



# Overview

- Introduction
- Challenges - Technology
- Challenges – Study Design, Endpoints, Data
- Intercurrent Events and Estimands
- Handling Missing Data
- References

# Statistical Challenges, Technology



Technology Failure

Calibration

Computing Capabilities

Processing large amounts of real time data

Data Capture  
No EDC

Back-up Strategies

Device Configuration,  
Time Zones

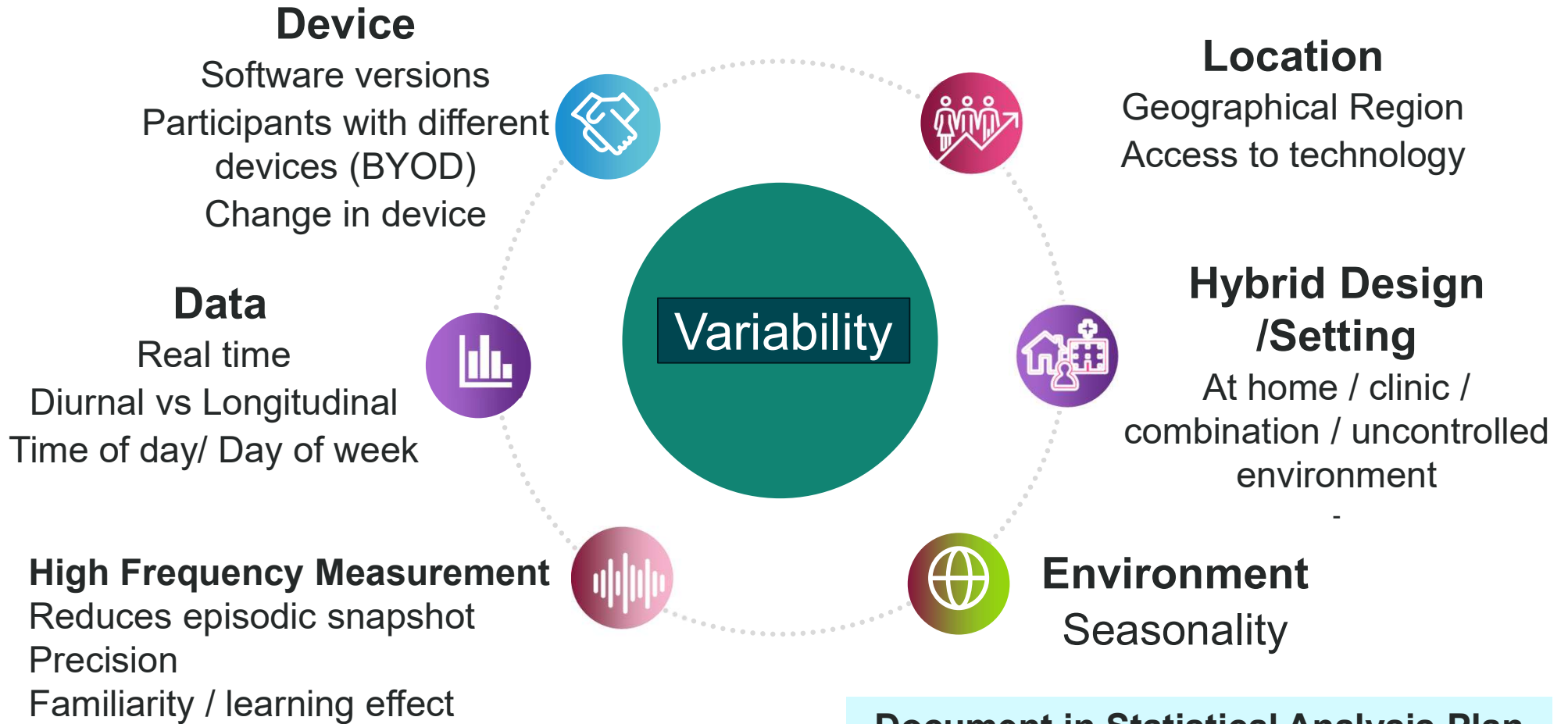
SDTM/ADaM

Data Collection

Computational Considerations



# Digital Endpoints, Variability



# Study Design and Digital Endpoints

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Digital Health provides the opportunity for **novel** study designs and endpoints

## Study Design

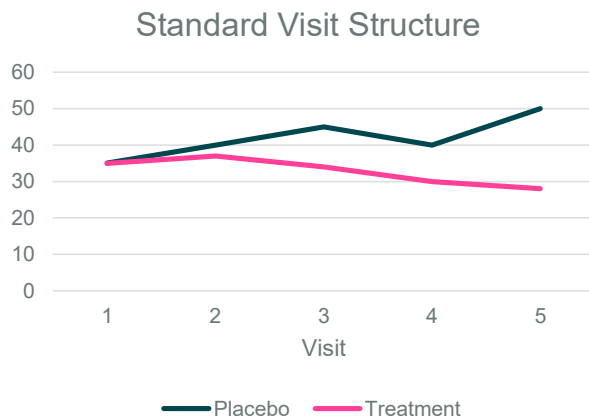
- Choice of **setting** (hybrid collection)
- Focus data collection on **necessary / sufficient**
- User **acceptability** of technology/ burden
- **Ethical** considerations
- **Blinding**
- **Estimands Framework**

## Endpoints

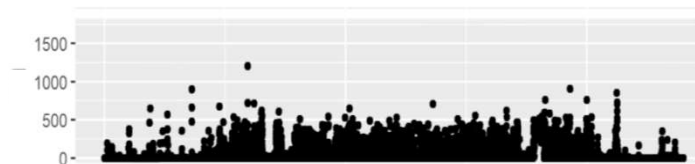
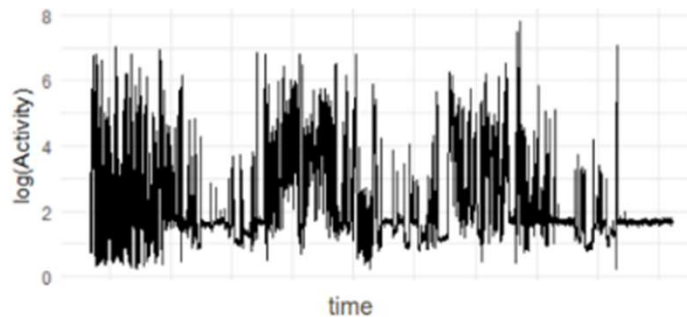
Variability  
Range  
Validated endpoints  
Regulatory approval for Primary/Secondary  
Effect Size/Power  
Meaningful change



# Statistical Challenges – Data and Analysis



- Variability, diurnal vs longitudinal
- Innovative methods for data analysis of time series
- Beyond reliance on change from baseline
- Generalised Additive Models, Functional Data Analysis, Change point detection
- Granularity of Data (raw vs summaries)
- Proprietary Algorithms
- AI/Machine Learning for meaningful biomarkers/ prediction



→ Estimands / Intercurrent Events  
→ Missing Data / Compliance

# Estimands and Digital Health?

Scientific Question of Interest

Population

Treatment/ Intervention

Endpoint

Intercurrent Events

Summary Measure

Estimator

## Estimands Framework:

Inform study design and strategic thinking  
Can clarify added value, potential risks and opportunities for novel estimands of DCT

*What: Impact of DCT on each estimand attribute?*

*How: DCT impacts on estimator?*

# Digital Health and Intercurrent Events

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## Intercurrent Events

Post baseline events that impact the presence or interpretation of endpoints

### Common ICEs (Standard Trials)

- Treatment Discontinuation / Treatment Non-Adherence
- Rescue Medication
- Prohibited Medication
- Death

### Specific to Digital Collection

- Frequency / likelihood / timing of identifying ICEs
- Change in Device
- Network interruption?



# Missing Data



## Likely to be common

### Classification **informative, non-informative**

- Technology related (internet connectivity, battery power, device malfunction)
- Person related (compliance, time in study, disease stage, symptom severity, activity level)
- Engagement
  - how invested is the investigator
- Compliance checks and technical support / notifications.

Missing data is likely to be missing **not** at random

## Missing Data Example - Wearables

Common approach: define a **day** as missing or observed using a threshold on wear time.

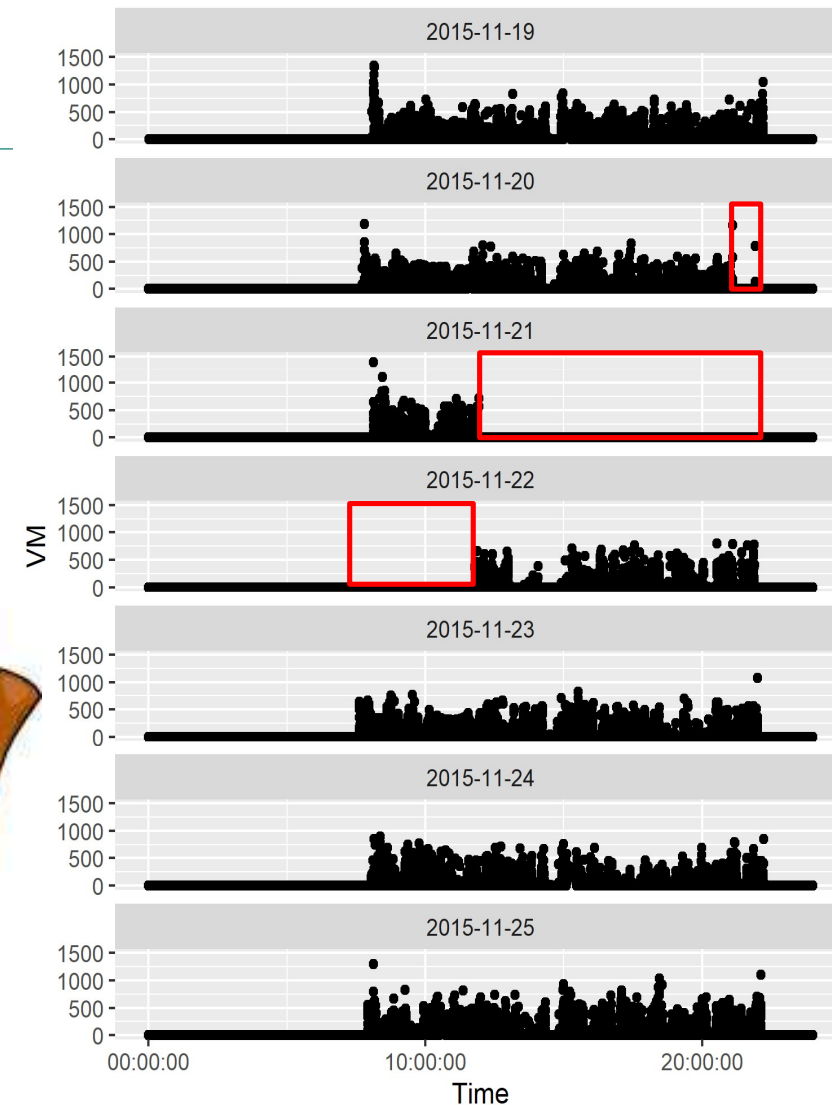
Using epoch-level data, **intervals** can be classified as inactivity, sleep or missing. Missing intervals can be handled with Multiple Imputation.

Most likely to be **missing not at random**.



Important to pre-specify how to handle missing data in SAP, and build in sensitivity analysis

Tackney et al, 2021, 2023



Harris et al, 2017

# References

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