PDUFAVII Updates: Data and Statistical Considerations when Submitting Analysis Data for DHT-Derived Endpoints

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EU CDISC

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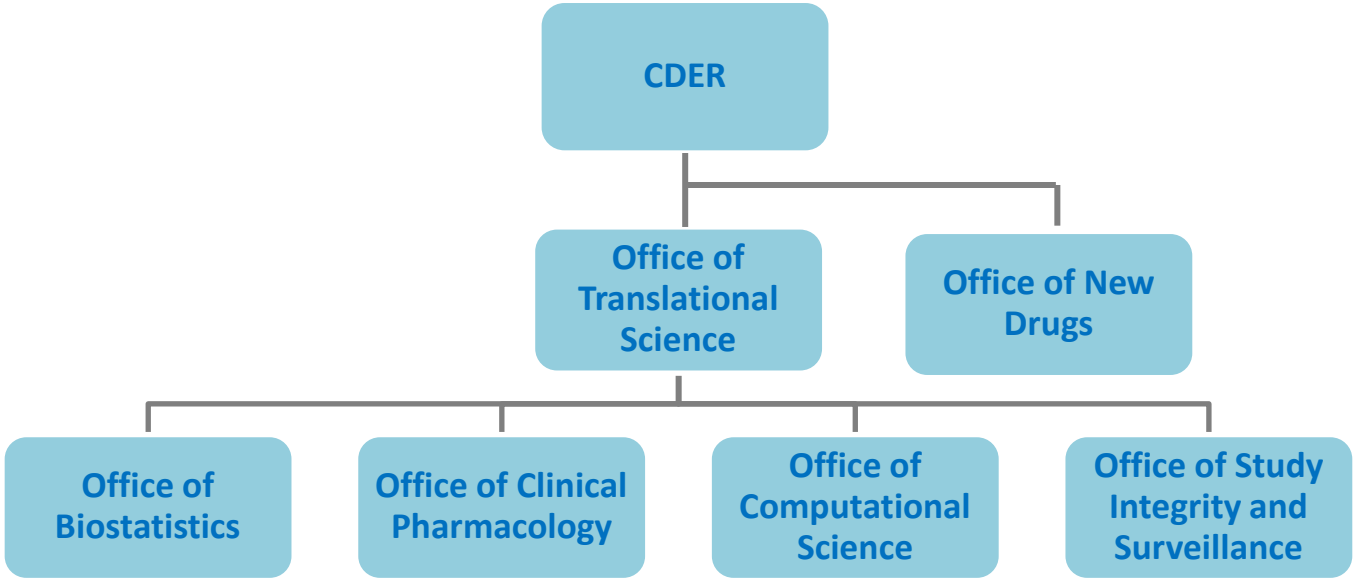
Disclaimer

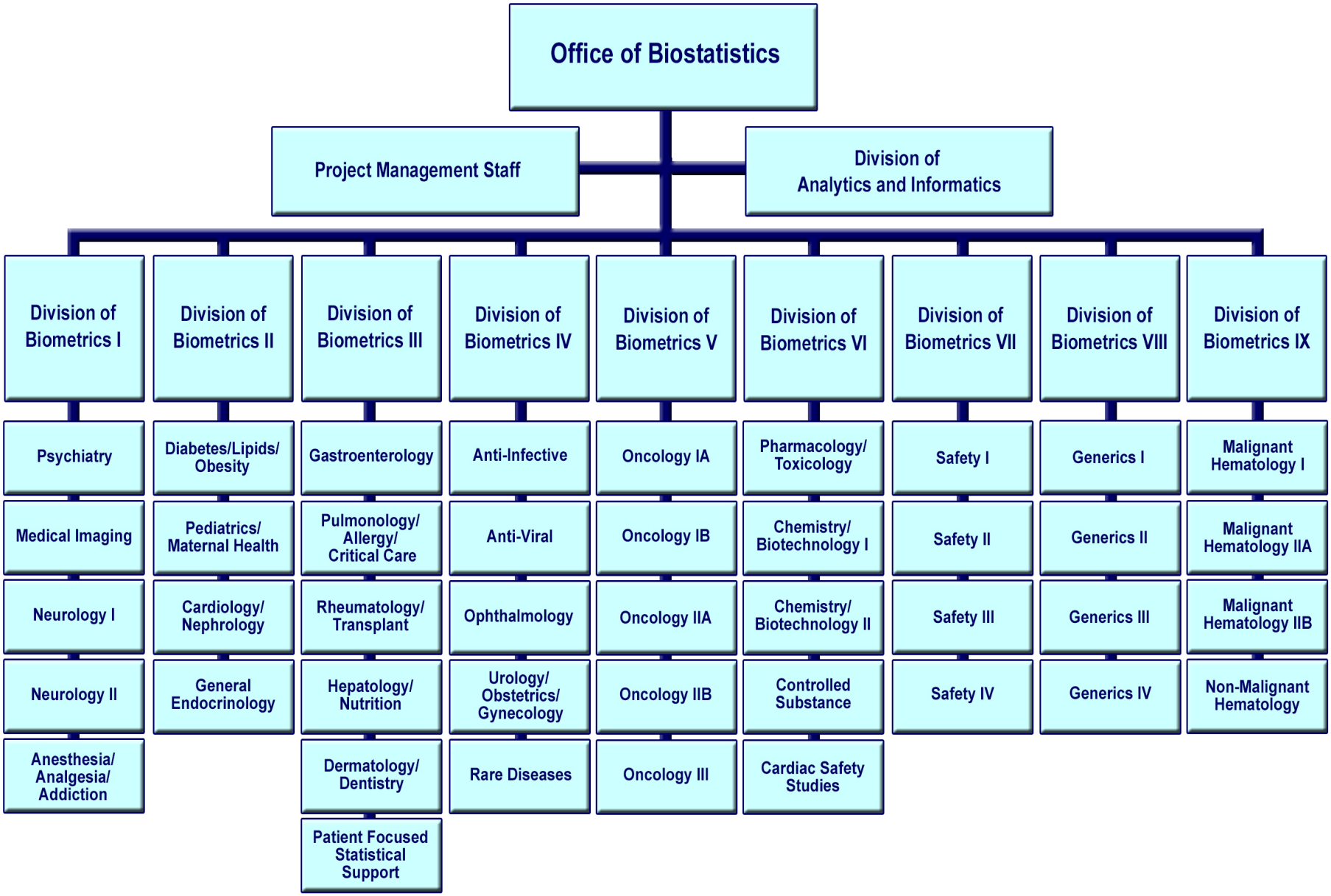
The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Outline

- Office of Biostatistics (OB) Overview
  - Division of Analytics and Informatics (DAI)
- Prescription Drug User Fee Act (PDUFA) VII Overview
- Digital Health Technologies (DHT)
- Summary
- References

Center for Drug Evaluation and Research (CDER) Organizational Chart




Office of Biostatistics
Project Management Staff
Division of Analytics and Informatics
Division of Biometrics I
Division of Biometrics II
Division of Biometrics III
Division of Biometrics IV
Division of Biometrics V
Division of Biometrics VI
Division of Biometrics VII
Division of Biometrics VIII
Division of Biometrics IX
Psychiatry
Medical Imaging
Neurology I
Neurology II
Anesthesia/ Analgesia/ Addiction
Diabetes/Lipids/ Obesity
Pediatrics/ Maternal Health
Cardiology/ Nephrology
General Endocrinology
Gastroenterology
Pulmonology/ Allergy/ Critical Care
Rheumatology/ Transplant
Hepatology/ Nutrition
Dermatology/ Dentistry
Patient Focused Statistical Support
Anti-Infective
Anti-Viral
Ophthalmology
Urology/ Obstetrics/ Gynecology
Rare Diseases
Oncology IA
Oncology IB
Oncology IIA
Oncology IIB
Oncology III
Pharmacology/ Toxicology
Chemistry/ Biotechnology I
Chemistry/ Biotechnology II
Controlled Substance
Cardiac Safety Studies
Safety I
Safety II
Safety III
Safety IV
Generics I
Generics II
Generics III
Generics IV
Malignant Hematology I
Malignant Hematology IIA
Malignant Hematology IIB
Non-Malignant Hematology

Division of Analytics and Informatics

- Works jointly with all 9 Divisions of Biometrics (DB)
- Provides leadership in the areas of:
  - Data Standards
  - Data Integrity and Data Quality
  - Data Visualization and other Data Tools
  - Scientific Computing and Statistical Programming
  - IT Tools Development and Support

Prescription Drug User Fee Act (PDUFA) VII

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027

This document contains the performance goals and procedures for the Prescription Drug User Fee Act (PDUFA) reauthorization for fiscal years (FYs) 2023-2027, known as PDUFA VII. It is commonly referred to as the "goals letter" or "commitment letter." The goals letter represents the product of FDA's discussions with the regulated industry and public stakeholders, as mandated by Congress. The performance and procedural goals and other commitments specified in this letter apply to aspects of the human drug review program that are important for facilitating timely access to safe, effective, and innovative new medicines for patients. While much of FDA's work is associated with formal tracked performance goals, the Agency and industry mutually agree that it is appropriate to manage some areas of the human drug review program with internally tracked timeframes. This provides FDA the flexibility needed to respond to a highly diverse workload, including unanticipated public health needs. FDA is committed to meeting the performance goals specified in this letter and to continuous improvement of its performance regarding other important areas specified in relevant published documents[1] that relate to preapproval drug development and post-approval activities for marketed products. FDA and the regulated industry will periodically and regularly assess the progress of the human drug review program throughout PDUFA VII. This will allow FDA and the regulated industry to identify emerging challenges and develop strategies to address these challenges to ensure the efficiency and effectiveness of the human drug review program.

- Split Real Time Application Review (STAR) Pilot Program
- Enhancing Capacity to Review Complex Innovative Designs
- Advancing RWE for Use in Regulatory Decision-Making
- Advancing Development of Drugs for Rare Diseases
- Enhancing Incorporation of Patient's Voice in Drug Development & Decision-Making
- Enhancing use of DHTs to Support Drug Development and Review

www.fda.gov

https://www.fda.gov/media/151712/download

Framework for Use of DHT in Drug and Biological Product Development

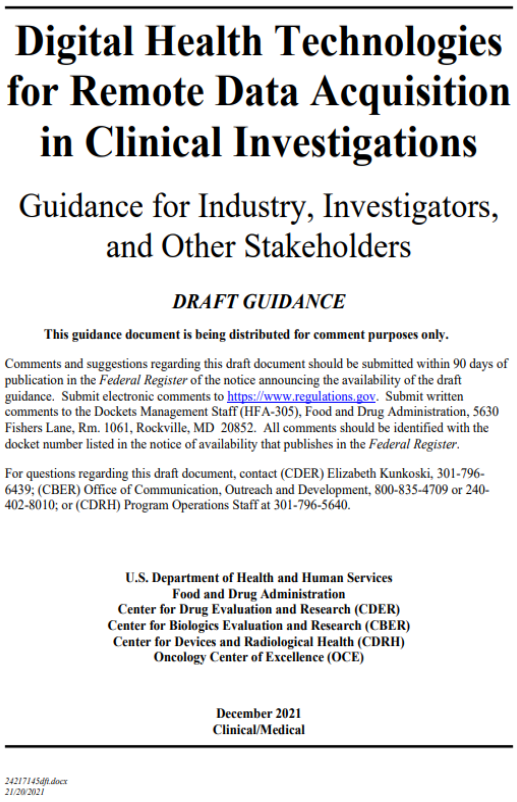
- Promote regulatory consistency and coordination across FDA regarding DHT-based policy, procedure, and analytic tool development
  - Establish a DHT Steering Committee
- Convene public workshops on the use of DHTs in regulatory decision-making
- Identify demonstration projects to inform methodologies for DHT evaluation
- Issue DHT-related guidances
- Enhance IT capabilities to support the review of DHT-generated data

DHT for Drug Development Website

https://www.fda.gov/science-research/science-and-research-special-topics/digital-health-technologies-dhts-drug-development

Tracking Submissions Containing DHT Data
Form 1571 and Form 356H

Draft 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

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) Elizabeth Kunkoski, 301-796-6439; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff 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)
Oncology Center of Excellence (OCE)

December 2021
Clinical/Medical

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21/20/2021

- This draft 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

Engage early with the appropriate Center to discuss the use of DHTs in a specific clinical investigation

Follow each FDA Center's procedures for engaging with the Agency in the context of a development program

If the medical product under investigation is:

Drugs and biological products

See these Draft Guidance for industry:

- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017);
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018).

Devices

See this Guidance for industry:

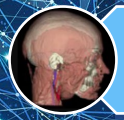
- FDA Staff Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (January 2021).

Digital Health Technology

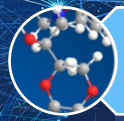
"A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses"*

Used as a medical product

Incorporated into a medical product (include a pharmacologic 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/

Potential Advantages of DHT

- Ability to make continuous or frequent measurements of clinical features
- Ability to record or measure novel clinical features that could not be captured during traditional study visits
- Ability to decentralize clinical trial activities by obtaining clinical data from study participants remotely

DHTs should be fit-for-purpose when used in a clinical investigation

Fit-for-purpose: a conclusion that the level of validation associated with a DHT is sufficient to support its proposed use in the clinical investigation

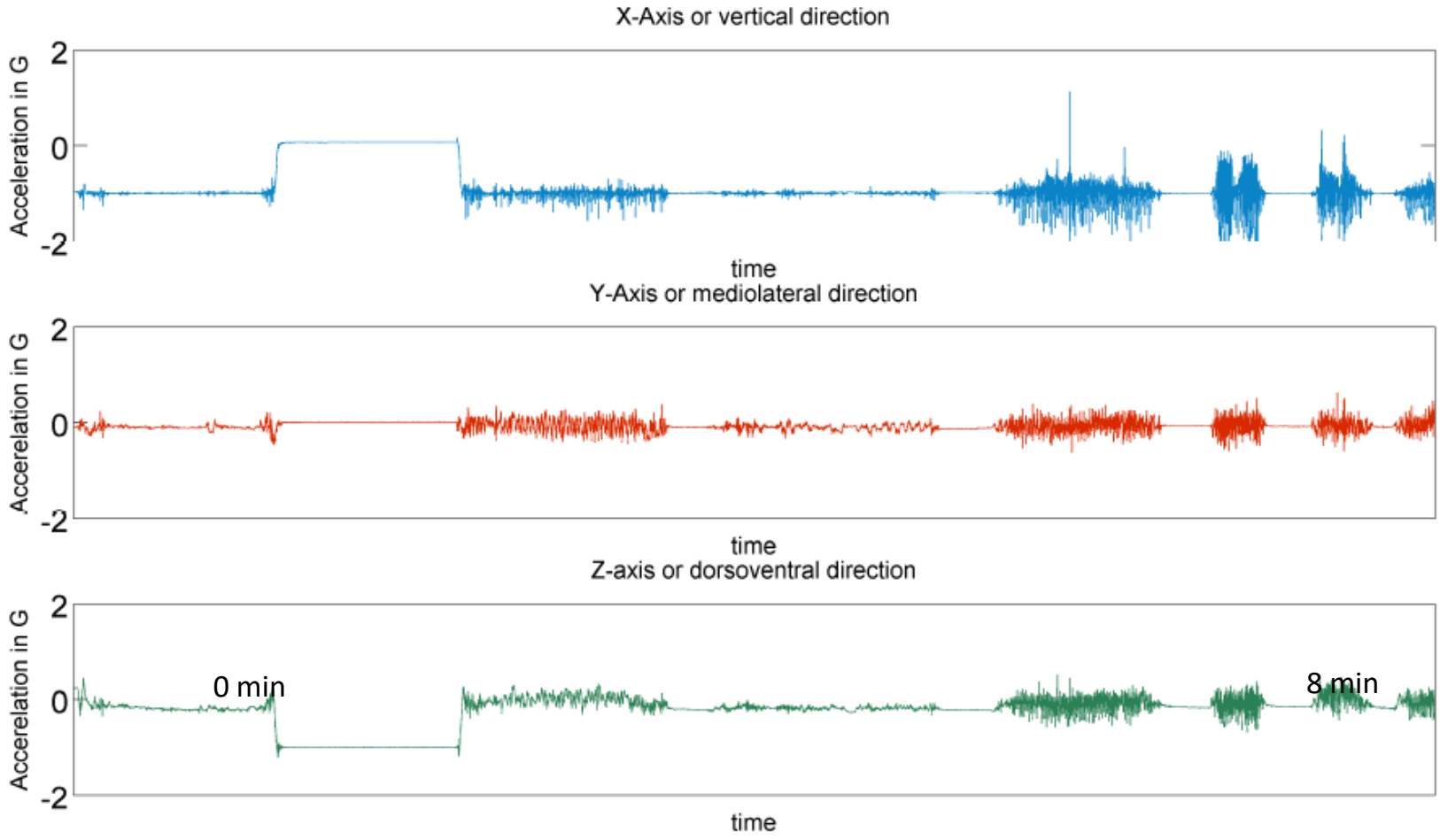
- Clinical event or characteristic of interest
- Ability of DHT to measure clinical event or characteristic of interest
- Population of interest, including age, technical aptitude, and education level, as appropriate
- DHT design and operation (for example, physical properties, power needs, alerts)

Applies regardless of if the participant is bringing their own DHT or general-purpose computing platform

Novel types of data obtained from continuous recording by biosensors

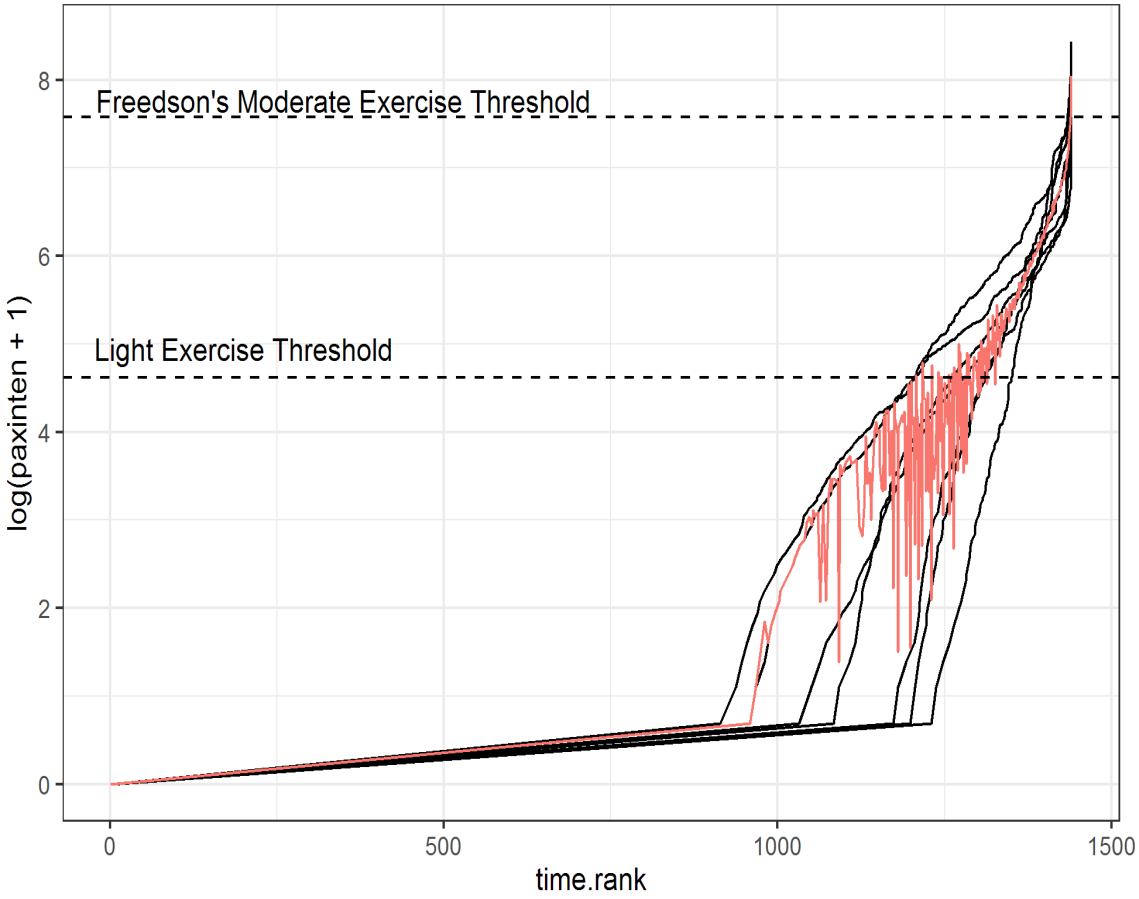
Opportunities	Examples
Richer data instead of snapshots	• Average steps per day vs 6MWD • CGM versus HbA1c
Ability to detect rare events	• arrythmias, seizures
Data from patient who cannot report	• Scratching in infants with atopic dermatitis
New types of measurements	• Accelerometer measurements of gait stability that may predict falls • Measurements of coughing, sneezing, tremor

Movement Data from Acceleration Sensors



Gyllensten, IC, Physical Activity Recognition in Daily Life using a Triaxial Accelerometer, Master's Thesis, 2010.

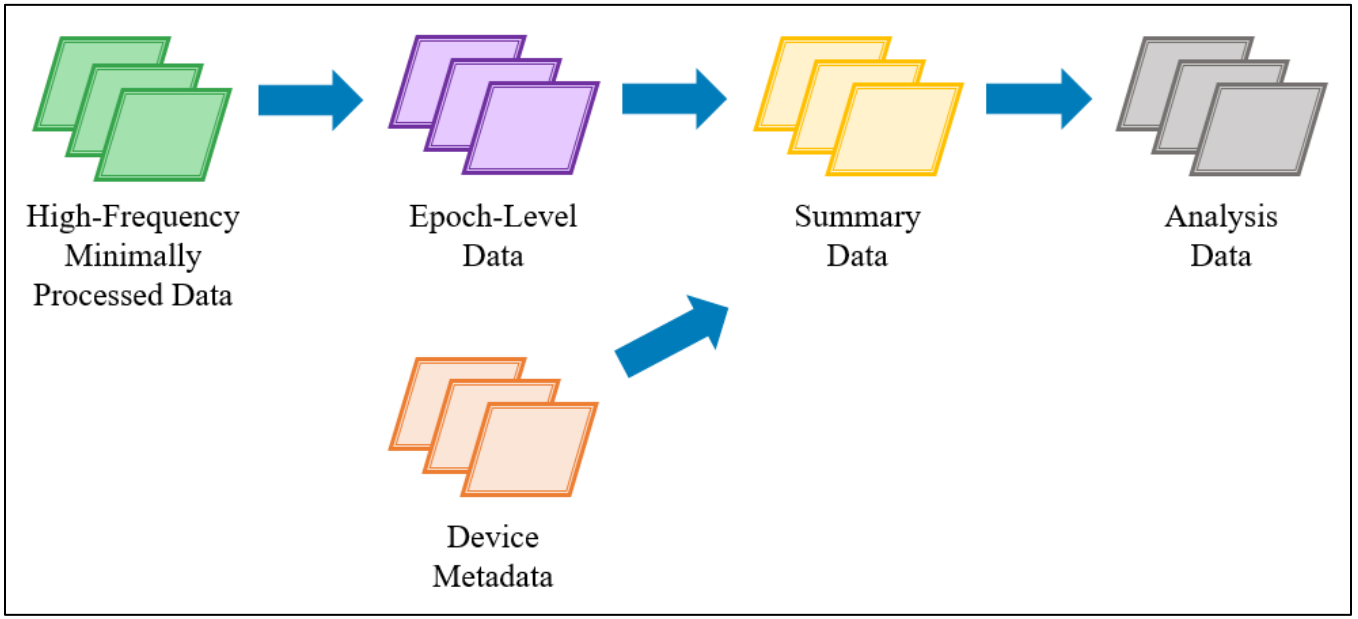
Example Daily Activity Counts



- Sample subject from NHANES 2003-2004 dataset
- Each curve – activity count at a minute
- Red curve is mean of daily curves
- How to summarize?
  - The entire curve?
  - Features of the curve?

Datasets and Submission

- Data Flow



- What to Submit?
  - Required: Summary Data, Analysis Data, Device Metadata
  - Recommended: Epoch-level Data
  - As needed: High-Frequency Minimally Processed Data

Data Considerations

- Epoch-level data (if submitted) represents aggregated or captured DHT data and is tabulated in SDTM format.
  - an actigraphy watch using a one-minute epoch length results in 1,440 epochs captured for each day of patient wear
  - a CGM device using a five-minute epoch length results in 288 epochs captured for each day of patient wear

Data Considerations (continued)

- Summary data represents the data summarized from the epoch-level data
  - Bridge the epoch-level data and the analysis data to address the clinical trial objectives
- Analysis data contains analysis-ready DHT data and are standardized using ADaM business rules and assumptions

Data Considerations (continued)

- Sponsor should provide a well-documented data flow and audit trail.
  - Each step can be traced back to its previous step
  - Aids in FDA's review and support data provenance and traceability within the data flow
- Sponsor should get agreement on which data needs to be submitted with NDA.
  - depends on the Agency's experience with the DHT, the DHT-derived endpoints proposed and whether they are novel, and the proposed patient population

Statistical Considerations

- Development of approaches to DHT validation
- Determination of minimum wear time and valid DHT data set, valid day and minimum number of valid days
- Definition of missing data and methods to handle missing data
- Choice of summary measures and definition of ‘complete’ summary measure

Statistical Considerations (continued)

- Gain understanding of the techniques used for processing DHT data, including ML algorithms
- Regulatory requirements for development of DHT-derived endpoints
- Develop data standards for DHT data
  - no standard formats for analysis and summarization of continuous data from DHTs
  - Summaries (activity counts, steps, calories) with the same name have different meaning
  - Companies does not want to disclose proprietary algorithms
  - Difficult to translate or generalize results

Summary

- PDUFA VII will play a critical role in advancing an effective, science-based regulatory review program.
- FDA recognizes the potential advantages of DHTs in supporting the assessment of patients by generating information outside of the traditional clinic visit.
- FDA is building capacity and expertise to support the use of DHT in drug development and review.
- DHT-based data need to be fit for the intended purpose to support new drug registration, label expansion and safety monitoring.
- The Office of Biostatistics participates in multidisciplinary efforts to advance DHTs, CID, PFDD, RWE, Rare Disease and other strategic FDA initiatives.

References

- DHT for Drug Development website

https://www.fda.gov/science-research/science-and-research-special-topics/digital-health-technologies-dhts-drug-development

- Framework for use of DHT in Drug and Biological Product Development

https://www.fda.gov/media/166396/download

- Draft Guidance: DHT for Remote Acquisition in Clinical Investigations

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations

- FDA Digital Health Center of Excellence

https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health