Digital health technologies and Decentralized clinical trials

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Digital health technology (DHT)

- A system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses

- All sorts of small or mobile instruments that make clinical measurements and/or acquire clinical data directly from patients
  - Sensors: wearable, ingestible, environmental, portable devices
    - glucose monitors, accelerometers, wearable cardiac monitors, pulse oximeters
  - Cameras and video recorders
  - Interactive apps
  - Electronic patient reporting platforms

Advantages and Challenges when using DHTs in Clinical Trials

Advantages

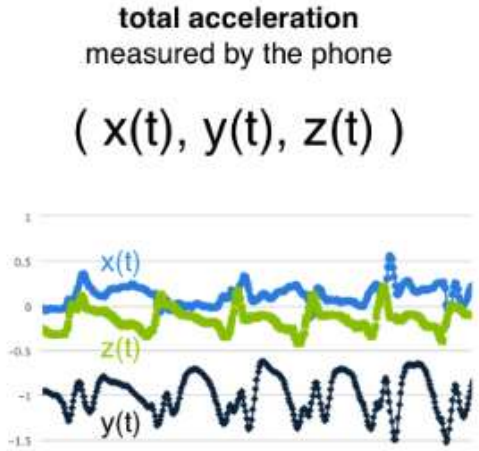
- Patients can be monitored from the comfort of their homes
- Quantifiable, objective measurements can be made
- Measurements can be made at any time of the day- not just during an office visit
- Continuous measurements may provide richer data than “snapshot” measurements
- Potential to capture rare events

Challenges

- Necessary to ensure the accuracy, precision and reproducibility of measurements
- Usability of DHTs is critical
- Data privacy and security must be ensured

Duchenne's drug evaluation-6MWD

Accelerometer



What do we need to know?

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.
  - usually bench testing to define performance specifications

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
  - clinical studies to confirm that the DHT measures the physiological characteristic or event accurately and precisely (e.g., steps, sleep, arrhythmia, tremor)

Justification of endpoints

- evidence to support the timing and nature of the endpoint as a clinically meaningful measurement of drug/device effect

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

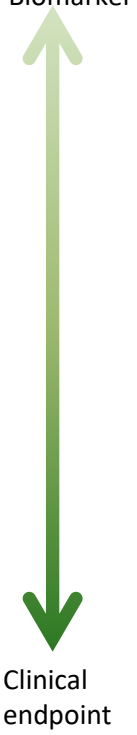
- The endpoint is a clinical observation (nothing to do with the DHT which is just a way to measure it)

- 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 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

Endpoints in registrational trials 2007-2015



Type of endpoint	NDAs N=280	Examples of endpoints measured
Chemistry	25%	HBA1c, pregnancy test, GFR
Hematology		Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
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)	17%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	9%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	19%	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	30%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Do all DHTs need to be cleared/approved by CDRH before use in a trial?

- DHTs not meeting the regulatory definition of a medical device do not require clearance/approval by CDRH

- DHTs meeting the definition of medical devices, but 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

- **A device is defined 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…*

Opportunities for interaction with FDA

CDER's Drug Development Tool Qualification Program and CDRH's Medical Device Development Tool Qualification Programs:

- DHTs may be used in different clinical investigations where the conditions of use are the same. Procedures for submitting DHTs to these programs are available on FDA's website.

DHTs not associated with specific drug –development programs may be discussed with FDA at a Critical Path Innovation Meeting

DHTs to be used in specific drug-development programs should be discussed early with review divisions

Regulatory references

- *CDER's Drug Development Tools Qualification Program* :https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm.
- *CDRH's Medical Device Development Tools Qualification Progra:* https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/.
- *Drug Development Tool Submissions Process* available at https://www.fda.gov/drugs/drug-development-tool-qualification-programs/drug-development-tool-submissions-process.
- *How to Participate in the MDDT Program* available at https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt#How_to_Participate_in_the_MDDT_Program.

Decentralized clinical trials

Source: Duchenne Foundation Australia

Can we do trials where some or all of the trial-related activities take place at locations remote from the investigator?

Why the interest in DCTs?

- Patient convenience
- Improved recruitment of patients with limited mobility
- Ability to study patients in widespread locations
- “Real world” data from patient’s environment
- Continuous data rather than snapshots
- Capturing rare events

Remote data acquisition and decentralized clinical trials

- Hybrid trials- where some activities take place at a trial site and others at the patient's home
- Some Concerns
  - Oversight of trials
  - Patient safety
  - Patient retention
  - Data privacy

Decentralized trial activities- what's new?

A package of practical solutions, supported by the best technology to allow us to get clinical trial data directly from patients in their real-world environment

- telehealth allowing remote visits using video and other interactive technologies
- remote informed consent
- study staff going to patient homes
- use of local healthcare services and providers (Xrays, drawing blood, EKGs)
- shipment of investigational drugs directly to patients' homes,
- use of digital health technologies to get physiological information directly from patients.

Telehealth study visit

- Regularly scheduled visits
- Easy access to study staff
- Reliable communication technology
- Accessible local health services

Electronic informed consent

- Paper-based informed consent involves long documents that are sometimes meaningless to patients. Why can't we show videos and interact electronically with patients?
- Regulations on informed consent (21CFR 50) describe the required content and the necessary documentation:
  - informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent.
- Electronic informed consent can satisfy these regulatory requirements and does not have to be done at a trial site

The opportunities for electronic informed consent are obvious

- Better patient comprehension
- Prompt documentation
- The opportunity for patients to review informed consent programs and sign consent at home with no duress

Oversight*

- Investigator
- Sub-investigator

FDA form 1572

- Local radiologist
- Local health provider
- Phlebotomist
- Visiting nurse

Responsibility log

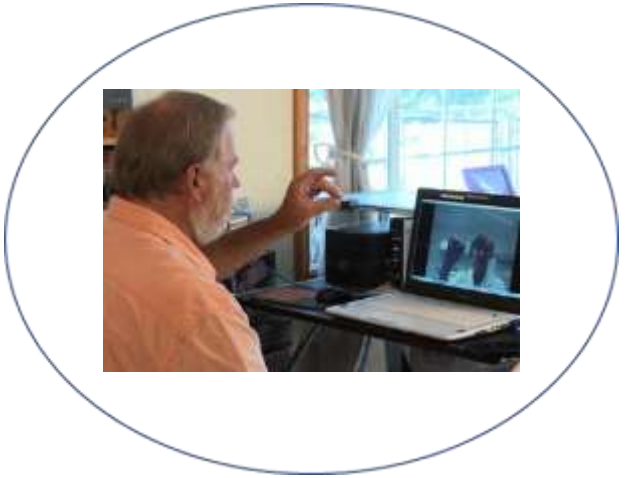
- Local emergency room
- Neighborhood clinic
- Pharmacy

Not part of study staff

*Guidance for industry-Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009

Safety

- High risk products and severe diseases may not be suitable for DCTs
- Patients should be able to contact study staff
- Local medical facilities should be available for urgent care



Inspection

- Investigator
- Sub-investigator

Site inspection
- where the data are
- where study staff can be interviewed

- Local radiologist
- Local health provider
- Phlebotomist
- Visiting nurse

Local inspection
- may be necessary if problems are found

- Local emergency room
- Neighborhood clinic
- Pharmacy

Trials in clinical practice settings

- Clinical practice settings have an infrastructure, equipment and medical staff that may be used in the conduct of clinical trials
- Conducting trials in clinical practice setting where patients receive their medical care may be convenient for participants who have trouble getting to research sites (e.g., elderly, minorities)
- Clinical practice settings may allow us to capture clinical events of interest that are serious enough and clear enough to be identified in routine practice (e.g., stroke, myocardial infarction, fractures)
- Consensus is that such trials will use a mixture of clinical practice and research specific data

This is just the beginning

- My prediction is that clinical trials in 10 years' time will be hard for us to recognize
- Increasingly they will occur at patient homes or at their private doctors. Patients may potentially wear their sensor devices, flash pictures of their lesions from their cellphones, submit patient reported outcomes on their tablet computers, perhaps even receive their study drugs by drone

Summary

- Discuss regulatory framework for using electronic systems
- Discuss the opportunities and challenges using electronic technologies to modernize clinical trials
- Discuss decentralization of clinical trial activities-advantages and concerns

Questions

- Do all DHTs need to be approved/cleared by CDRH before using them in clinical trials?
- Can informed consent be signed by subjects at home?
- List 4 components of a decentralized trial?