170

The Coalition Against Major Diseases: Expanding its Clinical Trial Database to Support a Disease Progression Model for Pre-dementia

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Background

- The Coalition Against Major Diseases (CAMD) utilizes the power of sharing non-competitive patient-level data from legacy trials, and transforming those data into generalizable and actionable knowledge for Alzheimer disease (AD) (**Figure 1**).
- CAMD's disease progression model in mild-to-moderate AD and simulation tools were endorsed as Drug Development Tools (DDT) by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) (**Figure 2**).
- Quantifying disease progression in Mild Cognitive Impairment (MCI) is also critical in order to define informed entry criteria, enrichment strategies and stratification approaches.

Drug Development Tools: Fit-for-Purpose Initiative

U.S. Department of Health and Human Services — FDA U.S. FOOD & DRUG ADMINISTRATION

Background

The Fit-for-Purpose (FFP) Initiative provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs. Due to the evolving nature of these types of drug development tools (DDTs) and the inability to provide formal qualification, a designation of 'fit-for-purpose' (FFP) has been established. A DDT is deemed FFP based on the acceptance of the proposed tool following a thorough evaluation of the information provided. The FFP determination is made publicly available in an effort to facilitate greater utilization of these tools in drug development programs.

Contact Us

For more information about the FFP Initiative, please contact DrugDevelopmentTools@fda.hhs.gov

Fit-For-Purpose Tools and Supporting Information:

Disease Area	Submitter	Tool	Trial Component	Issuance Date and Supporting Information
Alzheimer's disease	The Coalition Against Major Diseases (CAMD)	Disease Model: Placebo/Disease Progression	Demographics, Drop-out	Issued June 12, 2013 • Determination Letter. The tool is freely available at: https://bitbucket.org/metrumrg/alzheimers-disease-progression-model-adascog/wiki/Home

Figure 1. U.S. FDA fit-for-purpose initiative

Table 1. Studies currently integrated in the database

Study Name	Contributor	Type of Study	Number of MCI Subjects (Trial Total)
ADNI-1	ADNI	Observational	305 (400)
ADNI-2	ADNI	Observational	122 (163)
InDDEx (control arm)	Novartis	Clinical trial	394 (510)

MCI = Mild Cognitive Impairment
ADNI = Alzheimer's Disease Neuroimaging Initiative
InDDEx = Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon

Objectives

The goal of the present effort is the expansion of the CAMD database to support the development of a MCI progression model.

Methods

- The Clinical Data Interchange Standards Consortium (CDISC) standards have enabled the integration of the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon (InDDEx) datasets (**Table 1**).
- A coalition of industry, regulators, academics and patient advocacy groups is developing an analysis plan for a model-based clinical trial enrichment platform for MCI.
- A non-linear mixed-effects model is being proposed, where Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB) is the endpoint.
- The intended subjects' demographic, genetic, biomarker and clinical characteristics to be tested as predictors of disease severity at baseline and/or intrinsic rate of disease progression are presented on **Figure 3**.

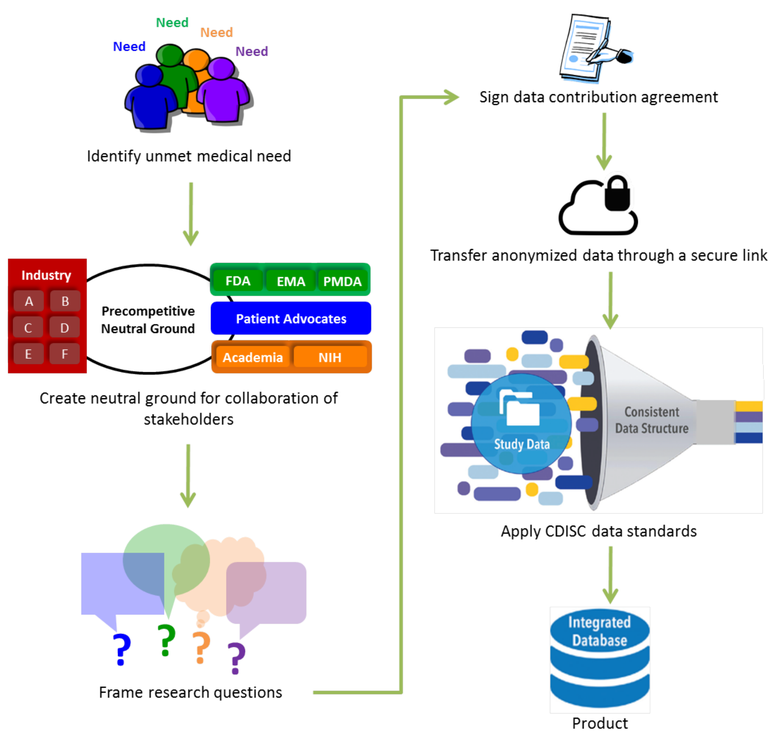

Figure 2. Schematic of an expanded data sharing initiative such as CAMD

Source: DJ Conrado, MO Karlsson, K Romero, C Sarrc, JJ Wilkins. Open Innovation: towards sharing of data, models and workflows (Submitted to European Journal of Pharmaceutical Sciences)

Envisioned Outcome

- The proposed expansion of the database and the model development plan for the DDT for MCI will be submitted to FDA and EMA for regulatory input and potential endorsement.
- A web-based simulator will be developed to aid with clinical trial enrichment and design. The tool will simulate disease progression based on user-defined patient characteristics at study entry (**Figure 4**).

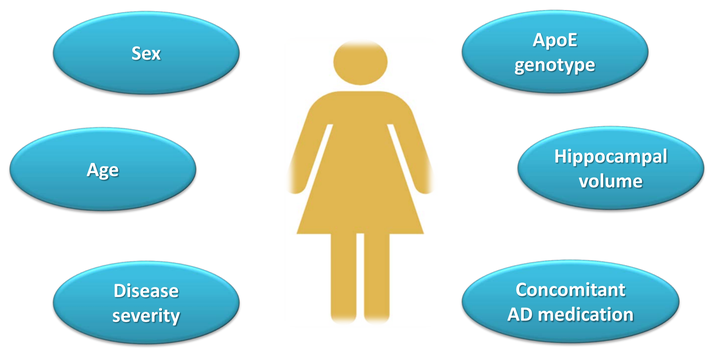

Figure 3. Examples of subject's characteristics to be tested as predictors of disease progression

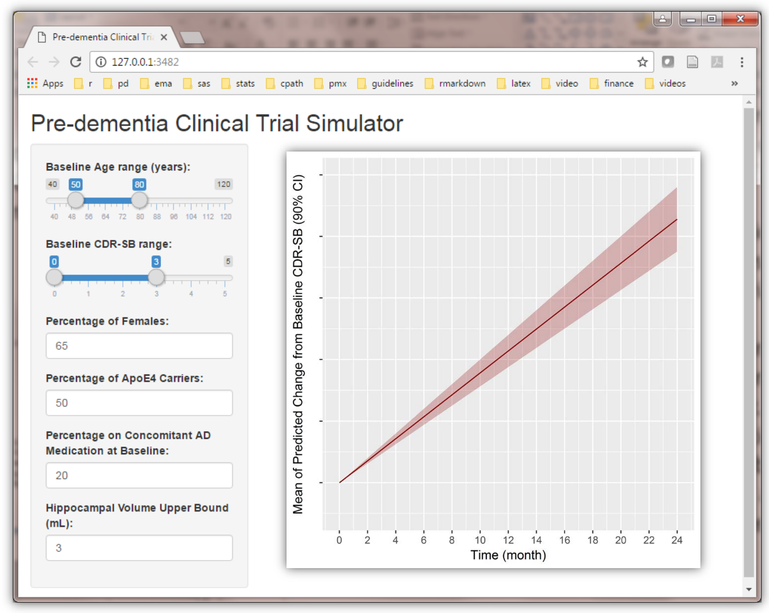

Figure 4. Mock-up of web-based pre-dementia clinical trial simulator

Conclusions

- The application of CDISC standards facilitates the integration of patient-level data across studies.
- Developing the quantitative drug development platforms for MCI through collaborative effort and regulatory review will enable optimized design of pre-dementia clinical trials.

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