

Enabling Integration of Alzheimer Disease (AD) Prevention Study

Data by Application of CDISC Standards: Extension to Biometric Monitoring Device (BMD) Assessments



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Background and Objectives

In December 2016, the U.S. Food and Drug Administration (FDA) initiated the requirement of submitting data conforming to Clinical Data Interchange Standards Consortium (CDISC) standards for all new drug applications, indicating that clinical trials initiated at the present time must adopt these standards. CDISC standards facilitate aggregation of clinical data from diverse sources, which has enabled the FDA to improve the efficiency of integrated data analyses for new drug applications by ~40%. Biometric Monitoring Devices (BMDs) (e.g., wearables, smartphones, remote monitoring biosensors) offer the potential of measuring biologic events that may predict disease progression, or monitor key biologic functions in response to treatment interventions. The Coalition Against Major Diseases (CAMD), a nonprofit public-private-partnership within the Critical Path Institute (C-Path) focused on delivering Drug Development Tools that accelerate innovative treatments for Alzheimer disease (AD), is coordinating the development of these standards for integration into registration trials. BMDs may lead to clinical assessments sufficiently sensitive to detect changes in the pre-symptomatic stages of the neurodegenerative diseases like AD.

Methods

A partnership/collaboration between C-Path and the Arizona Alzheimer's Consortium was formed in 2016 to lay the foundation for additional data standardization and integration of data from prevention trials. On March 10, 2017, an international workshop was held to:

1. Evaluate the existing standards that apply to mobile devices that could be implemented in clinical drug trials and longitudinal disease progression studies;
2. Identify/prioritize existing gaps;
3. Develop a plan to accelerate the creation/implementation of CDISC standards required for future registration studies that assess three concepts-of-interest: mobility/frailty, sleep, and cognitive performance.

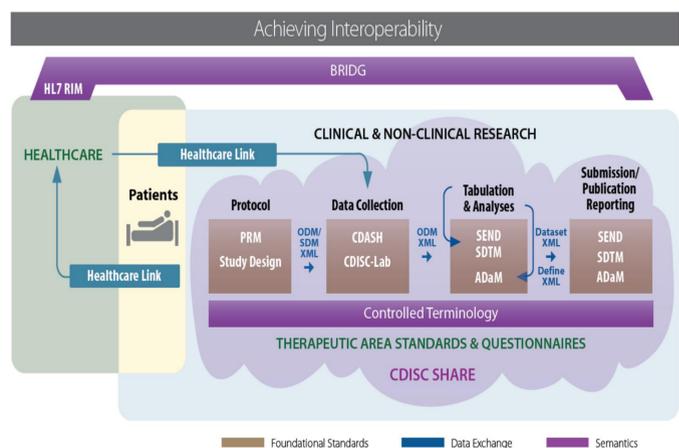
Presentations and detailed notes from this meeting are available ([LINK](#) on the right).



Results

- Many foundational standards already exist thanks to the work of CDISC. CDISC launched the Shared Health And Research Electronic (SHARE) library for developing, integrating and accessing CDISC standards metadata electronically ([Figure 1](#)). SHARE is a curated resource that makes it easier to implement CDISC standards in electronic systems such as clinical data management systems, mobile apps, and learning health systems.

Figure 1 CDISC SHARE library overview (Ref. 1)



- Increasingly, clinical trials in neurodegenerative diseases are focusing on the early stages of the disease ([Figure 2](#)), trying to identify individuals who are genetically, or otherwise susceptible prior to developing any symptoms ([Ref. 2](#) and [3](#)).
- High-level considerations were developed for all three concepts-of-interest (COIs), and how they interrelate ([Figure 3](#)). Ideally these COIs and corresponding standards, could be developed across neurodegenerative diseases.

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- More detailed considerations of data flow were outlined for each COI ([Figure 4](#)).
- Additional work needs to be completed in detailing data provenance, annotating contextual metadata, and compliance with Good Clinical Practices (GCP) to support the requirements for regulator submissions ([Figure 5](#)).

Figure 2

Alzheimer disease (AD) Stages: Framing the dilemma of what to measure and when

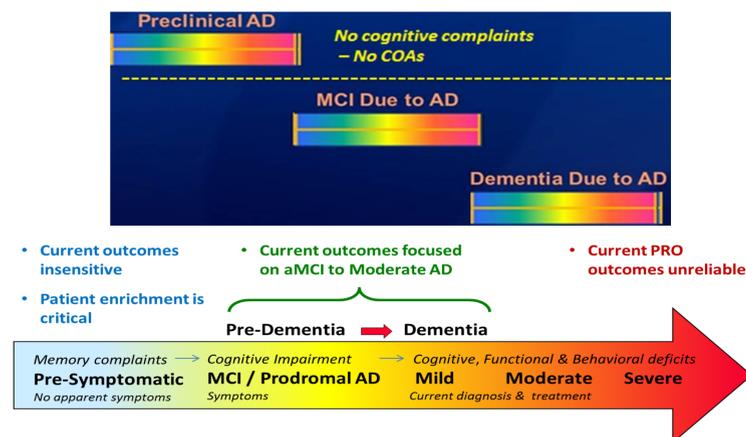


Figure 3

High level Concepts-of-Interest applicable across neurodegenerative diseases

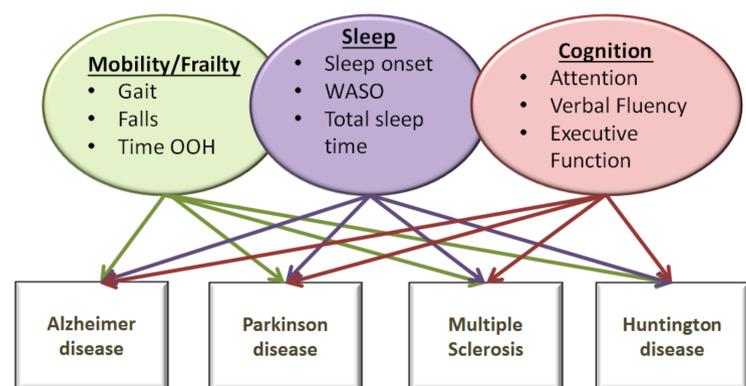


Figure 4

Data flow from Biometric Monitoring Devices (BMDs) assessing specific measures for each Concept-of-Interest: High-level information capture

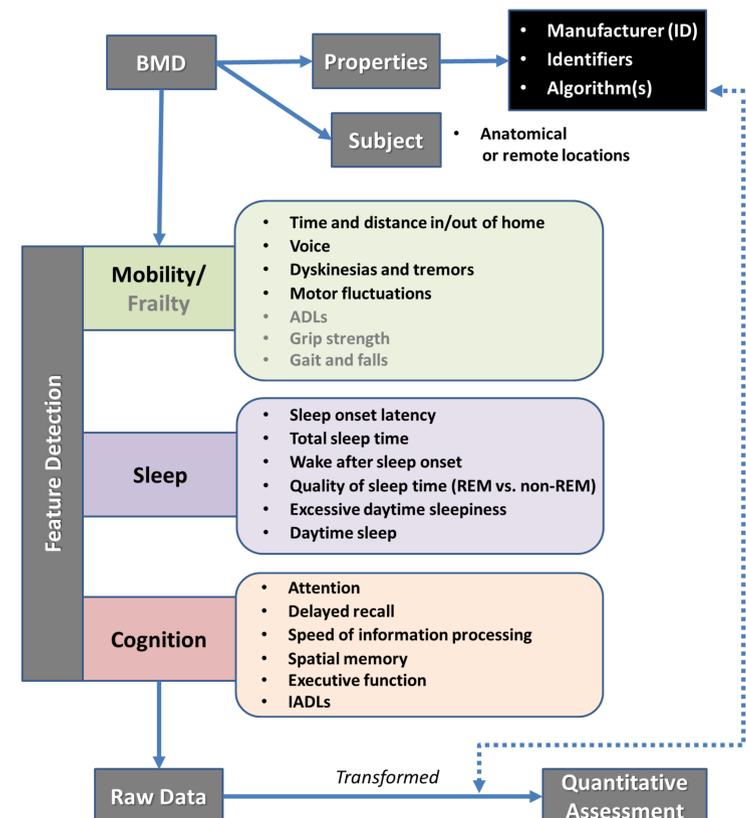
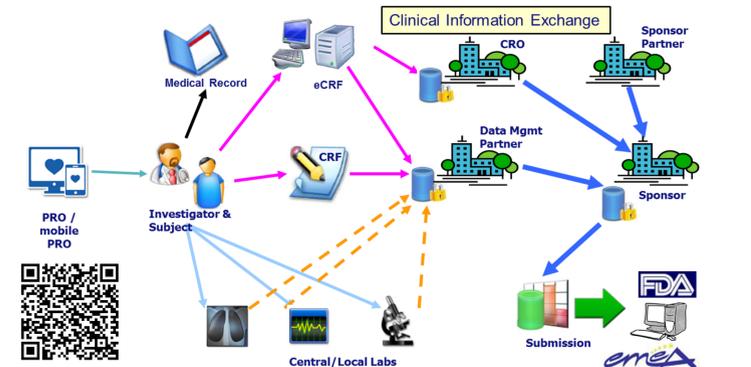


Figure 5

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

Acquisition, archive and interchange of metadata, data & audit trail for clinical research studies.



Discussion

- Continuous and passive monitoring of patient outcomes will likely provide greater ecological validity, improve statistical power to facilitate personalized therapeutics, reduce cost of lengthy trials, and enable tailored therapeutic approaches. This has great potential to facilitate clinical trial design, and reduce costs for preventative therapy trials started in the pre-symptomatic stages of AD.
- Many foundational data standards exist that will support the acquisition, tabulation, analysis and final reporting of data to the FDA ([Figure 1](#)). Some specific standards to align correlative metadata will likely be required.
- Understanding what dimensions of Quality-of-Life are most important to patients and their caregivers may help focus which biosensor assessment to focus on.
- Cross correlation of mobility/frailty, sleep, and cognition assessments may lead to more sensitive ways to understand disease progression and treatment responses.
- Various stakeholders will need to effectively collaborate to develop, validate, and secure regulatory endorsement of the use of Biometric Monitoring Devices in clinical trials for patients with AD and other neurologic disorders.

Conclusions

1. In the absence of more sensitive, regulatory-qualified patient assessment technologies, large, lengthy prevention trials (5-10 years) will be required to progress to MCI stages where existing assessments are available ([Figure 2](#)).
2. Developing and validating specific Use-Cases are required to gain confidence in their utility as viable Drug Development Tools.
3. Development of data repositories of structured data, using CDISC standards gathered from well-characterized patient populations, will be foundational to supporting the well defined Contexts-of-Use.
4. **Key Gaps Remaining:**
 - Capture critical contextual metadata to enable interpretation;
 - Use of uniform terminology regarding sensor, device, and measurement should be a focus;
 - High priority should be given to understanding which functional outcomes patients and caregivers prefer, and how these Concepts-of-Interest might relate to features captured by BMDs (those interested in contributing to CAMD's survey "[The Voice of Those Who Care](#)", please follow link on the right);
 - While the payer's perspective should not be ignored, this topic could be a later priority when alignment with regulators has been achieved.

References

- (1) Becnel, L. (2017) S28: An overview of CDISC standards and services, American Medical Informatics Association, 3/29/17, San Francisco.
- (2) Gray, B.B. (2016) Signs Before Symptoms, *NeurologyNow*, June/July, pp 33-36.
- (3) Mortamais, M. et al. (2017) Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility, *Alzheimer's & Dementia*, 13:468-492.

