Leveraging technology for better clinical endpoints

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FUTURE CLINICAL TRIALS – FROM TOMORROW TO 2030 – WHY CHOOSE THE NORDICS?
Problem statement:
Conventional clinical endpoints have high variability which leads to poor drug signal detection

Key strategy is to increase drug signal detection by reducing variability and bias through:

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

Future clinical trials

Healthy volunteer
- Technical verification in healthy controls
  - Go / no go

Methodology study in patients
- Operational feasibility in patients
  - Go / no go

Exploratory in PoC trials
- Sensitivity to drug treatment effects
  - Go / no go

Primary in PoC trial
- Run smaller, shorter and less expensive PoC!
1. Increase frequency of measurements
Cognition fluctuates

«Good» day: fresh and had a coffee

«Bad» day: no sleep the night before

Adapted from: Hassenstab et al., 2017
Today, pharma industry is measuring cognition very poorly.
True change needs frequent evaluation and patient follow-up
Daily measures of mood and cognition via chat bot app

Working memory fluctuations in depression
Separating health and disease by using repeated measures from digital devices

Accuracy = 97.5%
Sensitivity 95%
Specificity 100%

Adapted from: Sverdlov et al., 2021
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-Olsson et al. (1997)
Montero-Odasso et al. (2009)
Bridenbaugh and Kressig (2014)
Instrumented dual tasking – set up

1 minute

Distance: ~20 steps

Walking route

Recording walking with sensors on both feet

Recording counting with a microphone on the shirt

<table>
<thead>
<tr>
<th>Task</th>
<th>1 minute</th>
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<td>Walk</td>
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Dual task effect (DTE)

- Mutual facilitation
  - No dual-task interference ≤ 10% performance reduction
- Motor-priority trade-off
  - Low load (subtract by 3)
- Cognitive-priority trade-off
  - High load (subtract by 7)

Future clinical trials

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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)
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
3. Increase quality of measurements
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
Practical considerations when implementing technology into clinical trials
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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