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

May 9, 2017

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Fourteen global consortia collaborating with 1,450+ scientists and 84 organizations
C-PATH CLINICAL DATA CONTRIBUTIONS

Growing Clinical Data Contributions

- Clinical studies: 97
- Subjects: 54,044

Diseases:
- T1D
- Duchenne Muscular Dystrophy
- Kidney healthy volunteer study
- Polycystic kidney disease
- Multiple sclerosis
- Tuberculosis
- Parkinson's disease
- Alzheimer's disease

Note: Nonclinical 116 studies; 6296 subjects.
ReSeqTB: 3558 Individual solates
COALITION AGAINST MAJOR DISEASES (CAMD)

Mission
To develop, as a pre-competitive consortium, new technologies and methods to accelerate the development and review of medical products for treating Alzheimer’s Disease and dementias of related neurodegenerative diseases.

Focus
Advancement of regulatory science supporting Drug Development Tools (DDTs) for Alzheimer disease and related dementias with impaired cognition and function.
Integrated Data

Mixed Disparate Legacy Data

CDISC ‘Standardized Data’

STEP 2: AD DRUG-DISEASE-TRIAL MODEL

Integrating the Clinical Trialist’s World

- Natural History
- Interpatient Variability
- Patient Specific Factors
- Imaging and CSF Biomarkers

186 patients

Longitudinal Drug Disease Model

Trial Design Options Doses/N Duration/Sampling Enrichment (BMx, etc.) Dropouts

Integrated Knowledge Model

Statistics

Range of Possible Outcomes

Sponsor Proprietary Data
- Preclinical
- Related products
- Hypothesized effects of novel therapy

Literature Meta-Data
- 73 Trials (1990 to Present)
- Interstudy variability
- Effects of marketed therapeutics (magnitude onset, offset)

17,235 patients

CAMD Database
- 9 trials, 3223 patients
- Interpatient Variability
- Patient Specific Factors
- Placebo Effect

3223 patients

How to request access To CAMD database:
www.codr.c-path.org
Today >6500 patients

www.c-path.org/camd
STEP 3: USE

Balancing power, sample size, and duration, given varying effect magnitudes

- **Crossover**: 91 weeks
- **Parallel**: 78 weeks

- Better power
- ~50% Cost Savings
- Less time
AD DRUG DISEASE TRIAL MODEL –
THE REGULATORY PATH

The total journey took 1,317 days (3 years, 7 months and 9 days)

- On June 12, 2013 the **FDA** determined the CTS tool was “Fit for Purpose.”
- On September 19, 2013 the **EMA** determined the CTS tool was “Qualified for Use.”
CAMD’S ALZHEIMER’S DISEASE DATABASE
(OCTOBER 10, 2016) (% change over the last 4 months)

CAMD joined GAAIN – December 2015

CAMD’S ALZHEIMER’S DISEASE DATABASE

242 Organizations
Abbott
ALSTDI
ALZFORUM
BILL & MELINDA GATES foundation
GE Global Research
Genentech
GlaxoSmithKline
National Institutes of Health
The Michael J. Fox Foundation
...and others
+3%

343 Individuals
+3%

89 Academic Institutions
+3%

...and others

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CAMD CLINICAL TRIAL SIMULATION TOOL (OCTOBER 10, 2016) (% change over the last 4 months)

CAMD’S CLINICAL TRIAL SIMULATION TOOL FOR ALZHEIMER’S DISEASE

- **Organizations**: 58 (+7%)
  - AstraZeneca
  - Biogen
  - Bristol-Myers Squibb
  - Lilly
  - Merck
  - Pfizer
  - Takeda
  - ...and others

- **Individuals**: 72 (+7%)

- **Academic Institutions**: 18 (+13%)
  - ...and others

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MAXIMIZING THE USE OF PRE-COMPETITIVE DATA

Accelerate new drug development tools and data acquisition

- CDR-SB
- ICV-vMRI
- Biomarkers

Drug effects
Drop-out rates
Placebo effect
ALZHEIMER’S DISEASE (AD) STAGES

Our dilemma: What to measure and when?

- Current outcomes insensitive
- Patient enrichment is critical
- Current outcomes focused on aMCI to Moderate AD
- Current PRO outcomes unreliable

Memory complaints → Cognitive Impairment → Cognitive, Functional & Behavioral deficits
Pre-Symptomatic → MCI / Prodromal AD → Mild
Preclinical AD

No cognitive complaints – No COAs

MCI Due to AD

Dementia Due to AD

Pre-Dementia → Dementia

MCI / Prodromal AD
Mild

Current diagnosis & treatment

Severe

No apparent symptoms
Symptoms
IMPAIRED MOBILITY/FRAILTY, SLEEP AND COGNITION ARE PROMINENT ACROSS NEURODEGENERATIVE DISEASES

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

Alzheimer’s Disease
- Cognitive impairments
- Speech problems
- Depression
- Sleeping changes
- Gait slowed
- Dizziness/vertigo
- Swallowing (advanced stages)
- Pain

Parkinson’s Disease
- Tremor
- Walking & gait impairment
- Spasticity
- Pain
- Depression
- Bowel/bladder problems
- Fatigue
- Sleeping impaired
- Dizziness/vertigo
- Cognitive impairments
- Speech problems

Multiple Sclerosis
- Depression
- Pain
- Numbness/tingling
- Sexual dysfunction
- Fatigue
- Spasticity
- Lower & upper extremity impairments
- Walking impairment
- Bowel/bladder problems
- Dizziness/vertigo
- Cognitive impairments
- Speech problems
- Sleeping impaired

Huntington’s Disease
- Irritability
- Depression
- Pain
- Fatigue
- Sleeping problems
- Spasticity
- Walking impairment
- Upper & lower extremity impairments
- Dizziness/vertigo
- Cognitive impairments
- Speech problems

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AGE-RELATED NEURODEGENERATIVE DISEASES

Tsunami of Elderly

“Alzheimer's disease is the sixth-leading cause of death in the United States and the only cause of death among the top 10 in the United States that cannot be prevented, cured or even slowed”
- Alzheimer’s Association

~477,000 new AD patients diagnosed each year in the U.S.

Figure 1: Number of Persons 65+, 1900 to 2060 (numbers in millions)

“Increasing population of people with Alzheimer's disease”

Approximately 5.5 million Americans have Alzheimer's disease.

Approximately 50 million Americans aged 50 or older have mild cognitive impairment.

Since 2000, deaths from heart disease have decreased by 14% while deaths from Alzheimer's disease have increased by 89%.

Since 2000, the number of people aged 65 and older has increased by 40%.

1 in 3 seniors dies with Alzheimer’s or another dementia.

~477,000 new AD patients diagnosed each year in the U.S.

14
DEFINING DISEASE

Requires a composite assessment =

**Signs** + **Symptoms**

**Observer / Performance Outcomes**
- Genetics
- Examination
- Temperature
- Vision
- Forgetfulness
- Infection
- Mobility
- GI/Lung/Glucose tests
- Kidney function
- EKG
- HR/BP
- EEG/Sleep/Fatigue

**Patient & Physician Reported Outcomes**
- Cognition (MMSE, CDR-SB, etc.)
- Behavior (sleep/mood scales – QOL-AD, GDS)
- Motor function (UDPRS)
- Sensation (NRS, etc.)
- Balance & Coordination
- Autonomic

**Outcome decisions**
- Diagnoses
- Treatment algorithm
WHAT ELEMENTS CAN BE USED FOR BMD ASSESSMENTS?

Roadmap to PATIENT-FOCUSED OUTCOME MEASUREMENT in Clinical Trials

1. Understanding the Disease or Condition
   - A. Natural history of the disease or condition
     - Onset/Duration/Resolution
     - Diagnosis
     - Pathophysiology
     - Range of manifestations
   - B. Patient subpopulations
     - By severity
     - By onset
     - By comorbidities
     - By phenotype
   - C. Health care environment
     - Treatment alternatives
     - Clinical care standards
     - Health care system perspective
   - D. Patient/caregiver perspectives
     - Definition of treatment benefit
     - Benefit-risk tradeoffs
     - Impact of disease

2. Conceptualizing Treatment Benefit
   - A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
     - Survives
     - Feels (e.g., symptoms)
     - Functions
   - B. Define context of use (COU) for clinical trial:
     - Disease/Condition entry criteria
     - Clinical trial design
     - Endpoint positioning
   - C. Select clinical outcome assessment (COA) type:
     - Patient-Reported Outcome (PRO)
     - Observer-Reported Outcome (ObsRO)
     - Clinician-Reported Outcome (ClinRO)
     - Performance Outcome (motor, sensory, cognition)

3. Selecting/Developing the Outcome Measure
   - A. Search for existing COA measuring COI in COU:
     - Measure exists
     - Measure exists but needs to be modified
     - No measure exists
     - Measure under development
   - B. Begin COA development:
     - Document content validity (qualitative or mixed methods research)
     - Evaluate cross-sectional measurement properties (reliability and construct validity)
     - Create user manual
     - Consider submitting to FDA for COA qualification for use in exploratory studies
   - C. Complete COA development:
     - Document longitudinal measurement properties (construct validity, ability to detect change)
     - Document guidelines for interpretation of treatment benefit and relationship to claim
     - Update user manual
     - Submit to FDA for COA qualification as effectiveness endpoint to support claims

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BMDs HAVE THE POTENTIAL TO PROVIDE ObRO and PerfO ASSESSMENTS
HIGH LEVEL CONCEPTS-OF-INTEREST (COI) ACROSS NEURODEGENERATIVE DISEASES

PREFERRED OBJECTIVE:
Create standards with utility across diseases

**Mobility/ Frailty**
- Gait
- Falls
- Time OOH

**Sleep**
- Sleep onset
- WASO
- Total sleep time

**Cognition**
- Attention
- Verbal fluency
- Executive function

Alzheimer disease
Parkinson disease
Multiple Sclerosis
Huntington disease
CDISC STANDARDS FOR BMDs

Concepts-of-Interest (COIs): Mobility/Frailty, Sleep & Cognition across neurodegenerative diseases

**DRAFT** Timeline of activities:

1Q 2017

- Determine existing standards and gaps
- Devise plan to address
- Identify funding sources

2Q 2017

- Understand BMD landscape for COIs
- Highlight regulatory considerations
- Socialize plan forward

3Q 2017

- Engage dedicated Subject Matter Experts (SMEs) to develop CDISC standards for existing gaps (12-18 mo. process)
- Contingent on getting into pipeline with CDISC!
CDISC STANDARDS ARE REQUIRED FOR REGISTRATION SUBMISSIONS

When will eSTUDY data be required?

*36 months for INDs  **Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = STDTC).
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.
CDISC STANDARDS ARE BECOMING GLOBAL REQUIREMENTS

Announcements

https://www.cdisc.org/resources/impending-regulatory-requirements

From FDA:

- Data Standards Catalog (September 2016) specifies using CDISC Controlled Terminology, SEND, SDTM, ADaM, and Define-XML standards.
- Study Data Technical Conformance Guide (March 2017) specifies rules for using CDISC standards on submissions to FDA CDER and CBER.
- Study Data Standards: What You Need to Know (June 2016)
- Section 5 of Prescription Drug User Fee Act (PDUFA) VI Proposed Commitment Letter addresses “Enhancing Capacity to Support Analysis Data Standards for Product Development and Review.”
- Guidance on Providing Regulatory Submissions in Electronic Format (December 2014) requires submissions in an electronic format specified by the agency beginning 24 months from the issuance of this document.

From PMDA:

- Advanced Review with Electronic Data Promotion Group
- Notification on Practical Operations of Electronic Study Data (April 2015)
- Question and Answer Guide Regarding Notification on Practical Operations of Electronic Study Data Submissions (April 2015)
- Technical Conformance Guide on Electronic Study Data Submissions (April 2015)
- PMDA Data Standard Catalog (July 2015)

From China FDA (CFDA):

- CFDA has endorsed CDISC standards in their Clinical Trial Data Management Technology Guide (July 2016)
## Concepts covered by the Alzheimer's CDISC User Guide

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<thead>
<tr>
<th>Topic</th>
<th>Details</th>
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<tr>
<td>ApoE Genotype</td>
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<td>Family History of AD</td>
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<td>Volumetric MRI</td>
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<td>PET, PET/CT (FDG, Florbetapir, PiB)</td>
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<tr>
<td>CSF Biomarkers and Sampling</td>
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<td>Outcome Assessment Scales</td>
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<td>ADAS-COG</td>
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<td>CDR</td>
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<td>AVLT</td>
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<td>FAQ</td>
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<td>Modified Hachinski</td>
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<td>DAD</td>
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<td>ADCS-ADL MCI</td>
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<td>NPI</td>
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<td>CGI</td>
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<tr>
<td>GDS</td>
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*www.cdisc.org/therapeutic*
# AVAILABLE CDISC STANDARDS

## Status of CDISC Standard Development for Key Brain Diseases

All CDISC Therapeutic Area User Guides can be accessed free at: [www.cdisc.org](http://www.cdisc.org)

<table>
<thead>
<tr>
<th>Disease TAUGs</th>
<th>Available</th>
<th>In Planning</th>
<th>In Progress</th>
<th>Comments</th>
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<tr>
<td>Alzheimer’s (AD) V2.0</td>
<td>YES</td>
<td>V3.0</td>
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<td>Structural and fluid biomarkers integrated into V2.0; Future plans for presymptomatic stages of the disease that include biometric monitoring devices (V3.0)</td>
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<td>Amyotrophic Lateral Sclerosis (ALS)</td>
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<td>Autism Spectrum Disorder (ASD)</td>
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<tr>
<td>Depression</td>
<td>YES</td>
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<td></td>
<td>Biomarkers not included.</td>
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<td>Huntington’s Disease (HD)</td>
<td>NO</td>
<td>YES</td>
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<td>Plans to integrate biomarkers across modalities</td>
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<tr>
<td>Multiple Sclerosis (MS)</td>
<td>YES</td>
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<td>Contains imaging biomarkers</td>
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<tr>
<td>Parkinson’s Disease (PD) V1.0</td>
<td>YES</td>
<td>YES</td>
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<td>Plans to integrate CSF biomarkers and PET standards into V2.0</td>
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<tr>
<td>Traumatic Brain Injury</td>
<td>YES</td>
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<td>Imaging and fluid biomarkers included</td>
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MEASURES TO SUPPORT CONCEPTS-OF-INTEREST

KEY LEARNINGS

- Many fundamental CDISC standards exist
- **Metadata is critical to understand context of an assessment**
- Composites may provide a more powerful and contextually meaningful assessment
- Mood (e.g., depression) and pain may be important factors in assessments
- Need to understand the priorities of Patients and Caregivers

FRAILTY: HOW IS IT DEFINED?

• Frailty was defined as a clinical syndrome in which three or more of the following criteria were present:
  1. unintentional weight loss (10 lbs in past year)
  2. self-reported exhaustion
  3. low physical activity
  4. weakness (grip strength)
  5. slow walking speed

• 5,317 men and women 65 years and older

  Not Frail (0 criteria): 48%
  Intermediate (1-2): 45%
  Frail (3-5): 07%


• Frailty is a hyperinflammatory geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to resist stress.

FRAILTY = Biological Aging

IMPORTANCE OF FRAILTY ASSESSMENT

- More sensitive predictor of outcomes than is age \(^1,2\)
- Frail patients are 2.5 times longer length of stay, and 20 times as likely to be discharged to a nursing home \(^2\)
- American College of Surgeons guidelines: “frailty score” for optimal perioperative decision-making, management, and discharge strategy \(^3\)
- Elders underrepresented in clinical trials (esp. those >70. We can’t assume they are equal to younger patients\(^4\)

ASSESSMENTS OF FRAILTY

HISTORICAL

- **Single Markers**
  - Grip strength
  - Walking speed
- **Phenotypic Frailty Indices**
  - CHS (Fried) index
  - SOF index
  - FRAIL index
- **Multi-dimensional Indices**
  - Rockwood
  - FI-CGA-10
  - MPI
  - SHERPA
  - HARP

**Functional Decline Instruments**

- ADL
- CCI

SENSOR - BASED

<table>
<thead>
<tr>
<th>Inertial Sensors (gyroscopes &amp; accelerometers)</th>
<th>Greene, BR, 2014</th>
<th>TUG</th>
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<tbody>
<tr>
<td>Inertial Sensors (gyroscopes &amp; accelerometers) Upper Extremity Based</td>
<td>Schwenk, M. 2014</td>
<td>Gait speed Walking bout duration variability</td>
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<tr>
<td>Merchant, R.A., 2016</td>
<td>Trunk posture</td>
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<td>Najafi, B, 2014</td>
<td>Stand and Flop</td>
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<tr>
<td>Bahureksa, L, 2017</td>
<td>Gait speed Stride length Stride time</td>
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<tr>
<td>Toosizadeh, N.</td>
<td>Upper extremity function</td>
<td></td>
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</tbody>
</table>

- Dynamometer
  - Schwenk, M. 2014; Greene, BR, 2014
  - Grip strength

- ECG
  - Parvaneh, 2017
  - Heart rate variability

Dr. Jane Mohler
University of Arizona

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FRAILTY IS ASSOCIATED WITH MCI

Figure 1. Simple frailty score and the presence of mild cognitive impairment. The closed column indicates the number of participants with mild cognitive impairment (MCI), and the open column indicates those without MCI. The number in the column represents the number of participants. The odds ratio on the right side indicates the odds ratio of a simple frailty (SF) score of 1 and a SF score of 2 to an SF score of 0 for the presence of MCI. Adjustment 1: adjusted for age and sex. Adjustment 2: adjusted for age, sex, body mass index, mean blood pressure, triglyceride, total cholesterol, high-density lipoprotein cholesterol, glucose, insulin, use of antihypertensive drugs, antidyshlipidemic drugs, diabetic drugs, current smoking, physical activity and the presence of silent cerebral infarctions and white matter hyperintensity. Adjustment was performed by logistic regression analyses for the presence of MCI. OR, odds ratio; CI, confidence interval.
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

I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning.
Cognition AND “INSTRUMENTAL ACTIVITIES OF DAILY LIVING”

Premise: Cognition is a key lens through which we ‘view the world’, and how we can focus/functionally organize our “instrumental activities of daily living”.

Hypothesis: Changes or increased variance in the key functional domains of “instrumental activities of daily living” should reflect current (and potentially future) changes in cognitive function.
BIOMETRIC MONITORING DEVICES (BMDs)

Measuring ‘Signs’ Related to QoL

BMDs have the potential to measure signs related to all domains of function comprising what is viewed as Instrumental Activities of Daily Living (IADLs – Quality of Life Surrogate)

- **Mental Function**
  - Working memory
  - Attention
  - Wakefulness/sleep
  - Long-term memory

- **Social Engagement**
  - Friends/family
  - Mood
  - Social interaction/employment

- **Physical Function**
  - Mobility
  - Frailty
  - Homeostatic physiology
  - Drug disposition/metabolism

- **Health Maintenance**
  - Injury & sickness
  - Surgery
  - Disease

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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
CORE SIGNS & SYMPTOMS

Sleep
- Total sleep time
- Sleep efficiency
- Wake after sleep onset
- Sleep onset latency
- Excessive daytime sleepiness

Core Disease Symptoms
- Disease stage
- Treatment effect

Mood
- Depression
- Anxiety
- Agitation

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

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

GOAL:
To develop appropriate Contexts-of-Use
SUMMARY OF THE POTENTIAL FOR BMDs

Ability to:

• Improve sensitivity to detect/assess disease progression and treatment interventions
• Support label claims for innovative treatments
• Create novel assessments of pre-manifest disease
• Provide assessments in compliance of Good Clinical Practice
• Provide novel quantitative composite assessments of QoL, and health care delivery
## TECHNOLOGY ATTRIBUTES AND GAPS

### Concept-of-Interest measured:

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<tr>
<th>CONSIDERATION</th>
<th>ATTRIBUTE</th>
<th>GAP</th>
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<td>Biometric validation of user</td>
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<td>Secure data transfer</td>
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<tr>
<td>GCP compliant for audit trail</td>
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WORKSHOP DELIVERABLES

- Identify current gaps in data standards and approaches to validation required to advance clinical Drug Development Tools that assess Physical Function/Frailty, Sleep and Cognition using Biometric Monitoring Devices (BMDs)
- Fill these gaps to enable the use of BMDs in Registration Studies, and the creation of actionable databases of disease progression, and treatment responses across neurological & psychiatric diseases
- Create a publication outlining the state of the field and considerations for advancement of these devices for use in clinical registration trials
DAY 2: METADATA FOR ASSESSMENT INTERPRETATION
DISCUSSION