Digital Health Technologies
&
Decentralized Clinical Trials

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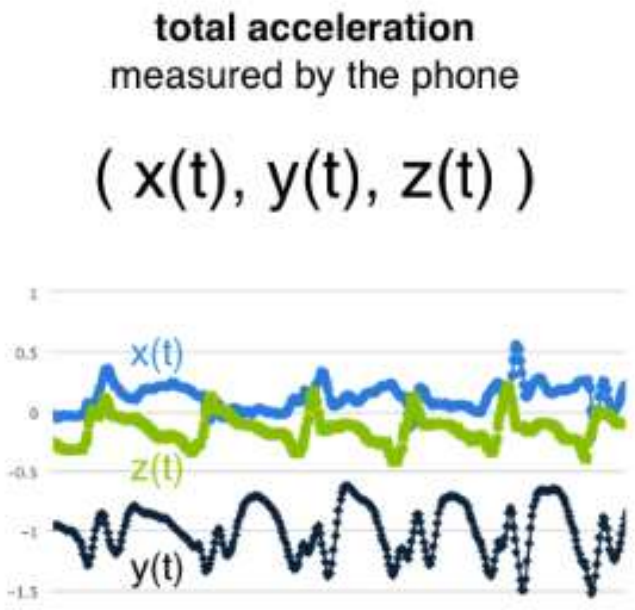
Technology enabled clinical trials

- Significant progress in biosensor and communication technologies
- Opportunities for remote data acquisition are remarkable
- These technologies are playing an ever increasing role in clinical care.
- **Digital Health Technologies** and **electronic communication platforms** can play a role in evaluation medical products

Why bother?

Duchenne’s drug evaluation-6MWD

Accelerometer



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

Measuring functionality

- They capture objective data on **functionality** which has traditionally been challenging in clinical trials
- Useful in neuromuscular and cardiorespiratory diseases, muscular dystrophy, Parkinson's, heart failure, COPD, pulmonary hypertension,
- Potential role in neuropsychiatric diseases, depression, ADHD, schizophrenia

As far as biosensors go, they measure clinical features

Discrete events

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

Continuous readings

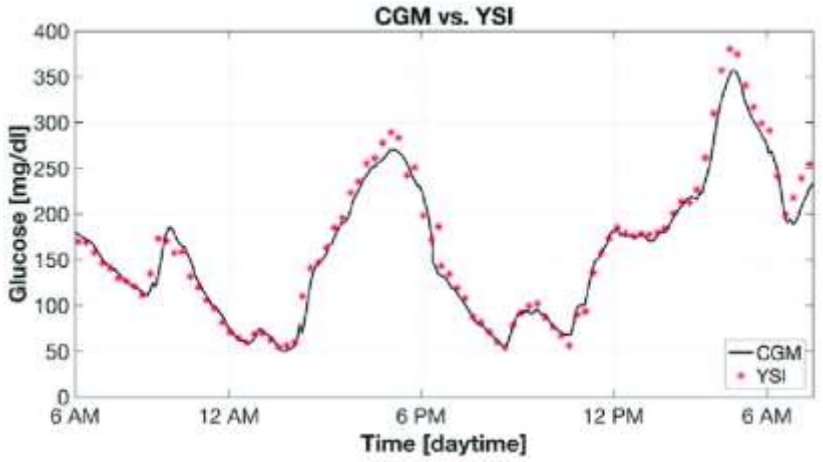
- Glucose
- pO_2
- Temperature
- ECG
- Blood pressure

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	

Discrete events versus continuous measurements

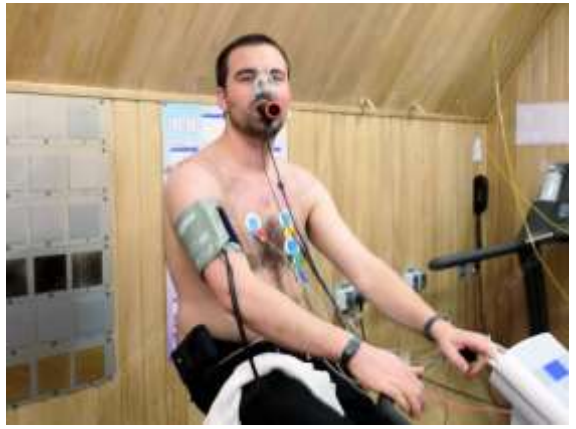
Discrete events

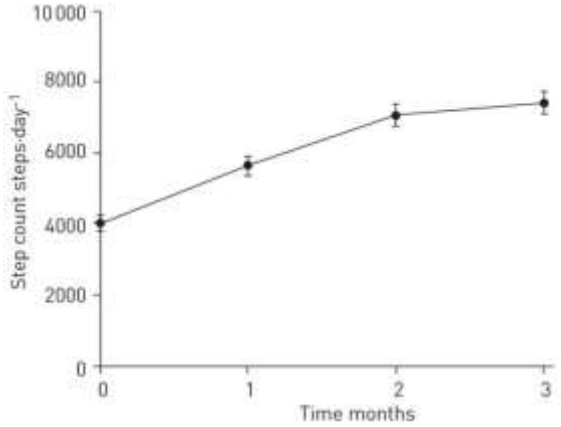
Continuous measurements



Can we rely on the DHT?

- **Verification** in the laboratory
  - How accurate and precise is the DHT in measuring the targeted feature?
  - Is it reliable in different environments- temperature, humidity
  - Does the algorithm used to interpret the raw signal reliably represent the clinical characteristic or event we are trying to capture (e.g. steps, breaths)?





Can we rely on the DHT?

- **Validation** in the field
  - How suitable is the DHT for its intended use?
  - Are the data recorded by the DHT in patients the same as the data we would report if we were looking at the patient? (steps in a patient with Duchenne's, Parkinson's disease,)?
  - 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?

Mobile applications

Patient reported outcome on cellphone

Coordination test in Parkinson's

Cellphone camera to capture lesion

Vision test on cellphone

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

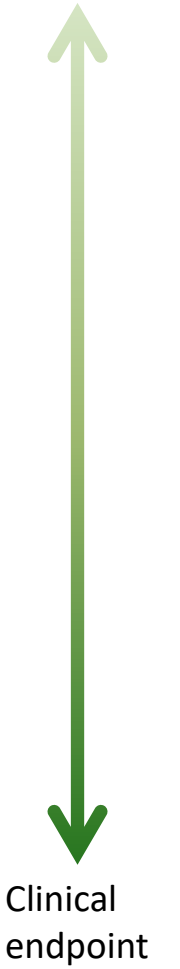
- Is the endpoint clinically meaningful measurement of drug effect?
  - Comparison with existing benchmarks of performance- UPDRS, other Patient reported outcomes, 6MWD
  - Input from patients, caregivers, professional societies, disease experts, regulators

Endpoints versus method of measurement

- Validation and verification 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 how well the **clinical feature** of interest represents a meaningful response to treatment (nothing to do with the DHT).

Summary of endpoints in registrational trials 2015-2020



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
- Performance assays
  - Stamina, strength, coordination, abnormal movements, sleep, cognition

Novel types of data that continuous recording by biosensors can provide

Opportunities	Examples
Richer data instead of snapshots	average steps per day v.s. 6MWD, continuous glucose monitoring v.s. HBA1C
Ability to detect rare events	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	Accelerometer measurements of gait stability that may predict falls Measurements of coughing, sneezing, tremor Behavior patterns in dementia or depression

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

- Regulations do not directly address the use of digital health technologies in clinical trials
- 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

Decentralized clinical trials

Source: Duchenne Foundation Australia

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

- 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
  - Video and telemedicine visits
  - Digital health technologies
  - Direct distribution of product
  - Electronic informed consent
  - Home visits
  - Use of local HCPs 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

Remote data acquisition and decentralized clinical trials

- Some Concerns
  - Oversight of trials
  - Device failure
  - Patient safety
  - Patient retention
  - Data privacy

Decentralized trial procedures are not new

- Patient diaries
- Interactive Voice Response System
- Telephone follow-up
- Electronic informed consent 2016

Use of Electronic Informed Consent

Questions and Answers

Guidance for Institutional Review Boards, Investigators, and Sponsors

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						

Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial

Miguel Orri [a,*,1], Craig H. Lipset [b], Bradly P. Jacobs [c,d], Anthony J. Costello [c], Steven R. Cummings [c,d,e]

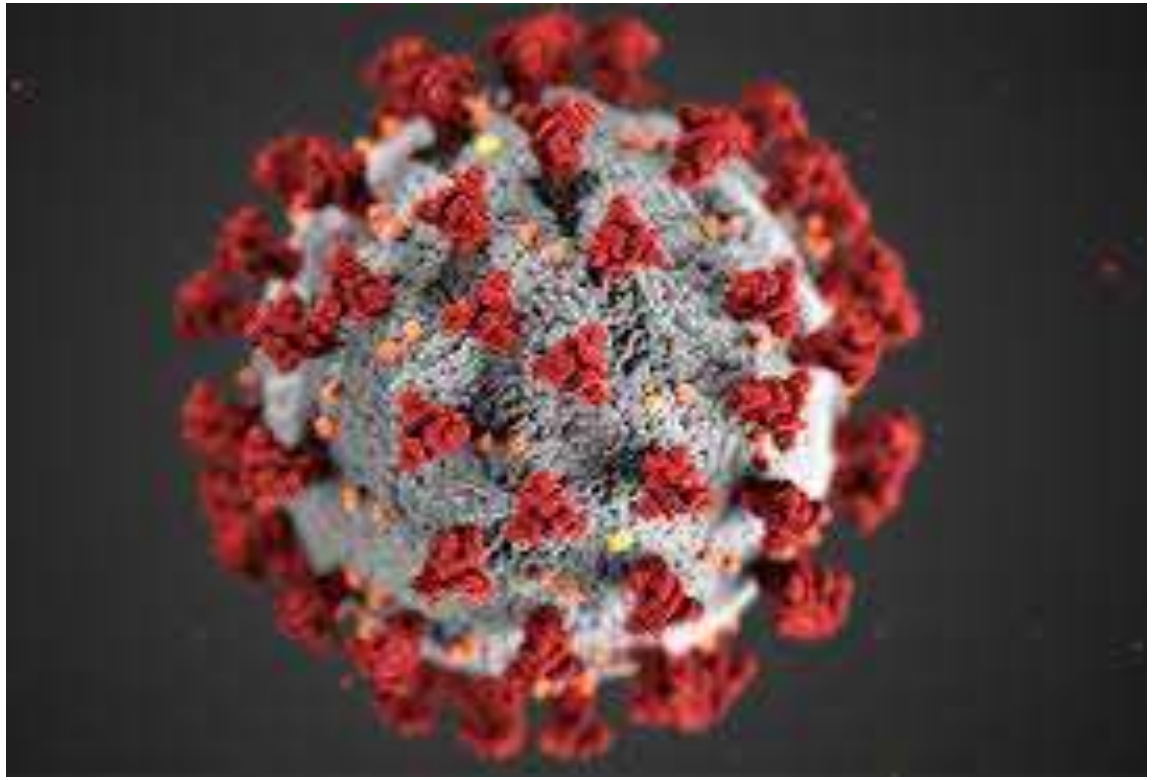
[a] Pfizer Ltd, Tadworth, United Kingdom
[b] Pfizer Inc, New York, NY, USA
[c] University of California-San Francisco, San Francisco, CA, USA
[d] Mytrus, San Francisco, CA, USA
[e] California Pacific Medical Center Research Institute, San Francisco, CA, USA

- First entirely web based trial under IND in 2014
- 5157 patient registered, 456 signed consent, 188 in placebo run in, 18 randomized to treatment
- Electronic informed consent
- Randomized to tolterodine 4mg daily X 12 weeks vs placebo
- Electronic diaries
- Decreased micturition/24 hours:tolterodine -2.4 placebo -0.8
- treatment difference (95% CI): − 1.6 (− 3.9, 0.6)].

Contemporary Clinical Trials
Volume 38, Issue 2, July 2014, Pages 190-197

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



COVID 19 and the decentralization of trials procedures

- The guidance emphasized activities to ensure the safety of participants, including
  - use of remote visits
  - direct mailing of investigational products to patients
  - techniques to obtain informed consent without in person contact- using witnesses and photographs
- Some of the strategies to prevent transmission of COVID 19 may no longer be applicable, but many of the strategies mentioned in the guidance are very important in extending the reach of our trials far beyond the typical demographic into a much more diverse and representative population.

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

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

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
- Task logs allow investigators to keep a record of who is doing what
- Regular review of data

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

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

Digital Health Technologies

- Access to continuous or frequent data
- Ability to detect sporadic events- e.g., seizures, arrhythmias, falls
- Patient reported outcomes “Ecological momentary assessments”
- Real world environment- work, exercise, sleep
- Objective record of functionality
- *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations-guidance for industry*, January 2022

Oversight*

- Investigator
- Sub-investigator

FDA form 1572

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

Task 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

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
- Supervision- local healthcare providers and local facilities
- Records- allowing inspectors to recreate the trial

Trials in the clinical practice setting, point-of-care trials

- 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

Conclusions

- Important opportunity to improve trial efficiencies, convenience for patients, access to diverse participants, rare diseases
- Electronic technology has broadened the scope of decentralized activities

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?
- All local health care providers participating in a clinical trial would need to be listed on Form 1572 (Statement of investigator) True/False?