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R01AG070897, R01AG067546, R01AG058687

Consulting:
Biogen, Inc.
PRESENTATION OUTLINE

I. Advantages of using digital biomarkers as clinical trial outcomes

II. Selection bias within minority cohorts?
   Lessons learned from the I-CONECT project
Advantages of Digital Biomarkers as Trial Outcomes
CHALLENGES IN DEMENTIA TRIALS

• Large intra-individual variability & fluctuations
  Fluctuations within a short time duration (i.e., morning vs. at night, or good day vs. bad day) can easily override the long-term changes which occur gradually in one year or even several years.

• Large inter-individual variability
  Pathological burden ≠ Symptoms (due to variability in inter-individual levels of cognitive reserve and resilience)

Comparing average changes in outcomes by trial groups does not work!!

-- hard to obtain high signal-to-noise ratios
Advantage of Digital Biomarkers (1)

Top line: “annual assessment” indicates that the measured function is declining.

Bottom line: “annual assessment” indicates that the measured function is stable.

Precision improves by monitoring intra-individual variability.

If we had more frequent assessments....

Precision improves by monitoring intra-individual variability.
Distribution can be generated for EACH individual within short duration of data accrual periods
Your walking speed ≠ my walking speed
Your computer use ≠ my computer use

Using continuously monitored data:

In-Home Walking Speed Observed During the 90 days for 2 subjects
Transforming Clinical Trials with High Frequency, Objective, Continuous Data: “Big Data” for Each Subject

### MCI Prevention Trial – Sample Size Estimates

<table>
<thead>
<tr>
<th></th>
<th>Current Method</th>
<th>Using Subject-Specific Cutpoint as outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LM Delayed Recall*</td>
<td>Computer Use**</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 50% EFFECT</td>
<td>688</td>
<td>10</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 40% EFFECT</td>
<td>1076</td>
<td>16</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 30% EFFECT</td>
<td>1912</td>
<td>26</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 20% EFFECT</td>
<td>4300</td>
<td>58</td>
</tr>
</tbody>
</table>

- Reduces required sample size
- Reduces exposure to harm (fewer needed/ fewer exposed)
- More precise estimates of the trajectory of change; allows for intra-individual predictions.
- Provides the opportunity to substantially improve efficiency and inform go/no-go decisions of trials.

Walking Speed Declines Prior to PD Diagnosis

Subject P, stopwatch speed at in-person visit

Subject P, mean in-home walking speed

Peer group, normal mean in-home speed (n=100)

Data from Oregon Center for Aging and Technology (ORCATECH), PI: Kaye
Walking Speed Declines Prior to PD Diagnosis

Subject P, stopwatch speed at in-person visit
Subject P, mean in-home walking speed
Peer group, normal mean in-home speed (n=100)

Data from Oregon Center for Aging and Technology (ORCATECH), PI: Kaye
## Continuous activity monitoring approach

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome</th>
<th>group effect on slope (Normal vs Incidence)*</th>
<th>(SE)</th>
<th>p-value</th>
<th>Treatment Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linear Mixed Effects Model</strong>*</td>
<td>walking speed</td>
<td>0.0038</td>
<td>0.0115</td>
<td>0.74</td>
<td>92600 41156 23150 14816</td>
</tr>
<tr>
<td></td>
<td>computer usage**</td>
<td>0.0007</td>
<td>0.0003</td>
<td>0.01</td>
<td>1100 490 276 176</td>
</tr>
<tr>
<td></td>
<td>walking speed variability</td>
<td>0.0021</td>
<td>0.0022</td>
<td>0.34</td>
<td>7550 3356 1888 1208</td>
</tr>
<tr>
<td><strong>Generalized Mixed Model</strong></td>
<td>walking speed (likelihood of hitting 10th%tile low)</td>
<td>-0.0008</td>
<td>0.0005</td>
<td>0.1</td>
<td>588 262 148 94</td>
</tr>
<tr>
<td>(with Random Intercept)</td>
<td>computer usage (likelihood of hitting 40th%tile low)</td>
<td>-0.0016</td>
<td>0.0002</td>
<td>&lt;.0001</td>
<td>58 26 16 10</td>
</tr>
<tr>
<td></td>
<td>walking speed variability (70th%tile high)</td>
<td>-0.0009</td>
<td>0.0003</td>
<td>0.0009</td>
<td>184 82 46 30</td>
</tr>
</tbody>
</table>

Dodge et al., Plos One 2015
Use person-specific thresholds

Dodge Threshold Model (DTM)


Wu et al., A & D: TRCI (2021)
Advantage of Digital Biomarkers (2)

• Use each subject as their own universe in order to identify subtle changes or deviations from their own pre-morbid stage (i.e., use subject-specifically defined normative stage).

• “Big Data” for Each Subject

  Eliminate inter-individual variability → Increase signal-to-noise ratio > reduced sample size
Advantage of Digital Biomarkers (3)

Digital biomarkers are relevant for patients’ daily function and well-being, i.e., *clinically relevant and meaningful*. Which one matters more for participant and his/her family and “clinical” diagnosis?

- My CSF Ab42 went up by 0.02 SD
- My MMSE score improved by 0.5 point
- My medication adherence improved: I do not often forget taking medications
- I sleep better at night and therefore am more active during daytime
Advantage of Digital Biomarkers (4)

Digital biomarkers are relevant for patients’ daily function and well-being, i.e., **clinically more relevant and meaningful**

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- My CSF Ab42 went up by 0.02 SD
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- My medication adherence improved: I do not often forget taking medications
- I sleep better at night and therefore am more active during daytime

Translational effects are measurable using digital devices
Advantage of Digital Biomarkers (3)

Current Regulatory Perspective

Gold Standard Outcomes:
CDR, CDRSoB, Incidence, Traditional NP tests

Biomarkers
Targeted by a specific compound:
Clear mechanistic hypothesis

Digital Biomarkers
Indicators of daily functions, clinically meaningful
Sensitive secondary endpoints (or even primary endpoints in the future)
Digital Biomarkers as Trial Outcomes: ADVANTAGES

- Non invasive (cost effective, low participants’ burden)
- Clinically meaningful (closely tied with daily functions and well-being, clinical diagnosis)
- High-frequency data
  - Improve precision, increase signal-to-noise ratio
  - *Use each subject as their own universe* so that we can *identify subtle changes or deviations* from their own pre-morbid stage (e.g., DTM)
- Potentially reduce trial duration (e.g., changes in CDR or incidence of MCI take a long time, digital biomarker changes can be observed sooner)
Current Limitations

• Not many trials are using digital biomarkers as outcomes.
• A big effort is needed to implement digital biomarkers as trial outcomes to establish more evidence (e.g., show higher efficacy than traditional outcomes).

More trials need to include digital biomarkers as secondary or exploratory outcomes.
The theme of the ADC meeting: Diversity/Equity/Inclusion

SELECTION BIAS WITHIN MINORITY GROUPS ??

A Lesson learned from the I-CONECT Project Recruitment
The most recent report by the Lancet Commissions (Livingstone, et al., 2020) estimates that 4% of dementia cases can be prevented by eliminating social isolation (larger than 2% estimated for physical inactivity and 1% for diabetes.)
RCT Aimed to Enhance Cognitive Functions through Stimulations from Social Interactions Using Video Chats among the Older Old

- Can start without much motivation
- Can be done at home (be delivered to those with chronic illness/homebound)
- Can assess translational effects
- Can be sustainable for the long long term

PI: Dodge

I. NIA R01 AG0033581 (2010-2014) Completed (ClinicalTrials.gov: NCT01571427)
II. NIA R01 AG051628 (2016-2021) Ongoing (Normal)
III. NIA R01 AG056102 (2017-2022) Ongoing (MCI)

www.i-conect.org (ClinicalTrials.gov: NCT02871921)
RCT Aimed to Enhance Cognitive Functions through Stimulations from Social Interactions Using Video Chats among the Older Old

In this series of RCTs

- Participants in the experimental group engaged in 30 minutes of conversation with trained interviewers (conversational staff) using internet/webcam (control: only 10 mts weekly phone calls)
- Conversations: semi-structured in order to standardize interactions, yet require participants to understand interviewers, organize and convey their own thoughts in a natural conversational setting like talking with their friends.
- Expose participants to different conversational staff each week (if possible) to enhance novelty of the experience
Challenge: Recruiting Socially Isolated Older Old

Overall Recruitment

- Contact Attempted N=29,664
- Telephone Screenings N=1,139
- Eligible N=394
- Consented/Screened N=265
- Randomized/Enrolled N=186

Socially Isolated 75+ yrs, Normal or MCI

Caucasians:
- 96% of the targeted (149/160)

African Americans (AA):
- 23% of the targeted (37/160)

TOTAL: 186 randomized (20% AA)

Data collection completion/un-blinded: 8/2021
Methods

- Emotion characteristics were compared between the AA and Caucasians using NIH toolbox emotion battery (NIHTB-EB), including 3 domains and 17 subscales.

- Baseline data from the Internet-Based Conversational Engagement Clinical Trial (I-CONECT)

- Linear regression models comparing the NIHTB-EB outcomes between Caucasian and AA participants
Table 1. Linear regressions compare NIH toolbox emotion battery domain scores of AA and Caucasian participants (N=163, Reference group – Caucasian participants)

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Three domains of NIHTB-EB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Affect</td>
<td>-2.573</td>
<td>1.597</td>
<td>0.109</td>
</tr>
<tr>
<td>Psychological Wellbeing</td>
<td>5.670</td>
<td>1.589</td>
<td>0.000***</td>
</tr>
<tr>
<td>Social Satisfaction</td>
<td>7.915</td>
<td>1.804</td>
<td>0.000***</td>
</tr>
<tr>
<td><strong>B. Subscales of the Negative Affect domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger Affect</td>
<td>-2.195</td>
<td>1.634</td>
<td>0.181</td>
</tr>
<tr>
<td>Anger Hostility</td>
<td>-0.432</td>
<td>1.630</td>
<td>0.791</td>
</tr>
<tr>
<td>Sadness</td>
<td>-5.394</td>
<td>1.969</td>
<td>0.007**</td>
</tr>
<tr>
<td>Fear Affect</td>
<td>-1.749</td>
<td>1.987</td>
<td>0.380</td>
</tr>
<tr>
<td>Perceived Stress</td>
<td>-1.245</td>
<td>1.689</td>
<td>0.462</td>
</tr>
<tr>
<td><strong>C. Subscales of the Psychological Wellbeing domain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Affect</td>
<td>4.742</td>
<td>1.580</td>
<td>0.003**</td>
</tr>
<tr>
<td>Meaning and Purpose</td>
<td>7.698</td>
<td>1.553</td>
<td>0.000***</td>
</tr>
<tr>
<td>General Satisfaction</td>
<td>1.606</td>
<td>1.797</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Note: *p<.05, **p<.01, ***p<.001. All models controlled for age, sex, education, MCI status, marital status and depressive symptoms. NIHTB-EB: population mean=50, SD=10.
Selection Bias in Recruitment

Function/cognition/emotion
The findings comparing NIBTB-EB outcomes show that AA participants were better off than their Caucasian counterparts in psychological wellbeing and social satisfaction.

**Selection bias** among the minority groups since it’s more difficult to recruit them??

Merely increasing the proportion of minority participants might introduce some unexpected bias in trial results.
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www.i-conect.org, www.iconnectfoundation.org
THANK YOU!!

Contact e-mail: hdodge@mgh.Harvard.edu
I-CONECT project: digital biomarker (linguistic characteristics) as trial outcomes: the results will be presented in the Data Blitz by Dr. Asgari
Operational Definition of Isolation in I-CONECT

• The participants were considered socially isolated if they met **any one of the following three criteria:**
  1) Scoring <12 on the 6-item Lubben Social Network Scale (LSNS-6)
  2) Engaging in conversations lasting 30 minutes ≤ twice per week
  3) Answering "often" to at least one question of the three-item UCLA Loneliness Scale.