Data Sharing and Standardization to Expand a Patient-Level Database for the Update of a Regulatory Endorsed Clinical Trial Simulator for Alzheimer Disease

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Background

- The Coalition Against Major Diseases (CAMD), a public-private partnership, previously developed a regulatory-endorsed (FDA (1) & EMA) clinical trial simulation tool (CTS) for Alzheimer's disease (AD), using integrated standardized data from control arms of legacy trials in mild to moderate AD
- Contemporary datasets acquired within CAMD after the initial regulatory endorsement warrant an update of the CTS

Objectives

- Acquire, standardize, and integrate contemporary patient-level datasets into the CAMD database according to the Clinical Data Interchange Standards Consortium (CDISC) standards
- Utilize expanded database to update the existing CTS for mild-to-moderate AD using a Bayesian mixed effects modeling framework

Methods

Data Sharing Initiative (Figure 1):

- Consortia, such as CAMD, are initiated by collaborating with stakeholders to address an unmet medical need
- Research questions are framed and data sources are identified.
- Acquisition of relevant data sets from data contributors is initiated with a legally binding data contribution agreement
- An encrypted transfer is used to send data to a secure storage server
- A comprehensive data remapping effort to CDISC standards is performed in conjunction with a thorough data curation
- Standardized data sets are integrated into the consortium database.

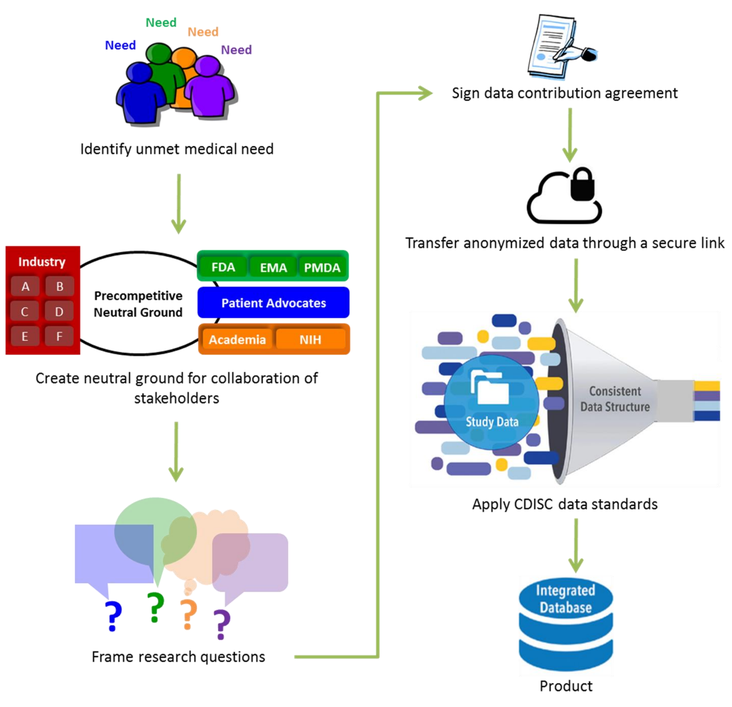

Figure 1. Schematic of an expanded data sharing initiative such as CAMD

Source: DJ Conrado, MO Karlsson, K Romero, C Sarrc, JJ Wilkins. Open Innovation: towards sharing of data, models and workflows. Eur J Pharm Sci. 2017 [epub ahead of print]

Preliminary update of the CTS:

- Compared to the original CTS tool, modifications and additional aspects to be investigated include:
  1) Use of patient-level data exclusively
  2) Bayesian framework using the Hamiltonian Monte Carlo method to estimate the posterior
  3) Investigate an additive allele effect for APOE4
  4) Include stable background medication as a covariate
  5) Use of a generalized logistic regression mixed effects approach following the framework of Conrado et al. (2) to describe the nonlinear natural progression of AD measured by the ADAScog11 scale :

$$ADAScog(t) = \frac{70 \cdot ADAScog_0}{\left[ADAScog_0^{\beta} + \left(70^{\beta} - ADAScog_0^{\beta}\right) e^{-\beta r t}\right]^{1/\beta}}$$

- Random effects on baseline $ADAScog_0$ and rate of progression r
- Beta distributed residual variability to ensure predictions of ADAScog11 are bounded
- Covariates: age, gender, number of APOE4 alleles, and concomitant medication use

Results

Expanded database overview :

- The contemporary CAMD database contains 15 studies of control data from legacy trials, an increase of 6 studies since the development of the original CTS (**Table 1**)

Table 1 **Summary level statistics comparing original and contemporary CAMD database**

Variable	Original database	Expanded database
Number of studies	9	15
Individuals	3255	4575
Mean age	73.9	74.1
% female	55.1%	55.4%
Mean years since dX	2.07	2.46
Mean baseline ADAScog11	23.4	24.0
Info on number of APOE4 alleles	1486	1895
Concomitant medication info	2483	3271

Preliminary Results on the CTS Update

- The observed temporal trajectory of ADAScog11 in control arm individuals and mean predicted progression are in **Figure 2**

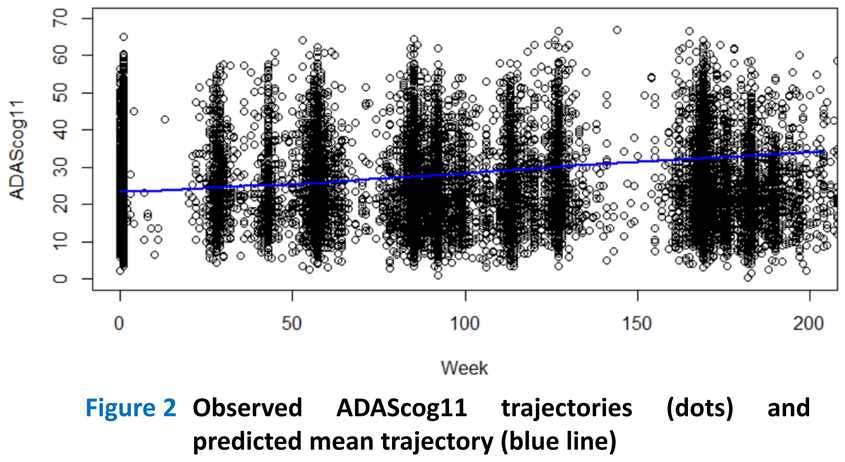

Figure 2 **Observed ADAScog11 trajectories (dots) and predicted mean trajectory (blue line)**

- The estimated parameters, including progression rate, covariate effects, and between subject variability are shown in **Table 2.**

Table 2 **Parameter estimates for natural progression of AD measured by ADAScog11**

Parameter	Description	Estimate	95% CI
$\theta_{baseline}$	Population mean baseline score	21.4	(19.8, 23.2)
θ_{rate} (year^{-1})	Population mean progression rate	0.145	(0.072, 0.22)
θ_{age}	Effect of age of progression rate	-0.025	(-0.049, -0.013)
θ_{sex}	Effect of sex on baseline	0.003	(8e-5, 0.011)
θ_{Apoe4_b}	Effect of number of Apoe4 alleles on baseline	0.034	(0.009, 0.062)
θ_{Apoe4_r}	Effect of number of Apoe4 alleles on rate	0.204	(0.066, 0.411)
θ_{Comed}	Effect of stable background medication on rate	-0.41	(-0.75, -0.22)
$\omega^2_{patient\_b}$	Variance of inter-individual variability on baseline	0.411	(0.402, 0.420)
$\omega^2_{patient\_r}$	Variance of inter-individual variability on rate	0.202	(0.194, 0.211)

- Estimated population baseline severity and rate of progression are in good agreement with previous studies (2),(3)
- Note worthy results indicate an additive allele affect for APOE4 that correlates with increased rate of progression and stable medication use correlating with faster rate of progression

Envisioned outcome

- A completed update of the CTS will involve the following milestones:
  - Separation of natural progression and placebo effect component by incorporating observational longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database
  - Confirm the additive allele effect of APOE4 and background medication use related finding with the ADNI data
  - Develop a user-friendly interface to provide accessibility of the tool to all members of a clinical development team
- Regulatory endorsement for the updated CTS will be pursued in order to provide the most up to date tool for clinical trial design and simulation for mild to moderate AD.

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