Digital Health Technologies
&
Decentralized Clinical Trials

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What is a trial with decentralized elements?

- A trial where some or all of the trial-related activities take place at locations that are convenient for patients and that do not require visits to research sites

Why bother?

- Study visits every six weeks.
- Child must leave school
- Parent must leave work and arrange care for patient's brother
- Organize flights, transport of wheelchair
- Airport transport.
- Hotel accommodation
- Transport to study site.
- Return journey

Duchenne's drug evaluation-6MWD

Can't some, or all of the trial-related activities take place remotely, at the patients' homes or some other convenient location?

Decentralized trial procedures are not new

- Patient diaries
- Interactive Voice Response System
- Telephone follow-up
- Electronic informed consent

Start Date: ___/___/___			1	2	3	4
1. Physical Activity						
No limitation	0	Marked limitation 2				
Slight limitation	1	Unable to carry on any 3				
2. Tiredness						
None	0	Marked amount 2				
Slight amount	1	Severe fatigue 3				
3. Shortness of Breath Sitting						
None	0	Marked amount 2				
Slight amount	1	Severe breathlessness 3				
4. Ankle Swelling						
None	0	Marked amount 2				
Slight amount	1	Severely swollen 3				
5. Body Weight Kg						
6. How many times did you get up last night to urinate? 0, 1, 2, 3, etc.						
7. DRUGS	**Name of drug**	**Dose prescribed**				
No. of doses taken during the past 24 hours						

Use of Electronic Informed Consent Questions and Answers
Guidance for Institutional Review Boards, Investigators, and Sponsors

Why are regulators interested in DCTs?

- 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

Importance for trials in rare diseases

Common disease (Diabetes mellitus trial)

- Number of patients
- Number of sites
- Number of countries participating
- Time to complete study

Rare disease

(Myasthenia gravis trial)

Decentralized clinical trials- a package of strategies to bring the trial to the patient

- Video and telemedicine visits
- Direct distribution of product
- Electronic informed consent
- Home visits, mobile trial units
- Use of local healthcare providers and facilities
- Digital health technologies

Remote trial visits

Investigators can conduct trial visits remotely

Challenges

- Local regulations on telemedicine
- Physical examinations
- Video photography - 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., for infusion reaction

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, pharmacists
- Packing and handling
- Disposal of unused product

Electronic informed consent

- Already in widespread use
- Allows patients to review and sign at home
- May provide videos and graphics to make the process more informative and more easily understood
- Signed consent must be obtained before enrollment

Home visits, mobile trial units

- Novel approach
- Either trial staff or local healthcare providers
- Mobile trial units are being developed
- Extend the physical reach of the trial

Use of local healthcare providers and facilities

- There are resources and qualified healthcare providers in the clinical care environment who may be used in trials
- Delegation of clinical activities to patients' local clinic or healthcare provider for routine procedures- e.g., X ray, clinical examination, laboratory tests)
- Ensuring appropriate qualifications/credentials
- Regular review of data by investigators

U.S. FOOD & DRUG ADMINISTRATION

Digital Health Technologies

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There is a large spectrum of DHTs available for potential use in clinical and home use settings

DHTs can include hardware and/or software to perform one or more functions

Consumer general wellness product (e.g., sleep monitor, basic pedometer)

Electronic patient-reported outcome (ePRO) instrument

Continuous blood glucose monitor

Digital therapy virtual reality device

Electrocardiograph (ECG) software for over-the-counter use

Portable electroencephalogram (EEG)

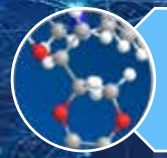
Digital Health Technology (DHT)

"A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses"*

Used as a medical product

Incorporated into a medical product

Used to develop a medical product



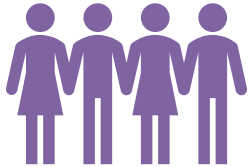
Used to study a medical product

Used as a companion or adjunct to a medical product, including diagnostics and therapeutics

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

DHTs can be used in a variety of ways when evaluating medical products

Remote data collection



Clinical investigation enrichment strategies

Electronic informed consent

Novel types of data that continuous recording by DHTs can provide

Opportunities	Examples
Richer data instead of snapshots	Average steps per day versus 6 Minute Walk Distance (*Duchenne Muscular Dystrophy*) Continuous glucose monitoring versus HBA1C (*Rabson-Mendenall Syndrome*)
Ability to detect intermittent events	Abnormal heart rhythms (*Long QT Syndrome*), seizures (*Dravet Syndrome*), apneic spells
Data from patients who cannot report	Patients with "locked in syndrome" (*ALS*), sleep in patients with dementia, scratching in infants with atopic dermatitis
Dose response information	On/off effects in Parkinson's
New types of measurement	Accelerometer measurements of gait stability that may predict falls (*Duchenne Muscular Dystrophy*) Measurements of coughing, sneezing, tremor Behavior patterns in dementia or depression

DHTs can transform how we study and use medical products

Enable Remote Data Collection in Decentralized Clinical Investigation

- More frequent or continuous monitoring compared to traditional methods
- Longitudinal view of participant's health status
- Improved recruitment and retention of participants leading to less missing data

Improve Access to Clinical Investigations

- Meet a participant where they are at for a clinical investigation
- Fewer visits to a study site places less burden on participants
- Reach a more diverse population, advancing health equity

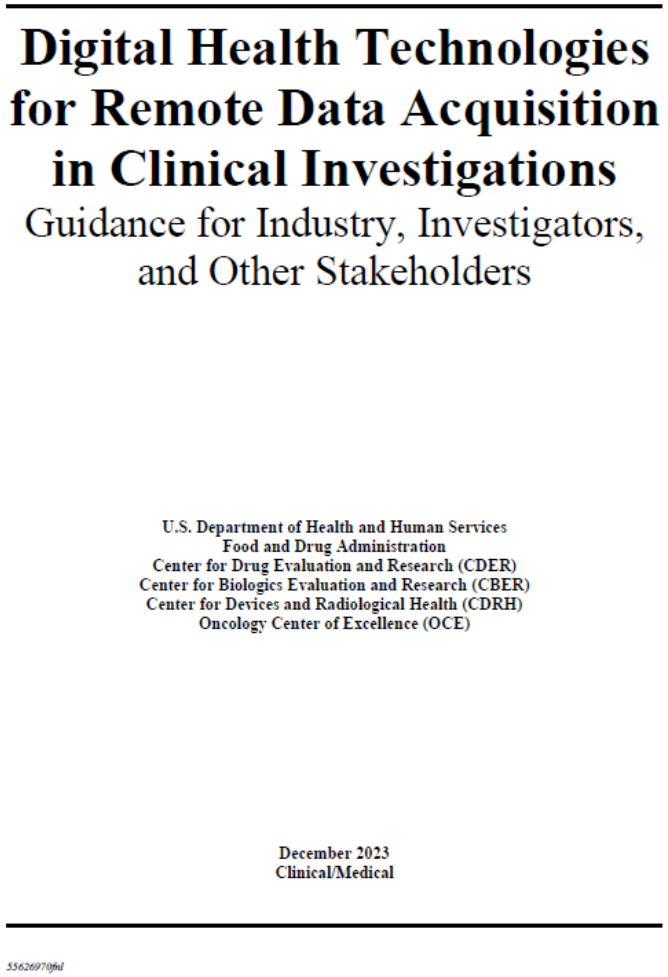
Facilitate Innovative Clinical Investigation Endpoints

- New types of data to inform novel endpoints
- Complementary to other forms of data used to support a regulatory submission

Capture Real-World Data (RWD) and Patient-Generated Health Data (PGHD)

- Data reflects a participant's daily life
- Remote and longitudinal follow-up with participants beyond the clinical investigation
- More detailed picture of the impact of a medical product on a participant
- Potential to capture infrequent clinical events (e.g., arrhythmia, apnea)

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



Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

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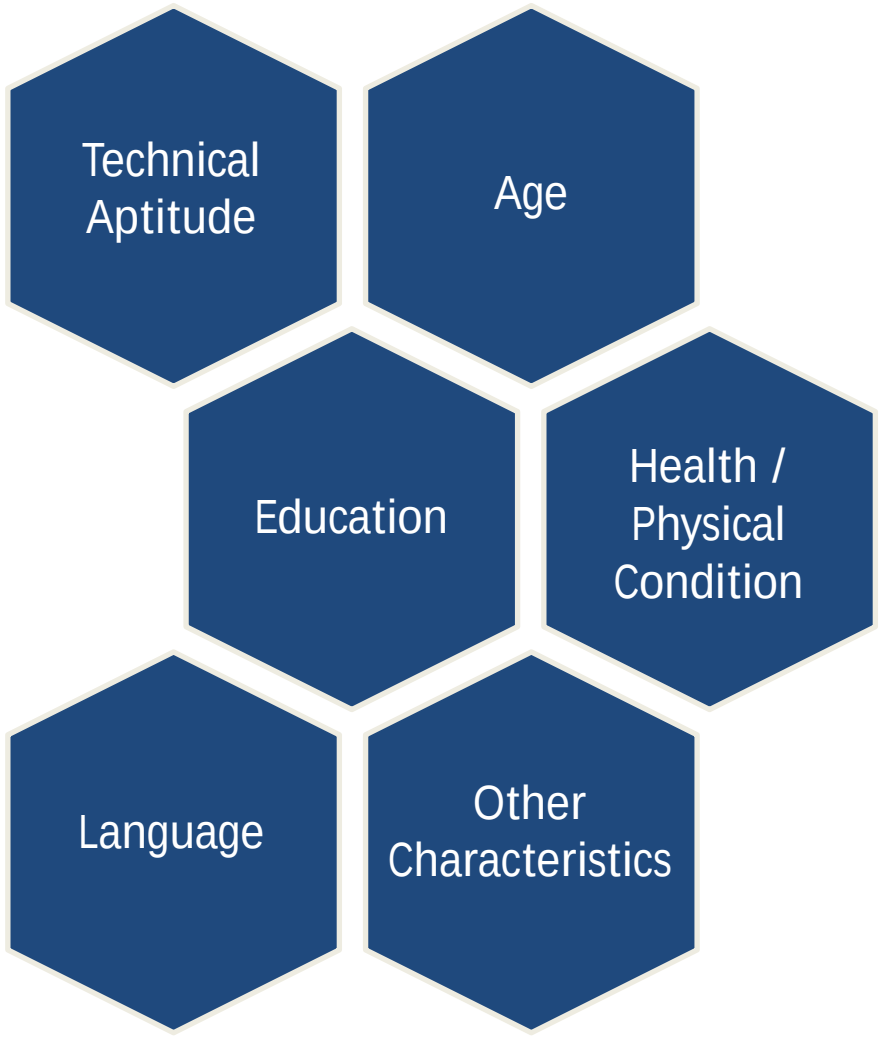
- This guidance provides recommendations to facilitate the use of DHTs in clinical investigations
- It is designed to help accelerate efficient medical product development to help bring new innovations and advances to patients
- It builds on the launch of the Digital Health Center of Excellence to empower digital health stakeholders and provide regulatory clarity and collaboration across FDA

When selecting a DHT, consider the proposed population who will be using the DHT

Also consider the impact using a DHT may have on cohort



Is the DHT suitable for use in the trial?
(Operational issues)

- Bulky or elegant?
- Easy to put on?
- Easy to operate?
- Comfortable to wear for the required time period?
- Battery life?
- Syncing data?
- “Bring your own” devices?

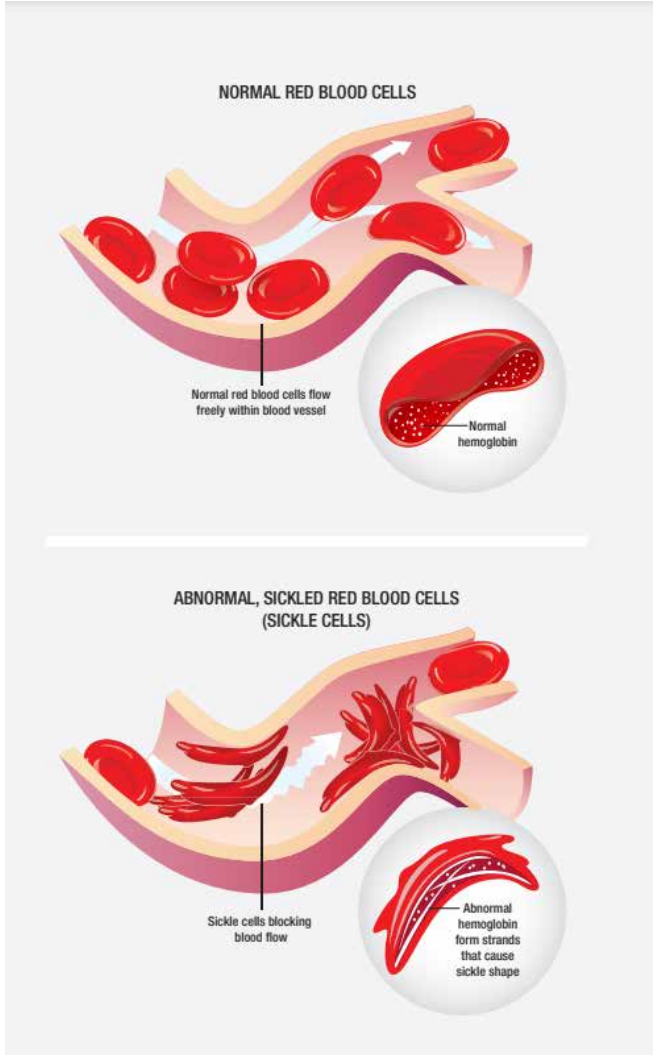
DHT Fit for Purpose

- Verification and validation are technological assessments. They address how well the **technology** measures the performance and clinical feature of interest.

- Justification of an endpoint (or a clinical outcome assessment) is a clinical issue. It addresses how well the **clinical feature** of interest represents a meaningful response to treatment

Example of DHT use in a clinical trial - SCD

- Sickle cell disease (SCD)
  - An inherited red blood cell disorder affecting ~ 100,000 people in the US
    - Mainly affects African American or Black individuals
    - Sickle-shaped RBCs get stuck in small blood vessels and die early
      - "Pain Crisis"
      - Acute chest syndrome
      - infections
      - stroke



https://www.nhlbi.nih.gov/health/sickle-cell-disease

Example of DHT use in a clinical trial - SCD

- Daily electronic diary reporting sickle cell pain crisis, worst pain, worst fatigue, ability to perform daily activities for 6 months (SCD electronic patient reported outcome)
  - Sickle cell patients on therapy vs. sickle cell patients not on therapy

https://clinicaltrials.gov/study/NCT05407805

In summary, DHTs can revolutionize the ability to remotely obtain clinically relevant information from diverse individuals

Potential for continuous or more frequent data collection

Opportunities to record data directly from trial participants wherever the participants may be

Can facilitate the direct collection of information from participants who are unable to report their experiences