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

May 9, 2017

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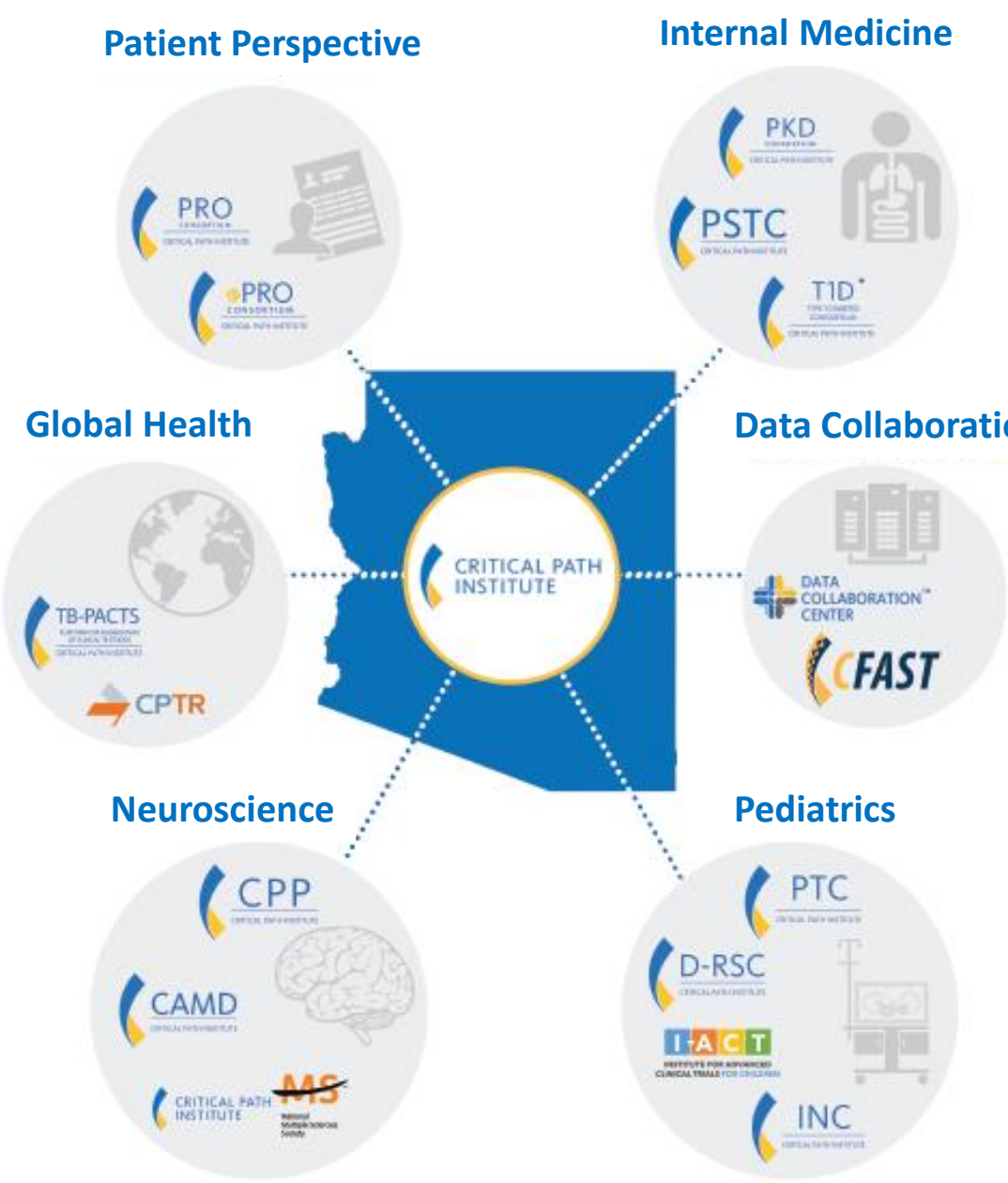
ARIZONA ALZHEIMER'S CONSORTIUM

CAMD CRITICAL PATH INSTITUTE

C-PATH CONSORTIA

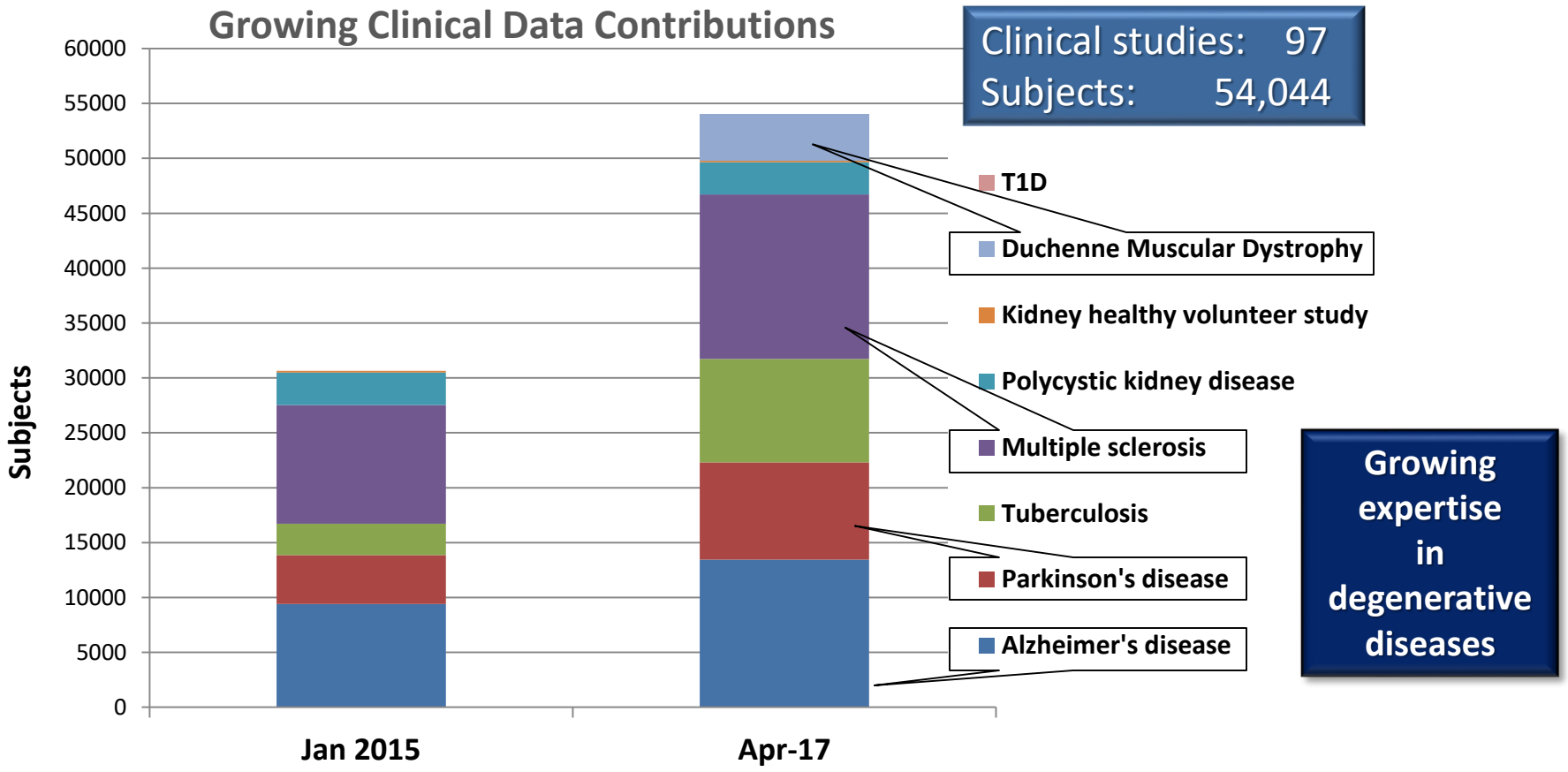


- ✓ Data standards
- ✓ *In vitro* tools
- ✓ Clinical trial simulation tools
- ✓ Biomarkers
- ✓ Clinical outcome assessment instruments

Fourteen global consortia collaborating with 1,450+ scientists and 84 organizations

www.c-path.org/camd

C-PATH CLINICAL DATA CONTRIBUTIONS

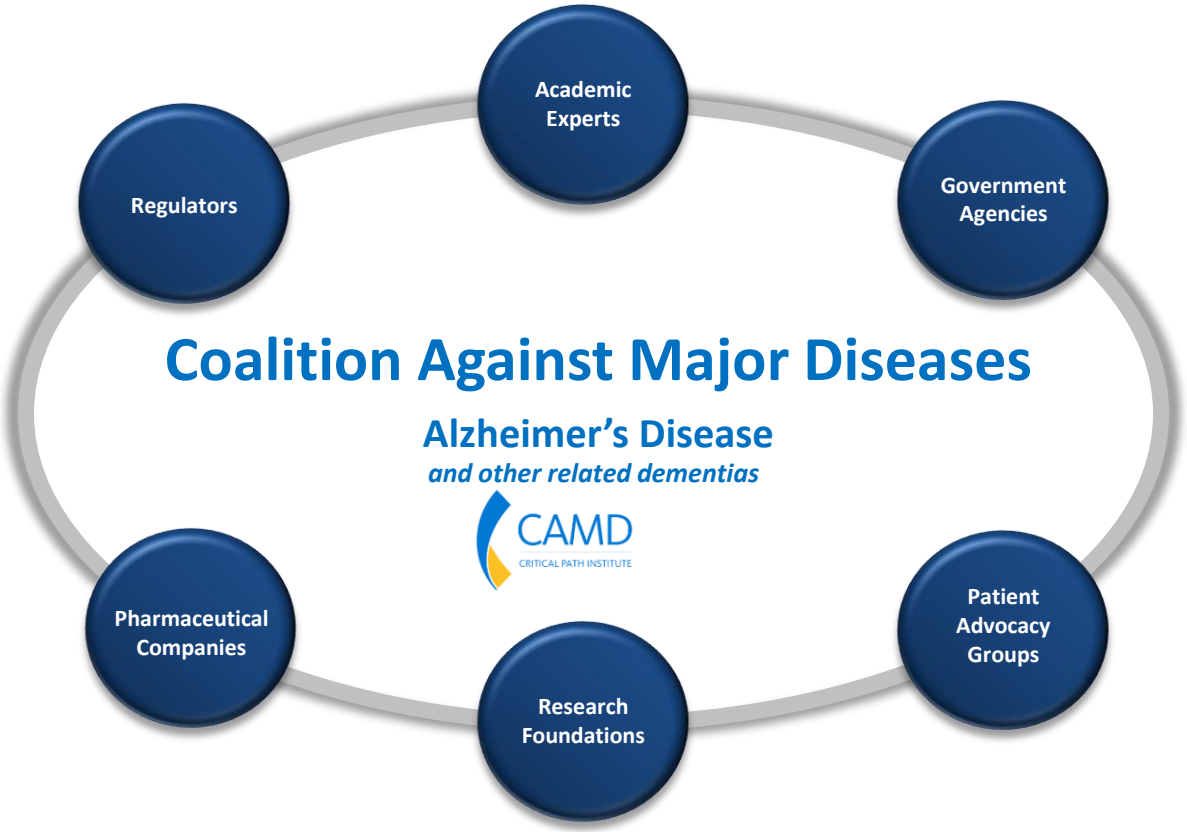


Note: Nonclinical 116 studies; 6296 subjects.
ReSeqTB: 3558 Individual solates

COALITION AGAINST MAJOR DISEASES (CAMD)

Mission

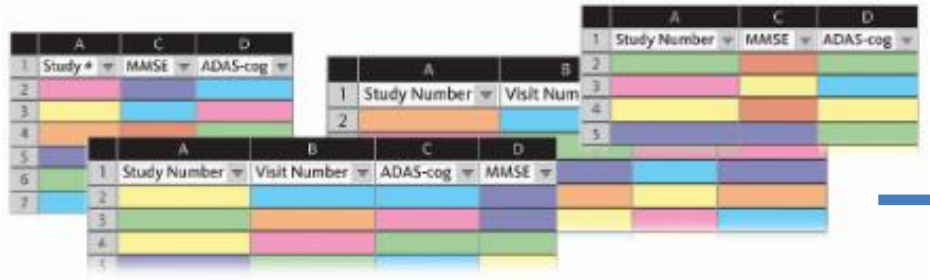
To develop, as a pre-competitive consortium, new technologies and methods to accelerate the development and review of medical products for treating Alzheimer's Disease and dementias of related neurodegenerative diseases.



Focus

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

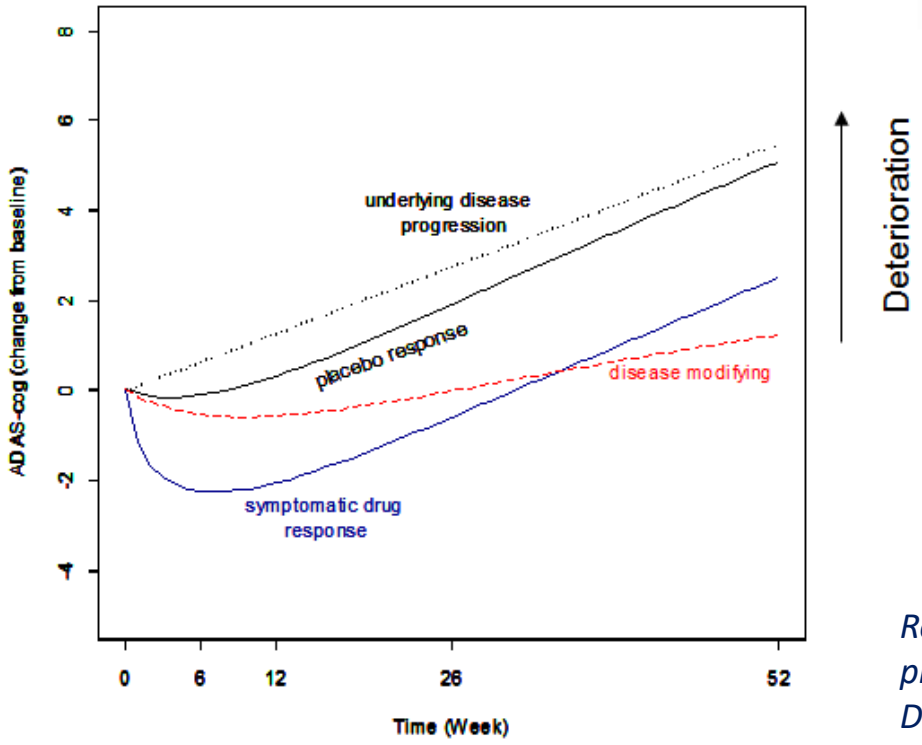
STEP 1: DATA STANDARDS



Mixed Disparate Legacy Data

CDISC
'Standardized Data'

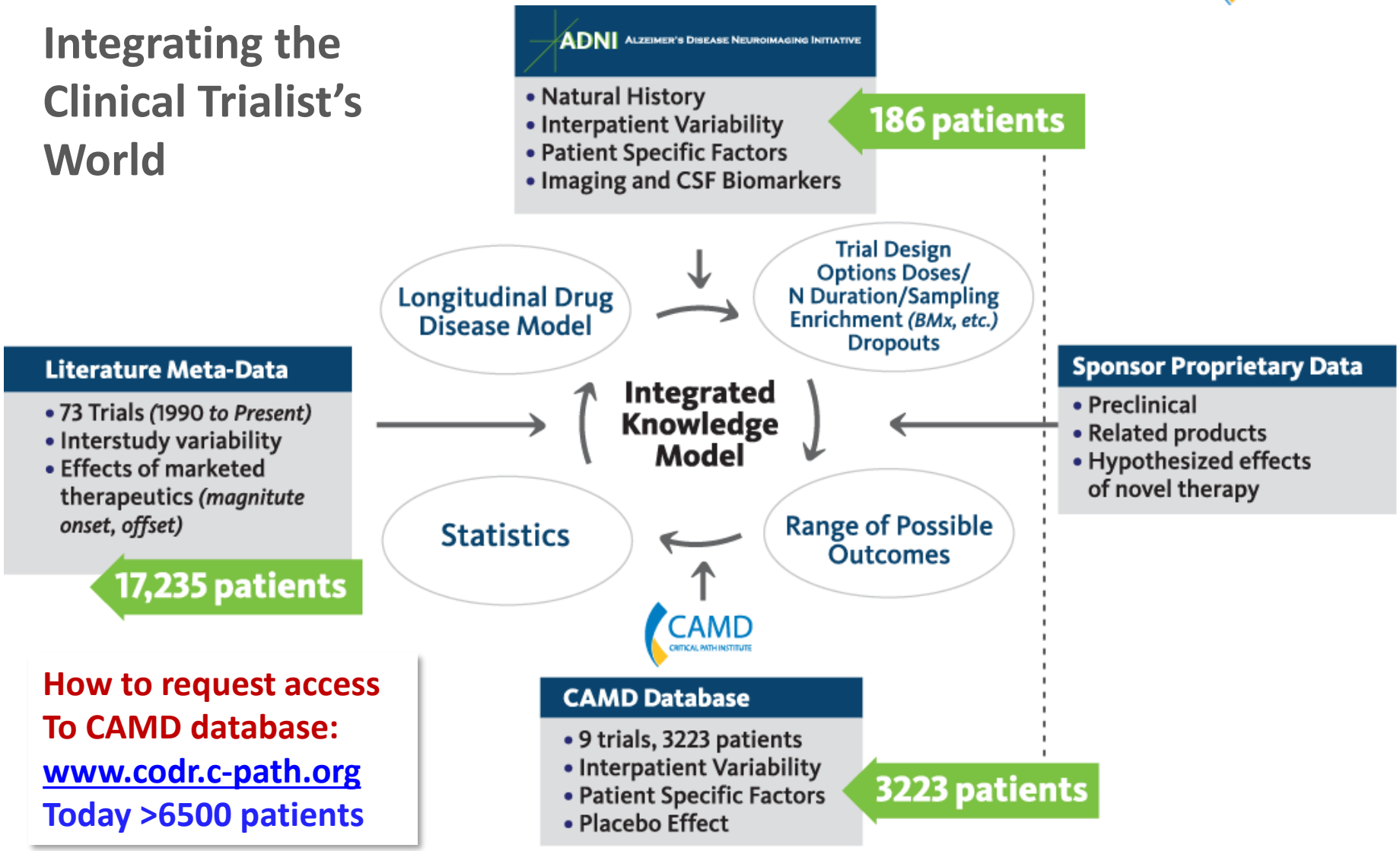
Integrated Data



Romero K., et al. Striving for an integrated drug development process for neurodegeneration: The Coalition Against Major Diseases. Neurodegen. Dis. Manage. 2011;1(5): 379-85.

STEP 2: AD DRUG-DISEASE-TRIAL MODEL

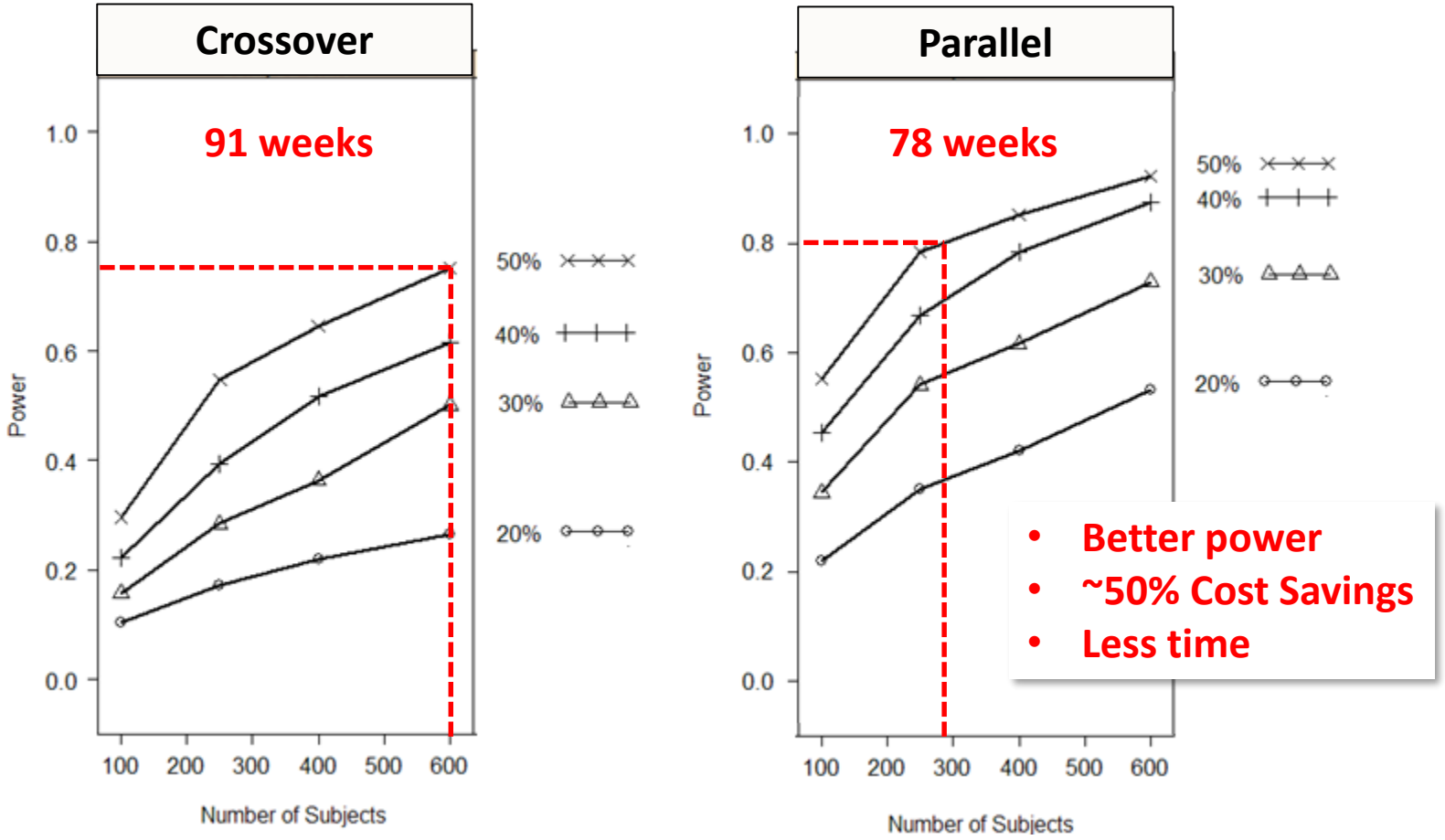
Integrating the Clinical Trialist's World



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

STEP 3: USE

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

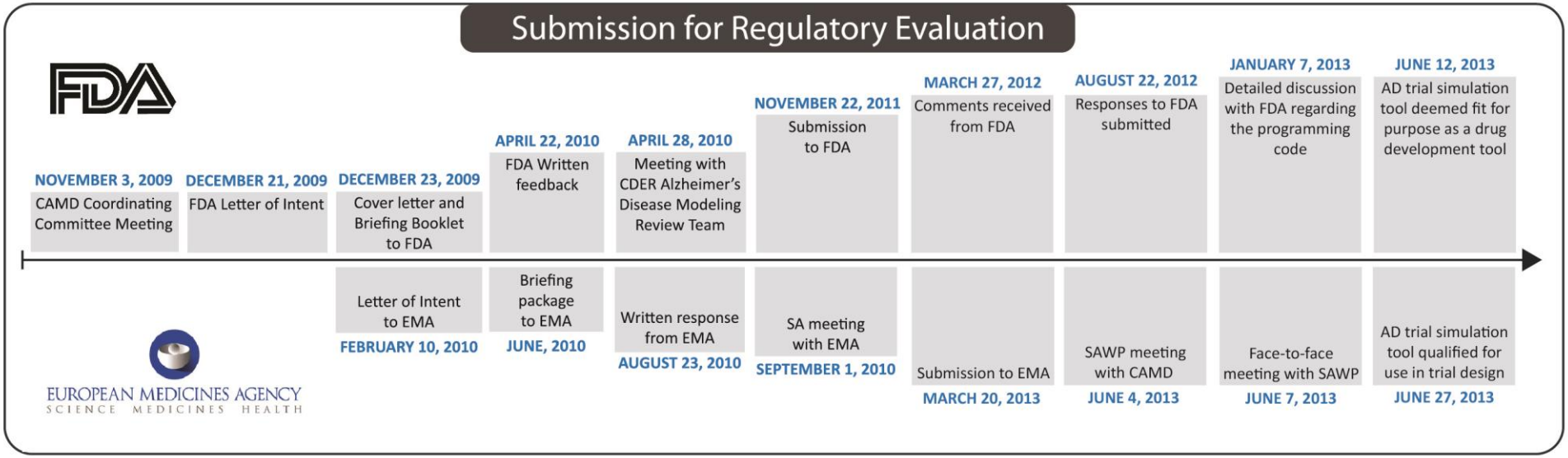


AD DRUG DISEASE TRIAL MODEL – THE REGULATORY PATH

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)

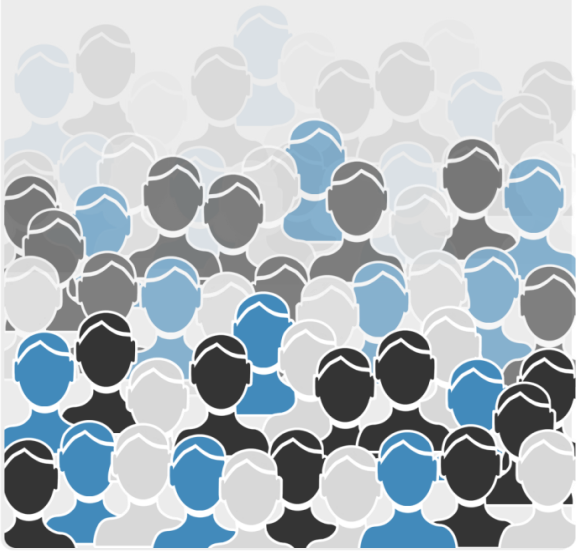
CAMD joined GAAIN – December 2015

CAMD'S ALZHEIMER'S DISEASE DATABASE

242 Organizations +3%

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

343 Individuals +3%



89 Academic Institutions +3%

Amherst College
Duke University School of Medicine
Emory University
Goethe Universität Frankfurt am Main
Harvard Medical School
Georgetown University Georgetown University Medical Center
Johns Hopkins University
Seoul National University
University of Aberdeen
The University of Auckland
University of Cape Town
Universitäts Klinikum Freiburg
…and others

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

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

58 Organizations **+7%**

AstraZeneca
Biogen
Bristol-Myers Squibb
Lilly
Merck
Pfizer
Takeda

...and others

72 Individuals **+7%**

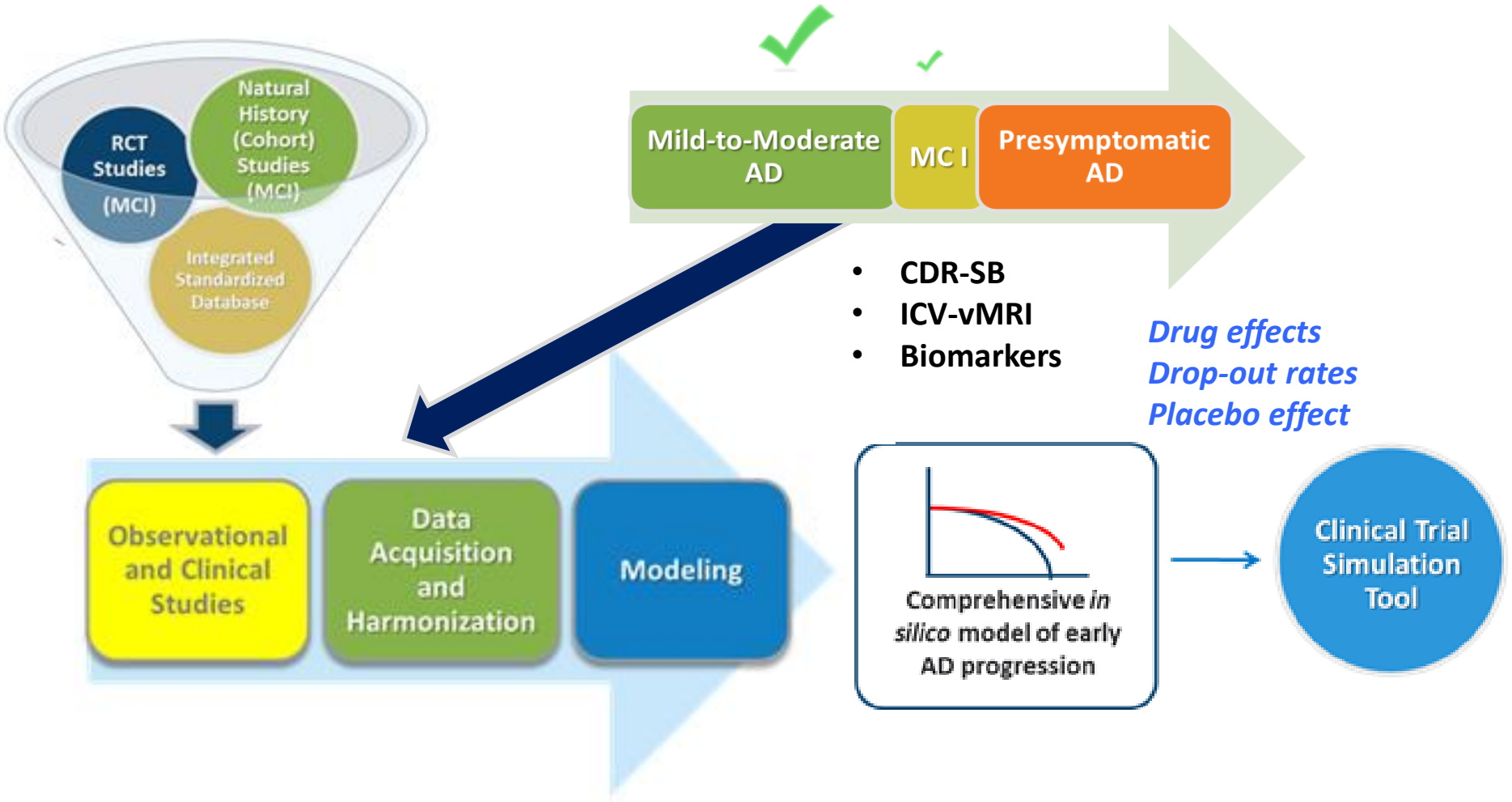
18 Academic Institutions **+13%**

Harvard University
Karolinska Institutet
LSE The London School of Economics and Political Science
Imperial College London
UF University of Florida
Manchester 1824 The University of Manchester
Penn University of Pennsylvania
USC University of Southern California

...and others

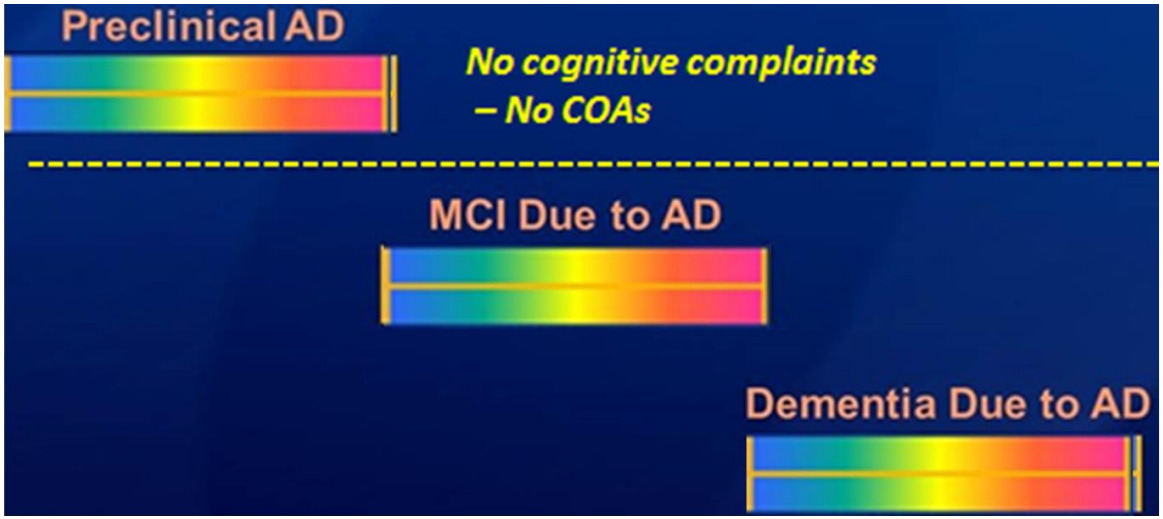
MAXIMIZING THE USE OF PRE-COMPETITIVE DATA

Accelerate new drug development tools and data acquisition



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 — *No apparent symptoms*

MCI / Prodromal AD — *Symptoms*

Mild **Moderate** **Severe** — *Current diagnosis & treatment*

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

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

AGE-RELATED NEURODEGENERATIVE DISEASES

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Tsunami of Elderly

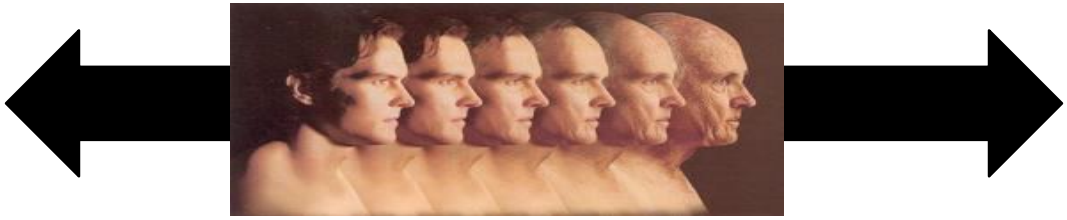
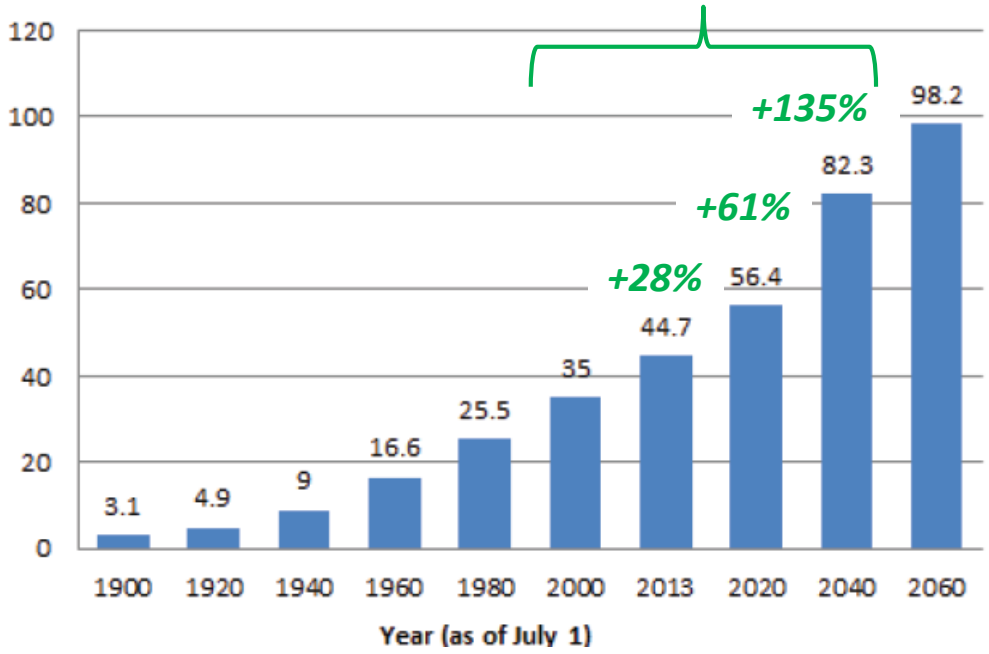


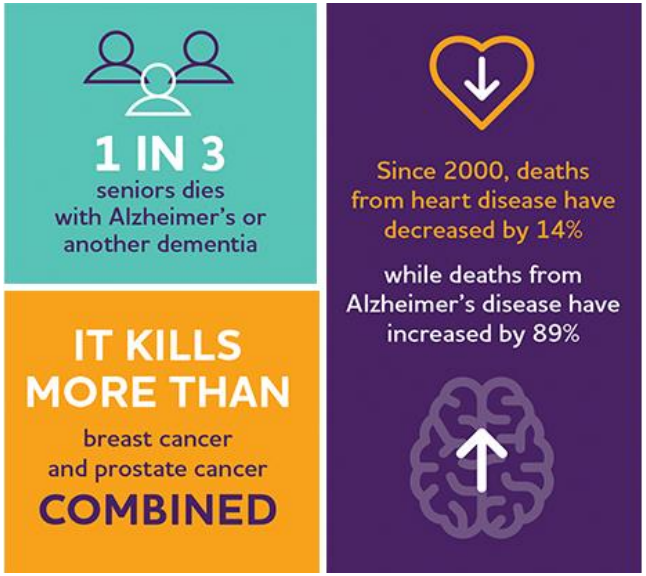
Figure 1: Number of Persons 65+, 1900 to 2060 (numbers in millions)



NOTE: INCREMENTS IN YEARS ARE UNEVEN.
SOURCE: U.S. CENSUS BUREAU, POPULATION ESTIMATES AND PROJECTIONS.

"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.



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

Imaging Modalities

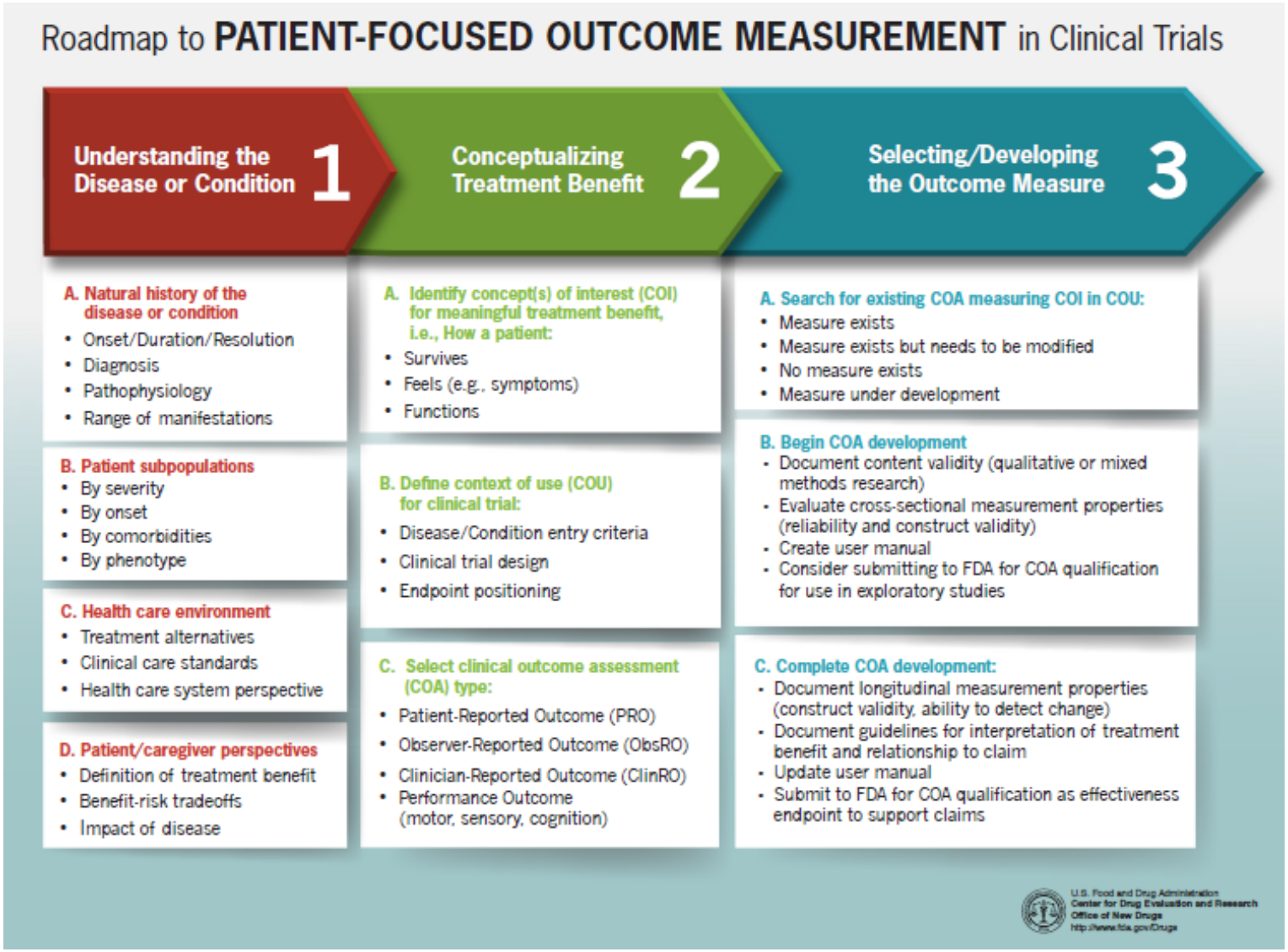
Patient & Physician Reported Outcomes

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

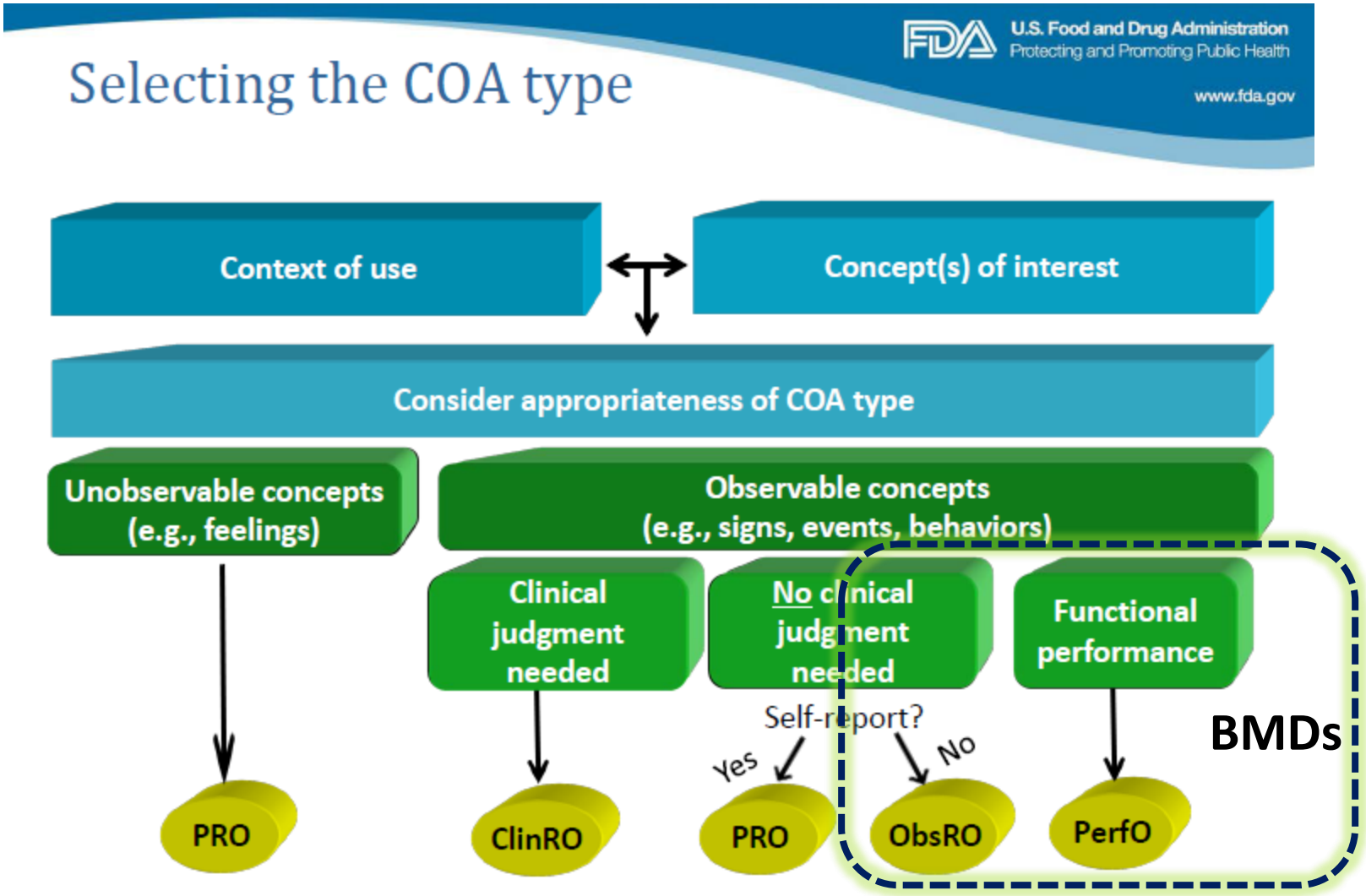
Outcome decisions

- Diagnoses
- Treatment algorithm

WHAT ELEMENTS CAN BE USED FOR BMD ASSESSMENTS?

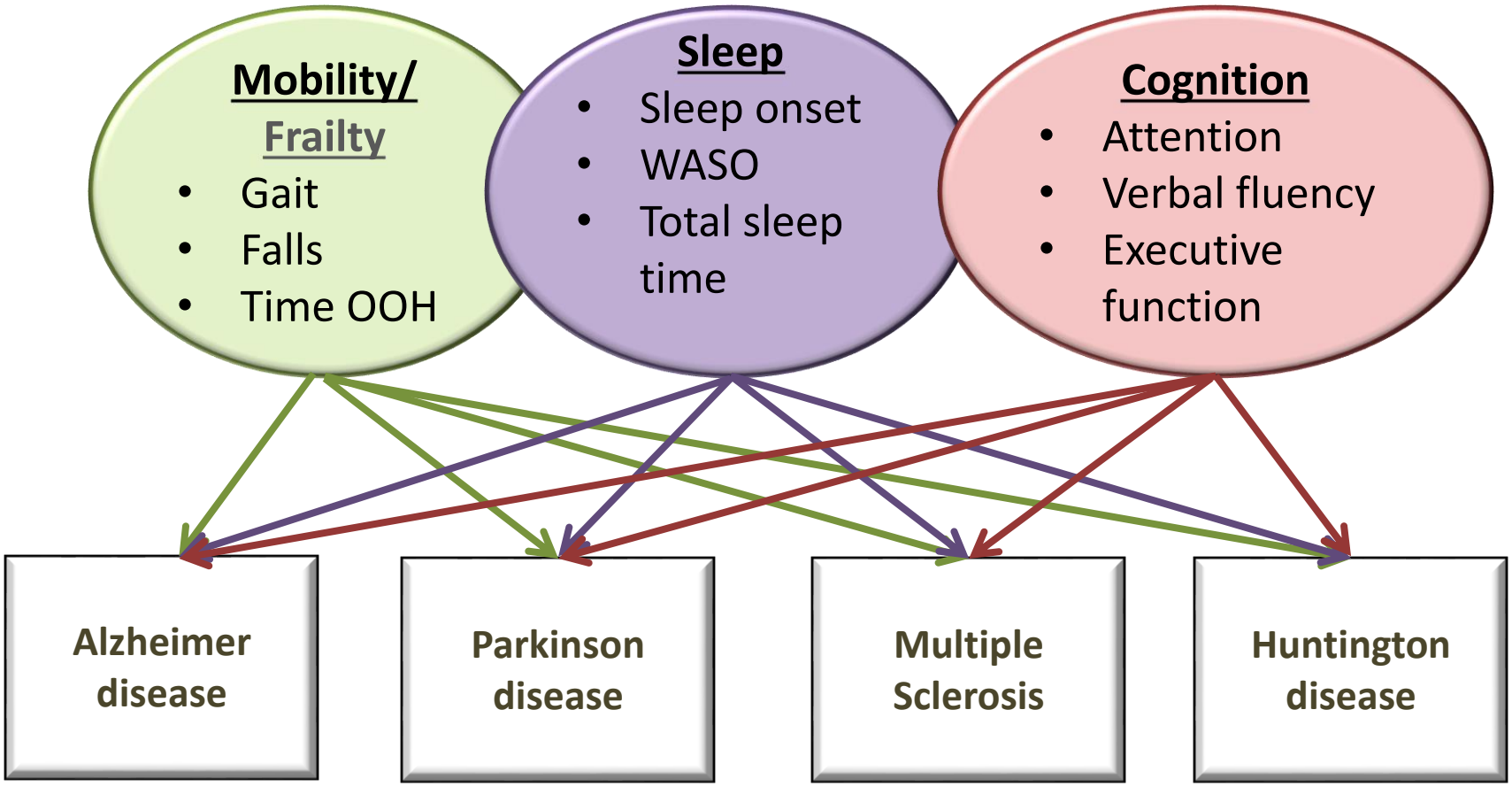


BMDs HAVE THE POTENTIAL TO PROVIDE ObRO and PerfO ASSESSMENTS



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

PREFERRED OBJECTIVE:
Create standards with utility across diseases

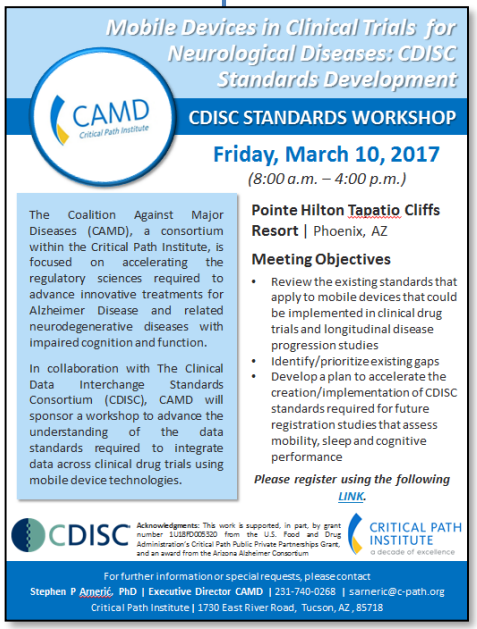


CDISC STANDARDS FOR BMDs

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

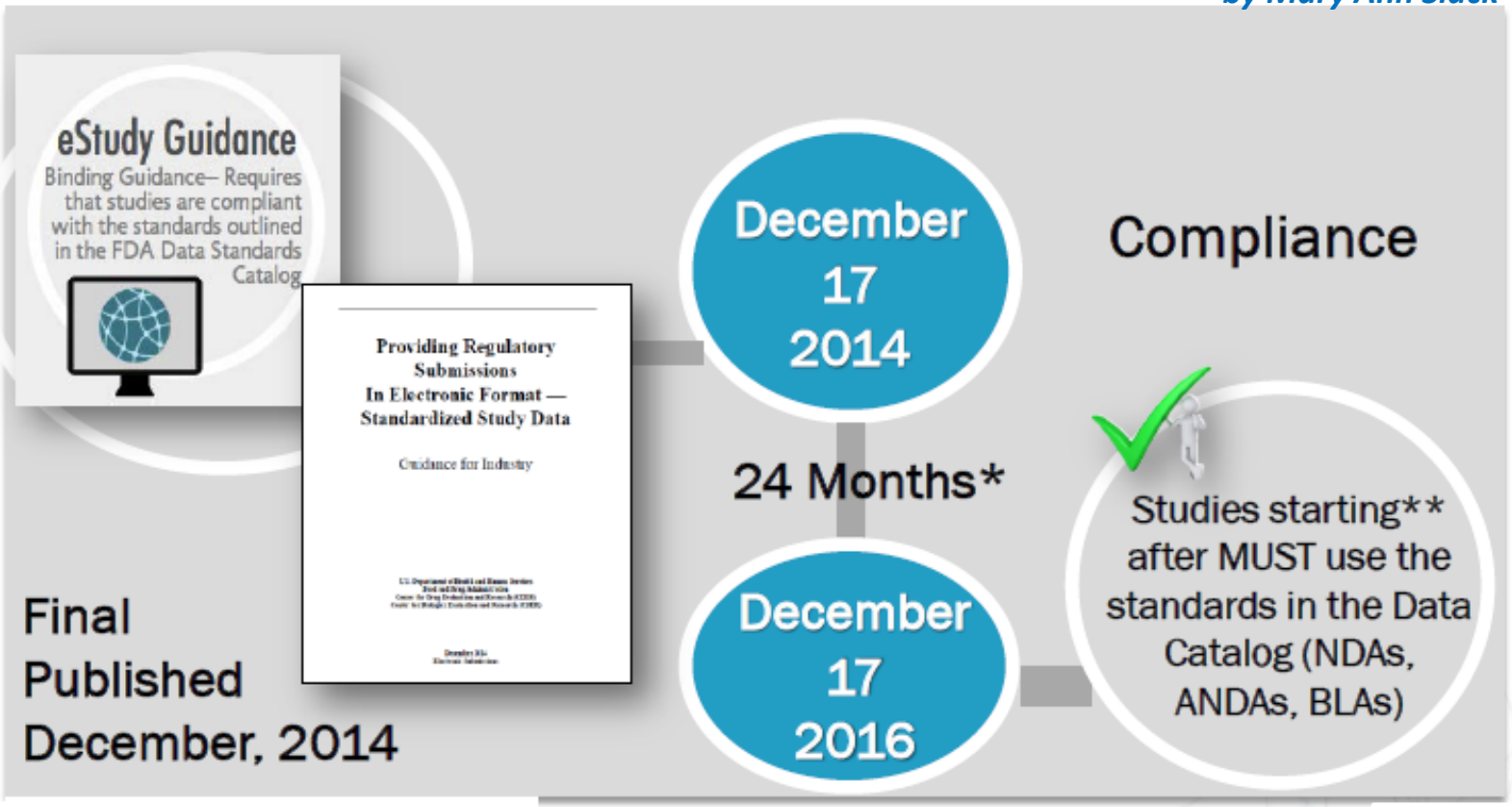
3Q 2017

- **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?

From presentation by Mary Ann Slack

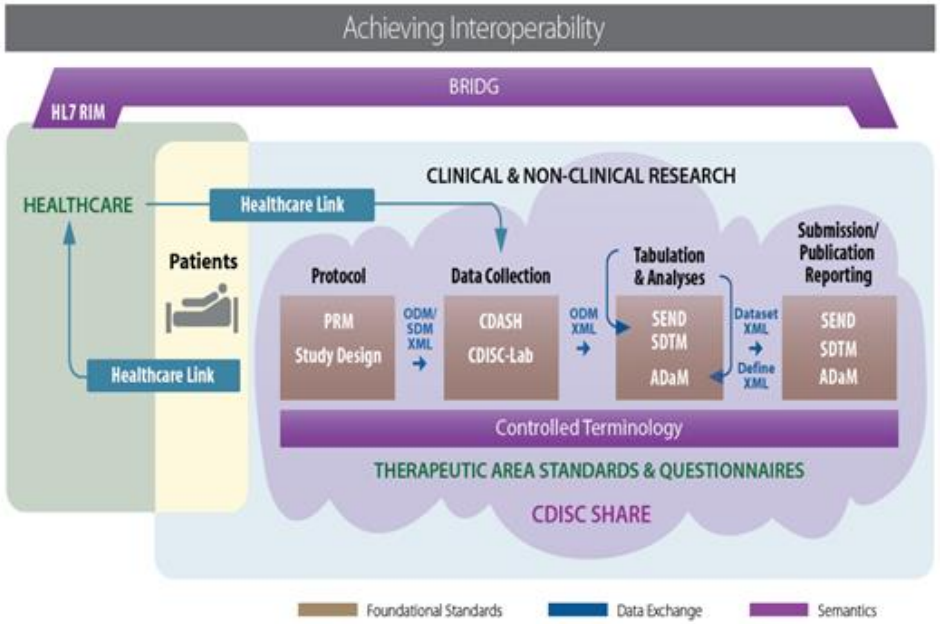


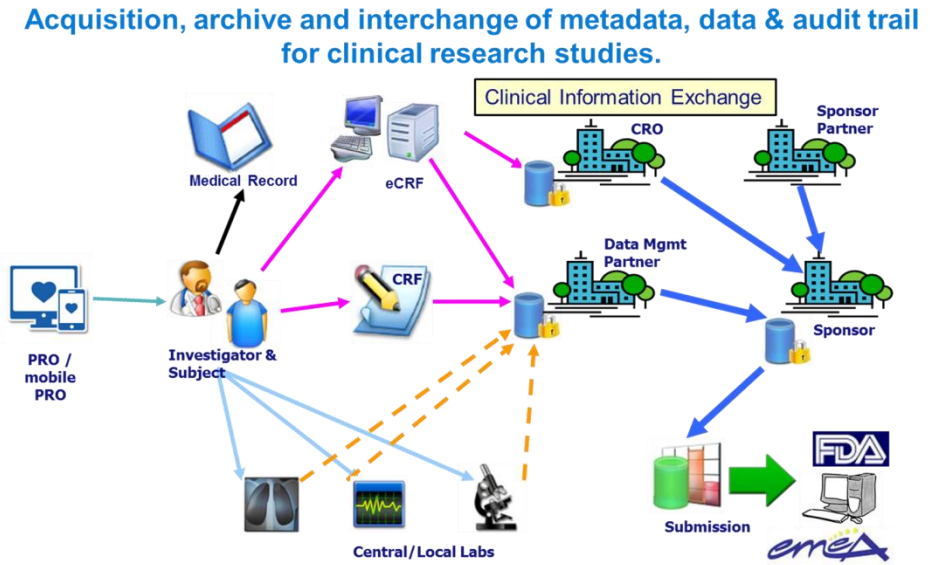
*36 months for INDs **Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC).

CDISC STANDARDS ARE FOUNDATIONAL IN CREATING ACTIONABLE DATABASES

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 SHARE library overview





CDISC standards are required for registrations studies at FDA, PMDA, etc.

CDISC STANDARDS ARE BECOMING GLOBAL REQUIREMENTS

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CDISC Strength Through Collaboration

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Global Regulatory Requirements

CDISC updates this page with announcements from regulatory authorities (FDA, PMDA, EMA, etc.). We encourage readers to check for new announcements directly with the appropriate agency.

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)

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

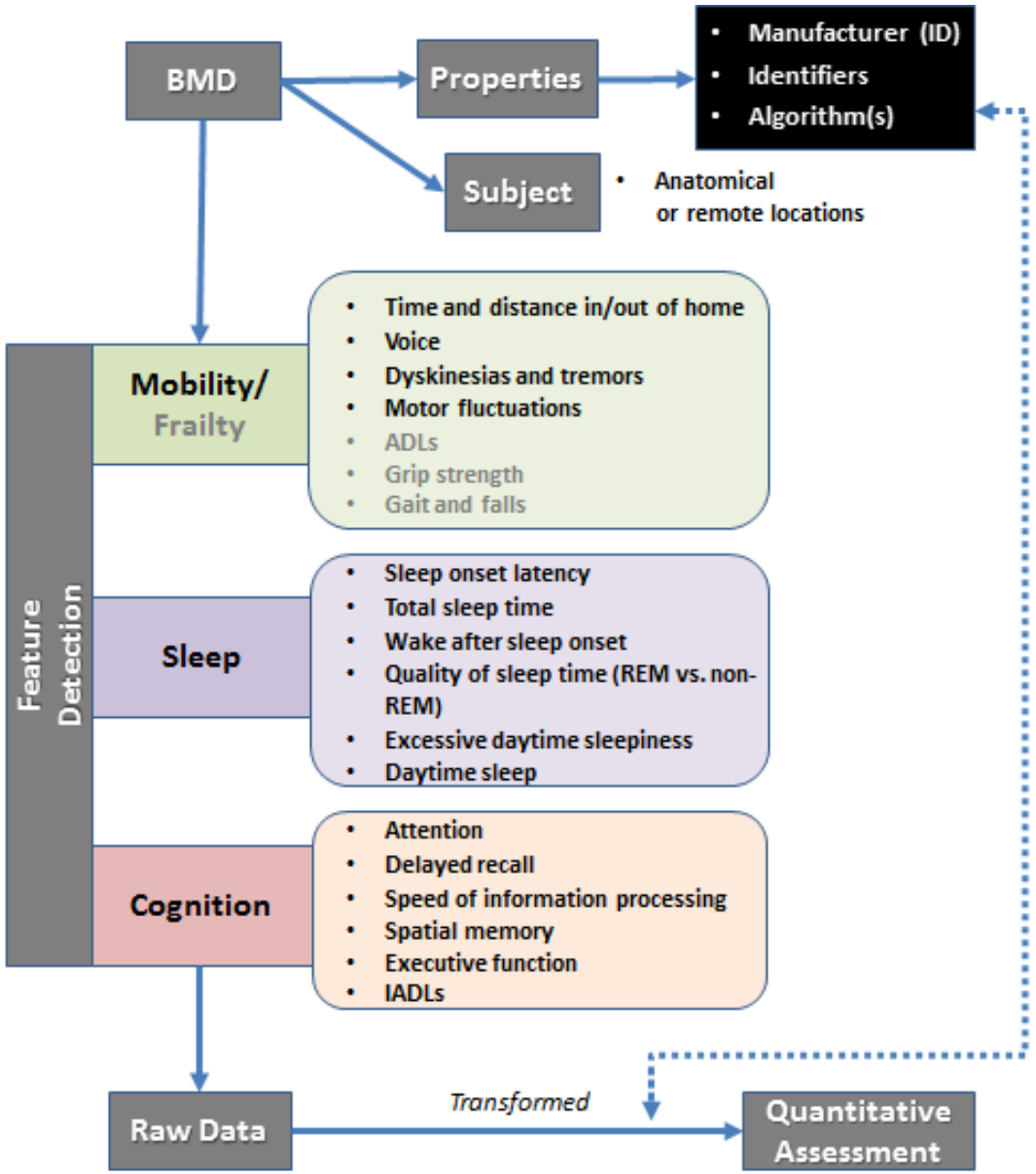
AVAILABLE CDISC STANDARDS

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

MEASURES TO SUPPORT CONCEPTS-OF-INTEREST



KEY LEARNINGS

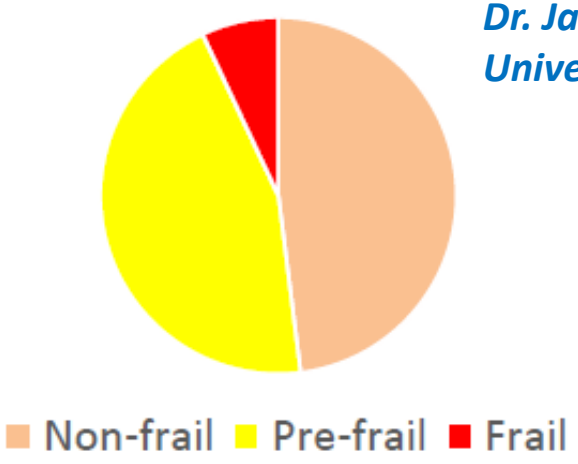
- **Many fundamental CDISC standards exist**
- ***Metadata is critical to understand context of an assessment***
- **Composites may provide a more powerful and contextually meaningful assessment**
- **Mood (e.g., depression) and pain may be important factors in assessments**
- **Need to understand the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

https://c-path.org/mobile-devices-in-clinical-trials-for-neurological-diseases-cdisc-standards-development/

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

Dr. Jane Mohler
University of Arizona

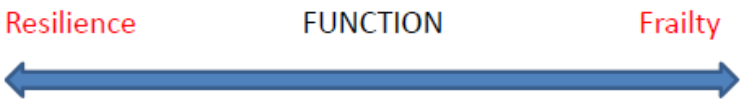


- 5,317 men and women 65 years and older

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

1: Fried LP, et al., (2001)

- 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

Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol a-Biol 2001;56:M146-M56.

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]

Dr. Jane Mohler
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1: Winograd CH, et al. (1991); 2: Makary MA, et al. (2010); 3: Chow WB et al., (2012); 4:JCO November 15, 2004 vol. 22 no. 22 4626-4631

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

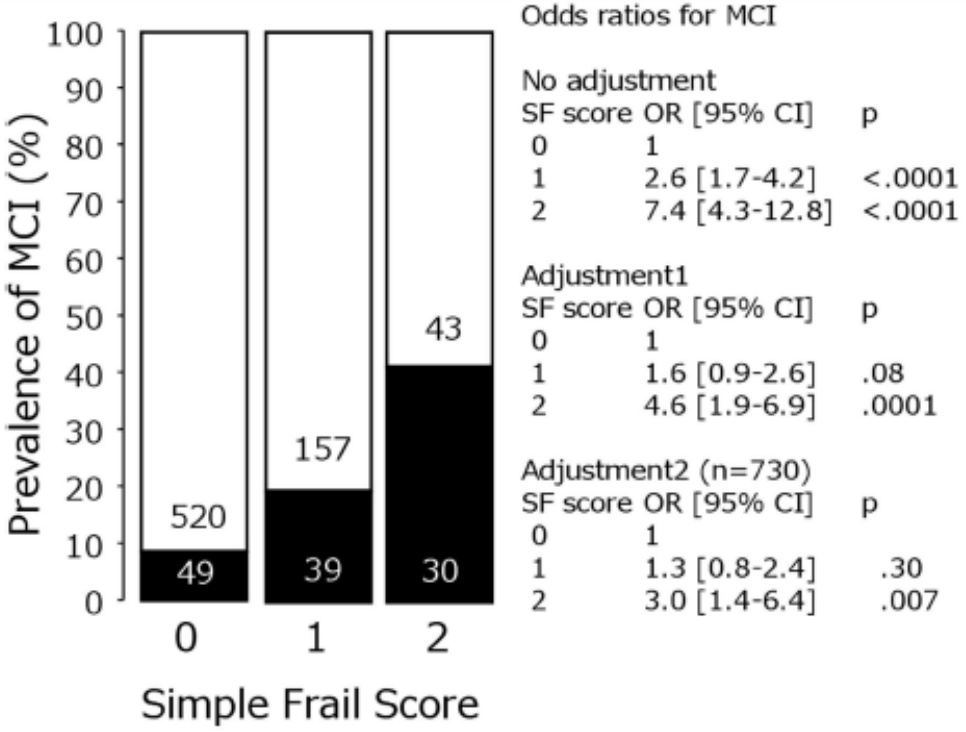
- Functional Decline Instruments
  - ADL
  - CCI

SENSOR - BASED

Inertial Sensors (gyroscopes & accelerometers) Gait-based	Greene, BR, 2014	TUG
	Schwenk, M. 2014	Gait speed Walking bout duration variability
	Merchant, R.A., 2016	Trunk posture
	Najafi,B, 2014	Stand and Flop
	Bahureksa, L, 2017	Gait speed Stride length Stride time
Inertial Sensors (gyroscopes & accelerometers) Upper Extremity Based	Toosizadeh,N.	Upper extremity function
Dynamometer	Schwenk, M. 2014; Greene, BR, 2014	Grip strength
ECG	Parvaneh, 2017	Heart rate variability

Dr. Jane Mohler
University of Arizona

FRAILTY IS ASSOCIATED WITH MCI



Odds ratios for MCI

No adjustment

SF score	OR [95% CI]	p
0	1	
1	2.6 [1.7-4.2]	<.0001
2	7.4 [4.3-12.8]	<.0001

Adjustment1

SF score	OR [95% CI]	p
0	1	
1	1.6 [0.9-2.6]	.08
2	4.6 [1.9-6.9]	.0001

Adjustment2 (n=730)

SF score	OR [95% CI]	p
0	1	
1	1.3 [0.8-2.4]	.30
2	3.0 [1.4-6.4]	.007

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, antidyslipidemic 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.

SCIENTIFIC REPORTS

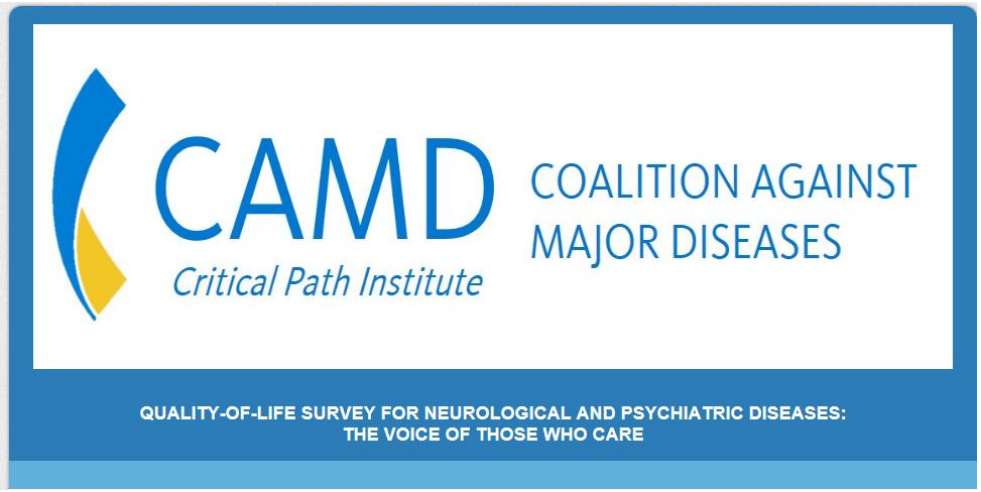
OPEN

Received: 31 October 2016
Accepted: 15 March 2017
Published: 13 April 2017

Office-based simple frailty score and central blood pressure predict mild cognitive impairment in an apparently healthy Japanese population: J-SHIPP study

Maya Ohara[1], Katsuhiko Kohara[2], Yoko Okada[1], Masayuki Ochi[1], Tokihisa Nagai[1], Yasumasa Ohyagi[1], Yasuharu Tabara[3] & Michiya Igase[1]

SURVEY: THE VOICE OF THOSE WHO CARE



LINK:
https://www.surveymonkey.com/r/quality-of-lifesurvey

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.

DIGITAL DRUG DEVELOPMENT TOOLS

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

WHAT

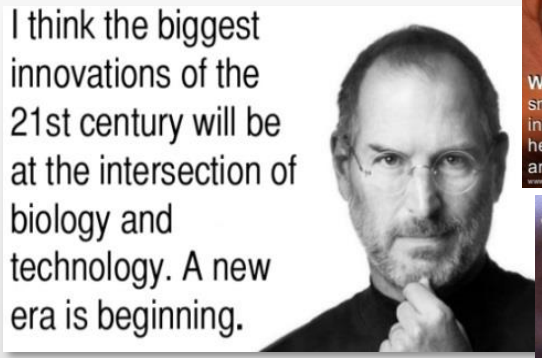
Data (signal output) collected from a biosensor that measures a biological response

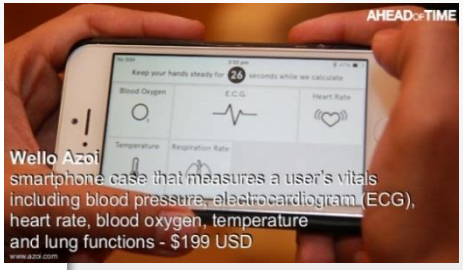
HOW

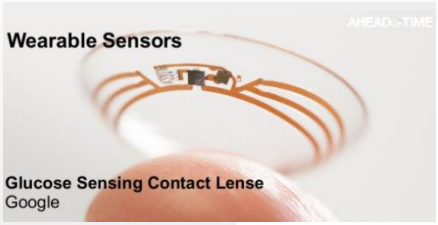
Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestible, remote biosensors)

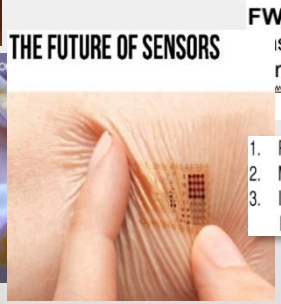
WHY

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



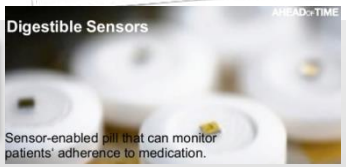






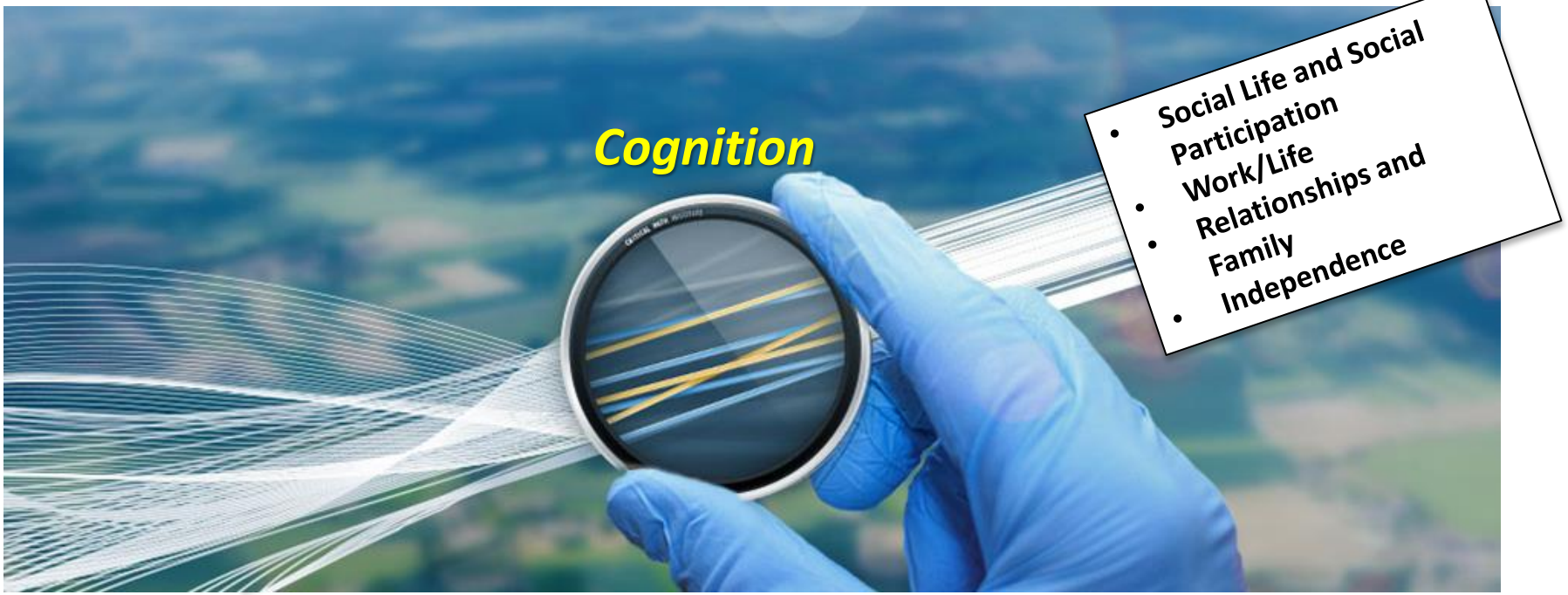
FWD Health
ishboard Tracks Exercise Regimes
r Lowered Insurance Prices

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



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".

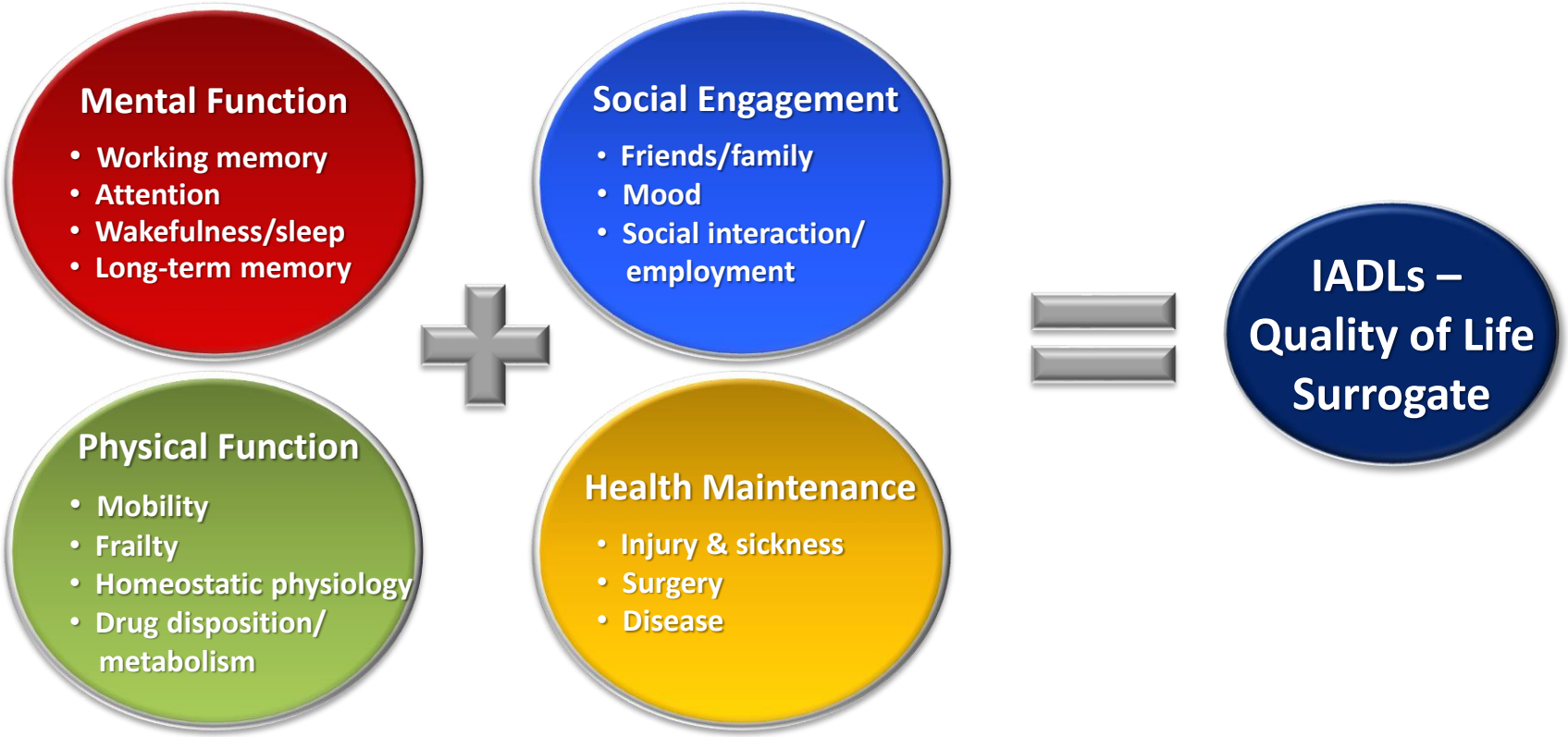


Hypothesis: Changes or increased variance in the key functional domains of "instrumental activities of daily living" should reflect current (and potentially future) changes in cognitive function.

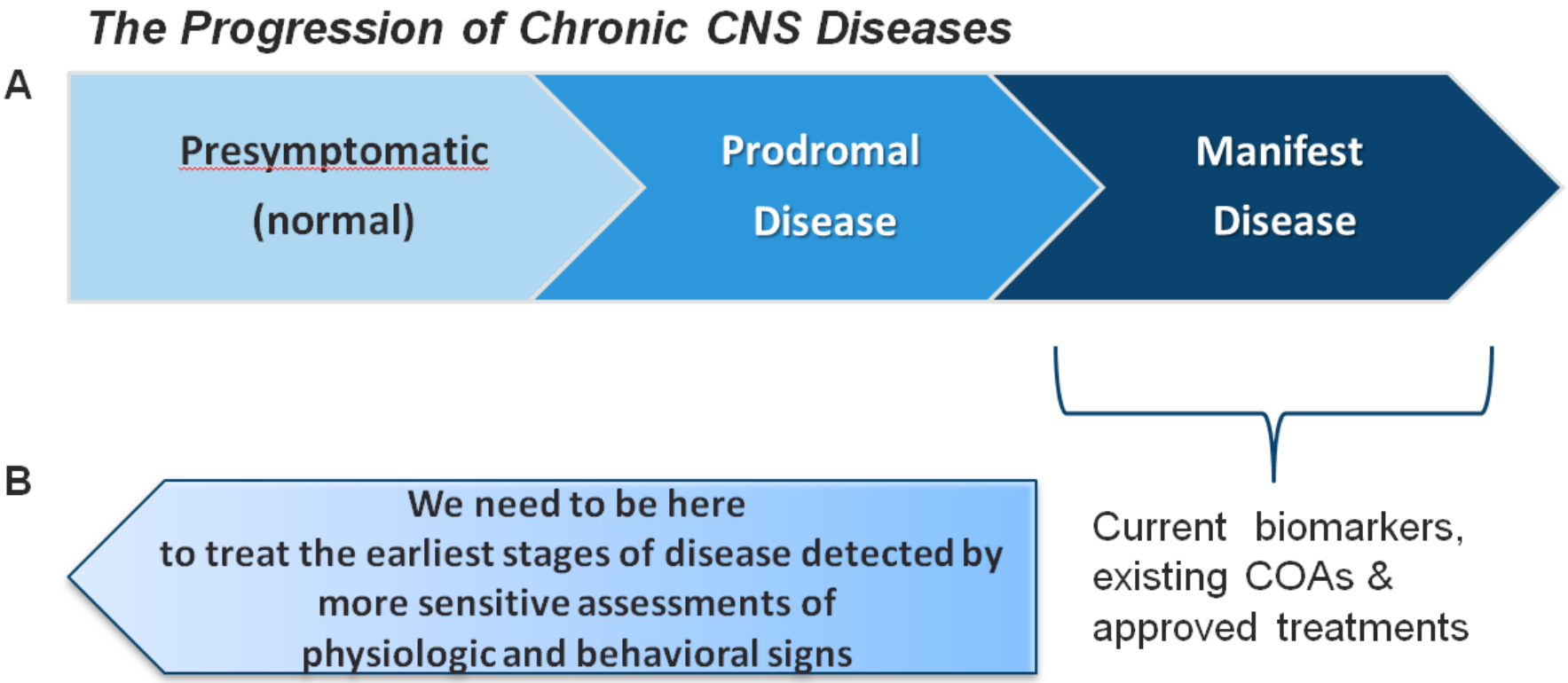
BIOMETRIC MONITORING DEVICES (BMDs)

Measuring 'Signs' Related to QoL

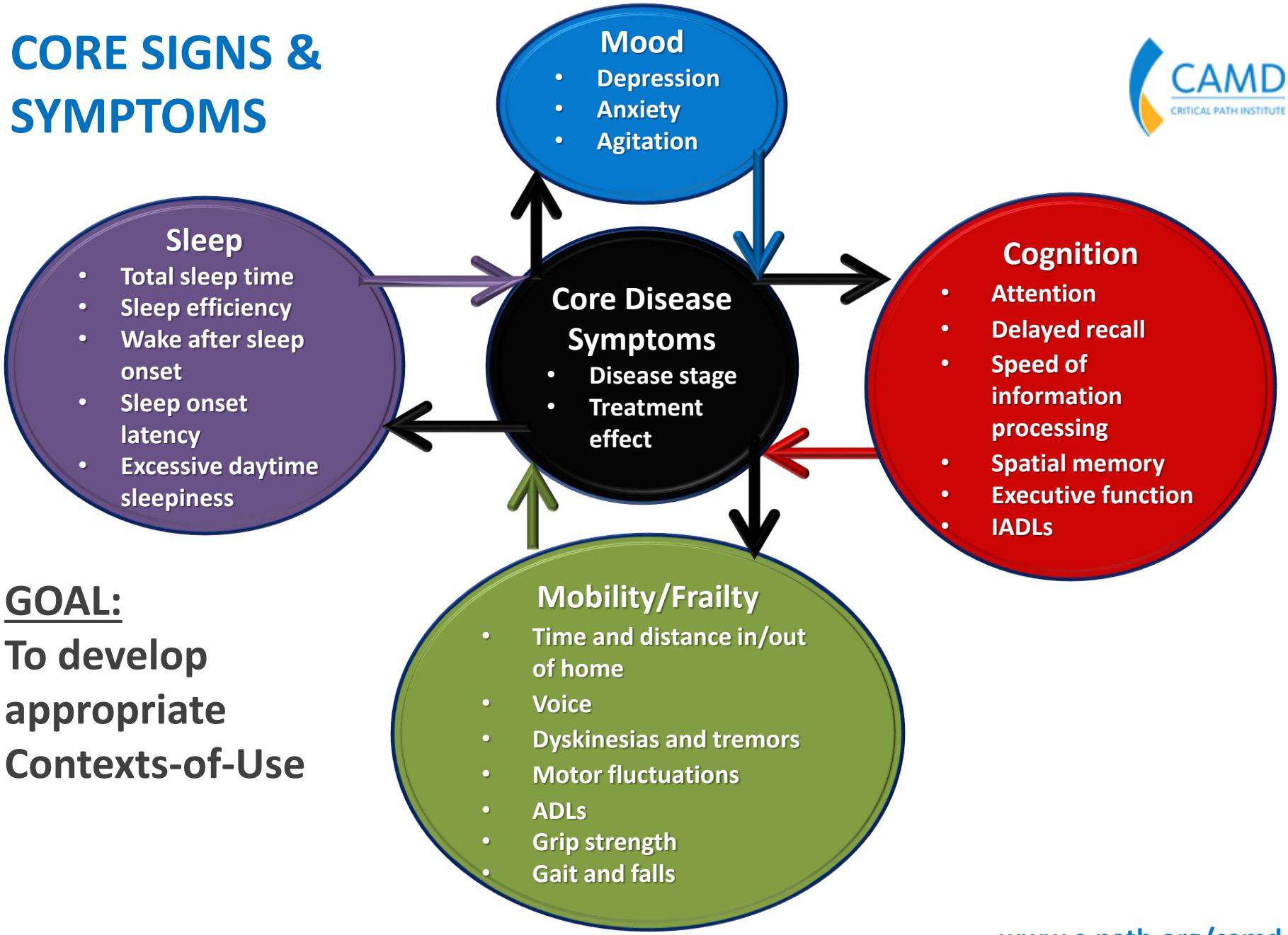
BMDs have the potential to measure signs related to all domains of function comprising what is viewed as Instrumental Activities of Daily Living



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



CORE SIGNS & SYMPTOMS



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

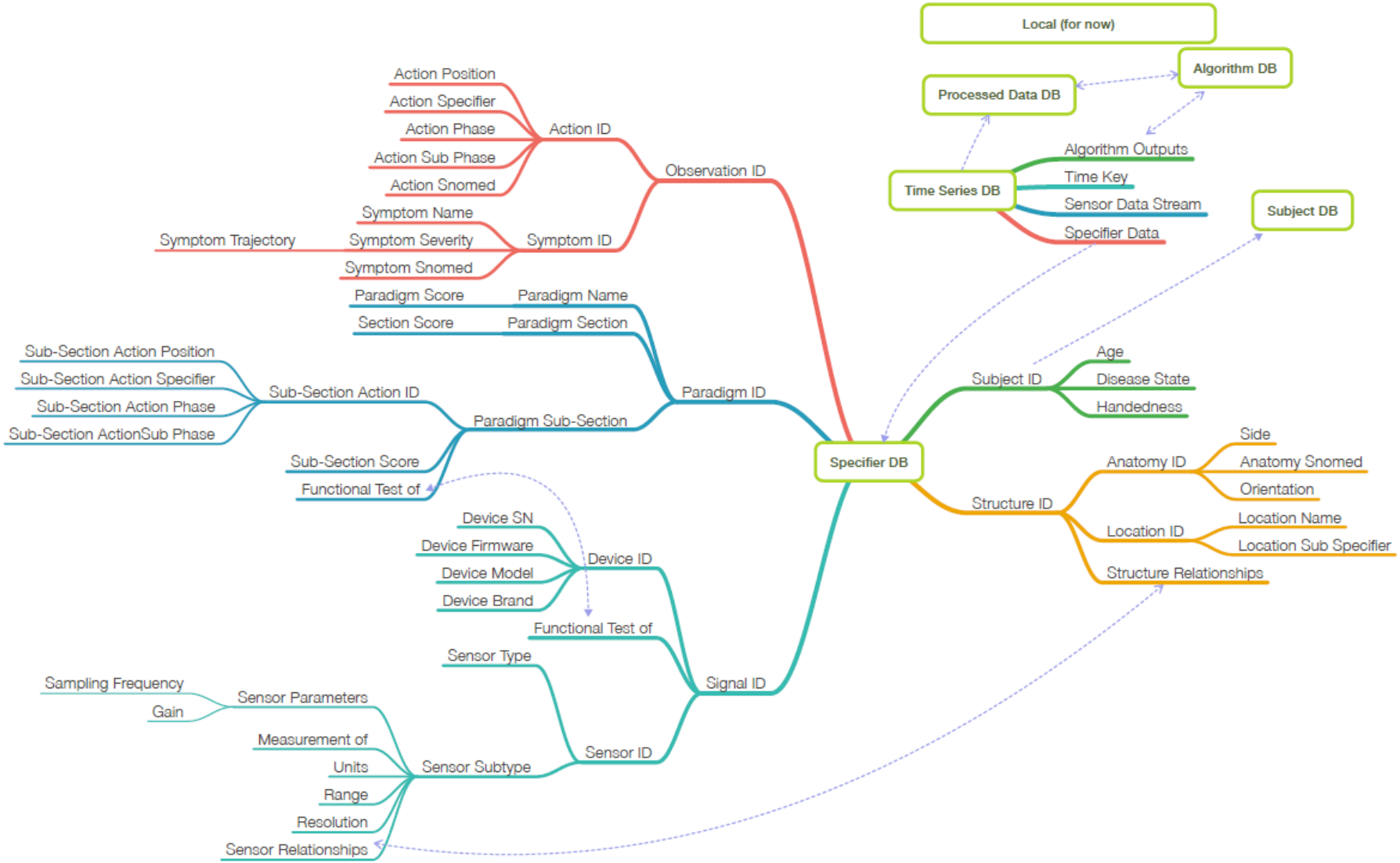
Concept-of-Interest measured:

CONSIDERATION	ATTRIBUTE	GAP	COMMENTS
510K compliant			
FDA cleared for specific use case			
Time stamp of data acquisition			
Biometric validation of user			
Analytical validation			
Clinical validation			
Secure data transfer			
GCP compliant for audit trail			

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



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

DISCUSSION