers in supporting clinical trials
- Patients seeking more convenient ways to participate in the research enterprise

Commitments and Mandates

- Prescription Drug User Fee Act of 2023 VII
  - IV.C. Enhancing use of DHTs to Support Drug Development and Review

- Food and Drug Omnibus Reform Act of 2022 (FDORA)
  - Sec. 3606 Decentralized Clinical Studies
  - Sec. 3607 Modernizing Clinical Trials

PDUFA VII DHT Commitments

IV.C. Enhancing use of DHTs to Support Drug Development and Review

C.1 Develop Framework
C.2 Establish DHT Steering Committee
C.3 Convene 5 public meetings
C.4 Identify 3 demonstration projects
C.5 Develop Guidance
C.6 Develop Prescription Drug User-Related Software (PDURS) Guidance
C.7 Expand review capabilities
C.8 Enhance IT capabilities to review DHT-generated data

https://www.fda.gov/media/151712/download

Published March 2023

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers

Guidance for Industry

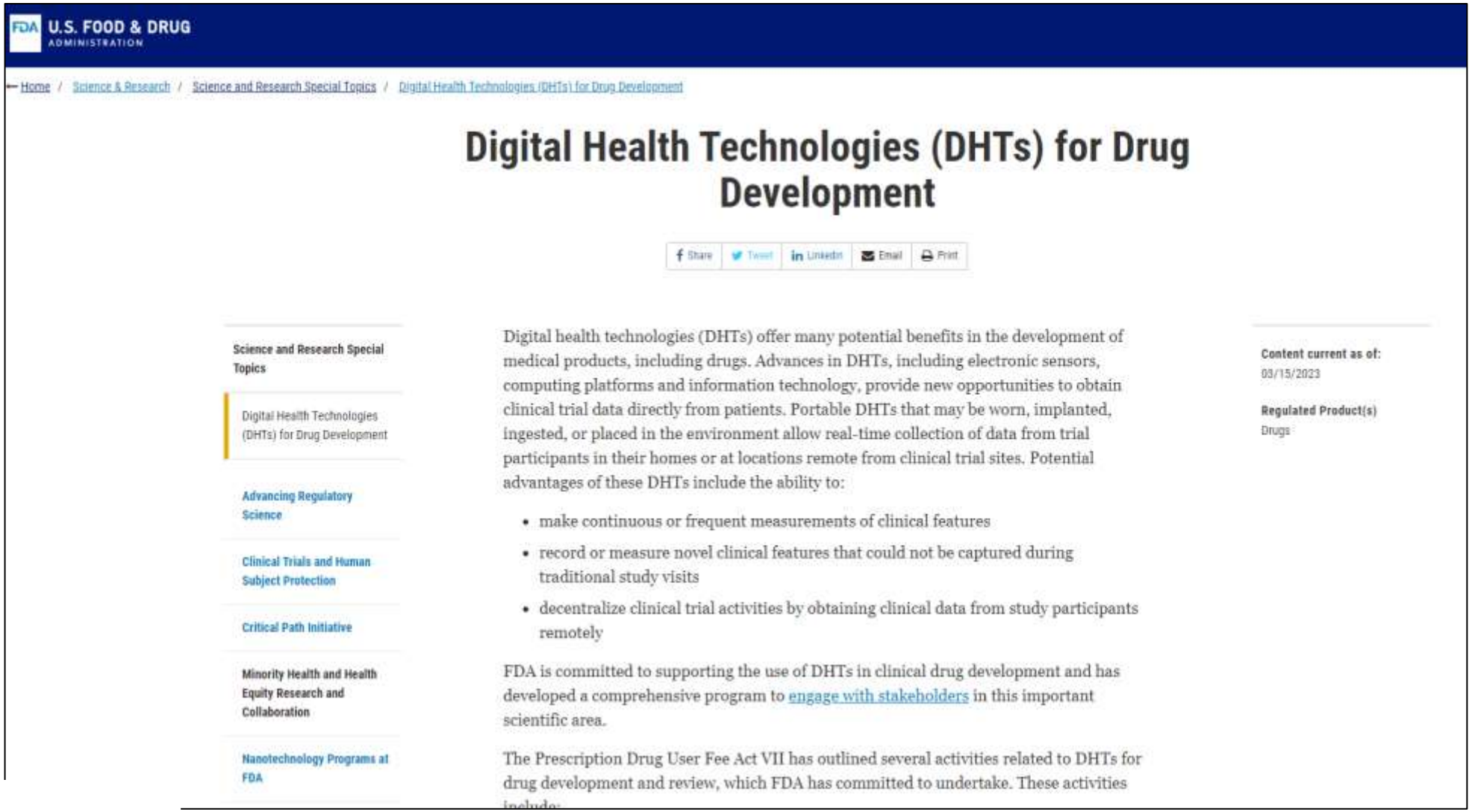
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Published March 16, 2023

Public Workshop

DHTs for Drug Development Webpage



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Digital Health Technologies (DHTs) for Drug Development

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- Digital Health Technologies (DHTs) for Drug Development
- Advancing Regulatory Science
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- Critical Path Initiative
- Minority Health and Health Equity Research and Collaboration
- Nanotechnology Programs at FDA

Digital health technologies (DHTs) offer many potential benefits in the development of medical products, including drugs. Advances in DHTs, including electronic sensors, computing platforms and information technology, provide new opportunities to obtain clinical trial data directly from patients. Portable DHTs that may be worn, implanted, ingested, or placed in the environment allow real-time collection of data from trial participants in their homes or at locations remote from clinical trial sites. Potential advantages of these DHTs include the ability to:

- make continuous or frequent measurements of clinical features
- record or measure novel clinical features that could not be captured during traditional study visits
- decentralize clinical trial activities by obtaining clinical data from study participants remotely

FDA is committed to supporting the use of DHTs in clinical drug development and has developed a comprehensive program to engage with stakeholders in this important scientific area.

The Prescription Drug User Fee Act VII has outlined several activities related to DHTs for drug development and review, which FDA has committed to undertake. These activities include:

Content current as of:
03/15/2023

Regulated Product(s)
Drugs

Tracking Submissions Containing DHT Data Form 1571 and Form 356H

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

12B. Does the submission contain: Digital Health Technology (DHT) data or a proposal to collect DHT data?

☐ Yes ☐ No

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulatio

25. Does the submission contain:

Only Pediatric data?	Digital Health Technology (DHT) data?
☐ Yes ☐ No	☐ Yes ☐ No

Conclusions

Modern clinical trials provide opportunities:

- To improve trial efficiencies, convenience for patients, access to diverse participants, and participants with rare diseases
- To broaden how we conduct clinical trials
- To collaborate with many different stakeholders
- To facilitate drug development

Engaging with the FDA

- Sponsors of applications who are considering the use of DHTs or DCTs for a specific drug development program, should contact the therapeutic review division and request that a representative from the DHT Steering Committee participate in the discussions.
- Sponsors or other stakeholders who are considering the use of DHTs or DCTs not associated with a specific drug development program and would like to discuss general feasibility for their proposed DHT, DCT or have general questions should email DHTsforDrugDevelopment@fda.hhs.gov