Summary of Advancing CDISC Standards for BMD Use in Clinical Development of Neurologic and Psychiatric Treatments

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# IMPAIRED MOBILITY/FRAILTY, SLEEP AND COGNITION ARE PROMINENT ACROSS NEURODEGENERATIVE DISEASES

**Functional Impact:**
- Social life and social participation
- Work/life
- Relationships and family
- Independence

## Symptoms & Signs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptom/Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>Cognitive impairments, Speech problems, Depression, Sleeping changes, Gait slowed, Dizziness/vertigo, Swallowing (advanced stages), Pain</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>Tremor, Walking &amp; gait impairment, Spasticity, Pain, Depression, Bowel/bladder problems, Fatigue, Sleeping impaired, Dizziness/vertigo, Cognitive impairments, Speech problems</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Depression, Pain, Numbness/tingling, Sexual dysfunction, Fatigue, Spasticity, Lower &amp; upper extremity impairments, Walking impairment, Bowel/bladder problems, Dizziness/vertigo, Cognitive impairments, Speech problems</td>
</tr>
<tr>
<td>Huntington’s</td>
<td>Irritability, Depression, Pain, Fatigue, Sleeping problems, Spasticity, Walking impairment, Upper &amp; lower extremity impairments, Dizziness/vertigo, Cognitive impairments, Speech problems</td>
</tr>
</tbody>
</table>

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[www.c-path.org/camd](http://www.c-path.org/camd)
DEFINING DISEASE & TREATMENT RESPONSE

Disease (ICD-10 code) = Symptoms + Signs

Use in Drug Development & Reimbursement
- Alzheimer’s disease
- Parkinson’s disease
- Huntington’s disease
- Multiple Sclerosis

Patient Reported Outcomes
- Cognition
- Behavior (sleep/mood)
- Motor function
- Sensation
- Balance and coordination
- Autonomic

Observer / Performance Outcomes
- Cognition
- Behavior (sleep/mood)
- Motor function
- Sensation
- Balance and coordination
- Autonomic

Functional Impact Domains

Cross-correlation of functional biosensor measurements with fluid and imaging biomarkers and PROs


www.c-path.org/camd
MEASURES TO SUPPORT CONCEPTS-OF-INTEREST

- BMD
  - Properties
    - Manufacturer (ID)
    - Identifiers
    - Algorithm(s)
  - Subject
    - Anatomical or remote locations

- Mobility/Frailty
  - Time and distance in/out of home
  - Voice
  - Dyskinesias and tremors
  - Motor fluctuations
    - ADLs
    - Grip strength
    - Gait and falls

- Sleep
  - Sleep onset latency
  - Total sleep time
  - Wake after sleep onset
  - Quality of sleep time (REM vs. non-REM)
  - Excessive daytime sleepiness
  - Daytime sleep

- Cognition
  - Attention
  - Delayed recall
  - Speed of information processing
  - Spatial memory
  - Executive function
  - IADLs

Raw Data → Transformed → Quantitative Assessment
“DIGITAL BIOMARKERS: SENSING LIFE KINETICS”
Dr. Jeffrey Kaye, Director, Oregon Center for Aging & Technology

**Every Day Cognition:**
Medication adherence as a measure of cognitive function

- Adherence assessed continuously x 5 wks with MedTracker taking a
- Mean Age - 83 yrs
- Based on ADAS cog: Lower Cognition Group vs Higher Cognition Group


Significantly Worse Adherence in Lower Cognition Group

- Median time within 53.4 mins of goal
- Median time within 12.0 mins of goal

**Differentiation of early MCI:**
Total Activity & Walking

Activity patterns associated with mild cognitive impairment


Trajectories of walking speed over time


MCI cases 9X more likely in Slow Group

**Differentiation of early MCI:**
Night-time Behavior & Sleep


**Routine home PC use over time (without formal tests or queries) detects change in those with MCI**

- Mean 1.5 hours on computer/per day at baseline month
- Over time:
  - Less use days per month
  - Less use time when in session
  - More variable in use pattern over time

Kaye, et al. AAIC, 2011

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Correlations with Validated Outcome Assessments

Raw Sensor Data
- Motion Detectors
- Location Tracking
- Load Cells / Bed Sensors
- Contact/Door Switches
- Phone Sensors
- Computer
- Medication Tracker
- Weight Scale

Direct Assessment
- Gait Velocity
- Location Estimation
- Sleep
- Departures/Arrivals
- Phone Use
- Computer Interactions
- Medication Events
- Weight

Inference
- Mobility
- Sleep Hygiene
- Socialization
- Depression
- Memory
- Pain
- Medication Adherence
- Physical Impairments

Change Detection

Cross-correlation of functional biosensor measurements with fluid & imaging biomarkers & PROs to develop more sensitive Outcome Assessments

Quality of Life Surrogate
- Independence
- Social life & social participation
- Work life
- Relationships & family
TRANSFORMING CLINICAL TRIALS WITH HIGH FREQUENCY, OBJECTIVE, CONTINUOUS DATA: “Smart Data” for Each Subject

<table>
<thead>
<tr>
<th>Continuous Measures</th>
<th>LM Delayed Recall*</th>
<th>Computer Current Method Use**</th>
<th>Walking Speed**</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMPLE SIZE TO SHOW 50% EFFECT</td>
<td>688</td>
<td>10 [1.5%]</td>
<td>94 [13.7%]</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 40% EFFECT</td>
<td>1076</td>
<td>16 [1.5%]</td>
<td>148 [13.7%]</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 30% EFFECT</td>
<td>1912</td>
<td>26 [1.4%]</td>
<td>262 [13.7%]</td>
</tr>
<tr>
<td>SAMPLE SIZE TO SHOW 20% EFFECT</td>
<td>4300</td>
<td>58 [1.4%]</td>
<td>588 [13.7%]</td>
</tr>
</tbody>
</table>

- Reduces required sample size and/or time to identify meaningful change
- 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. <14% of current patient costs with standard measures.

BMDs THE POTENTIAL TO CREATE MORE SENSITIVE ASSESSMENTS OF PHYSIOLOGICAL AND BEHAVIOR SIGNS OF HEALTH AND DISEASE

The Progression of Chronic CNS Diseases

A

Presymptomatic (normal)

Prodromal Disease

Manifest Disease

B

We need to be here to treat the earliest stages of disease detected by more sensitive assessments of physiologic and behavioral signs

Current biomarkers, existing COAs & approved treatments

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SURVEY: THE VOICE OF THOSE WHO CARE

Understanding what is most valued by the patient and their caregivers regarding innovative treatments for chronic diseases is of growing importance to regulators [e.g., U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japan’s Pharmaceutical and Medical Device Agency (PMDA)], healthcare providers (i.e., medical professionals and insurers), and the healthcare industry (i.e., pharmaceuticals and medical devices).

Chronic neurological and psychiatric diseases including Alzheimer’s disease, Parkinson’s disease, Multiple Sclerosis, Huntington’s disease, Amyotrophic Lateral Sclerosis, Depression and Schizophrenia share some common core symptoms. As these symptoms can vary during the course of these diseases, the Coalition Against Major Diseases (CAMD) has focused this survey on three areas that can profoundly influence the individual’s quality-of-life (QoL): mobility, sleep and cognition (i.e., memory).

CAMD is a consortium of non-profit and for-profit organizations working to improve and accelerate drug development for brain diseases (https://c-path.org/programs/camd/). CAMD has experienced first-hand how the ability to share key data can accelerate and improve the delivery of effective therapies to patients.

Please answer the following questions to help us understand what is most important to you in developing, approving and providing “medicines that matter”. All answers will remain anonymous.

LINK:
https://www.surveymonkey.com/r/quality-of-lifesurvey
DIGITAL DRUG DEVELOPMENT TOOLS

Qualifying Biometric Monitoring Devices (BMDs) for specific Contexts-of-Use

**WHAT**
Data (signal output) collected from a biosensor that measures a biological response

**HOW**
Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestible, remote biosensors)

**WHY**
Improve our understanding of real-time changes in FUNCTION during the progression of life in health & disease

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I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning.

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Visit: www.c-path.org/camd
Many consortia have more than one focus area. However, a majority (68%) focus on one (41%) or two (27%) areas.

80% of consortia choose not to invest in data sharing; of the 20% that do, not all make data available outside the consortium.

4% focus on advancing regulatory sciences.
CDISC STANDARDS ARE FOUNDATIONAL IN CREATING ACTIONABLE DATABASES

CDISC SHARE library overview

Many aspects of the infrastructure required to understand disease progression and treatment impact in clinical drug trials already exist (from CDISC 2017 Training Materials)

CDISC Standards are required for registrations studies at FDA, PMDA, etc.
A need for understanding all sources of variability

Different data produces different results
THE FUTURE OF HEALTH CARE

Increasing the probability of success for early interventions of chronic diseases (e.g., AD) will rely upon advancing regulatory science related to BMDs & modeling of standardized GLOBAL clinical data and RWE

THE VISION OF BMD USE IN CLINICAL TRIALS

• All clinical trials will involve continuous remote monitoring of participant physiology/performance
• Data is streamed from the participant to the cloud, and analyzed in real-time for automated change detections
• Earlier & automated identification of adverse events, and therapeutic response are SOP
• Algorithm-driven notifications/assessments to participant/health care professional will enable timely changes in health care delivery
Thank you!

Pharmaceutical Industry
- AbbVie Inc.
- Biogen
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Eisai
- Eli Lilly and Company
- Roche/Genentech
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Merck, Sharp & Dohme Corp.
- Novartis Pharmaceutical
- Pfizer, Inc.
- Takeda

Government and Regulatory Agencies
- European Medicines Agency (EMA)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute on Aging (NIA)
- U.S. Food and Drug Administration (FDA)
- National Institutes of Health (NIH)

Non-profit Research Organizations
- Alzheimer’s Association
- UsAgainstAlzheimer’s Network
- Alzheimer’s Research UK
- Alzheimer’s Drug Discovery Foundation
- CHDI Foundation