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

March 10, 2017

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ARIZONA ALZHEIMER'S CONSORTIUM

CAMD
CRITICAL PATH INSTITUTE

DIGITAL DRUG DEVELOPMENT TOOLS

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

WHAT

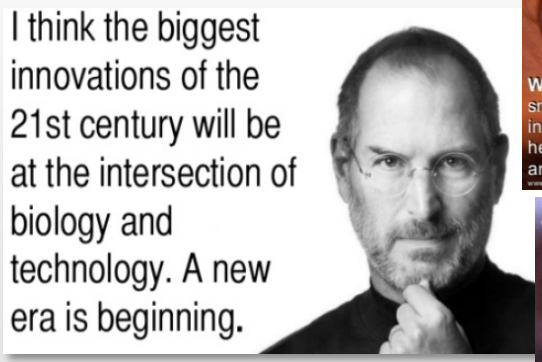
Data (signal output) collected from a biosensor that measures a biological response

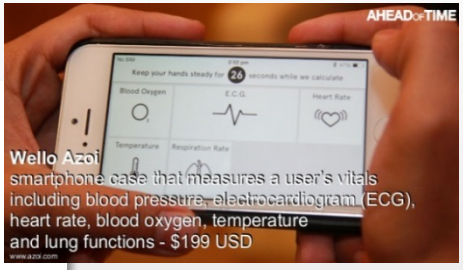
HOW

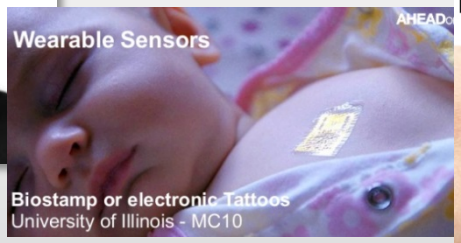
Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestible, remote biosensors)

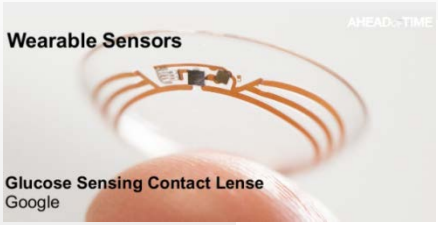
WHY

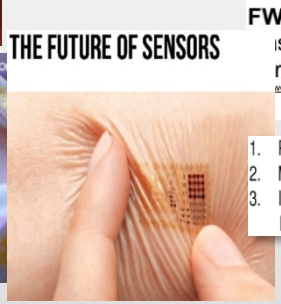
Improve our understanding of real-time changes in FUNCTION during the progression of life in health & disease











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

Imaging Modalities

Symptoms

Patient & Physician Reported Outcomes

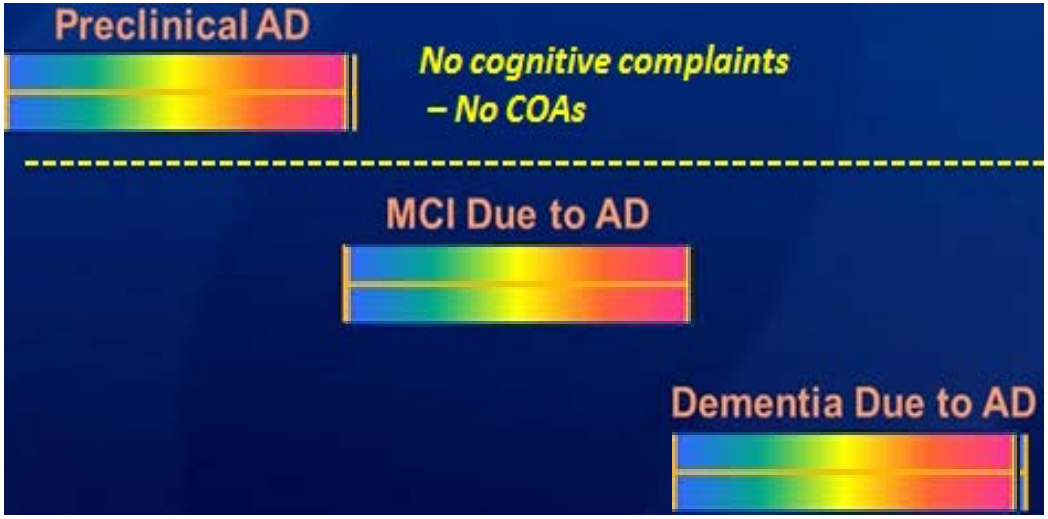
- Cognition (MMSE, CDR-SB, etc.)
- Behavior (sleep/mood scales – QOL-AD, GDS)
- Motor function (UDPRS)
- Sensation (NRS, etc.)
- Balance & Coordination
- Autonomic

Outcome Decisions

- Diagnoses
- Treatment Algorithm

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

Pre-Dementia → Dementia

Memory complaints → *Cognitive Impairment* → *Cognitive, Functional & Behavioral deficits*

Pre-Symptomatic | **MCI / Prodromal AD** | **Mild** | **Moderate** | **Severe**

No apparent symptoms | *Symptoms* | *Current diagnosis & treatment*

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

Symptoms & Signs

- **Cognitive Impairments**
- Speech Problems
- **Depression**
- **Sleeping Changes**
- **Gait slowed**
- Dizziness/Vertigo
- Swallowing (advanced stages)
- Pain

Parkinson's Disease

Symptoms & Signs

- Tremor
- **Walking & Gait Impairment**
- Spasticity
- Pain
- **Depression**
- Bowel/Bladder Problems
- Fatigue
- **Sleeping Impaired**
- Dizziness/Vertigo
- **Cognitive Impairments**
- Speech Problems

Multiple Sclerosis

Symptoms & Signs

- **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**

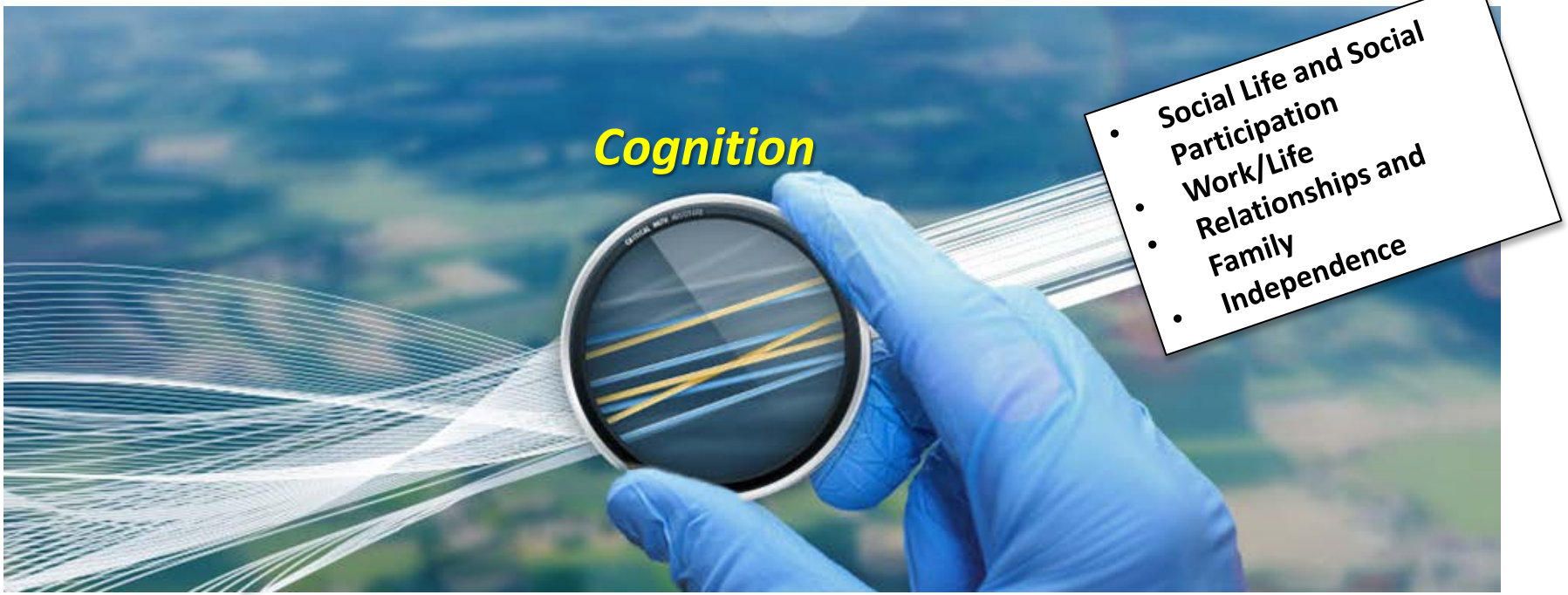
Huntington's Disease

Symptoms & Signs

- Irritability
- **Depression**
- Pain
- Fatigue
- **Sleeping Problems**
- Spasticity
- **Walking Impairment**
- Upper & Lower Extremity Impairments
- Dizziness/Vertigo
- **Cognitive Impairments**
- Speech Problems

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".

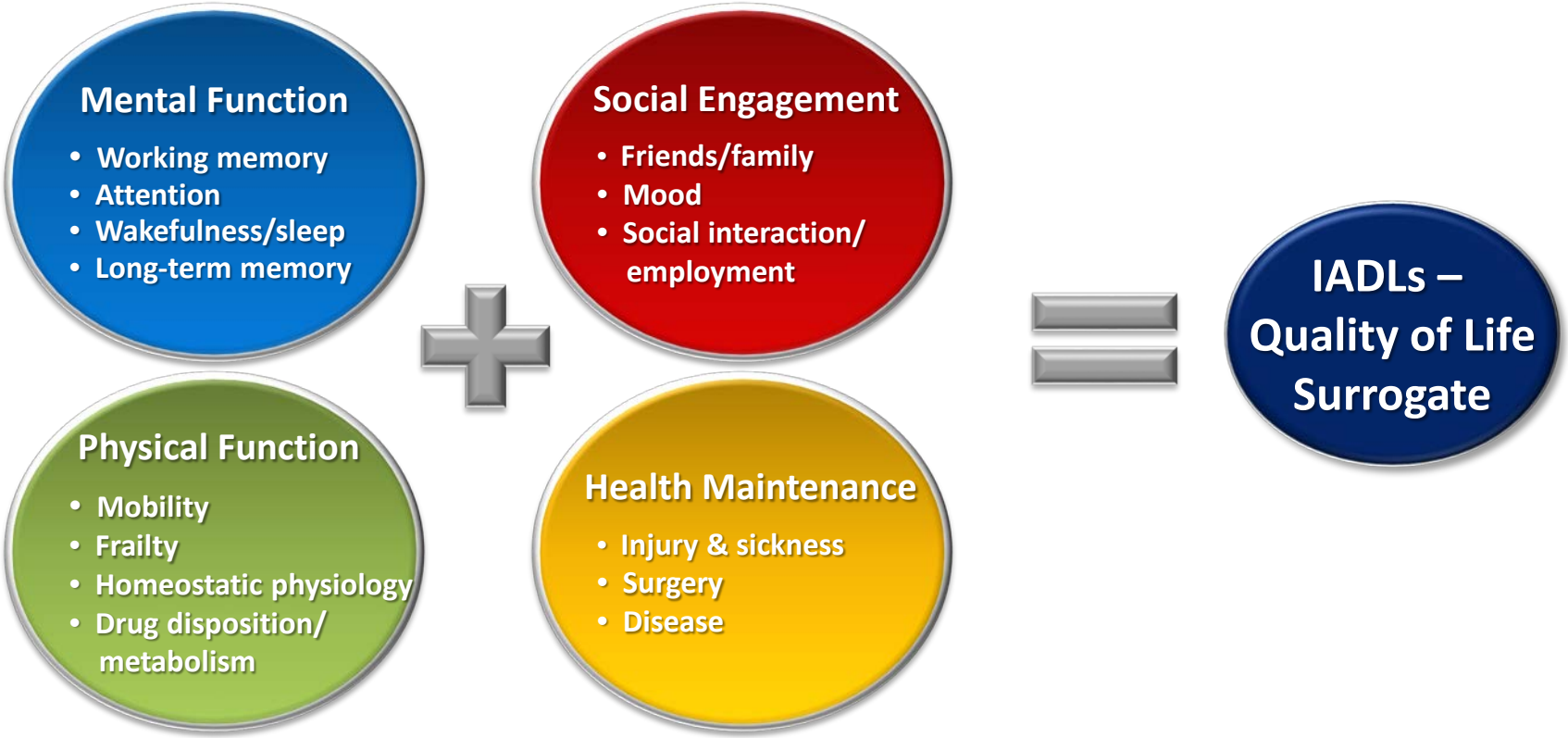


Hypothesis: Changes or increased variance in the key functional domains of "instrumental activities of daily living" should reflect current (and potentially future) changes in cognitive function.

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



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

Continental Breakfast (7:30 – 8:00 am)	
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: Sleep	
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: Mobility	
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	
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)	
3:50 – 4:50 p.m.	**Summary and Next Steps** *Barrie Nelson, Jon Neville, Stephen Arnerić*

Attendees:

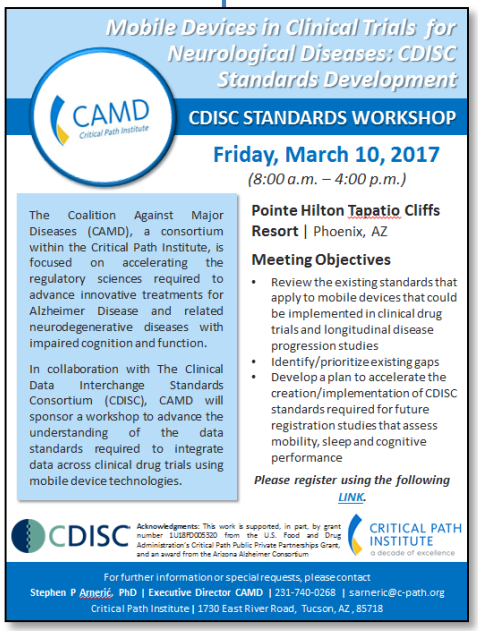
Steve Arnerić (CAMD/C-Path)
Jenny Barnett (Cambridge Cognition)
Ray Dorsey (Univ. of Rochester)
Jenn Downs (CAMD)
Farhan Hameed (Pfizer)
Derek Hill (IXICO)
Lynn Hudson (C-Path)
Michael Ibara (CDISC)
Daniel Karlin (Pfizer)
Jeffrey Kaye (Oregon Health Sciences Univ.)
Volker Kern (CAMD/C-Path)
Adria Martig (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 | **2Q 2017** | **3Q 2017**



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

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

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

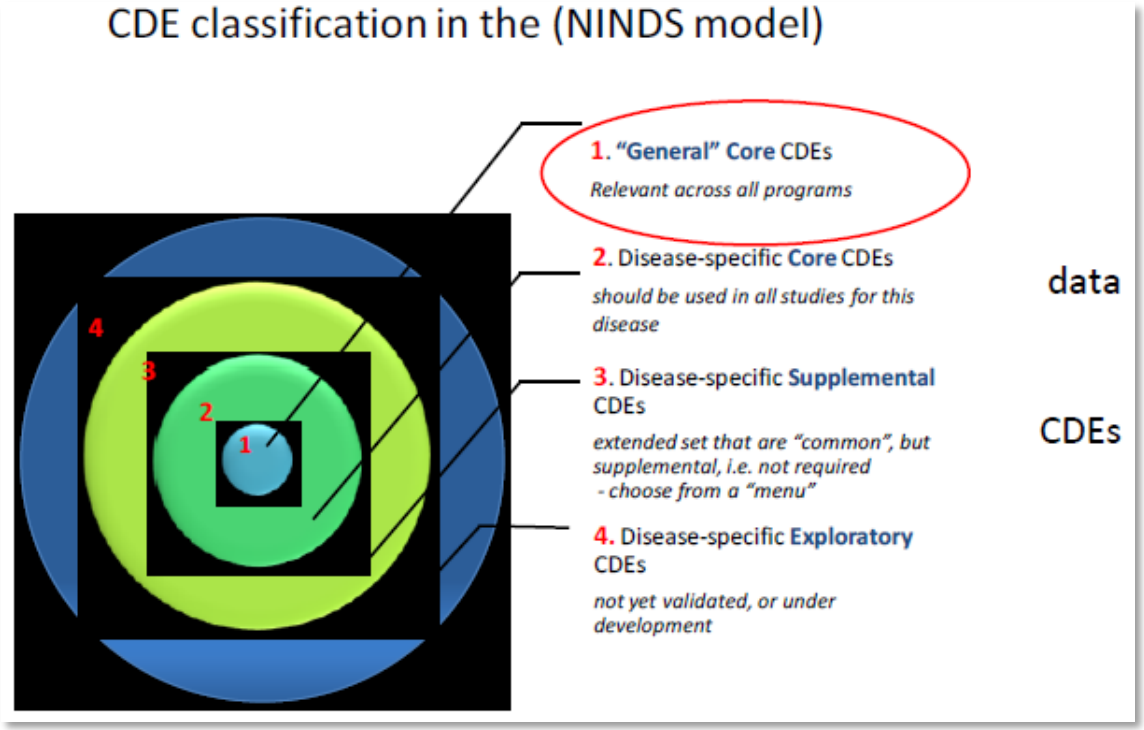
AVAILABLE CDISC STANDARDS

Status of CDISC Standard Development for Key Brain Diseases

All CDISC Therapeutic Area User Guides can be accessed free at : www.cdisc.orgwww.cdisc.org

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

COMMON DATA ELEMENTS (CDEs)

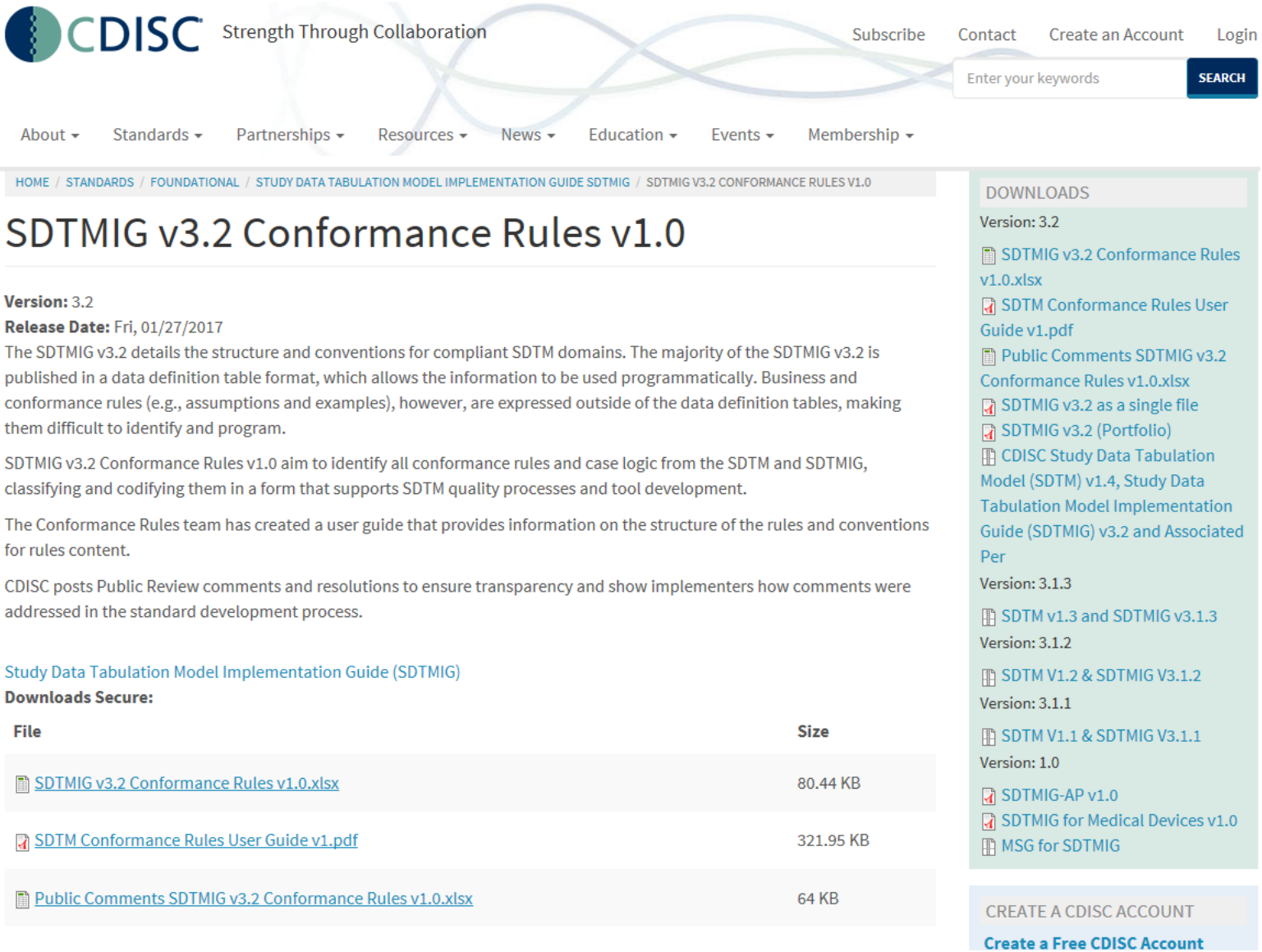


Brain-CODE Common Data Elements: Development of Core Demographic and Clinical Standards to Facilitate Data Aggregation, Sharing and Analyses
Report of the Brain-CODE Common Data Elements Committee

https://www.braincode.ca/sites/default/files/about/BrainCODE%20Demographic%20and%20Clinical%20CDE%20Committee%20Report.pdf

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.

CDISC – SDTM DOMAINS



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HOME / STANDARDS / FOUNDATIONAL / STUDY DATA TABULATION MODEL IMPLEMENTATION GUIDE SDTMIG / SDTMIG V3.2 CONFORMANCE RULES V1.0

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:

File	Size
SDTMIG v3.2 Conformance Rules v1.0.xlsx	80.44 KB
SDTM Conformance Rules User Guide v1.pdf	321.95 KB
Public Comments SDTMIG v3.2 Conformance Rules v1.0.xlsx	64 KB

DOWNLOADS
Version: 3.2
SDTMIG v3.2 Conformance Rules v1.0.xlsx
SDTM Conformance Rules User Guide v1.pdf
Public Comments SDTMIG v3.2 Conformance Rules v1.0.xlsx
SDTMIG v3.2 as a single file
SDTMIG v3.2 (Portfolio)
CDISC Study Data Tabulation Model (SDTM) v1.4, Study Data Tabulation Model Implementation Guide (SDTMIG) v3.2 and Associated Per
Version: 3.1.3
SDTM v1.3 and SDTMIG v3.1.3
Version: 3.1.2
SDTM V1.2 & SDTMIG V3.1.2
Version: 3.1.1
SDTM V1.1 & SDTMIG V3.1.1
Version: 1.0
SDTMIG-AP v1.0
SDTMIG for Medical Devices v1.0
MSG for SDTMIG

CREATE A CDISC ACCOUNT
Create a Free CDISC Account

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

ADNI Alzheimer's Disease Neuroimaging Initiative

CDISC

Therapeutic Area Data Standards
User Guide for Alzheimer's Disease
and Mild Cognitive Impairment
Version 2.0

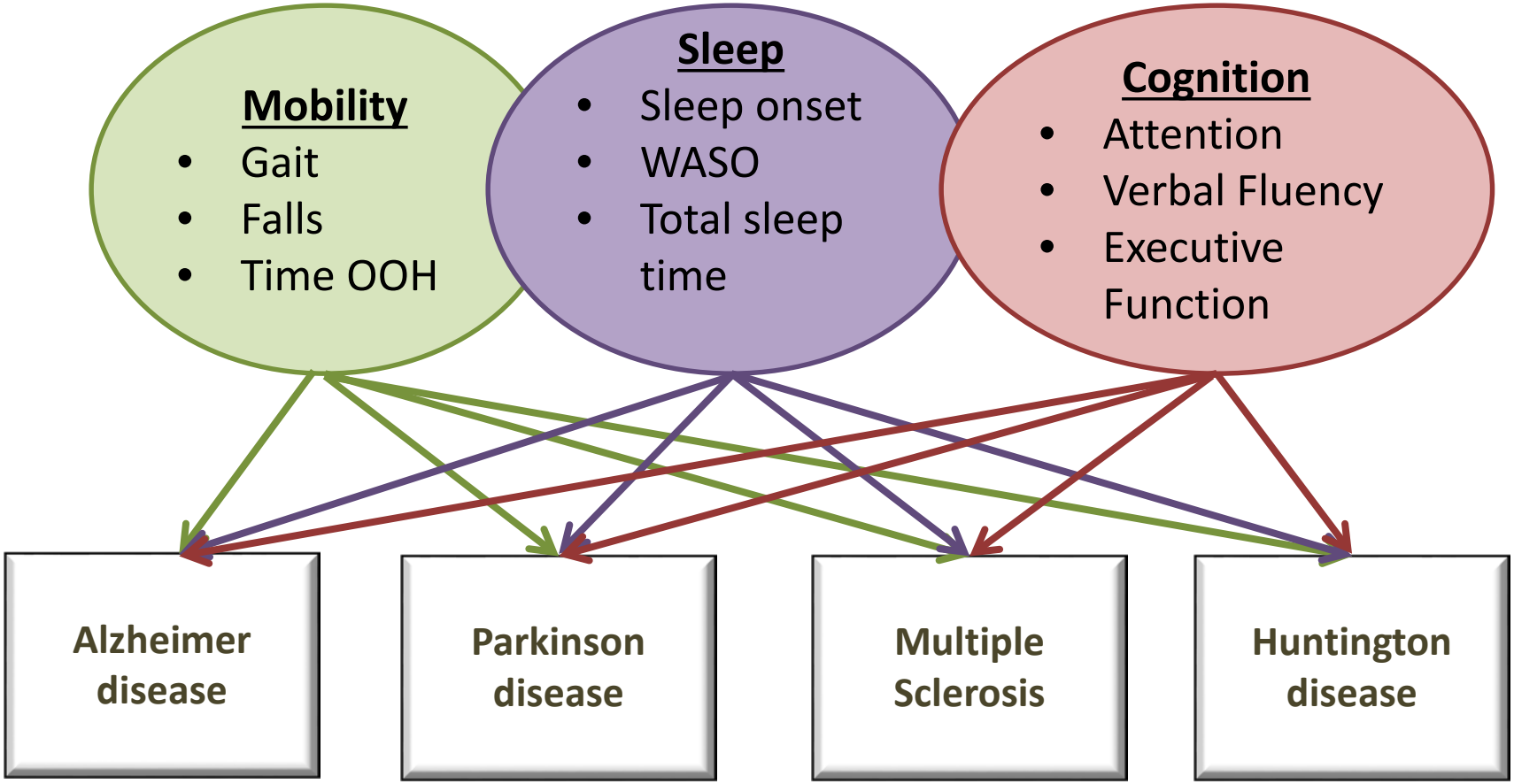
Prepared by the
CFAST Alzheimer's Development Team

[redacted]

www.cdisc.org/therapeutic

HIGH LEVEL CONCEPTS-OF-INTEREST (COI) ACROSS NEURODEGERATIVE DISEASES

PREFERRED OBJECTIVE: Create Standards with Utility Across Diseases



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:

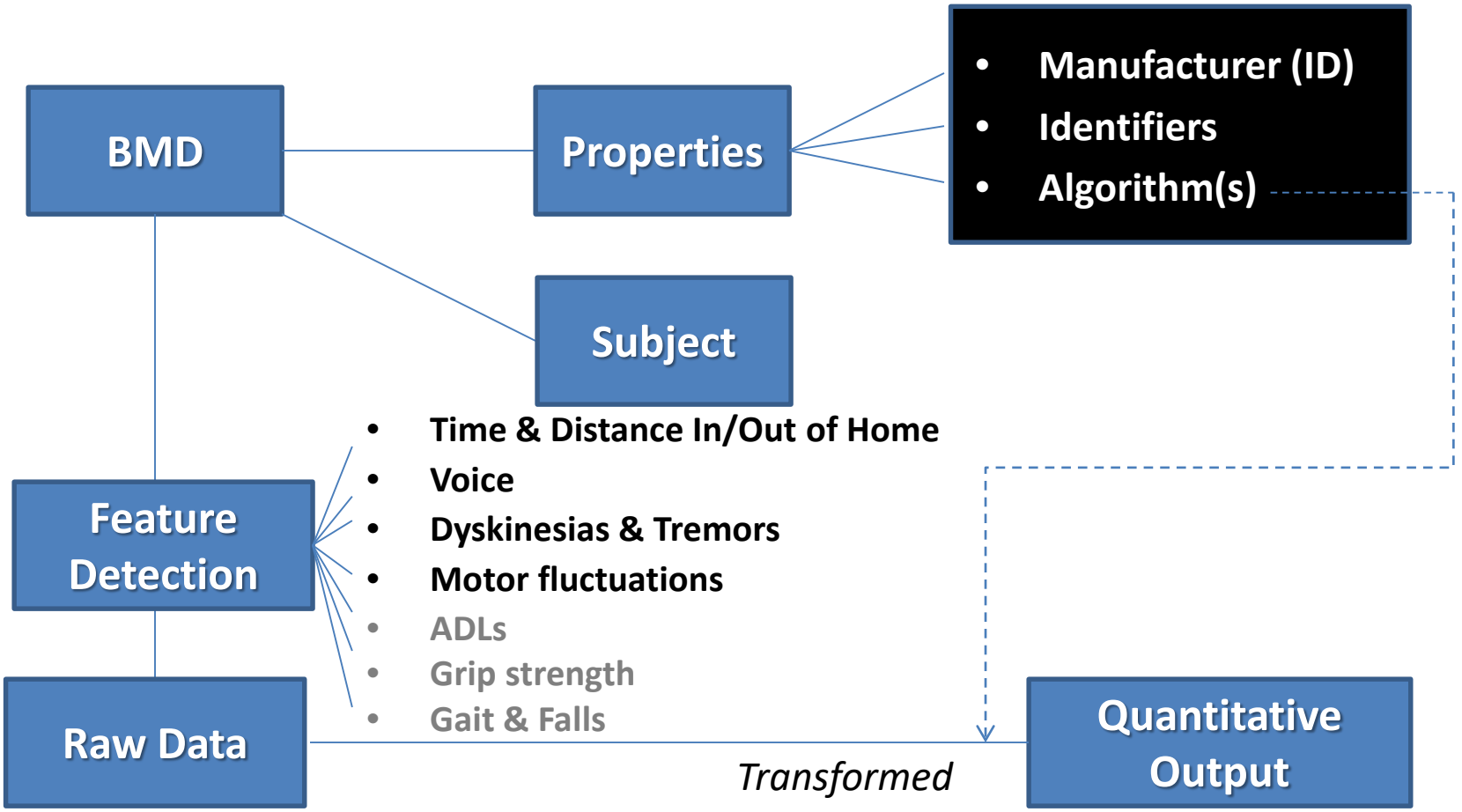
- Ability to impact QoL, and improve health
- Ability to address unmet needs
- Ability to achieve label claim
- Ability to use as use as pre-manifest disease outcome assessment

MOBILITY/FRAILTY: CONCEPTS TO CONSIDER

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

MOBILITY/FRAILTY: INFORMATION CAPTURE

High Level Considerations

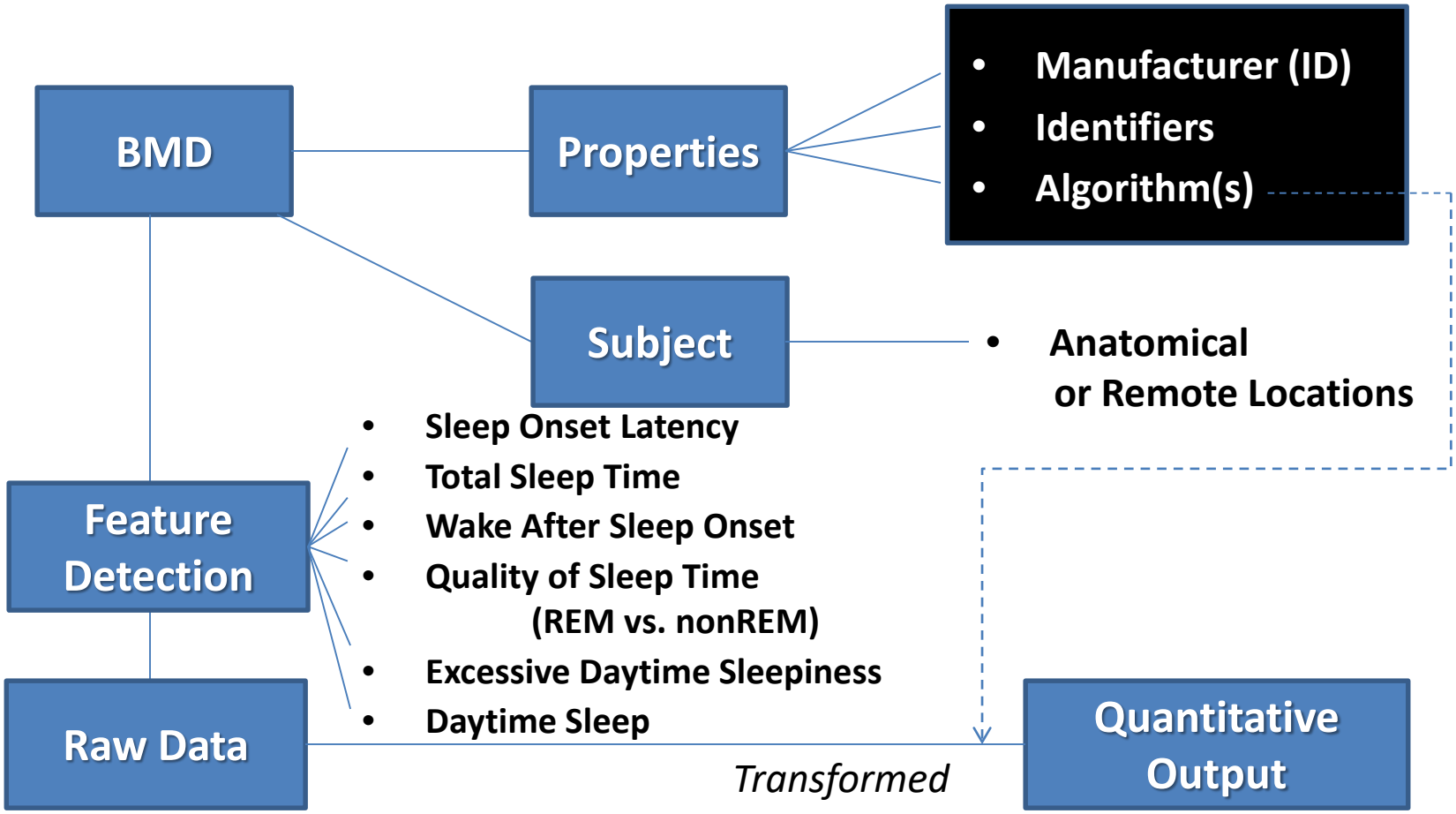


SLEEP:
CONCEPTS TO CONSIDER

Acronym	Definition	Concept
SOL	Sleep Onset Latency	Latency to fall asleep
TST	Total Sleep Time	Total hours asleep
WASO	Wake After Sleep Onset	Time spent awake after sleep onset
QST	Quality of Sleep Time	Time spent in various stages of sleep (e.g. REM/NREM)
EDS	Excessive Daytime Sleepiness	Indicator of poor night-time sleep quality
DS	Daytime Sleep	Indicator of poor night-time sleep quality

SLEEP: INFORMATION CAPTURE

High Level Considerations



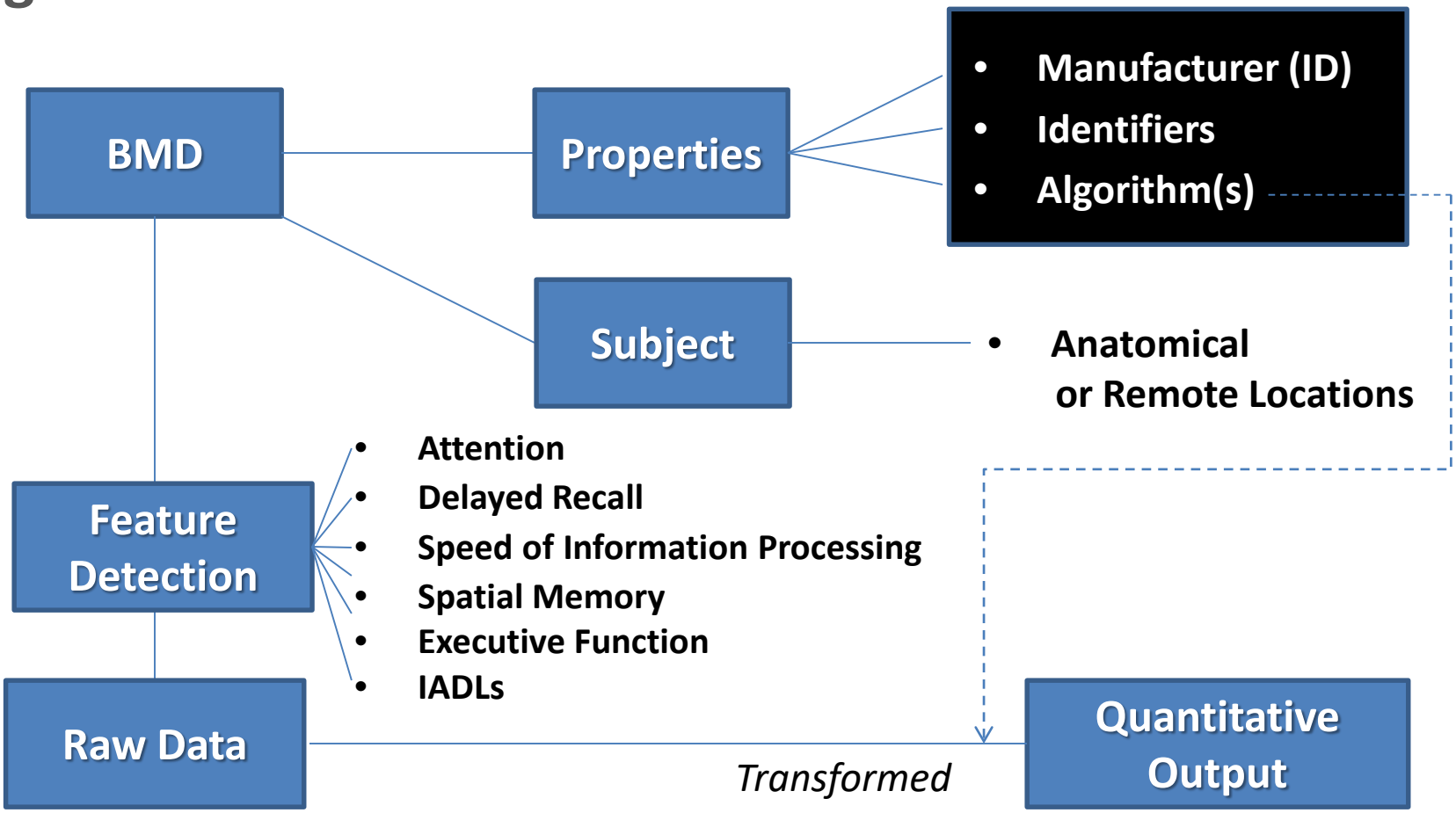
COGNITION: CONCEPTS TO CONSIDER

Acronym	Definition	Concept
SAT	Sustained Attention Task	Ability to focus; cognitive process of selectively concentrating on a discrete aspect of information
DMR	Delayed Memory Recall	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
IPS	Information Processing Speed	Time to remember or accomplish a task or make a decision based on information presented
SMT	Spatial Memory Task	Ability to recall spatial location of an object
EF	Executive Function	Mental processes that enable us to plan, focus attention, remember, and juggle multiple tasks
IADLs	Instrumental Activities of Daily Living	Ability to independently care for oneself including financial management

How important will it be to assess a depression using GDS?

COGNITION: INFORMATION CAPTURE

High Level Considerations



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

May 9

May 10

Keynote Speakers:

Jeffrey Kaye (Oregon Health Science University)

David Levine (PD patient in multiple mobile device trials & former Pharma Executive)

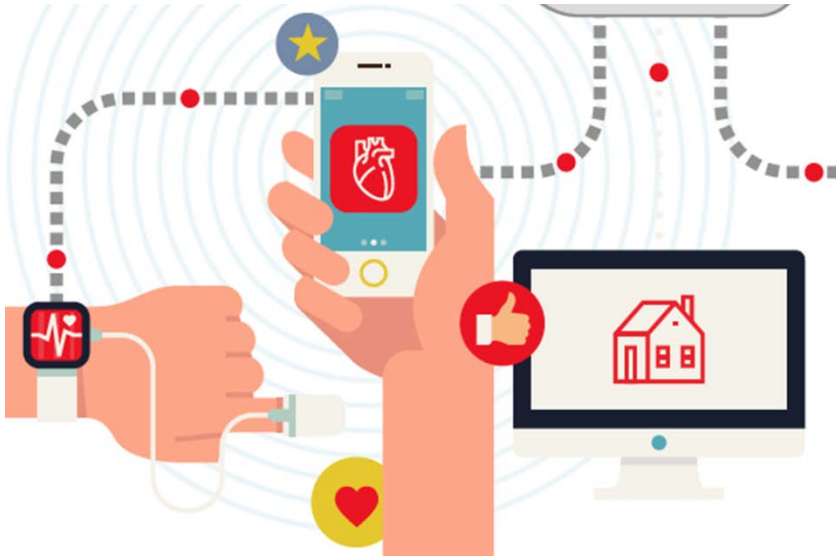
Mobility/Frailty
APDM
MJFF
Verily
Regulatory Panel

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!

ARIZONA ALZHEIMER'S CONSORTIUM

www.c-path.org/camd

CRITICAL PATH INSTITUTE

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