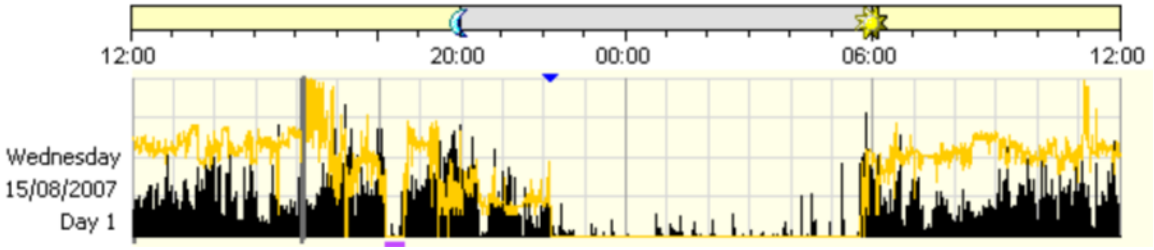
Actigraphy-based Clinical Study Endpoints: A Regulatory Perspective



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- The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.
- I have no actual or potential conflict of interest in relation to this activity.

Objectives

- To Discuss:
  - Actigraphy methodological considerations
  - Regulatory considerations for use of actigraphy-based clinical trial endpoint(s)
  - Key considerations for evaluating actigraphy data: challenges and next steps

Actigraphy:
A Measure of Patient Functioning

- Actigraphy is a noninvasive method of estimating activity patterns through the monitoring of movement
- Often, a small, watch sized device is worn on the wrist and a built-in accelerometer collects data on gross motor activity. These data are subsequently translated to data points (e.g., epochs of wakefulness or sleep) using a device-specific algorithm
- Common Concepts of Interest
  - Physical activity and activity capacity
  - Sleep (Disturbance, Wakefulness)

Measuring How Patients Feel or Function

- **Traditional approaches** (e.g., clinical outcome assessments) are an important part of clinical trials and likely continue to play a pivotal role
- **Novel approaches** such as those using wearable technology (e.g., actigraphy) may ***complement*** traditional clinical trial measurement approaches to help demonstrate clinical benefit
  - Wearable technology (e.g., actigraphy) may reflect certain aspects of patient **"functioning"** (e.g., ambulation) in real-world settings, however, it might not be able to measure how patients **"feel"**

Actigraphy-based Measurement

- Actigraphy can be used to measure binary movement detection (presence or absence) or movement intensity (allowing for threshold setting)
- Advantages:
  - Minimizes recall bias related to total activity assessment through continuous, objective measurement of total activity time
  - Extensive evidence to support the validity and reliability of accelerometer estimates of physical activity and sleep-wake patterns in numerous patient populations

Actigraphy-based Measurement

- Limitations:
  - Limited experience in aggregating and summarizing data into a clinically meaningful endpoint
  - Methodological issues surrounding:
    - The definition of intensity and duration of activity
    - Parameters for determining assessment periods in a day
    - Minimal time requirements for device wearing during a day
    - Aggregating data over numerous days
  - Sensitivity and specificity are dependent on the intended patient population and use
    - Examples:
      - Lack of sensitivity and specificity in sleep conditions not accurately evaluable through limb movement
      - Lack of specificity in childhood sleep measurement

Actigraphy-based Endpoints in Clinical Trials

Evidentiary Considerations for Actigraphy-based Endpoints

- Evidentiary considerations – broadly similar to other types of outcome measures and modes of administration
  - **Well-defined and reliable** (21 CFR 314.126)
  - **Compliance** with FDA regulatory requirements for record keeping, maintenance, and access (21 CFR Part 11)

Evidentiary Standards

- Is the assessment ***well-defined and reliable*** (21 CFR 314.126)? It should measure:
  - The ***right thing (concept)***
  - In the ***right way***
  - In a ***defined patient population***
  - A ***score*** that ***accurately and reliably quantifies*** positive changes that can be interpreted as a clear improvement due to treatment (***clinical benefit***).
- Does the endpoint score represent something meaningful to patients?
- How much within-patient change in a score/variable makes a difference in patients lives?

Evidentiary Standards

- Is the device compliant with regulatory standards for record keeping, maintenance and access (21 CFR Part 11)?
  - Direct actigraphy data transmission from the data collection device to the sponsor, clinical investigator, or other 3rd party ***must*** include an electronic audit trail that documents all changes to the data after it leaves the electronic data collection device.

Device Design, Implementation & Analysis Factors

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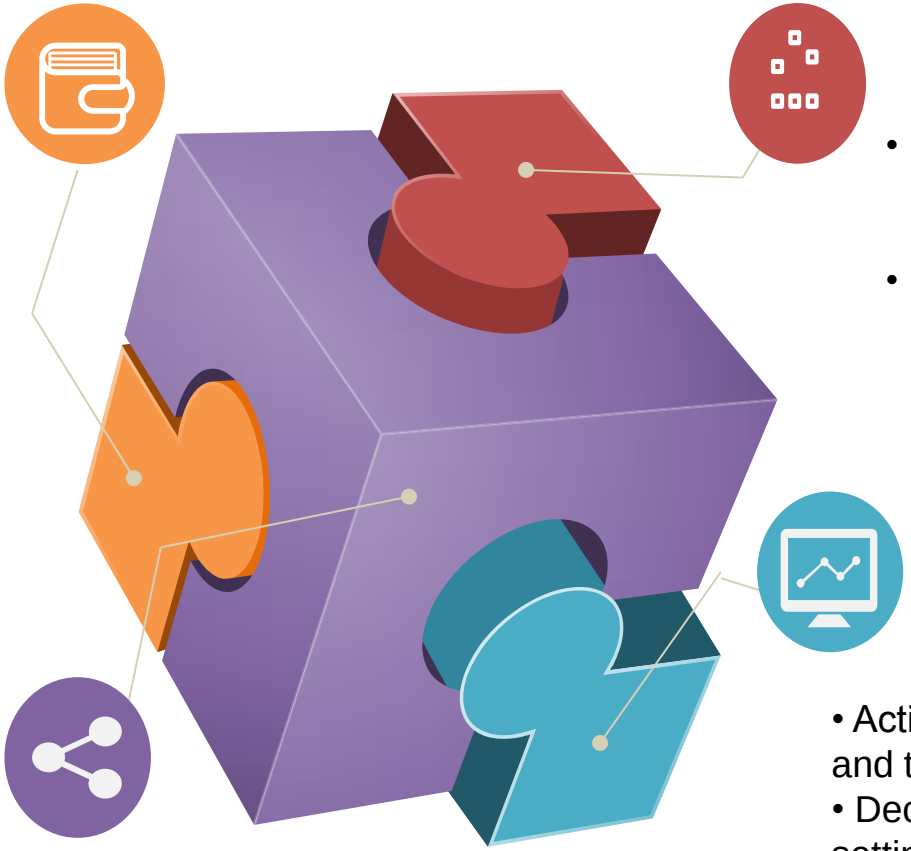
Instrumentation and Validation

- Device model and manufacturer
- Documentation of instrument validation

Data Collection

- Data collection environment
- Duration of data collection period
- Days of the week for monitoring
- Sampling epoch length
- Mode of data collection (ZCM, TAT, PIM, or TRI-mode)



Variable Selection and Definition

- Sleep and/or physical activity/activity capacity variables to be assessed
- Clear definitions of selected variables

Data Processing and Analysis

- Actigraphy data file preparation and transfer
- Decisions regarding time interval setting (diary, event marker, cascading counts)
- Scoring algorithm
- Missing data rules

Adapted from Berger AM, Wielgus KK, Young-McCaughan S, et al. Methodological Challenges when using actigraphy in research. J Pain Symptom Manage 2008 August;36(2):191–199.

Instrumentation and Validation

- Proper **documentation** of actigraphy device development and validation is necessary to support labeling claims
- Additional documentation important for review:
  - Design features (model, technical capabilities, alarm and reminder programming, etc.)
  - Usability testing
  - Training materials

Variable Selection and Definition

- Relevant variables for measuring clinical benefit should be identified and defined *a priori*
- Variables should appropriately reflect the pre-specified endpoints and represent concepts that are likely to detect clinical benefit

Data Collection Procedures and Parameters

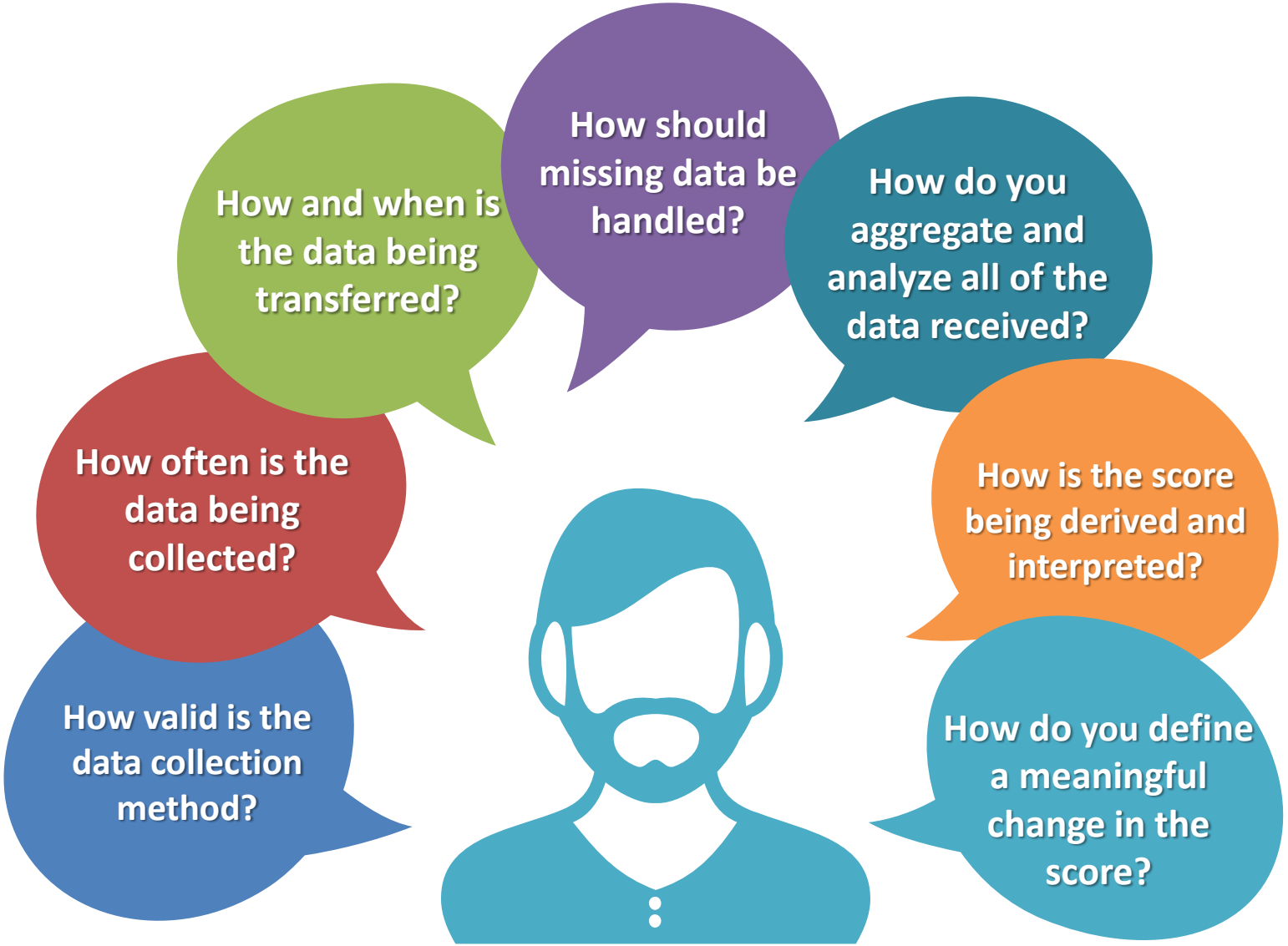
- Common considerations include:
  - Data collection environment
  - Duration of the data collection period (and volume of data to be collected)
  - Selection of days of the week for monitoring
  - Epoch length (for studying sleep patterns)
  - Mode of data collection (e.g., tri-mode accelerometry vs. proportional integrating measure [PIM])

Data Processing and Analysis

- **Data Processing:** Criteria for data processing and data transfer should be specified by the Sponsor prior to study implementation; nightly data transfer is better than data transfer at the end of a trial.
- **Data Analysis:** The following should be pre-specified
  - Data analysis plans according to data characteristics (intensity, frequency, event, etc.)
  - Scoring algorithm
  - Missing data rules

Regulatory Challenges for Evaluating Actigraphy Data

Questions, Questions, and more Questions!



Regulatory Challenges: Sensitivity vs. Specificity

- As compared with polysomnography (PSG), actigraphy is known to overestimate sleep and underestimate wake time.
  - Actigraphy and PSG record the beginning of sleep periods in different ways.
  - Actigraphy may have poor specificity to detect wakefulness after sleep among pediatric patients.

Marino YL, Rueschman MN, Winkelman JW, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep 2013;36(11):1747-1755.

Meltzer LJ, Montgomery-Downs HE, Insana SP, Walsh CM. Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev*. 2012;16(5):463-75.

Regulatory Challenges: Scoring

- Scoring:
  - Most algorithms are proprietary
  - Different devices will employ different algorithms producing potentially different numbers for the same activity
  - The algorithm used within one device might change/be updated while the device is used in a clinical trial

Regulatory Challenges: Missing Data

- Missing data:
  - What to do when you have missing data? Is imputation acceptable?
  - Best way to minimize missing data is to prospectively avoid it (e.g., usability testing, data monitoring, alarms, reminders)
  - Imputing data can yield biased results

Regulatory Challenges: Interpretation of Clinically Meaningful Change

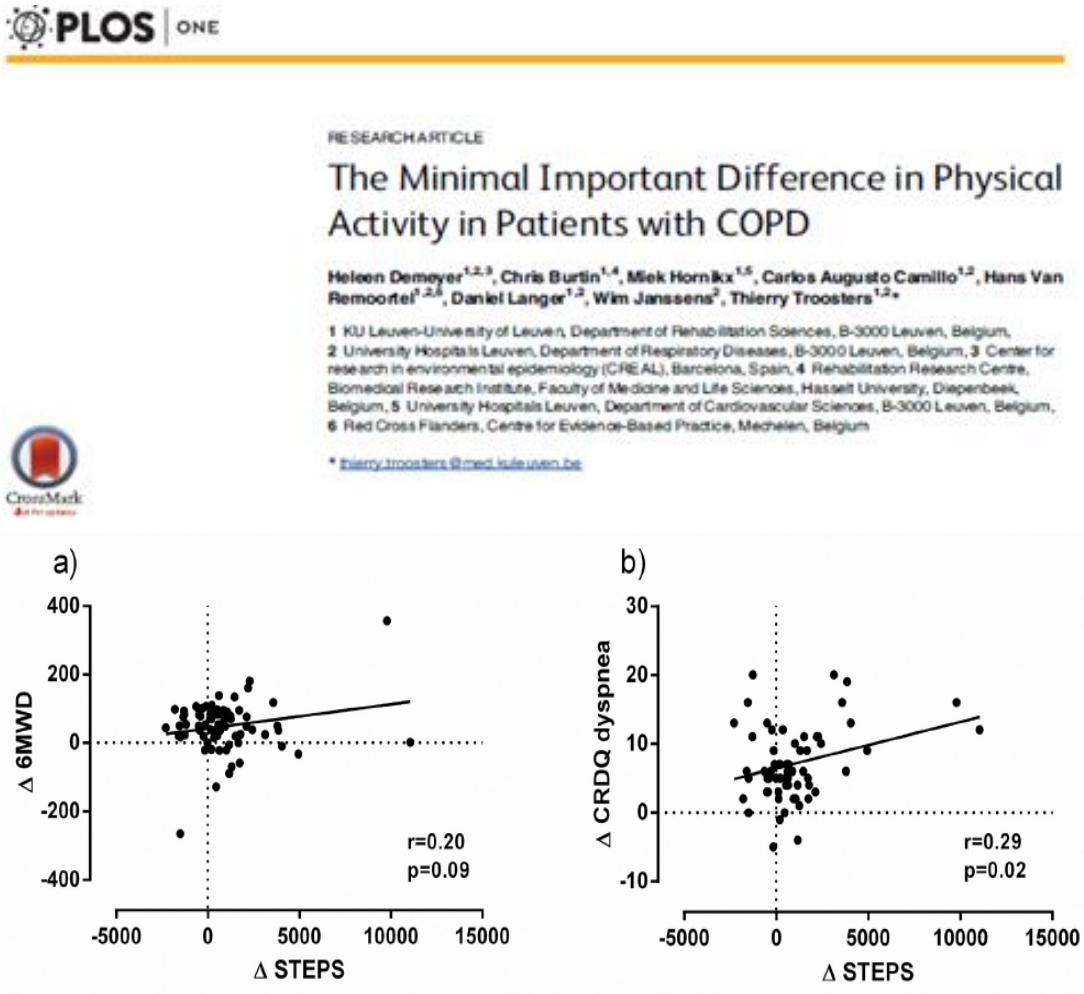
- Statistical significance alone is not sufficient; changes have to reflect a positive clinically meaningful effect of an intervention (i.e., clinical benefit - a positive effect on how an individual functions)

- To establish clinical benefit we consider two questions:
  1. Does the assessment measure or reflect something of significance to patients?
  2. Is the magnitude of change at the individual level sufficiently large to affect how patients feel or function in daily life?

Regulatory Challenges: Interpretation of Clinically Meaningful Change

- The Problem?
  - Difficult to determine what constitutes a clinically meaningful within-patient change on an actigraphy score because it is difficult to identify the right/a good anchor to compare the actigraphy results to.
  - Need to explore what constitutes a suitable anchor.

Example: Poorly correlated Anchors



PLOS ONE

RESEARCH ARTICLE

The Minimal Important Difference in Physical Activity in Patients with COPD

Heleen Demeyer[1,2,3], Chris Burtin[1,4], Miek Hornikx[1,5], Carlos Augusto Camillo[1,2], Hans Van Remoortel[1,2,6], Daniel Langer[1,2], Wim Janssens[2], Thierry Troosters[1,2]*

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Fig 1. Correlation between change in daily step count and possible anchors. a) 6MWD and b) $CRDQ_{dyspnea}$ in the rehabilitation sample (n = 74); 6MWD after 3 months was missing in 3 patients, $CRDQ_{dyspnea}$ scores were missing in 10 patients.

- Anchor-based estimation could not be obtained because of the lack of a sufficiently related anchor
- Neither the change in 6MWD (r = 0.20, p = 0.09), nor the change in CRDQdyspnea score (r = 0.29, p = 0.02) or CRDQtotal score (r = 0.16, p = 0.27) were even moderately correlated with the change in physical activity and could therefore not be used as reliable anchors.

Summary

- Actigraphy data has the potential to be useful as an objective measure to complement traditional COA data
- Despite longstanding use of actigraphy in clinical trials, many questions remain regarding the utility of actigraphy in regulatory decision-making.
- Further discussion is necessary surrounding topics related to:
  - Measurement concepts
  - Data analysis (e.g., What's the endpoint? How do we make sense of the large volume of data received?)
  - How to best derive scores
  - Identification of suitable anchors
  - Determining thresholds for meaningful within-patient change using those anchors
  - How to handle missing data

Helpful links

- Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf
- Guidance for Industry: Computerized Systems Used in Clinical Investigations
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf
- Guidance for Industry: Electronic Source Data in Clinical Investigations
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf
- Clinical Trials Transformation Initiative (CTTI) Novel Endpoints Project
  - https://www.ctti-clinicaltrials.org/projects/novel-endpoints


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