Advancing CDISC Standards for BMD Use in Clinical Development of Neurological Treatments

March 10, 2017

Stephen P. Arnerić, Executive Director
Volker D. Kern, Senior Project Manager
Jennifer Ashley E. Downs, Project Coordinator
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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Wearable Sensors

Glucose Sensing Contact Lens Google

FWD Health

Dashboard Tracks Exercise Regimes for Lowered Insurance Prices

THE FUTURE OF SENSORS

1. Passive data gathering
2. Meaningful interpretation
3. Internal sensors attached to body's organs

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Digestible Sensors

Sensor-enabled pill that can monitor patients' adherence to medication.
DEFINING DISEASE
Requires a Composite Assessment =

**Signs**

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

**Symptoms**

- 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

www.c-path.org/camd
ALZHEIMER’S DISEASE (AD) STAGES:

Our dilemma: What to measure and when?

- Current outcomes insensitive
- Current outcomes focused on aMCI to Moderate AD
- Current PRO outcomes unreliable
DIGITAL DRUG DEVELOPMENT TOOLS

Proposed Vision

**Years 1-3:** Develop, socialize, and implement a regulatory roadmap that would enable the advancement of regulatory science supporting the use of biometric monitoring devices (BMDs) in clinical trials.

**Years 2-5:** Create a data repository of de-identified, patient-level BMD data where quantitative disease-progress modeling and exploration of novel clinical outcome assessments could be examined at the earliest stages of disease to support specific contexts-of-use.

**FOCUS**

Identify relevant datasets to develop quantitative disease-progression models for three key domains of function influencing quality-of-life (QoL): mobility; sleep; cognition.

**OUT-OF-SCOPE**

Development of technology platforms or BMDs.
WHY MOBILITY, SLEEP AND COGNITION?

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

Symptoms & Signs
- Cognitive Impairments
- Speech Problems
- Depression
- Walking Changes
- Gait slowed
- Dizziness/Vertigo
- Swallowing (advanced stages)
- Pain
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._

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

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

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

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

_IADLs – Quality of Life Surrogate_
VISION OF FUTURE 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 and 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.
DELIVERABLES

• Identify current gaps in data standards 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 diseases
AGENDA – MARCH CDISC MEETING

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</table>
| 8:00 – 8:15 a.m. | Welcoming Remarks & Overarching Objectives for Concepts-of-Interest (COIs)  
Stephen P. Arnerić (Critical Path Institute) |
| 8:15 – 8:30 a.m. | CDISC Standards & Digital Health                                          
Michael Ibara (CDISC) |
| 8:30 – 9:00 a.m. | Data Flow: From COIs to Data Archiving                                    
Barrie Nelson (CDISC) |
| 9:00 – 9:15 a.m. | Representing Device Data Using CDISC Standards: Focus on Reusability       
Jon Neville (Critical Path Institute) |

Break (20 min)

SESSION I: Mobility

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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| 9:35 – 10:05 a.m. | BMDs for Sleep                                   
Rebecca Spencer (University of Massachusetts) - 20 min.  
Derek Hill (IXICO) - 10 min. |
| 10:05 – 11:15 a.m. | Capturing Key COIs & Data Flow                               
Barrie Nelson & Rebecca Spencer |

Lunch (45 min)

SESSION II: Cognition

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</table>
| Noon – 12:30 a.m. | BMDs for Mobility/Frailty                                      
Ray Dorsey (University of Rochester) - 20 min.  
Jane Mohler (University of Arizona) - 10 min. |
| 12:30 – 1:30 p.m. | Capturing Key COIs & Data Flow                               
Barrie Nelson & Lynn Hudson |

SESSION III: Cognition

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</thead>
</table>
| 1:30 – 2:10 p.m. | BMDs for Cognition                                              
Lee Ryan (University of Arizona) - 30 min.  
Jenny Barnett (Cambridge Cognition) - 10 min. |
| 2:10 – 3:30 p.m. | Key COIs & Data Flow                                           
Barrie Nelson & Lee Ryan |

Break (20 min)

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<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 3:50 – 4:50 p.m. | Summary and Next Steps                                          
Barrie Nelson, Jon Neville, Stephen Arnerić |

Attendees:

Steve Arnerić (CAMD/C-Path)  
Jenny Barnett (Cambridge Cognition)  
Ray Dorsey (Univ. of Rochester)  
Jenn Downs (CAMD)  
Farhan Hameed (Pfizer)  
Derek Hill (IXICO)  
Lynn Hudson (C-Path)  
Michael Ibara (CDISC)  
Daniel Karlin (Pfizer)  
Jeffrey Kaye (Oregon Health Sciences Univ.)  
Volker Kern (CAMD/C-Path)  
Adria Martig (MJFF)  
Jane Mohler (Univ. of Arizona)  
Barrie Nelson (CDISC)  
Jon Neville (C-Path)  
Jane Rhodes (Biogen)  
Lee Ryan (Univ. of Arizona)  
Rebecca Spencer (Univ. of Mass)  
Diane Stephenson (CPP/C-Path)
CDISC STANDARDS FOR BMDs

Concepts-of-Interest (COIs): Mobility/ Frailty, Sleep & Cognition
Across Neurodegenerative Diseases

DRAFT Timeline of Activities:

1Q 2017
- Determine existing standards & 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!
### 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>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s (AD) V2.0</td>
<td>YES</td>
<td>V3.0</td>
<td></td>
<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>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis (ALS)</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism Spectrum Disorder (ASD)</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>YES</td>
<td></td>
<td></td>
<td>Biomarkers not included.</td>
</tr>
<tr>
<td>Huntington’s Disease (HD)</td>
<td>NO</td>
<td></td>
<td>YES</td>
<td>Plans to integrate biomarkers across modalities</td>
</tr>
<tr>
<td>Multiple Sclerosis (MS)</td>
<td>YES</td>
<td></td>
<td></td>
<td>Contains imaging biomarkers</td>
</tr>
<tr>
<td>Parkinson’s Disease (PD) V1.0</td>
<td>YES</td>
<td>YES</td>
<td></td>
<td>Plans to integrate CSF biomarkers and PET standards into V2.0</td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td>YES</td>
<td></td>
<td></td>
<td>Imaging and fluid biomarkers included</td>
</tr>
</tbody>
</table>
In an effort to optimize the ability to aggregate and analyze data within Brain-CODE, Common Data Elements (CDEs) are being developed to provide standard definitions and formats so that investigators collect data consistently across studies. This will reduce variability in data collection and ultimately facilitate comparisons across diseases, merging of data sets and meta-analyses. Using the framework of the National Institute of Neurological Disorders and Stroke (NINDS) CDE Project as guidance [5], General Core CDEs Demographic and Clinical CDEs have developed. Critical to this process has been engagement of participating researchers through workshops and consensus methodologies. A summary of the approach, methodology, results and recommendations are presented here.

SDTMIG v3.2 Conformance Rules v1.0

Version: 3.2
Release Date: Fri, 01/27/2017

The SDTMIG v3.2 details the structure and conventions for compliant SDTM domains. The majority of the SDTMIG v3.2 is published in a data definition table format, which allows the information to be used programmatically. Business and conformance rules (e.g., assumptions and examples), however, are expressed outside of the data definition tables, making them difficult to identify and program.

SDTMIG v3.2 Conformance Rules v1.0 aim to identify all conformance rules and case logic from the SDTM and SDTMIG, classifying and codifying them in a form that supports SDTM quality processes and tool development.

The Conformance Rules team has created a user guide that provides information on the structure of the rules and conventions for rules content.

CDISC posts Public Review comments and resolutions to ensure transparency and show implementers how comments were addressed in the standard development process.

Study Data Tabulation Model Implementation Guide (SDTMIG)

Downloads Secure:

<table>
<thead>
<tr>
<th>File</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDTMIG v3.2 Conformance Rules v1.0.xlsx</td>
<td>80.44 KB</td>
</tr>
<tr>
<td>SDTM Conformance Rules User Guide v1.pdf</td>
<td>321.95 KB</td>
</tr>
<tr>
<td>Public Comments SDTMIG v3.2 Conformance Rules v1.0.xlsx</td>
<td>64 KB</td>
</tr>
</tbody>
</table>
AD TAUG v1.0/AD TAUG v2.0

Concepts covered by the Alzheimer's CDISC User Guide
ApoE Genotype
Family History of AD
Volumetric MRI
PET, PET/CT (FDG, Florbetapir, PiB)
CSF Biomarkers and Sampling
Outcome Assessment Scales
ADAS-COG
CDR
AVLT
FAQ
Modified Hachinski
DAD
ADCS-ADL MCI
NPI
CGI
GDS
HIGH LEVEL CONCEPTS-OF-INTEREST (COI) ACROSS NEURODEGENERATIVE DISEASES

PREFERRED OBJECTIVE: Create Standards with Utility Across Diseases

**Mobility**
- 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
KEY OBJECTIVES

Prioritize key specific outcomes into levels of need for delineating each COI

- Tier 1 – top ~3 must-haves
- Tier 2 – next 2
- Tier 3 – remaining

Considerations:
- Ability to impact QoL, and improve health
- Ability to address unmet needs
- Ability to achieve label claim
- Ability to use as use as pre-manifest disease outcome assessment
# MOBILITY/FRAILTY: CONCEPTS TO CONSIDER

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDT</td>
<td>Total Distance Traveled</td>
<td>Distance traveled per day</td>
</tr>
<tr>
<td>GS</td>
<td>Gait Speed</td>
<td>Time to travel 25 feet</td>
</tr>
<tr>
<td>6-MWT</td>
<td>6-Minute Walk Test</td>
<td>Distance traveled in 6 minutes</td>
</tr>
<tr>
<td>TIH</td>
<td>Time in Home</td>
<td>Time spent in home per day</td>
</tr>
<tr>
<td>TOOH</td>
<td>Time Out Of Home</td>
<td>Time spent out of home per day</td>
</tr>
<tr>
<td>VS</td>
<td>Voice Strength</td>
<td>Muscle modulation of voice</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
<td>Dressing; bathing; eating</td>
</tr>
<tr>
<td>TFM</td>
<td>Total Falls/Month</td>
<td>Number of falls per month</td>
</tr>
<tr>
<td>GS</td>
<td>Grip Strength</td>
<td>Muscle strength</td>
</tr>
</tbody>
</table>
MOBILITY/FRAILTY: INFORMATION CAPTURE

High Level Considerations

- **BMD**
- **Properties**
  - Manufacturer (ID)
  - Identifiers
  - Algorithm(s)
- **Subject**
  - Time & Distance In/Out of Home
  - Voice
  - Dyskinesias & Tremors
  - Motor fluctuations
  - ADLs
  - Grip strength
  - Gait & Falls

- **Feature Detection**
- **Raw Data**

**Quantitative Output**

Transformed
# SLEEP: CONCEPTS TO CONSIDER

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>Sleep Onset Latency</td>
<td>Latency to fall asleep</td>
</tr>
<tr>
<td>TST</td>
<td>Total Sleep Time</td>
<td>Total hours asleep</td>
</tr>
<tr>
<td>WASO</td>
<td>Wake After Sleep Onset</td>
<td>Time spent awake after sleep onset</td>
</tr>
<tr>
<td>QST</td>
<td>Quality of Sleep Time</td>
<td>Time spent in various stages of sleep (e.g. REM/NREM)</td>
</tr>
<tr>
<td>EDS</td>
<td>Excessive Daytime Sleepiness</td>
<td>Indicator of poor night-time sleep quality</td>
</tr>
<tr>
<td>DS</td>
<td>Daytime Sleep</td>
<td>Indicator of poor night-time sleep quality</td>
</tr>
</tbody>
</table>
SLEEP: INFORMATION CAPTURE

High Level Considerations

- **BMD**
  - Properties
    - Manufacturer (ID)
    - Identifiers
    - Algorithm(s)
  - Subject
    - Anatomical or Remote Locations
  - Feature Detection
    - Raw Data
    - Transformed
  - Quantitative Output
    - Sleep Onset Latency
    - Total Sleep Time
    - Wake After Sleep Onset
    - Quality of Sleep Time (REM vs. nonREM)
    - Excessive Daytime Sleepiness
    - Daytime Sleep
# COGNITION: CONCEPTS TO CONSIDER

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAT</td>
<td>Sustained Attention Task</td>
<td>Ability to focus; cognitive process of selectively concentrating on a discrete aspect of information</td>
</tr>
<tr>
<td>DMR</td>
<td>Delayed Memory Recall</td>
<td>Ability of participants to remember a stimuli (e.g., word, object, number, sound) and then, after a delay, are asked to remember characteristics of the stimulus</td>
</tr>
<tr>
<td>IPS</td>
<td>Information Processing Speed</td>
<td>Time to remember or accomplish a task or make a decision based on information presented</td>
</tr>
<tr>
<td>SMT</td>
<td>Spatial Memory Task</td>
<td>Ability to recall spatial location of an object</td>
</tr>
<tr>
<td>EF</td>
<td>Executive Function</td>
<td>Mental processes that enable us to plan, focus attention, remember, and juggle multiple tasks</td>
</tr>
<tr>
<td>IADLs</td>
<td>Instrumental Activities of Daily Living</td>
<td>Ability to independently care for oneself including financial management</td>
</tr>
</tbody>
</table>

How important will it be to assess a depression using GDS?
COGNITION: INFORMATION CAPTURE

High Level Considerations

BMD
- Properties
  - Manufacturer (ID)
  - Identifiers
  - Algorithm(s)

Subject
- Anatomical or Remote Locations
- Feature Detection
  - Attention
  - Delayed Recall
  - Speed of Information Processing
  - Spatial Memory
  - Executive Function
  - IADLs

Raw Data

Quantitative Output

Transformed
BMD WORKSHOP – Draft
BMDs in Clinical Trials

Concepts-of-Interest: Mobility/Frailty, Sleep, Cognition

May 9 & 10 (1.5 days), 2017

8:00 am to 5:15 pm (EDT)

Bethesda North Marriott Hotel & Conference Center,
5701 Marinetti Road, North Bethesda, MD

Keynote Speakers:
Jeffrey Kaye (Oregon Health Science University)
David Levine (PD patient in multiple mobile device trials & former Pharma Executive)

Mobility/Frailty
APDM
MJFF
Verily
Regulatory Panel

Sleep
Actigraphy
IXICO
Regulatory Panel

Cognition
Akili
Cambridge Cognition
Cognivue™
CogState
ImPACT™
Regulatory Panel

Standards
Michael Ibara (CDISC)
Barrie Nelson (CDISC)
Jon Neville (C-Path)
DISCUSSION
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