MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Digital Endpoints: Key themes from a Multi-stakeholder event

Mia Sato Tackney
Research Associate

Motivation

Stride Velocity 95th Centile was qualified by the EMA after a **10-year** journey and required a multi-stakeholder, cross-sector approach.

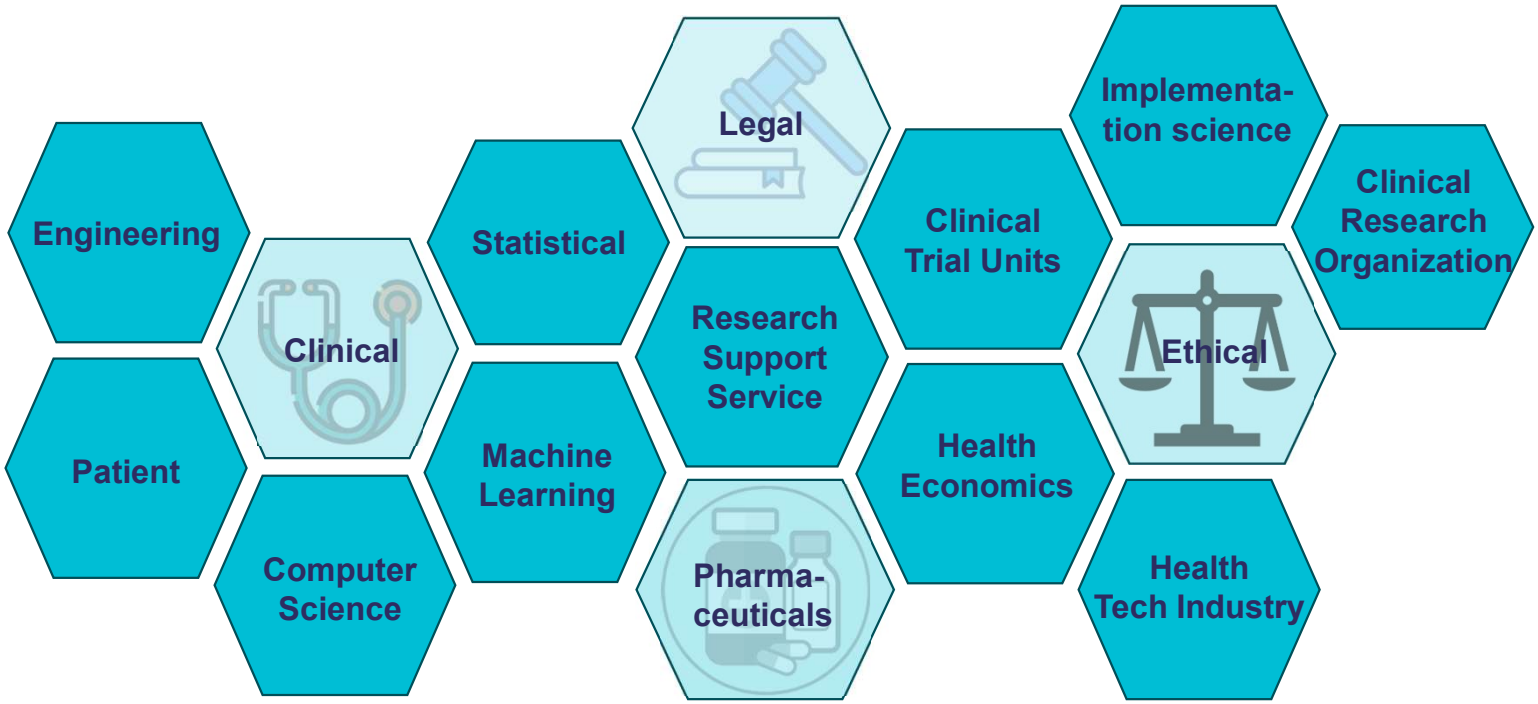
Dr. Sofía Villar
MRC-Biostatistics Unit

Statistical

Dr. Amber Steele
National Institute of Health Research

Research Support Service

Where are we at now? What challenges do we face?



Outline

Understanding Patient Engagement

Ongoing Ethical Reflection

Environmental Impact

Validation

Seasonal Variation

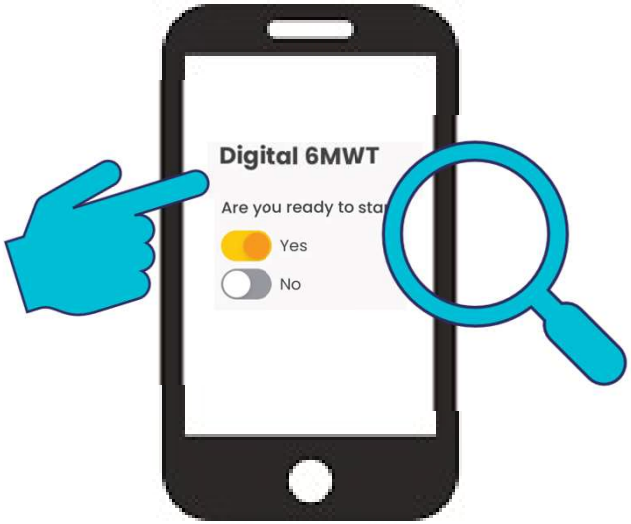
Missing Data

} Simulation Study

Understanding Patient Engagement

Joseph Newman
University of Cambridge &
Royal Papworth Hospital

Involving patients in design and testing of digital walk tests and ePROs for Pulmonary Hypertension:



Engagement typically:

- declines over time
- depends on disease severity (lower at the extremes)
- depends on investigator engagement (site level effect)

[Robertson et al, 2024]
[PPIE work by PHA UK]

Understanding Patient Engagement

Zarnie Khadjesari
University of East Anglia

- Gamification
- Investigator-in-the-loop
- Ongoing feedback to patients

Implementation Outcomes:

Acceptability: degree to which an intervention is perceived to be agreeable

Adoption: intention to adopt or initial implementation of intervention

Appropriateness: perceived suitability and usefulness of intervention to address problem

Feasibility: fit and suitability of the intervention for everyday use

Fidelity: the extent to which an intervention is implemented as intended

Implementation cost: costs associated with implementation, including cost of delivery of the intervention and cost associated with the implementation strategy used

Penetration: diffusion into practice

Sustainability: sustained use of the intervention

ImpRes Tool [Hull et al, 2019]

NASSS framework: Nonadoption, abandonment, scale-up, spread, and sustainability [Greenhalgh et al, 2017]

Ongoing Ethical Reflections

Federica Lucivero
Ethox, University of Oxford

Ethical reflection is needed **throughout** the study:

- Privacy of bystanders, e.g. family members when wearable cameras are used;
- Feedback to patients, e.g. if worsening health is identified by a remote device.

"Ethics clubs"

Regular discussions in Steering Committee

Feedback procedures with patients

[Muurling et al, 2023]

Environmental Impact

The carbon footprint due to digital devices in trials needs to be quantified.

Detailed guidance by Low Carbon Clinical Trials Group:

Manufacture

Transport

Use

Data Storage

6.3. Equipment and supplies provided to participants specifically for the trial

Smartphone: For a smartphone, account for 55 $kgCO_2e$ from manufacture and add 5.5 $kgCO_2e$ per year of usage.

Source: Examining the Carbon Footprint of Devices - Sustainable Software (microsoft.com) [19]

Tablet: For a tablet, account for 119 $kgCO_2e$ from manufacture and add 10kg CO_2e per year of usage. Assume a maximum lifetime of 3 years, therefore 30 kg CO_2e is the total possible carbon footprint that can be attributed to use.

Source: Examining the Carbon Footprint of Devices - Sustainable Software (microsoft.com) [19]

Wearables/smart watch: For a smart watch, account for 30.1 kg CO_2e for manufacture and add 1.633 kg CO_2e per year of usage. Assume a maximum lifetime of 3 years, therefore 4.9 kg CO_2e is the total possible carbon footprint that can be attributed to use.

Source: Apple Watch SE Product Environmental Report [22]

To calculate the carbon footprint associated with shipment of the devices, please refer to section 1.2.

[Griffiths et al, 2024]

Validation of Digital Endpoints

V3+ framework

- Accuracy
- Repeatability
- Robustness

- Known-groups validity
- Concurrent validity
- Sensitivity to disease progression
- Sensitivity to treatment

[Bakker et al, 2024]

Stride Velocity 95th Centile

Validation of Digital Endpoints

V3+ framework

- Accuracy
- Repeatability
- Robustness

- Known-groups validity
- Concurrent validity
- Sensitivity to disease progression
- Sensitivity to treatment

Methodological guidance needed for:

- Outcome granularity
- Length of measurement period
- Selection of summary measure
- How missing data is handled

[Bakker et al, 2024]

Seasonal Variation and Missing data

Bellerophon Phase II Study

Evaluated whether **inhaled nitric oxide** improves physical activity in patients with Pulmonary Hypertension associated with Interstitial Lung disease.

Primary endpoint: 6 Minute Walk Test
Exploratory endpoint: Moderate-to-Vigorous physical activity (used in a subsequent Phase III study)

Baseline: 1 Month

Randomisation:
30 Treatment
14 Control

3-Month Period

Follow-up: 1 Month

[King et al, 2021]

Simulation Study

Seasonal Variation: Recruitment between January-July
Suppose some individuals recruited in winter have a seasonal increase in MVPA at follow-up.

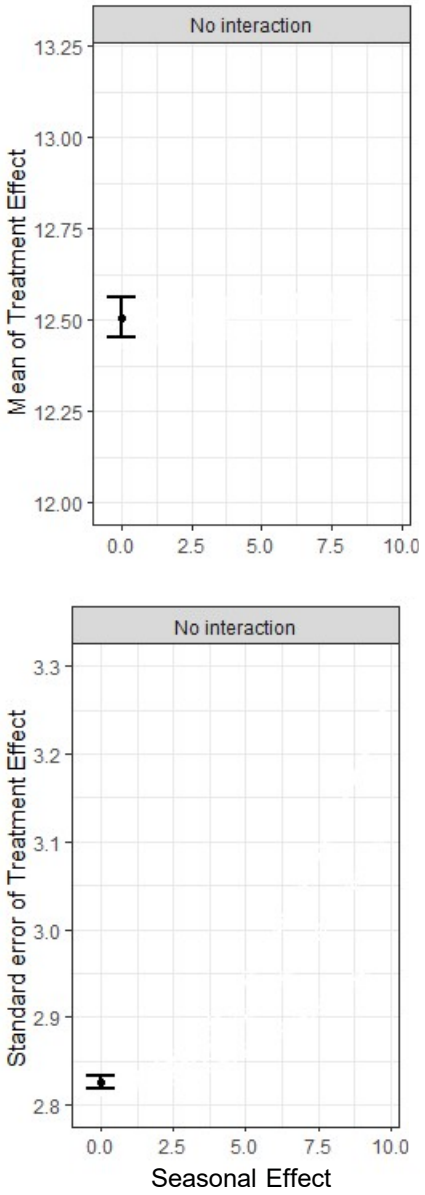
Missing data: Days are compliant if wear time $\geq$ 600 minutes.
Individuals are included in the analysis if $\geq$ 14 compliant days.
Suppose some individuals are:

- non-compliant on a random selection of days (MCAR)
- non-compliant on days when they are less active (MNAR)

$y_{i,j}$: daily time spent in MVPA for individual *i* on day *j*
$\overline{y_{i,\cdot}}$: average of spent in MVPA for individual *i* from compliant days
$\overline{y_{i,\cdot}} = \beta_0 + \beta_1 baseline_i + \beta_2 treat_i + \epsilon_i$ where $\epsilon_i \sim N(0, \sigma^2)$

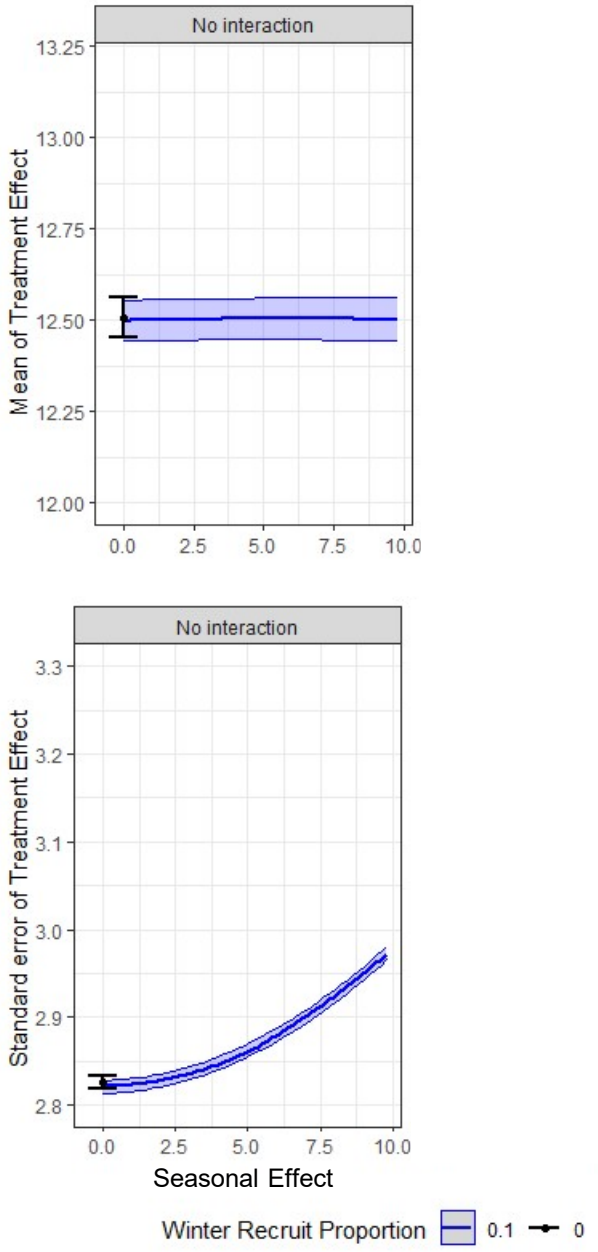
Seasonal Effect

- Effect of treatment: 12.5 min/day



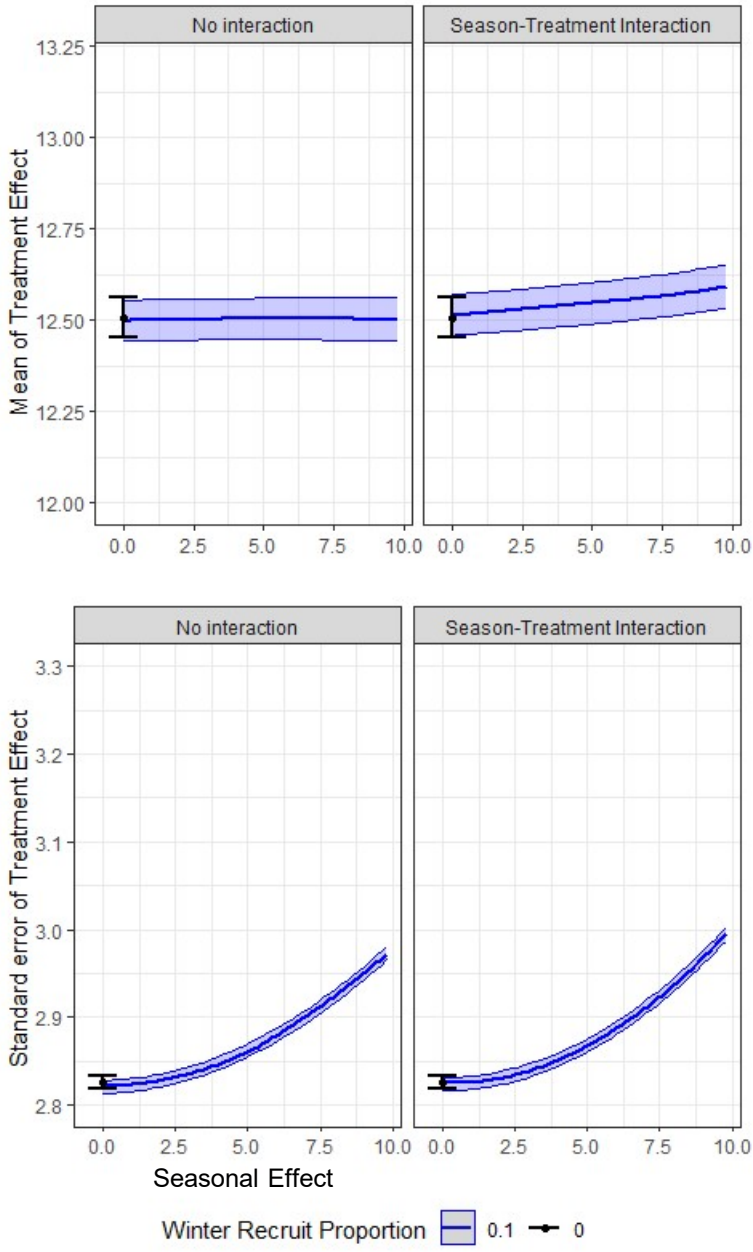
Seasonal Effect

- Effect of treatment: 12.5 min/day
- 10% of individuals experience seasonal effect: Increased **standard error**



Seasonal Effect

- Effect of treatment: 12.5 min/day
- 10% of individuals experience seasonal effect: increased standard error
- Interaction with treatment: **bias and increased standard error**

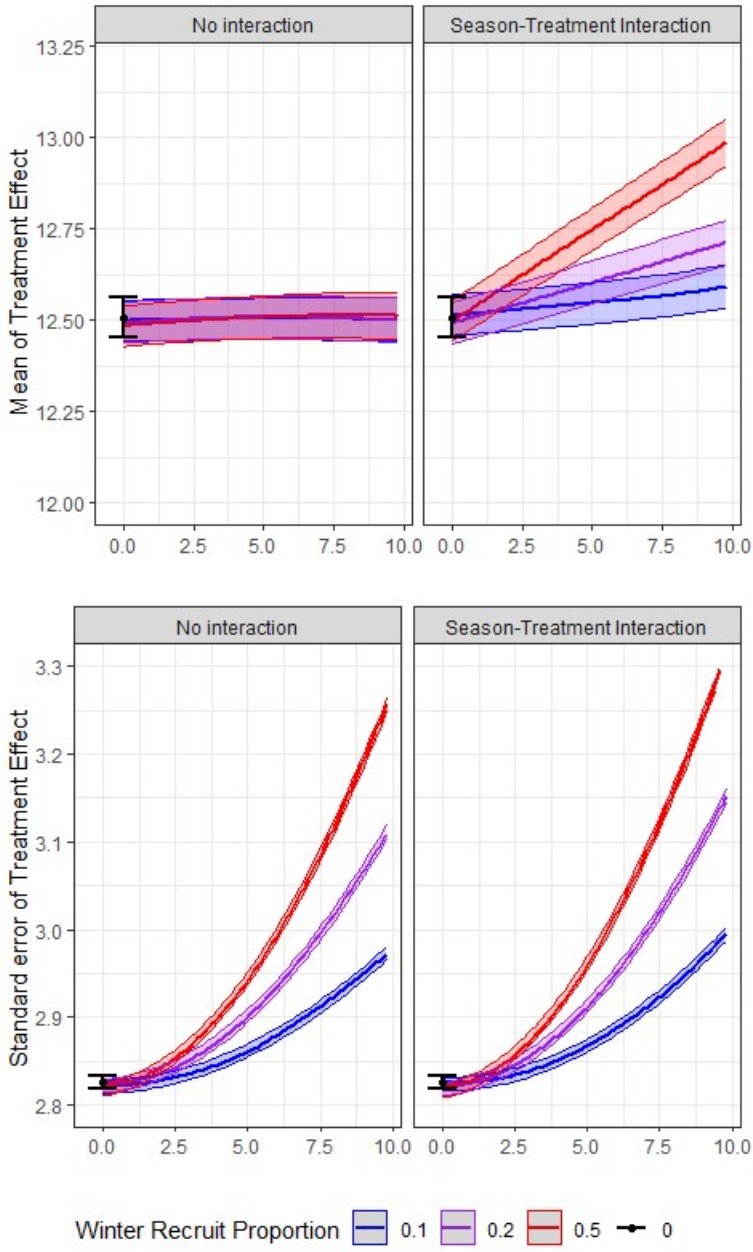


Seasonal Effect

- Effect of treatment: 12.5 min/day
- 10% of individuals experience seasonal effect: increased standard error
- Interaction with treatment: **bias and increased standard error**

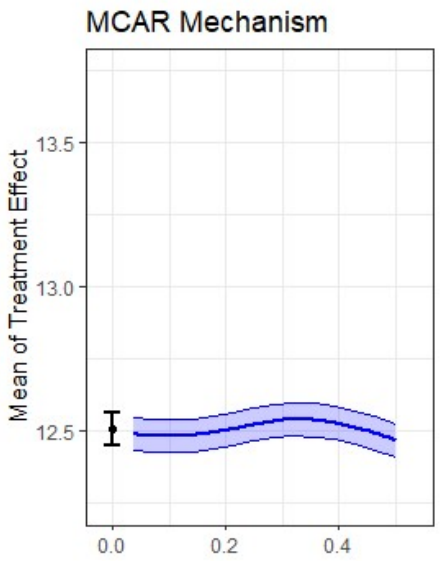
Strategies:

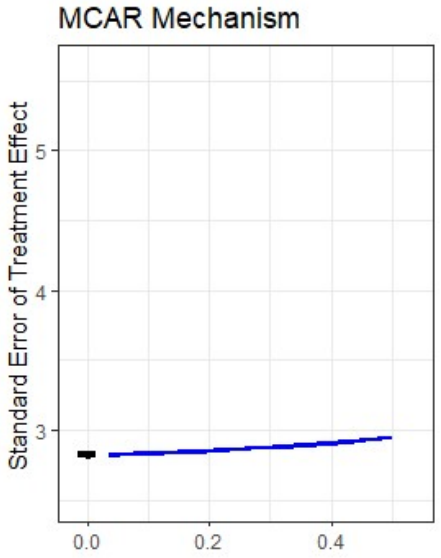
- ➢ Recruit at appropriate times of year
- ➢ Adjust for season in the analysis
- ➢ Randomisation procedures, e.g. Maximum Tolerated Imbalance

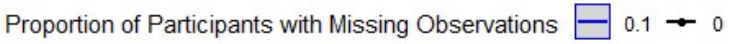


Missing data

- 10% of individuals have missing data:
  Under MCAR: increased **standard error**

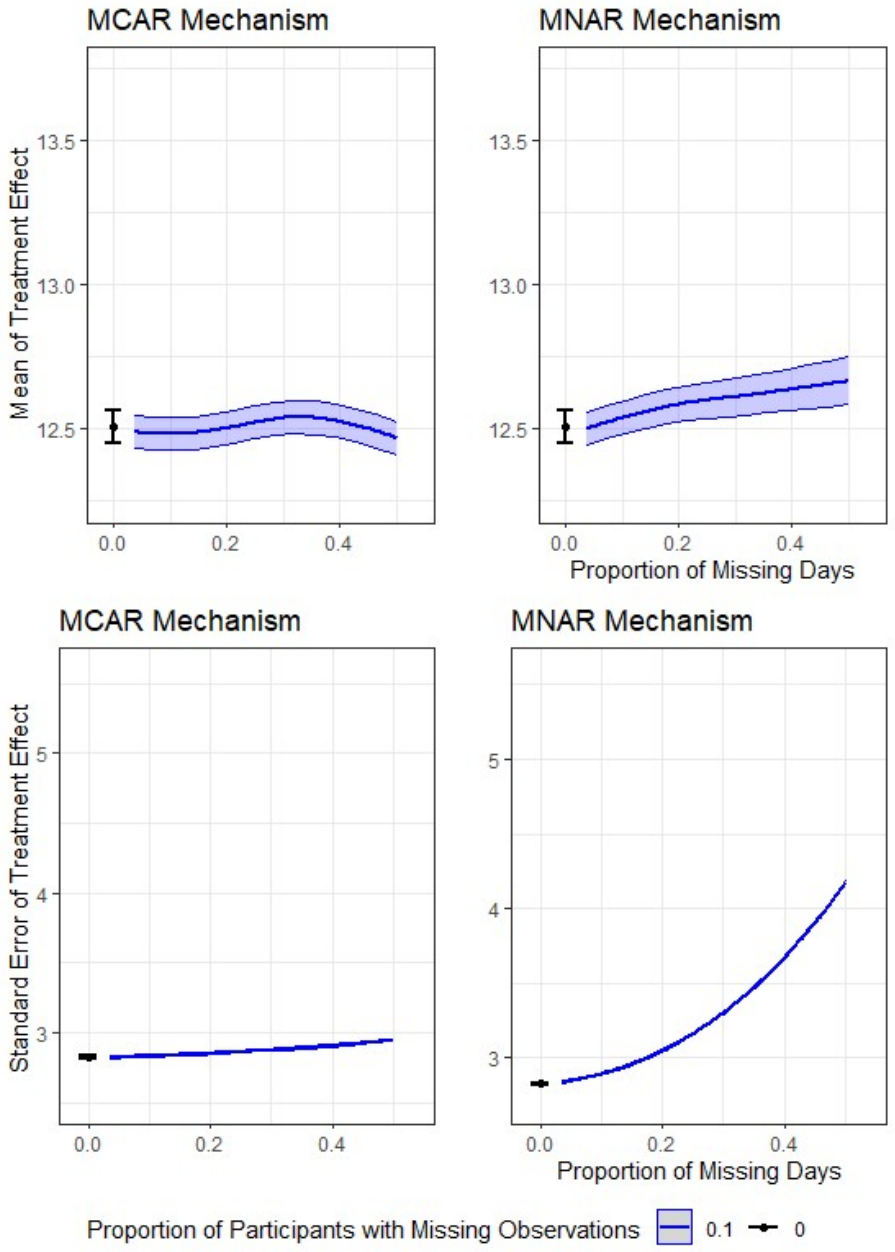






Missing data

- 10% of individuals have missing data:
  Under MCAR: increased standard error
  Under MNAR: **bias and increased standard error**



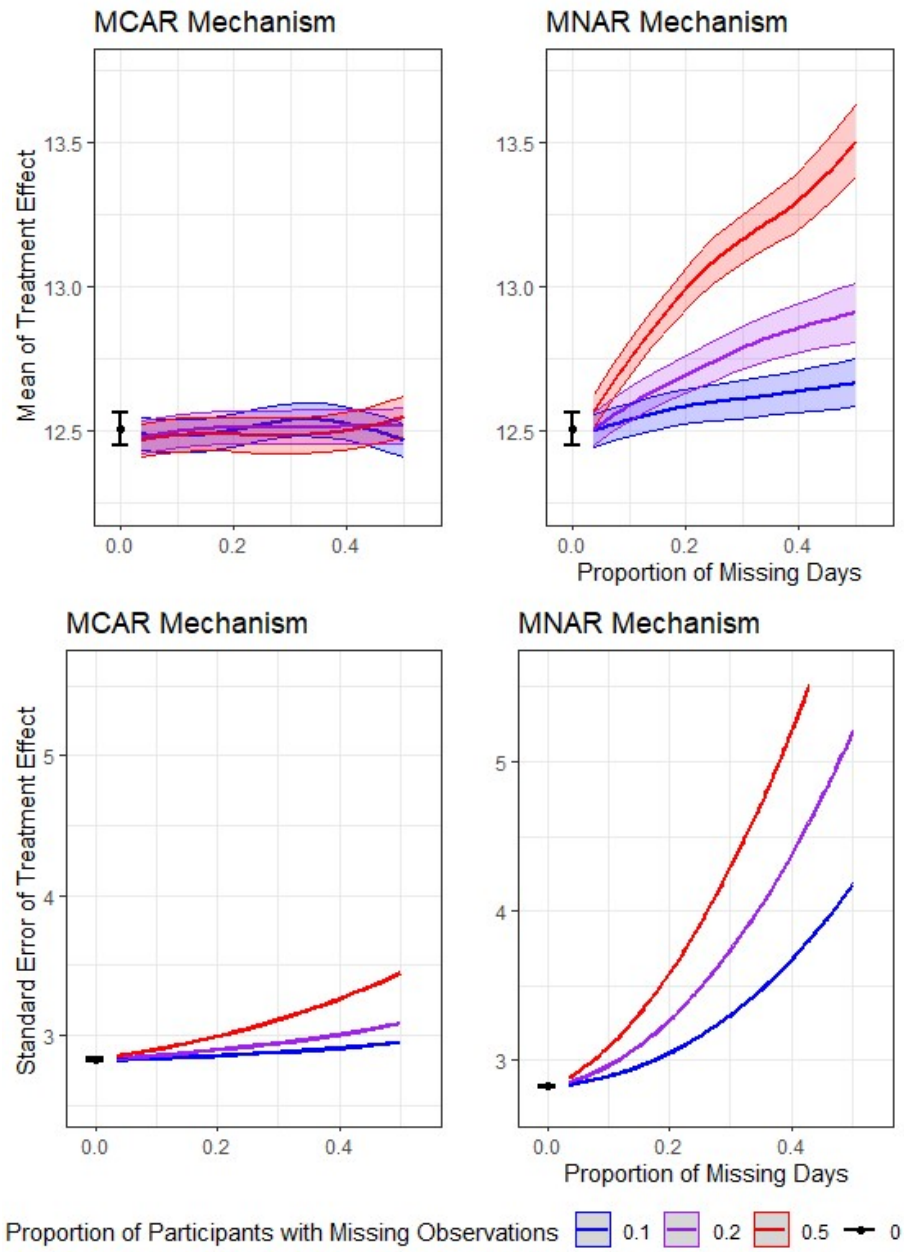
Missing data

- 10% of individuals have missing data:
  Under MCAR: increased standard error
  Under MNAR: **bias and increased standard error**

- Impact is greater when the proportion of missing data is increased

Strategies:

- ➢ Implementation strategies to reduce missing data
- ➢ Define/handle missingness at a granular level and sensitivity analyses



Discussion

- Pre-specification on digital endpoints and standardization in reporting
- Open-source software and standardised terminology
- Support from funders for interdisciplinary and cross-sector collaboration
- Early engagement between academics/funders and regulators

IDEA FAST

Mobilise-D

CLINICAL TRIALS TRANSFORMATION INITIATIVE

DiME DIGITAL MEDICINE SOCIETY

MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Research Article

Digital Endpoints in Clinical Trials: Emerging Themes from a Multi-stakeholder Knowledge Exchange Event

Under Review Trials BMC

Unleashing the Full Potential of Digital Endpoints: Eight Questions that Need Attention

Mia S. Tackney[1*], James R. Carpenter[2,3] and Sofía S. Villar[1]

Pre-prints available upon request:
Mia.Tackney@mrc-bsu.cam.ac.uk

References

Robertson et al, 2024. The Digital 1-Minute Walk Test: A New Patient-centered Cardiorespiratory Endpoint. doi: 10.1164/rccm.202310-1855LE

PHA UK. Clinical trials: What matters to you? https://www.phauk.org/clinical-trials-what-matters-to-you/

Greenhalgh et al, 2017. Beyond adoption: A new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies: doi: 10.2196/jmir.8775

Hull et al, 2019. Designing high-quality implementation research: development, application, feasibility and preliminary evaluation of the implementation science research development (ImpRes) tool and guide. doi: 10.1186/s13012-019-0897-z

Muurling et al, 2023. Ethical challenges of using remote monitoring technologies for clinical research: A case study of the role of local research ethics committees in the RADAR-AD study. doi: 10.1371/journal.pone.0294797

Griffiths et al, 2024. Quantifying the carbon footprint of clinical trials: guidance development and case studies. doi: 10.1136/bmjopen-2023-075755

Bakker et al, 2024. V3+: An extension to the v3 framework to ensure user-centricity and scalability of sensor-based digital health technologies.

King, et al, 2022. A Phase-2 Exploratory Randomized Controlled Trial of INOpulse in Patients with Fibrotic Interstitial Lung Disease Requiring Oxygen. doi: 10.1513/AnnalsATS.202107-864OC
[Phase II study: NCT01457781, Phase III study: NCT03267108]

MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Validation of Digital Endpoints

Analytical Validation	
Accuracy	Mean difference between digital and traditional endpoint, and its standard deviation
Repeatability	Intra-cluster correlation between repeated measurements
Robustness	Low variation over time Check differences in different conditions
Clinical Validation	
Known-Groups Validity	Comparison of medians of digital endpoint between patients with disease and healthy controls
Concurrent Validity	Compute correlations between digital and traditional endpoints.
Sensitivity to disease progression	Compute change in median of digital endpoint between baseline and follow-up. Compare with gold standard endpoints.
Sensitivity to treatment	Calculate change in median of digital endpoint in patients who have started on a treatment.