



U.S. FOOD & DRUG
ADMINISTRATION



Innovative approaches to clinical trials

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Why bother?



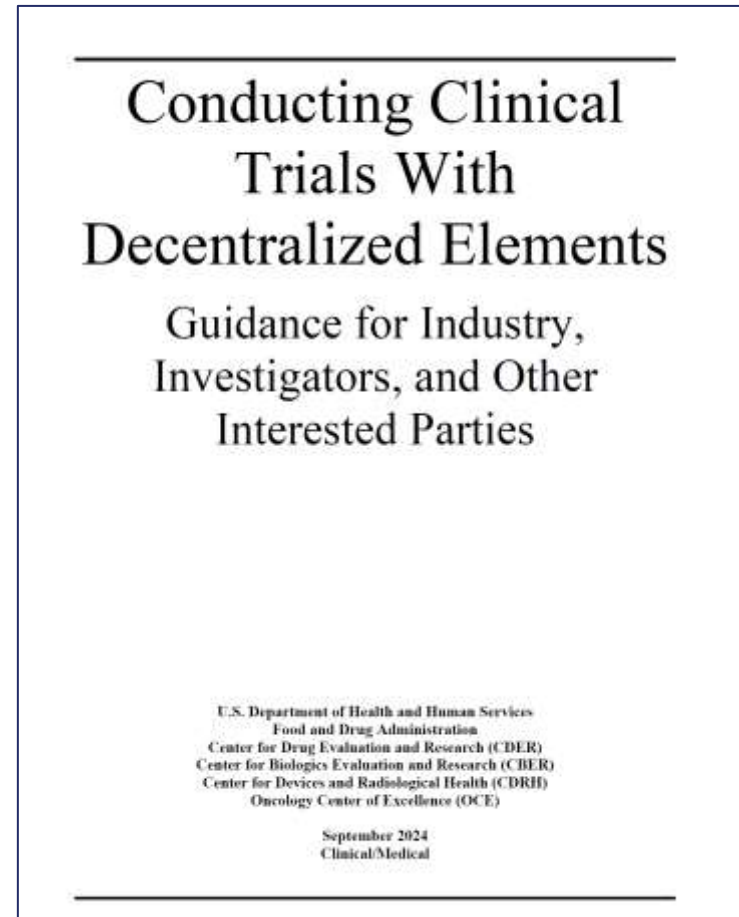
Technology-enabled clinical trials offer new opportunities

- ▶ Enormous progress
 - communication technologies and telemedicine
 - sharing of healthcare data/images/documents
 - biosensors
- ▶ Opportunities for remote data acquisition in clinical trials are remarkable
 - from trial participants
 - from healthcare providers
 - from clinical care institutions

Clinical Trials with Decentralized Elements



Decentralized elements allow trial-related activities to occur at locations other than traditional clinical trial sites that are convenient for trial participants



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



Decentralized trial procedures are not new



- In outpatient trials, once participants leave the study site, many trial-related activities take place remotely
 - Self administration of investigational product
 - Adverse events- present to local clinic or emergency rooms
 - Patient diaries
 - Interactive Voice Response Systems
 - Telephone follow-up
 - Electronic informed consent 2016

Decentralized clinical trials -a bundle of strategies



Remote telehealth visit with investigator



Digital Health Technology



Electronic informed consent



Home delivery of drug



Local clinic



Local Health Care Provider

Remote trial visits

Investigator can supervise 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

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 routine clinical activities to patient's local clinic or healthcare provider for routine procedures- e.g., X ray, clinical examination, laboratory tests)
- Ensuring appropriate qualifications
- Regular review of data



Home visits

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



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

Investigational Products suitable for DCTs



- The nature of the drug should be considered when determining whether administration outside of a clinical trial site in a DCT is appropriate
 - Complexity of administration
 - Safety profile
 - Stage of drug development
- May be appropriate for local HCPs or trial personnel working remotely to administer the IP at local health care facilities or participants' homes
- Hybrid DCTs may be considered for drugs that require supervised but infrequent administration

Investigator oversight

Investigator oversight

- Oversight of trials-
 - data provide by local health care providers needs to be reviewed on a regular basis by investigators
- Investigators should make sure the data they receive are complete, and consistent with requirements in the protocol
- It is the investigators who will need to decide if
 - a patient's complaint to a local health care provider represents an adverse event
 - if a finding reported by a local healthcare provider represents a study endpoint
 - if a protocol directed change in treatment is necessary
- Patient retention –jury is still out
- Data privacy

Safety Assessments

- Trial participants must be able to contact trial personnel to report adverse events and have pertinent questions answered
- Trial participants should be able to arrange for unscheduled visits using telehealth or an in-person visit, as appropriate
- If significant safety risks emerge because of remote administration or use of an IP, sponsors must discontinue remote administration or use
- If authorized in the protocol, routine safety monitoring involving laboratory testing and imaging may be performed using local clinical laboratory facilities
- Protocols should specify how adverse events identified remotely will be evaluated and managed, and how care will be provided for adverse events that require urgent or in-person attention

Sponsor's Responsibilities

- Sponsor responsibilities are the same for DCTs and traditional site-based clinical trials
- Should strive for diversity and inclusiveness in trial populations
- Must account for multiple sources of data collection in a DCT in the data management plan
- Should describe in the trial protocol how operational aspects of the DCT will be implemented

Other considerations

- Not everything can be accomplished remotely
- Many decentralized trials will end up as hybrids-combinations of remote visits and visits to investigator sites when procedures such as detailed physical exams and other in-person activities are required by the protocol

Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Heather Stone, 301-796-2274, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)
Oncology Center of Excellence (OCE)

September 2024
Real World Data/Real World Evidence (RWD/RWE)



Background

- Medical literature abounds with point-of-care trials, trials with pragmatic elements, large simple trials
- All these rely on integration of clinical research with clinical care
- These approaches have not been significantly adopted for regulatory submissions

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, tocilizumab, and baricitinib in treating patients hospitalized with COVID.
- Practice settings allow engagement of 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

Integrating RCTs into clinical practice



- Goal: to conduct clinical trials where participants get their routine care (sometimes referred to as point-of-care trials)
 - Trial design and activities are streamlined to align with clinical practice
 - Leverage established health care institutions and existing clinical expertise in the medical community to reduce startup times, speed up enrollment and improve accessibility and convenience for patients
 - Real-world data from electronic or other health care records may be used
 - Trial-related activities may be conducted as part of routine practice, with participation of local healthcare providers
 - Dedicated trial staff may participate if needed, to perform activities that require research-specific expertise



Digital Health Technologies

“Digital health technologies (DHTs) are systems that use computing platforms, connectivity, software, and/or sensors for health care and related uses”

In the context of clinical trials, we are interested in DHTs such as wearables, interactive applications, and instruments placed in the patient’s environment that measure clinical features of interest in a clinical trial

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)

December 2023
Clinical/Medical

Duchenne's muscular dystrophy

6-minute walk distance to evaluate drug efficacy

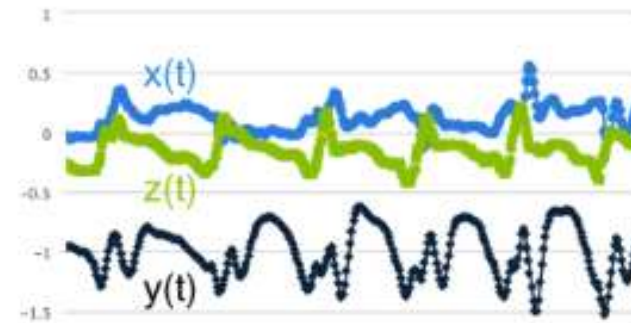


Accelerometer








total acceleration
measured by the phone

$(x(t), y(t), z(t))$



Accelerometers-versatile tools for Duchenne's and many other diseases

- ▶ Accelerometers are used all over- present in cellphones, smart watches, fit bits.
- ▶ Triaxial accelerometers give a good 3-dimensional picture of movement.
- ▶ They can be very helpful in measuring steps or other activities take by a Duchenne's patient, no need to depend on snapshot measurements and clumsy tests
- ▶ Measurements can be recorded over long periods of time
- ▶ Baseline comparisons can be made

Transducer	output	Clinical feature to be measured	Data processing	Clinical DHT
Galvanometer	voltage/ current/ impedance	Heart rhythm	Algorithm	
Accelerometer	Voltage/ current/ impedance	Walking, Scratching Sleep Tremor	Algorithm	
Photoelectric cell	Voltage/ current/ impedance	Blood oxygen saturation	Algorithm	
Electrochemical sensor	Voltage/ current/ impedance	Blood glucose	Algorithm/ calibration curves	
Thermocouple	Voltage/ current/ impedance	Temperature	Algorithm	

As far as biosensors go, they measure clinical features



Discrete events

- Steps
- Breaths
- Coughs
- Pulse beats
- Seizures
- Tremor
- FEV1

Continuous readings

- Glucose
- pO_2
- Temperature
- ECG
- Blood pressure

Novel types of data that biosensors can provide



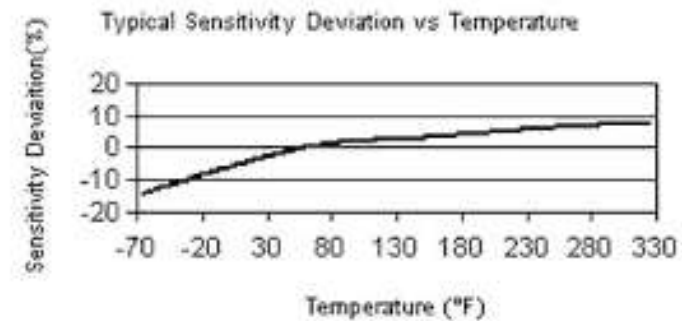
Opportunities	Examples
Rich continuous data instead of snapshots	average steps per day v.s. 6MWD, continuous glucose monitoring v.s. HBA1C
Ability to detect rare events	Falls, arrhythmias, seizures, apneic spells
Data from patients who cannot report	scratching in infants with atopic dermatitis, sleep in patients with dementia
Dose response information	on/off effects in Parkinson's
New types of measurement	gait stability that may predict falls, coughing, sneezing, tremor Behavior patterns in dementia or depression
Early detection of functional abnormalities	coordination, gait, reaction time

Verification-

confirms that the sensor is working as needed



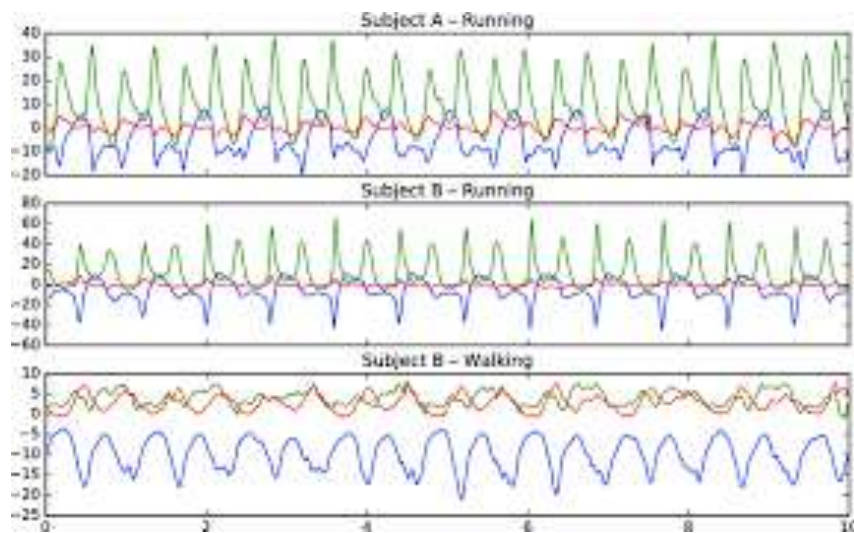
Shake table can confirm the accuracy of accelerometers



Example of Analytical Validation Study- confirms that the interpretative algorithm is working as needed



Raw signal



Ground truth



Interpretive Algorithm

Step count in 5 minutes = 480

Observer report

Step count in 5 minutes = 477

Confounders of the measurement



- Is the result affected by how the patient wears or uses the DHT?
- Are there things that a patient might do that would be misinterpreted by the DHT? (e.g., tapping a foot, riding a bike)

Is the DHT suitable for use in the trial?

(Operational issues)

- Ugly 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?



Interactive DHTs

Patient
reported
outcome on
cellphone



Coordination
test in
Parkinson's



Cellphone
camera to
capture
lesion



Mobile
spirometer



Vision test
on
cellphone



Portable fixed
dynamometer
to measure
muscle
strength



Measurement tool versus clinical endpoint



Important to distinguish between the instrument used to measure a clinical feature, and the clinical feature used to evaluate the effect of a drug

- **Verification and Validation** are technological assessments. They address how well the **technology** measures the clinical feature of interest.
- **Justification of an endpoint** (or a clinical outcome assessment) is a clinical issue. It addresses whether the **clinical feature** is a meaningful way to assess the response to treatment (nothing to do with the DHT).



EMA qualified 95th centile of stride velocity as primary endpoint in studies in ambulatory Duchenne muscular dystrophy

- ▶ The top 5% fastest strides a patient spontaneously takes in their normal daily environment over a pre-defined time period

Justification of the endpoint as a clinically meaningful measure of drug effect

Formulating the 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

Is the endpoint 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

Summary of endpoints in registrational trials

2015-2020

Biomarker



Clinical endpoint



Type of endpoint	NDAs N=218	Examples of endpoints measured
Chemistry	30%	HBA1c, pregnancy test, GFR
Hematology		Severe neutropenia
Pathology		Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology		Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	22%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	7%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	22%	Death, hospitalization, MACE, MS relapse
CRO/PRO	32%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Types of endpoints where Mobile Technology Tools may play a role

- ▶ Clinical laboratory measurements
 - Continuous glucose monitoring, pulse oximetry
- ▶ Physiological measurements
 - Heart rate and rhythm, breathing and lung function, seizures, syncope, temperature, weight, sleep
- ▶ Clinical events
 - Seizures, falls, arrhythmias, apneic spells
- ▶ Performance assays
 - Stamina, strength, coordination, abnormal movements, cognition

Uses for DHTs

- ▶ Enrollment screening and enrichment
 - Help us quantify disease severity, functional status at enrollment
- ▶ Safety monitoring
 - Identification of rare AEs, real time access to safety data
- ▶ Dose effect
 - Visualize response over dosing interval
- ▶ Endpoints
 - Most compelling in superiority studies. Non-inferiority studies may be challenging to interpret

Regulatory position

- ▶ DHTs used in clinical trials generally do not need to be approved/cleared by FDA for marketing unless they are medical devices
- ▶ Regulatory standard: Are the qualities of the data from a DHT adequate to provide substantial evidence of effectiveness?
- ▶ Are the data attributable to the patient, are there processes in place to ensure data integrity, data security in transit and during storage

* [Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers | FDA](#)

Conclusions

- Electronic technology provides many new opportunities to exchange information, obtain clinical data remotely, and make improved clinical measurements
- Interoperative electronic systems will support integration of clinical care and clinical research
- These advances will play an increasing role in improving trial efficiencies, convenience for patients and access for diverse participants including those with rare diseases

Contacting FDA

- If you are considering an innovative trial design for a drug-specific application, you should contact the relevant review division for a pre-IND meeting
- For engagement on **DHTs** or **decentralized clinical trial designs** that are not related to a specific drug development program, you can contact us at DHTSfordrugdevelopment@FDA.hhs.gov and we will determine the best forum to address this.

Questions

- All Digital Health Technologies for use in clinical trials need to be cleared/approved by FDA. True/False?
- Justification of an endpoint as clinically meaningful depends on the DHT used. True/False?
- Trial complexity is not a concern when trials are integrated into clinical practice True/False?

