U.S. FOOD & DRUG ADMINISTRATION

Mobile Technologies – Opportunities and Regulatory Considerations

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Presenter Disclosure Information

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FINANCIAL DISCLOSURE:

No relevant financial relationship exists

The views expressed herein are those of the author and should not be construed as FDA's views or policies

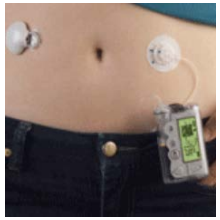
Overview

- **Opportunities for mobile clinical devices with regulated products**
- **Is it fit for use?**
  - What are we trying to measure?
  - Is it suitable for use for the population?
- **Data and Privacy Considerations**

Two big opportunities

- **Electronic data transmission**
  - Patient-centric, data can be transmitted from the patient at home
  - Data can be gathered from geographically dispersed patients, e.g. for rare diseases
  - Potential to reduce loss-to-follow-up
  - Convenience and increased participation

- **Unobtrusive measurement**
  - Sensors can be worn or attached to patient
  - Continuous monitoring (rare events- seizures, arrhythmias)
  - Capture real life situations (stress, sleep, exercise, eating)
  - Objective measurements



Commitments to Evaluate RWE

21st Century Cures

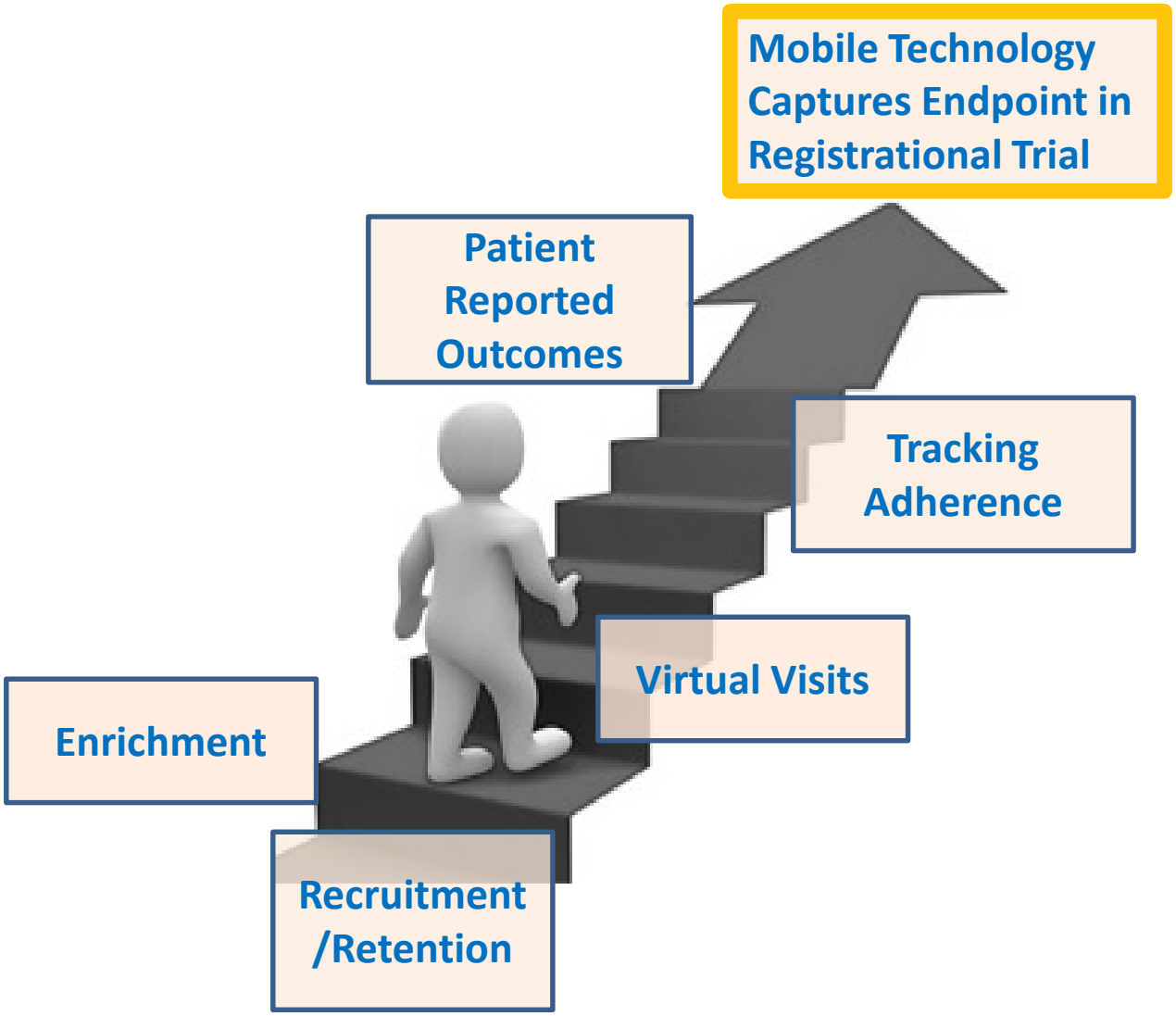
"FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:

- **A new indication for an approved drug**
- **Post-approval study requirements**

- **Real-World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources
- **Real-World Evidence (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

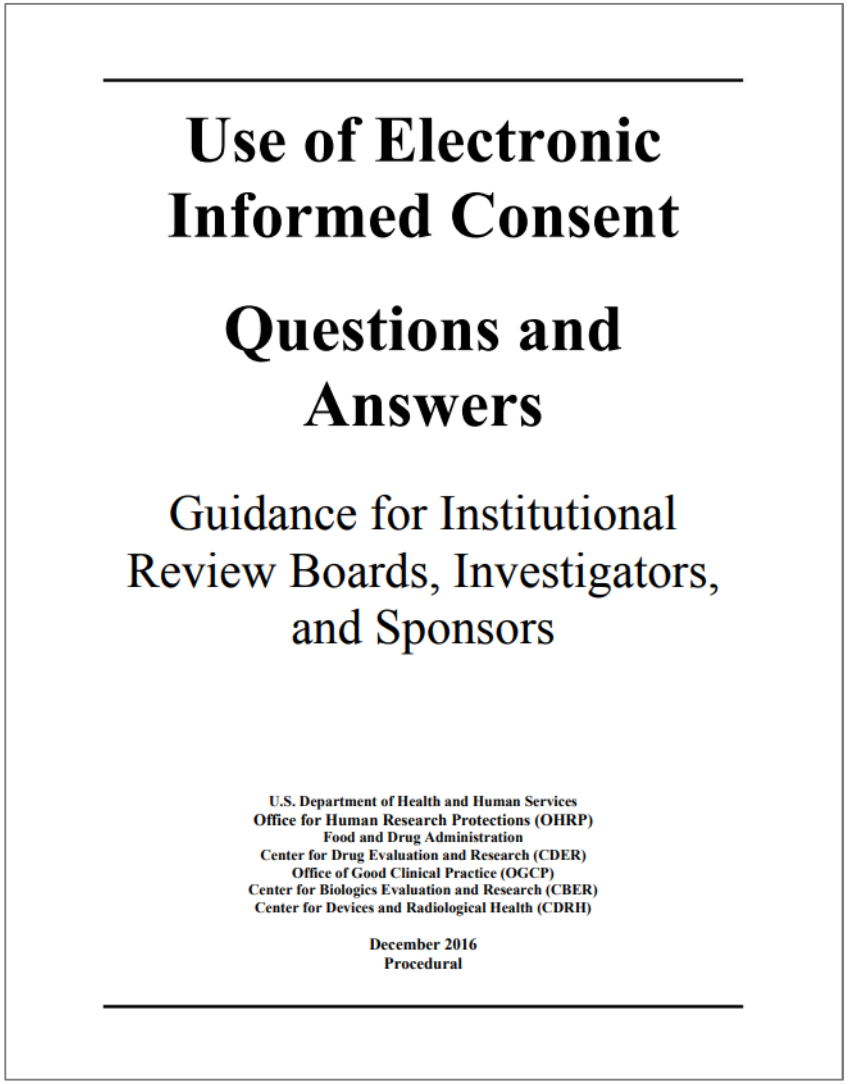
RWD include data derived from *electronic health records* (EHRs), *claims and billing data*, data from product and disease *registries*, AND patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices.

Many Potential Uses



Recruitment

- Can use audio visual presentation
- Can be obtained from patient at home
- Method needed to ensure the person signing the consent is the person in the trial
- Must have a facility to address patient's questions
- Must provide a suitable record to patient
- FDA needs to be able to inspect it.



Use of Electronic Informed Consent

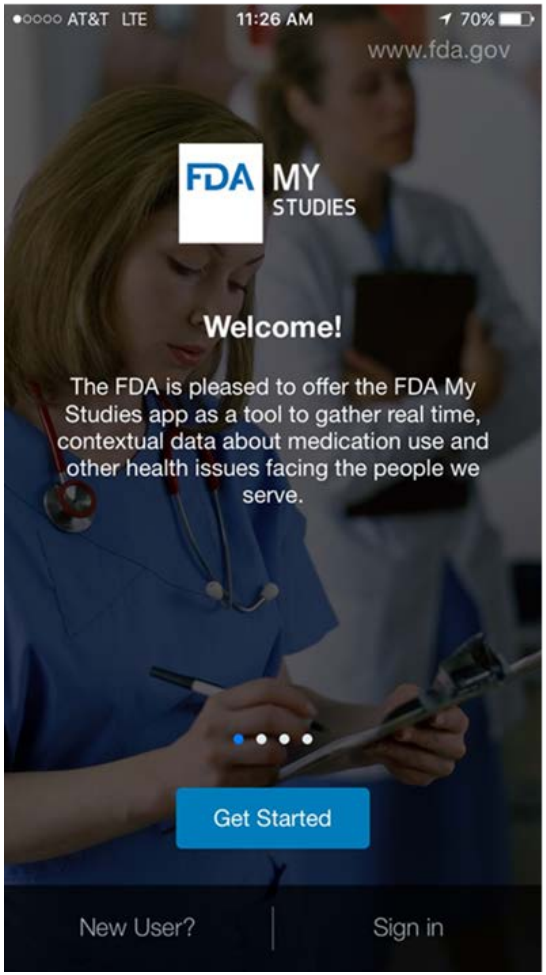
Questions and Answers

Guidance for Institutional Review Boards, Investigators, and Sponsors

U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2016
Procedural

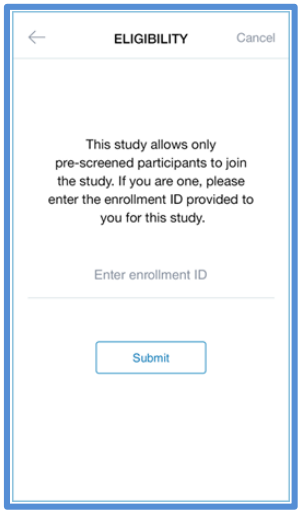
Recruitment

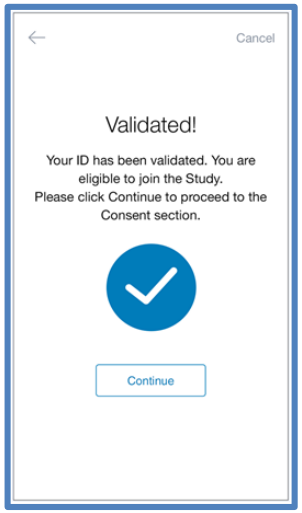


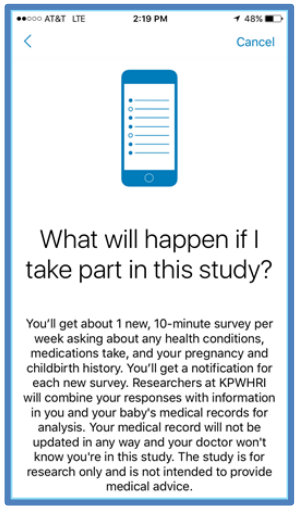
- Mobile App
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
  - Gateway capability
- Web-based configuration portal
- Secure Storage Environment
  - FISMA complaint
  - Partitioned for distributed research
  - Responses can be downloaded in broadly compatible formats (e.g., for use in SAS, Excel, etc.)

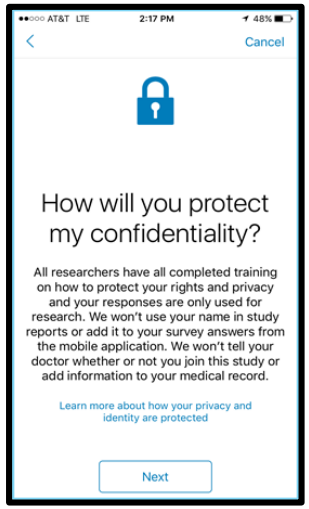
Developed by CAPT David Martin in collaboration with Sentinel

Recruitment and Consent



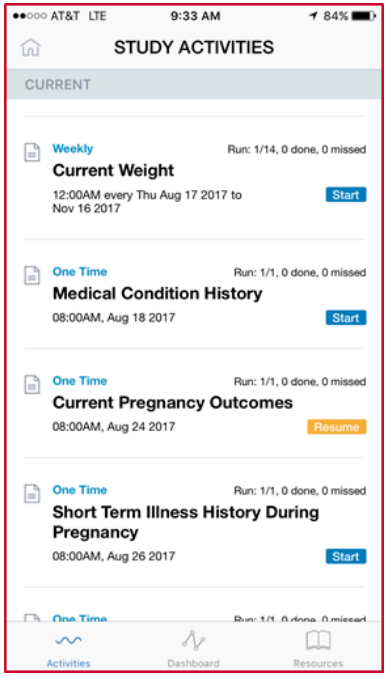


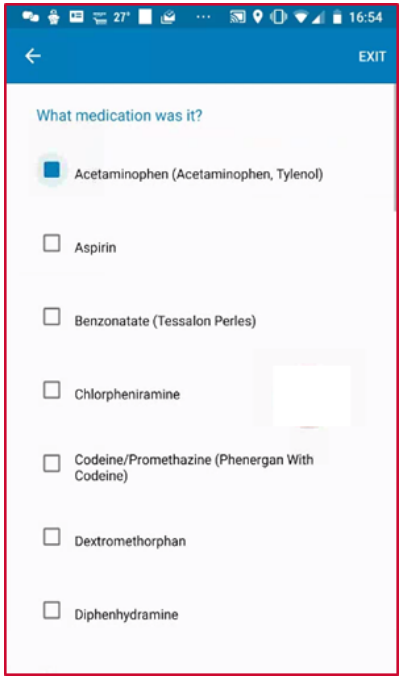


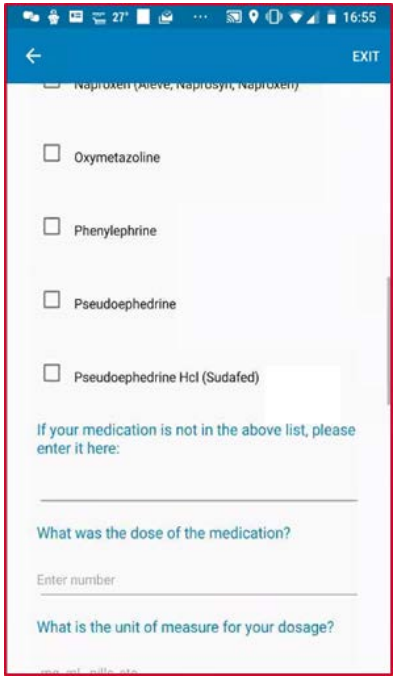


- **Pre-select a cohort from electronic health data**
- **Recruit and distribute enrollment tokens for pre-selected cohorts**
- **Participants download the app from iOS or Android app stores**
- **Participants review eligibility information and provide informed consent through the app**

Engage and Retain

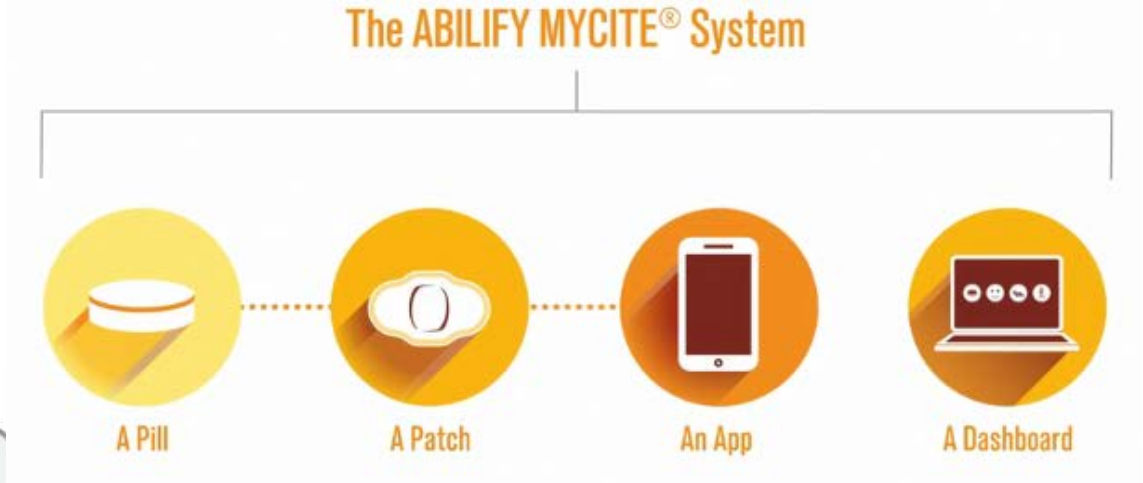


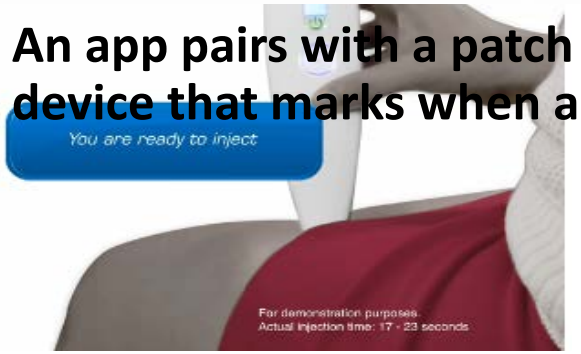




- **Participants respond when they choose within the study schedule**
- **Responses are securely transmitted to the Response Server**

Tracking Adherence





An app pairs with a patch that communicates with a device that marks when a pill has been ingested

MyBETAapp pairs with BETACONNECT autoinjector to record when medication is injected

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

Use of all trial medications or placebo during the double-blind period and of terbutaline during the run-in period was recorded electronically with the use of an inhaler monitor (Turbuhaler usage monitor, Adherium).

- Adherence to the twice-daily, blinded maintenance regimen did not differ significantly across the trial groups

An electronic diary was used to record the morning and evening peak expiratory flow, asthma symptoms, and nighttime awakenings due to asthma, and prompted use of the blinded maintenance inhaler. …….

- [A]pproach avoided retrospective data entry by patients and

may have resulted in a higher rate of reporting of symptoms, awakenings, and reliever use than has occurred in earlier studies in which patients used paper-based diaries

Duchenne's muscular dystrophy and the 6- minute walk test

- Just a snapshot
- Child may be having a bad day, feeling uncooperative
- Test may not capture the clinical benefit in advanced disease
- Is there a more reliable way of measuring drug benefit?

Type of Measurements

Interactive technologies

- Patients actively submit trial data
  - e.g., visual acuity tests, coordination tests, cognitive tests, audiology tests, patient reported outcomes

Electronic monitoring

- Data are obtained automatically by devices without relying on patient interaction.
  - Biosensors and pathophysiological measurement, e.g., accelerometers, fitbits, glucose monitors, EKGs, cellphone cameras

Types of Measurement

- **Use of Biosensors to capture more continuous endpoints**
  - Allows continuous monitoring
    - Is there an impact on behavior when there is continuous monitoring?
  - Reduces missing data
  - Quantifies performance before and during intervention
    - Can be used to enrich population
  - Captures rare or sporadic events
  - May require a plan for addressing clinically significant readings

What are the challenges?

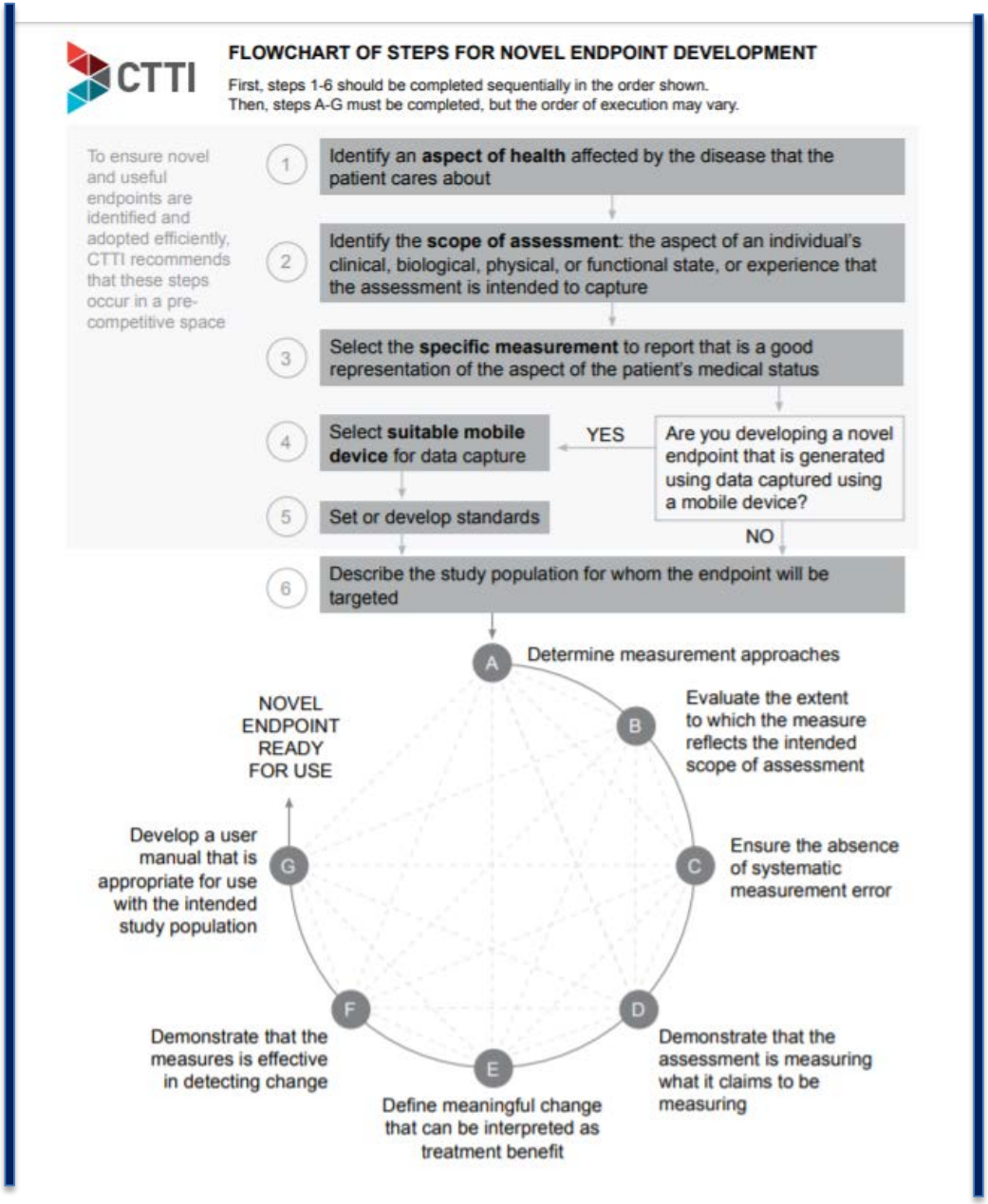
- **Reliability of the measurement**
  - CDRH cleared devices
  - Non-cleared devices-
    - prove the measurement is reliable, reproducible, sensitive, specific
- **Is it measuring the physiologic event of interest?**
- **What is the clinical meaning of the measurement (effect size, nature of the effect, relationship to the drug effect)**
  - Validation against traditional endpoints?
  - What are we measuring?
    - Is a patient with heart failure more active because they can breath better or are they pacing because anxious because can't lay flat and go to sleep

Is the Technology Fit for the Population

- **Age not necessarily a barrier**
  - In a study of use of on-line health care portals, patients in their 60s register for portal accounts at the same rate as those in their 30s, 40s, and 50s. Patients between 70 and 79 use portals at roughly the same rate as twenty-somethings*
- **Use of technology may not limit socioeconomic diversity**
  - Survey of 244 primary care patients regarding use of mHealth applications found 76% used mobile phone to search on health information and 79% surveyed had incomes less than $20,000 (JMIR Mhealth Uhealth 2016 4(2) e41)
- **Physical limitations may be more relevant, e.g. vision, dexterity**
- **For wearable sensors, are they non-intrusive, easy to use?**

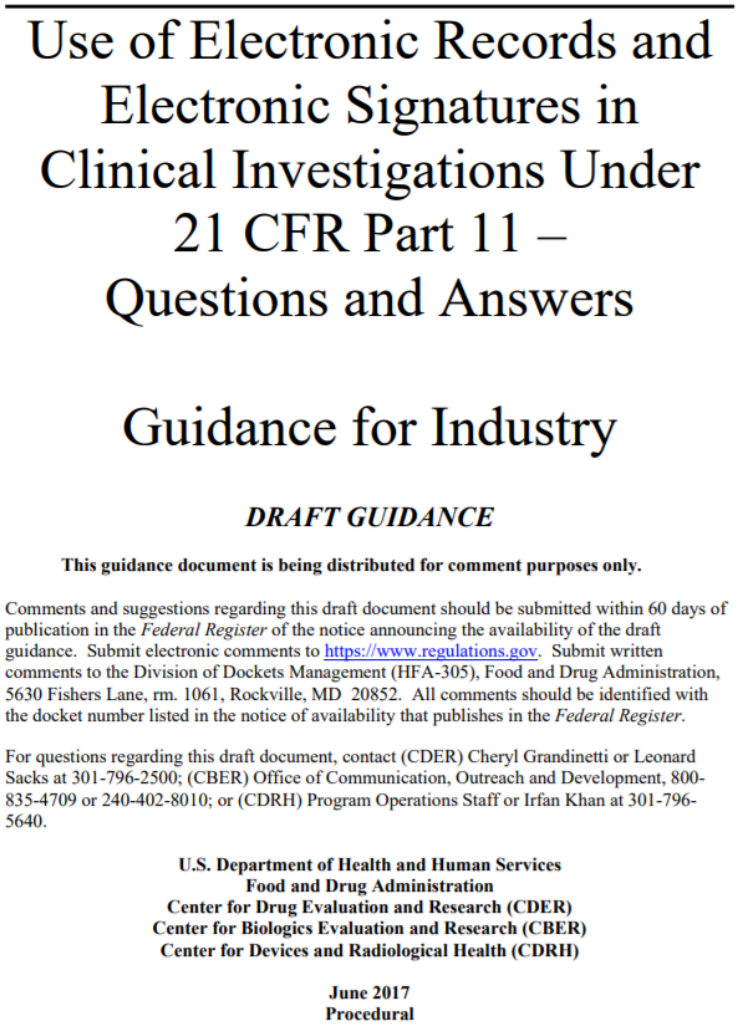
*Using Data to Increase Patient Engagement in Health Care, Harvard Business Rev. June 2015

A Potential Pathway



For regulatory trials engage FDA

Data Security, Privacy and Traceability



Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

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 60 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 Division of Dockets Management (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) Cheryl Grandinetti or Leonard Sacks at 301-796-2500; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff or Irfan Khan at 301-796-5640.

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)

June 2017
Procedural

- Mobile technology do not contain the source data – temporary storage place
- Retainable records is in the first durable database, e.g EDC, clinical investigational site database, EHR
- Data security to prevent access by intervening parties or malicious parties
- Clinical investigators need to have access to the data
  - Available for inspection
  - Meet regulatory requirements for maintaining adequate case histories

Change is good…

With Appropriate Data

Effect of a Home-Based Exercise Intervention of Wearable Technology and Telephone Coaching on Walking Performance in Peripheral Artery Disease
The HONOR Randomized Clinical Trial

JAMA. 2018;319(16):1665-1676. doi:10.1001/jama.2018.3275

Mary M. McDermott, MD; Bonnie Spring, MD; Jeffrey S. Berger, MD; Diane Treat-Jacobson, PhD, RN; Michael S. Conte, MD; Mark A. Creager, MD; Michael H. Criqui, MD, MPH; Luigi Ferrucci, MD, PhD; Heather L. Gornik, MD; Jack M. Guralnik, MD, PhD; Elizabeth A. Hahn, MA; Peter Henke, MD; Melina R. Kibbe, MD; Debra Kohlman-Trighoff, PhD, RN; Lingyu Li, MS; Donald Lloyd-Jones, MD, ScM; Walter McCarthy, MD; Tamar S. Polonsky, MD; Christopher Skelly, MD; Lu Tian, ScD; Lihui Zhao, PhD; Dongxue Zhang, MS; W. Jack Rejeski, PhD

Among patients with PAD, a home-based exercise intervention consisting of a wearable activity monitor and telephone coaching, compared with usual care, did not improve walking performance at 9-month follow-up. These results do not support home-based exercise interventions of wearable devices and telephone counseling without periodic onsite visits to improve walking performance in patients with PAD.

- Wearable measured activity throughout the day but intervention was designed to increase discrete walking episodes
- Frequency of walking exercise reported per day by participants in the intervention arm did not match the activity in the wearable device or the accelerometer reading

Questions/ Comments

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov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What endpoints are amenable to mobile technology assessment

Summary of endpoints in registrational trials from over 600 studies submitted to NDAs -- 2007-2015

Type of endpoint	Studies %	Examples of endpoints measured
Chemistry	**21%**	HBA1c, pregnancy test, GFR
Hematology	**4%**	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	**1%**	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	**9%**	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	**10%**	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	**10%**	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	**13%**	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	**31%**	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score