Novartis Institutes for Biomedical Research - NIBR

Leveraging technology for better clinical endpoints

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FUTURE CLINICAL TRIALS – FROM TOMORROW TO 2030 – WHY CHOOSE THE NORDICS?

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Strategy

Problem statement:
Conventional clinical endpoints have high variability which leads to *poor drug signal detection*

Key strategy is to increase drug signal detection by <u>reducing variability and bias through</u>:

1. Increase in frequency of measurements
2. Use of objective measures
3. Increase in quality of measurements

Roadmap

Technical verification in healthy controls

Go / no go

Operational feasibility in patients

Go / no go

Sensitivity to drug treatment effects

Go / no go

Run smaller, shorter and less expensive PoC!

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1. Increase frequency of measurements

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Cognition fluctuates

Adapted from: Hassenstab et al., 2017

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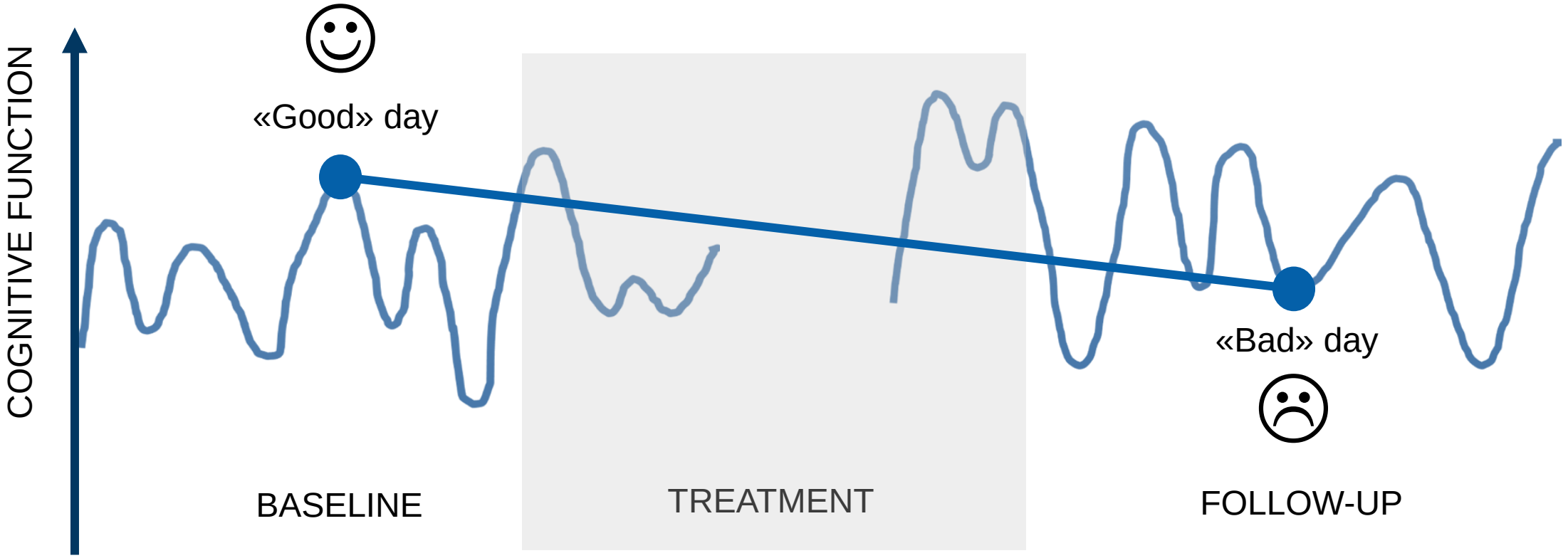
Today, pharma industry is measuring cognition very poorly



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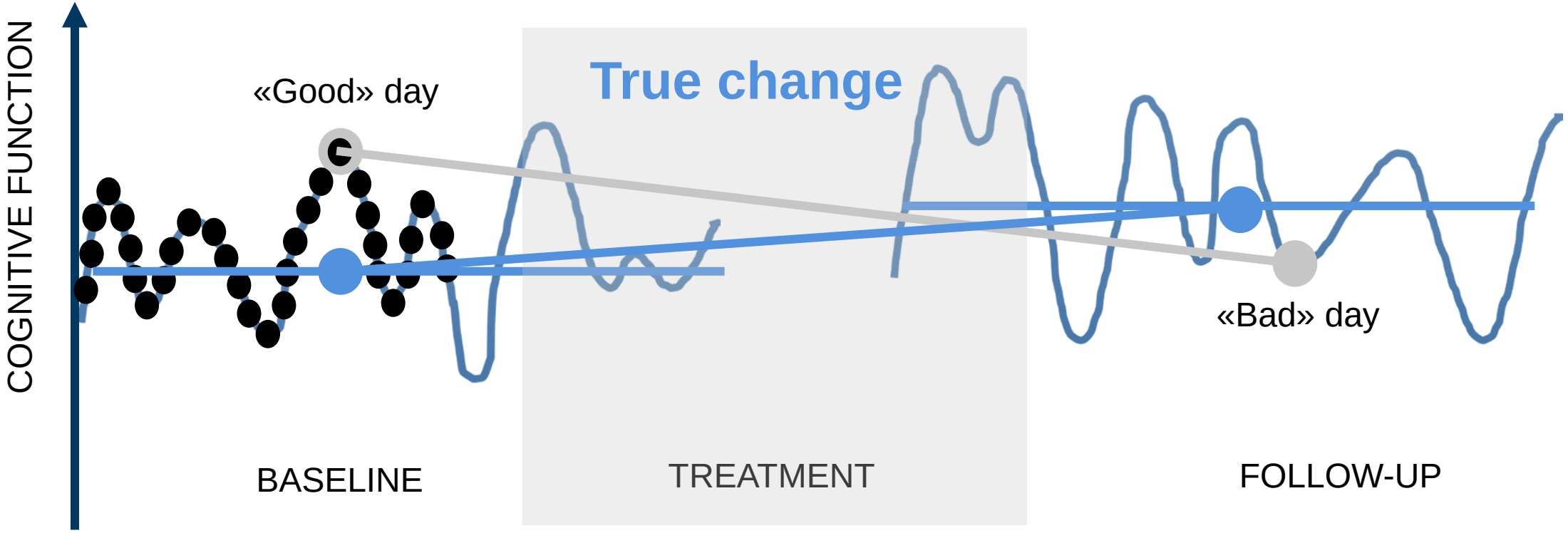
True change needs frequent evaluation and patient follow-up



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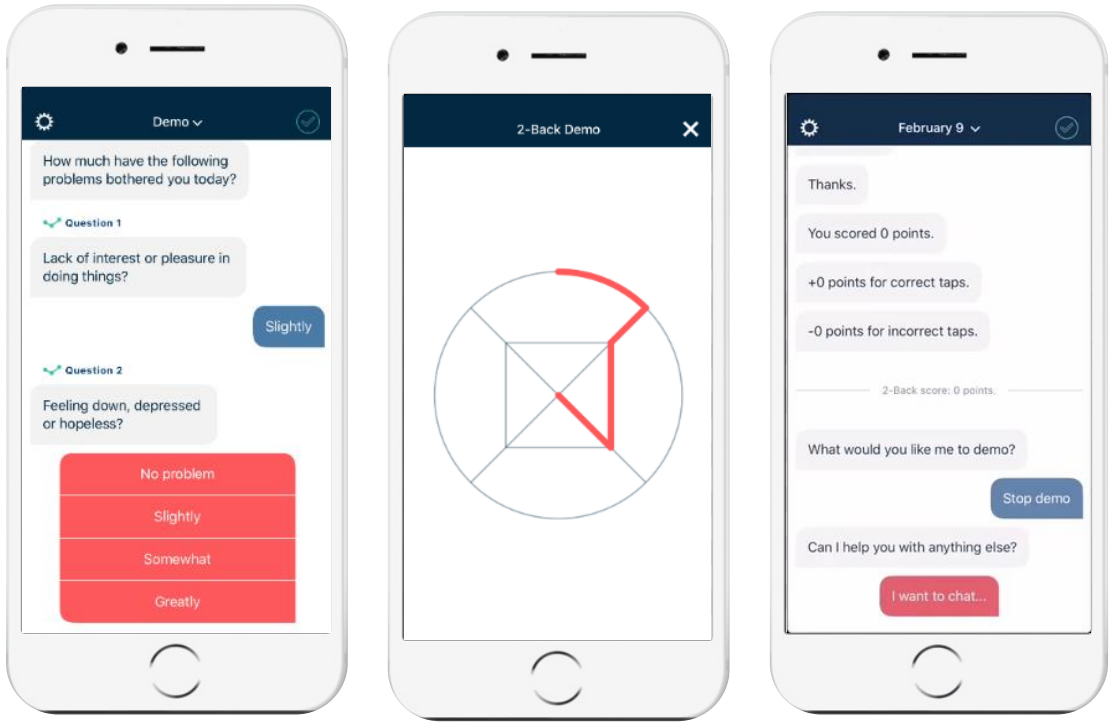
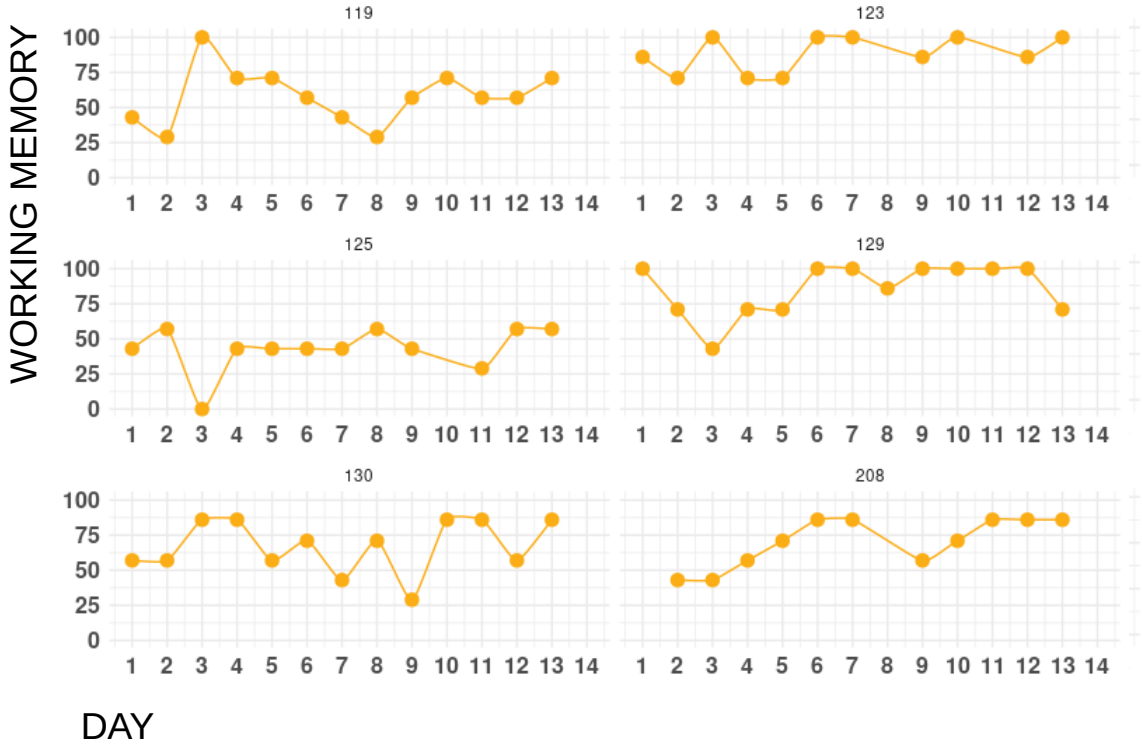
Daily measures of mood and cognition via chat bot app



Working memory fluctuations in depression



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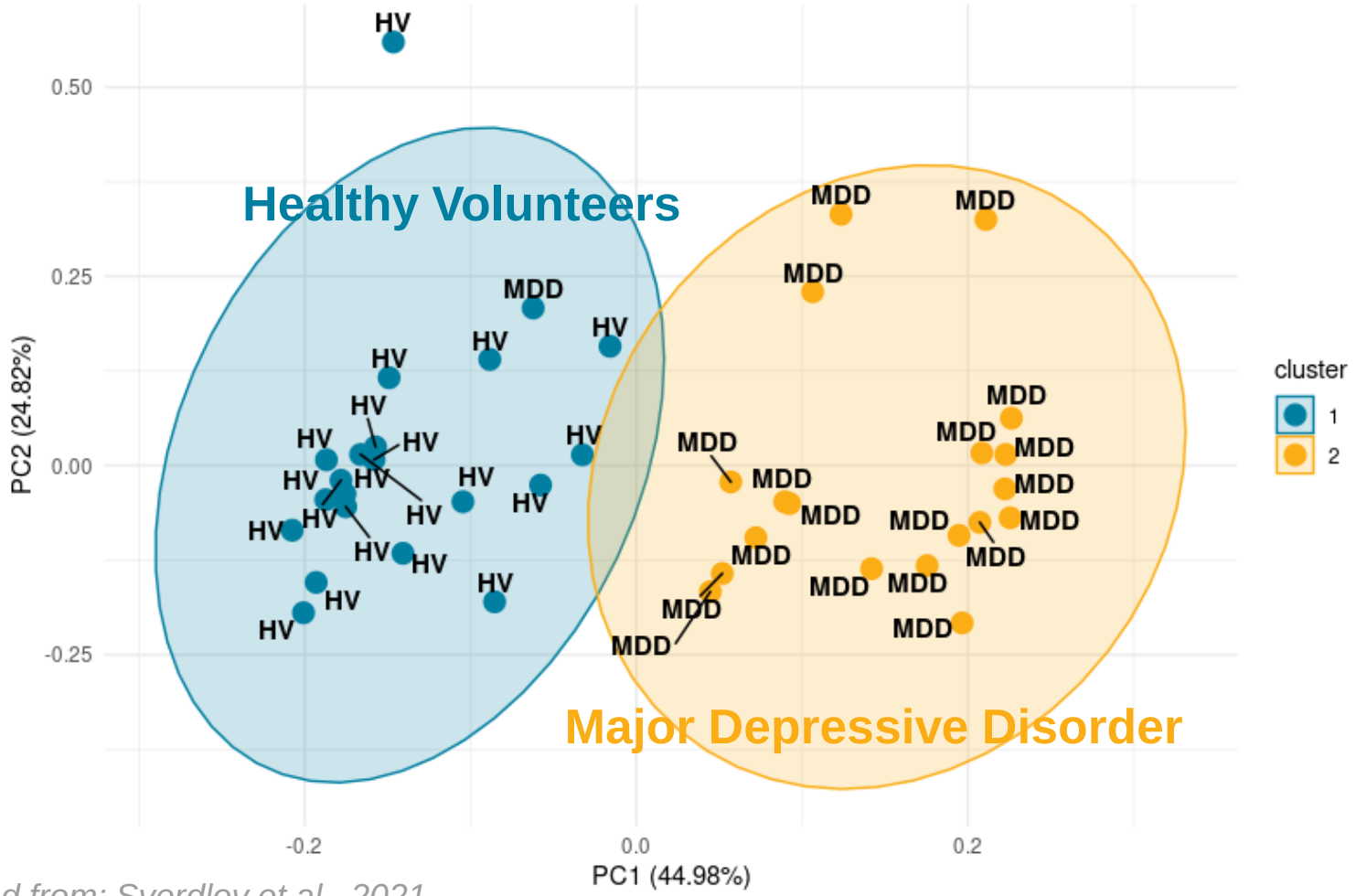
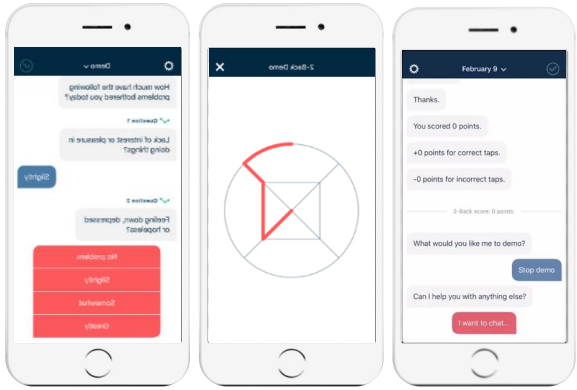
Separating health and disease by using repeated measures from digital devices





Accuracy = 97.5%

Sensitivity 95%
Specificity 100%

Adapted from: Sverdlov et al., 2021

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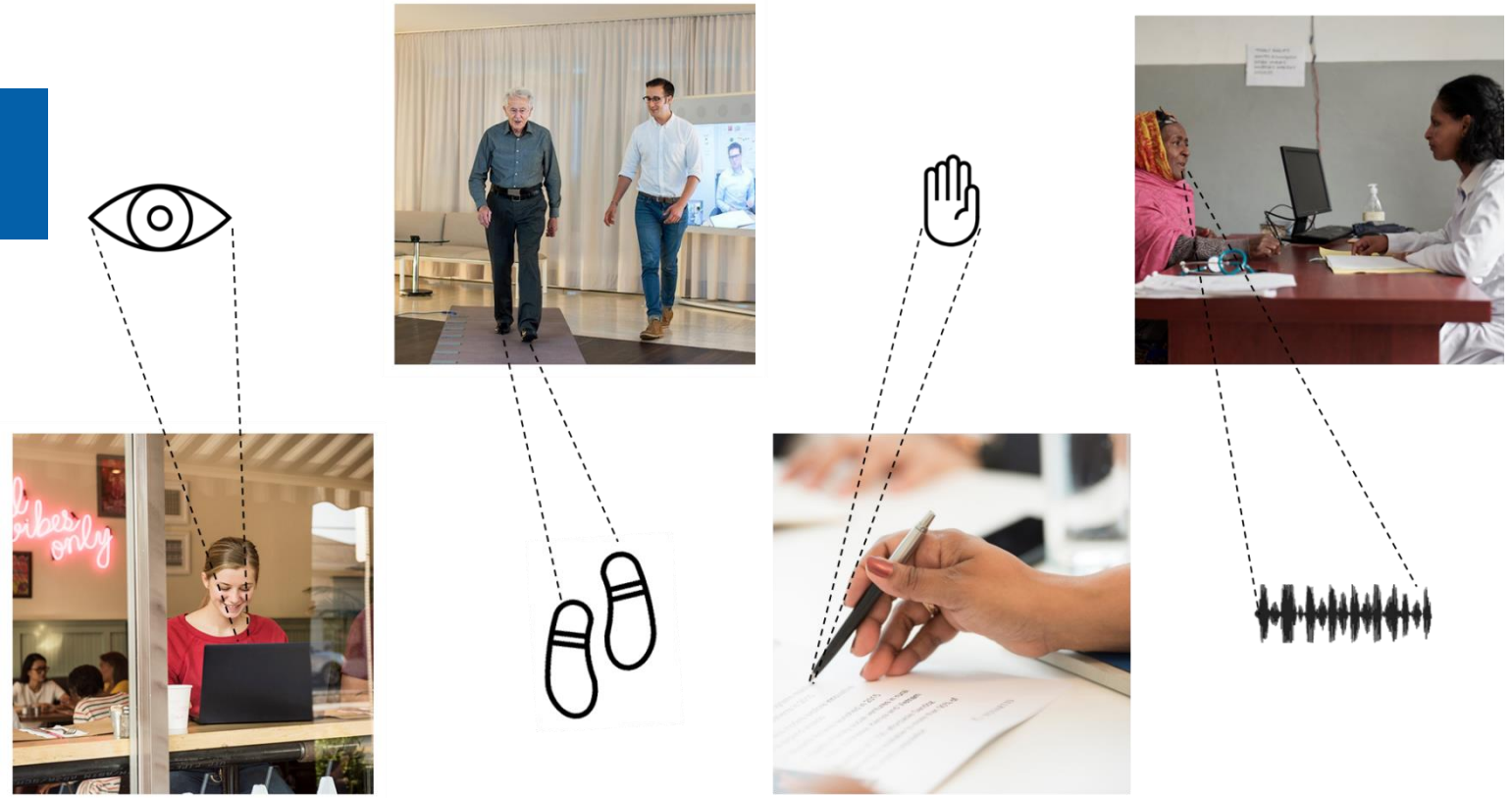
Leverage technology to increase frequency of endpoints that fluctuate

- Cognition
- Mood
- Various activity measures (e.g. step counts)
- Various subjective diaries (e.g. sleep, pain, fatigue...)

Reduction of variability



2. Use objective measures

Dual task interference

Motor-cognitive dual tasking

… the concurrent performance of two tasks that can be performed independently and have distinct and separate goals.

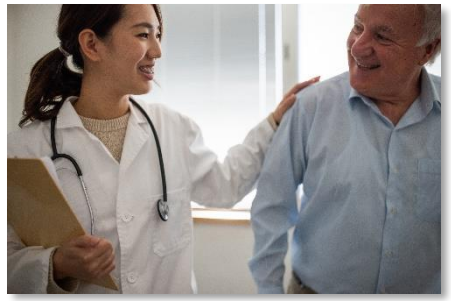
McIsaac et al. (2015)

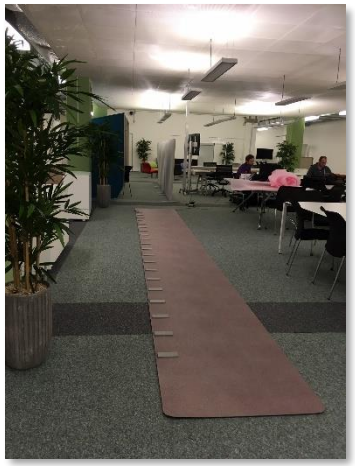
… ecologically valid test assessing quality of life and everyday function!

McFadyen et al. (2017)

In the clinic and in clinical trials

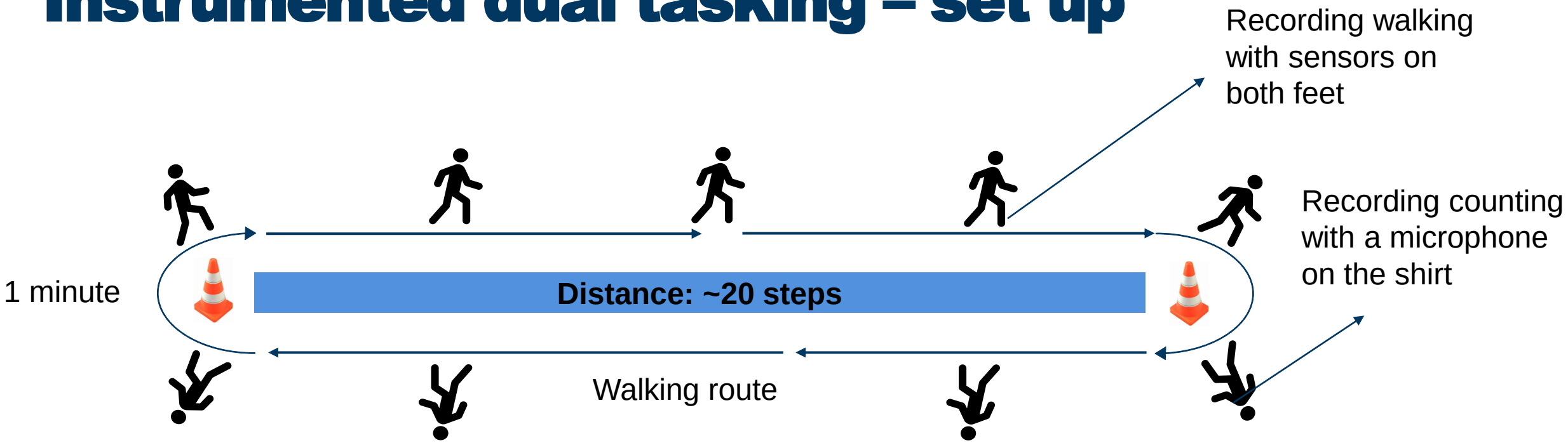
- The nurse or a doctor would ask the patient a question while walking to the examination room and observe if they stop to answer
- «Stops walking when talking» test predictor of falls in elderly
- GaitRite – sensorized walking mat
- Still research focuses on changes in walking while cognitive task is mostly ignored





Lundin-Olssen et al. (1997)
Montero-Odasso et al. (2009)
Bridenbaugh and Kressig (2014)

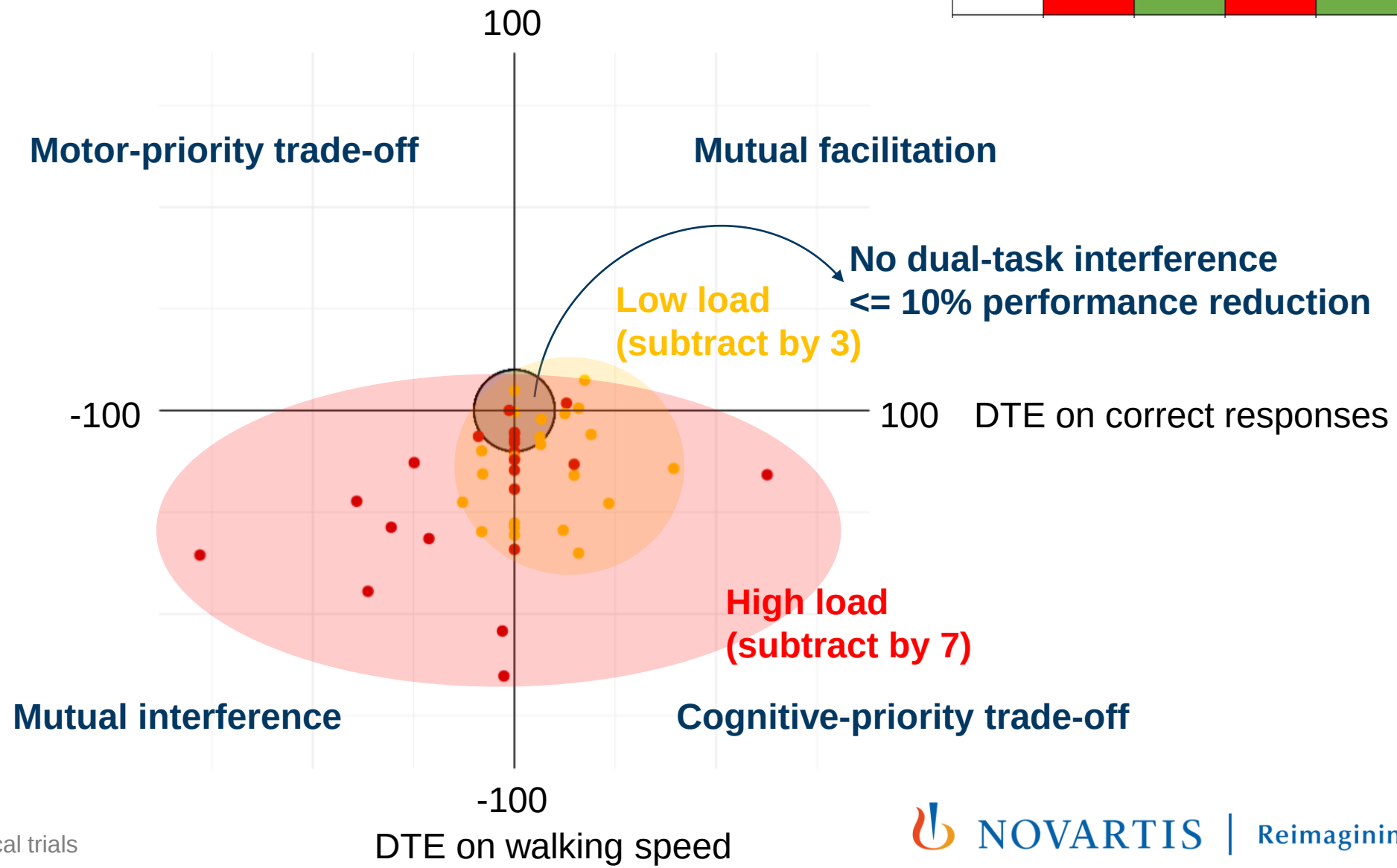
Instrumented dual tasking – set up



Task						
Cognitive	Rest	-3	-7	-7	-3	Rest
Motor	Walk	Sit	Walk	Sit	Walk	Walk

Dual task effect (DTE)

Task						
Cognitive	Rest	-3	-7	-7	-3	Rest
Motor	Walk	Sit	Walk	Sit	Walk	Walk



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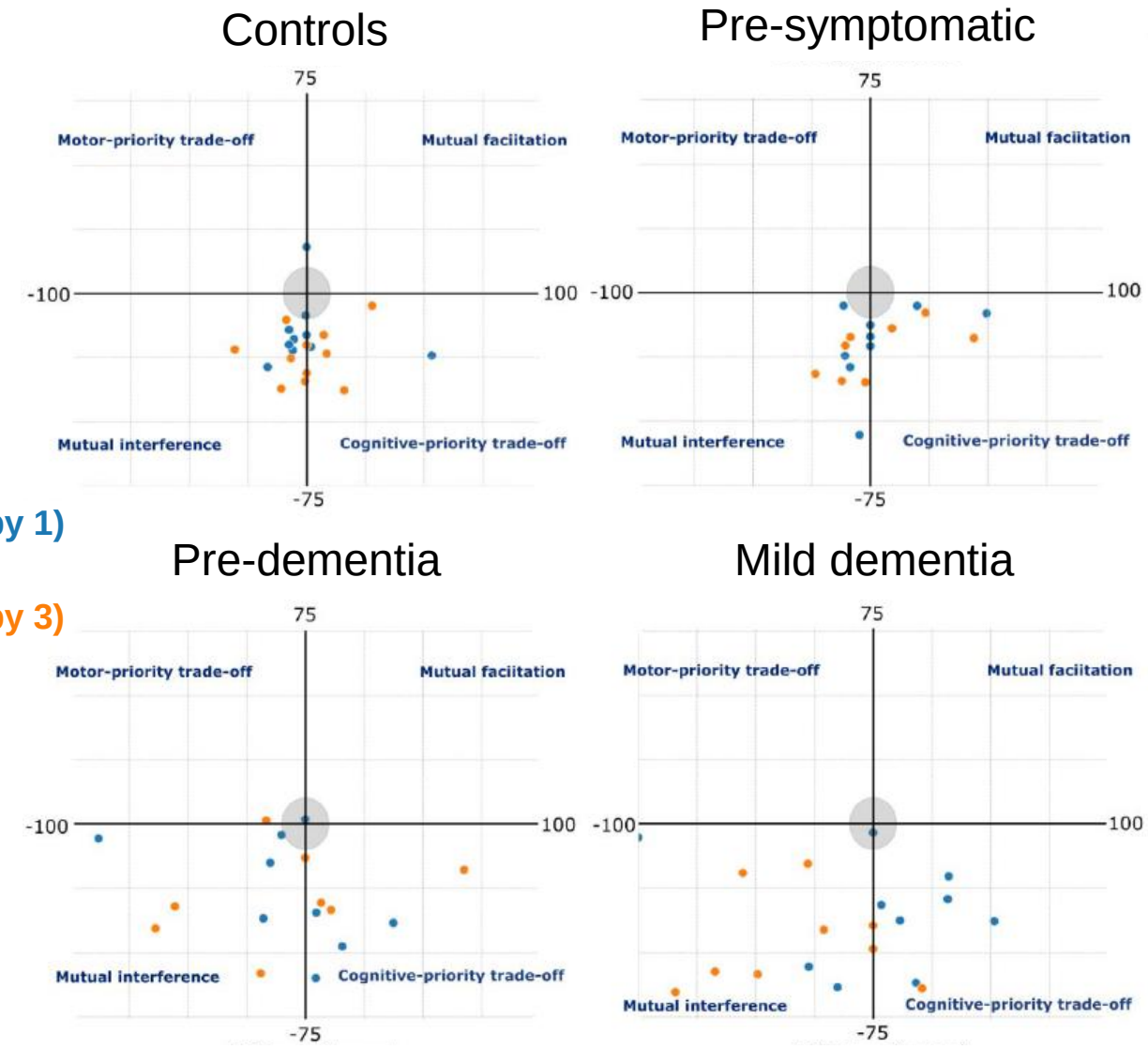
Preliminary results in Alzheimer's disease



All cohorts show cognitive-priority trade-off → better or stable responses while slower walking

Shift toward mutual interference → worsening of cognitive performance and slower walking especially in mild dementia and when cognitive load increases

Sorinas et al. AAIC (2022)

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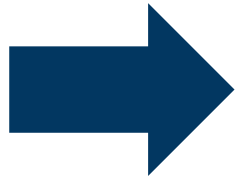
Leverage technology to enhance conventional clinical endpoints

- Recording hand movements while performing standard drawing tests
- Recording voice for voice, speech and language analytics
- Measuring walking and talking while dual tasking
- Recording eye movements while reading



Increase sensitivity

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3. Increase quality of measurements

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Digital endpoints suffer some of the same problems as conventional clinical endpoints

- Careful selection of technology providers
- Building relationship and partnership with technology providers
- Careful selection of sites and raters
- Building trust and partnership with sites and raters
- Careful training of sites, raters, participants and study partners
- Discuss selection of endpoints with Key Opinion Leaders
- Careful assessment of versions and translations of test instructions
- Reduce complexity for sites and participants by combining solutions

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Practical considerations when implementing technology into clinical trials

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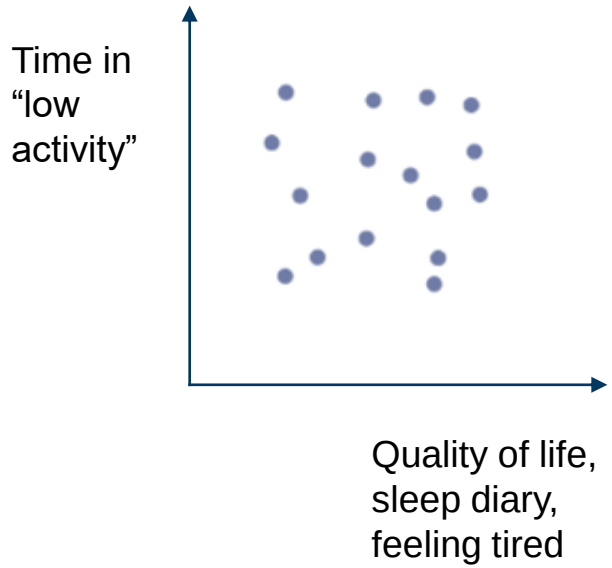
Correlation pitfall

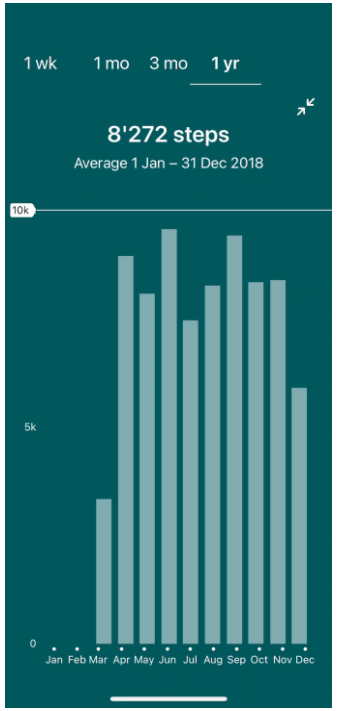
- Subjective cognitive measures like questionnaires (PRO) more often correlate with mood and not with objective measures of cognition (i.e. performance measures)
  - We advise clinical teams to measure together

- Time in “low activity” as measured by accelerometer on the wrist will not correlate with a sleep diary
  - We advise clinical teams on what the “device” is actually measuring and how to interpret results



Variability pitfall

- Based on internal datasets and biobank data measuring only acceleration with a wrist worn device has limited value (i.e. variability due to external factors and behavior is much more pronounced than medication effects)
  - We advise teams to always use multi-sensor wearable device measuring vital signs as well as acceleration (i.e. GSR, PPG, SPO2 etc)



Participant burden

- Frequency of assessments has to be carefully considered together with the study team based on study design
- Technology providers are developing short, efficient and repeatable tests
- Consider “burst” testing – e.g. every day one week before the visit

Thank you

Acknowledgement
We couldn't do this without you ☺

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