Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 273-283

Alzheimer's & Dementia

Featured Article

Accelerating drug development for Alzheimer's disease through the use of data standards

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Abstract

Introduction: The exceedingly high rate of failed trials in Alzheimer's disease (AD) calls for immediate attention to improve efficiencies and learning from past, ongoing, and future trials. Accurate, highly rigorous standardized data are at the core of meaningful scientific research. Data standards allow for proper integration of clinical data sets and represent the essential foundation for regulatory endorsement of drug development tools. Such tools increase the potential for success and accuracy of trial results.
Methods: The development of the Clinical Data Interchange Standards Consortium (CDISC) AD therapeutic area data standard was a comprehensive collaborative effort by CDISC and Coalition Against Major Diseases, a consortium of the Critical Path Institute. Clinical concepts for AD and mild cognitive impairment were defined and a data standards user guide was created from various sources of input, including data dictionaries used in AD clinical trials and observational studies.
Results: A comprehensive collection of AD-specific clinical data standards consisting of clinical outcome measures, leading candidate genes, and cerebrospinal fluid and imaging biomarkers was developed. The AD version 2.0 (V2.0) Therapeutic Area User Guide was developed by diverse experts working with data scientists across multiple consortia through a comprehensive review and revision process. The AD CDISC standard is a publicly available resource to facilitate widespread use and implementation.
Discussion: The AD CDISC V2.0 data standard serves as a platform to catalyze reproducible research, data integration, and efficiencies in clinical trials. It allows for the mapping and integration of available data and provides a foundation for future studies, data sharing, and long-term registries in AD. The availability of consensus data standards for AD has the potential to facilitate clinical trial initiation and increase sharing and aggregation of data across observational studies and among clinical trials, thereby improving our understanding of disease progression and treatment.

Keywords: Regulatory science; Translational science; Data science; Drug development and Alzheimer's disease; Data standards; Clinical trials; CDISC; Mild cognitive impairment; Biomarkers; Clinical outcome assessments; Therapeutic Area User Guide

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http://dx.doi.org/10.1016/j.trci.2017.03.006

1. Introduction

1.1. Data standards and the current landscape of Alzheimer's disease drug development

Drug development in Alzheimer's disease (AD) is increasingly being aimed at early intervention, with the recognition that such strategies hold the most promise to slow or halt disease progression [1]. New drug development tools such as disease progression models, biomarkers, and outcome measures that can easily and rapidly incorporate new and existing sources of information are urgently needed to accelerate drug development at all stages of the AD disease spectrum. The development and regulatory endorsement of these tools has been hampered by the lack of consensus data standards that cover both clinical and biomarker assessments allowing for rapid integrated analyses derived from multiple data sources.

The inability to compare data across different clinical trials arises in part because of differences between them, including data collection and format.

Data standards enable the integration and analysis of data from multiple sources. This, in turn, allows for development of common open-source tools [2,3]. Data standards provide the framework for consistent structure and understanding of data. Use of data standards results in an increase in efficiency of studies by maximizing data utility, minimizing reprocessing of data, and expediting regulatory review of new drug applications (NDAs). Standards also enable integrated analyses across different studies by allowing integration of data and reusability of programming statements within analysis software.

Research organizations have responded to the need for data standards by creating many different sets of standards [4]. Pharmaceutical companies have also created their own internal data standards, whereas government agencies have recommended and even required use of specific standards to funders [5].

Given the rapid increase in global data availability [6] and an increasing number of experimental treatment modalities, an efficient way to compare effects on clinically meaningful outcomes is critical for selecting the most promising therapeutics to advance to the clinic. To maximize the knowledge from the growing number of costly and high risk AD intervention studies, it is imperative that the field attend to the importance of data standardization, beginning at study start-up.

1.2. Clinical Data Interchange Standards Consortium data standards

The development and widespread dissemination of universally accepted global clinical data standards is the mission of the Clinical Data Interchange Standards Consortium (CDISC), which has been developing global, platform-independent standards to streamline medical research since 1997 [7]. CDISC is a global nonprofit organization that catalyzes productive collaboration to develop freely available, industry-wide clinical research data standards. The primary CDISC standard governing the structure of data collected in clinical studies is the Study Data Tabulation Model (SDTM), which defines the variables and rules associated with specific observation classes including events, interventions, and findings. SDTM is one of the required standards that sponsors must use for NDAs submitted for the U.S. Food and Drug Administration (FDA) review [8].

The implementation of consensus-based CDISC clinical data standards serves to improve medical research and health care [9]. Such standards support the acquisition, exchange, archiving, and reporting of electronic clinical research data. Notably, CDISC standards are recognized by the FDA and Japan's Pharmaceuticals and Medical Devices Agency as the preferred standards for submission of clinical trial data and enable regulatory reviewers to use sophisticated review tools and conduct more efficient reviews.

Public-private partnerships and precompetitive consortia have emerged as a common strategy to share the cost and risk of development of consensus data standards. The Alzheimer's Disease Neuroimaging Initiative (ADNI), formed in 2004, catalyzed awareness and external recognition of the importance of data standardization in the AD research community [10]. In a parallel effort, two nonprofit organizations, CDISC and the Critical Path Institute (C-Path), created the Coalition for the Acceleration of Standards and Therapies in 2012 to develop Therapeutic Area User Guides (TAUGs) for specific disease areas. The focus of the first CDISC therapeutic specific standard was AD, which used elements from ADNI. AD version 1.0 (V1.0) was completed in 2011. As of January 2017, a total of 27 TAUGs spanning a variety of different disease conditions have been developed by CDISC, most of them under the umbrella of Coalition for the Acceleration of Standards and Therapies.

There are a growing number of public-private partnerships focused on AD [11]. The Coalition Against Major Diseases (CAMD), whose mission is to accelerate the path of drug development, is one of many consortia of C-Path [12]. CAMD is a coalition of stakeholders including industry, government agencies, nonprofit organizations, advocacy organizations, academic experts, and regulatory agencies collaborating to improve the efficiency of drug development for memory disorders [13,14]. CAMD, in close partnership with CDISC and ADNI, represented the key groups that formed the collaborative framework for stakeholders working across consortia to successfully develop CDISC standards specific for AD.

This study discusses the development of the first therapeutic area-specific CDISC standard, how the CDISC standards are used, the need for additional standards, and, most importantly, the need to implement these standards across clinical studies to maximize knowledge gained from past, current, and future clinical trials.