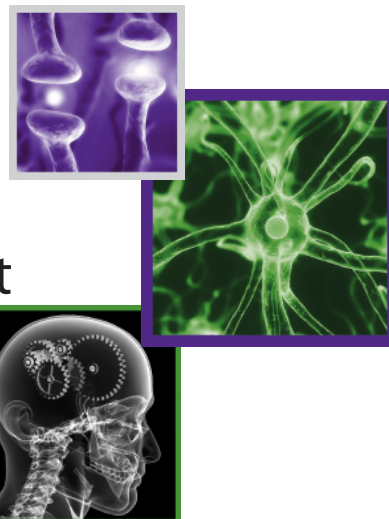


## SPECIAL REPORT

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# Striving for an integrated drug-development process for neurodegeneration: the coalition against major diseases



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### Practice Points

- The current drug development process for Alzheimer's and Parkinson's diseases has not produced the expected results, especially given the huge investments made.
- Drug development tools need to have a very specific context of use within the drug-development process, and the qualification process by regulatory authorities focuses on the proposed context of use.
- Such tools, in the form of biomarkers and modeling and simulation frameworks, once evaluated and qualified by the regulatory authorities, can help make the drug development process in these areas more efficient and increase the likelihood of success for go/no-go decisions for new compounds.
- The development of such tools is best completed by sharing precompetitive data, which can be leveraged in conjunction with additional data sources, provided that the right data standards are in place.

**SUMMARY** Alzheimer's and Parkinson's diseases are the two main neurodegenerative disorders and despite the public health need, drug development for these conditions has been plagued by a high attrition rate in the late phases of evaluation. In order to improve the efficiency of the drug development process for these conditions, the Coalition Against Major Diseases was formed by the Critical Path Institute in September 2008, in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution (Washington, DC, USA), with the aim of sharing precompetitive patient level data from legacy clinical trials, and transforming those data into generalizable and shareable knowledge in the form of drug development tools for Alzheimer's and Parkinson's diseases. As of May 2011, Coalition Against Major Diseases has 21 members (14 pharmaceutical companies and seven patient groups), joined by the US FDA, the European Medicines Agency, the National Institute of Aging and the National Institute of Neurological Disorders and Stroke. The drug development tools in development will take the form of biomarkers and modeling and simulation frameworks, and will be submitted for regulatory evaluation and qualification as 'fit for purpose' in the specific context of the drug development process for these diseases. This article constitutes a report of the progress of the work of the coalition in data standards, disease models and biomarkers.

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Alzheimer's disease (AD) and Parkinson's disease (PD) are the two leading neurodegenerative diseases; currently, AD alone affects 35 million patients worldwide, climbing to 150 million within a generation, unless disease-modifying treatments can be developed [101]. Despite large, long trials for AD modification, no treatment has proven positive, so the field is increasingly realizing that new tools and designs are urgently needed [1,2]. The landscape for PD is not much different, as results of clinical trials of new treatment options reported in the past decade have shown negative/unsatisfactory results [2], except perhaps for the Attenuation of Disease Progression With Azilect Given Once-Daily (ADAGIO) study, a complex delayed-start design that suggests a potential disease-modifying effect for rasagiline 1 mg/day (based on Unified Parkinson's Disease Rating Scale [UPDRS] progression-rate change) [3,4].

Although it is likely that the drugs tested a lack of efficacy, other potential explanations for such a high failure rate during late-phase development include trial design factors such as overestimation of treatment effects, lack of understanding of the underlying pathology and resultant clinical course, inadequate patient selection strategies, and the unsatisfactory performance of the outcome measures [4].

The Coalition Against Major Diseases (CAMD) was formed by the Critical Path Institute (AZ, USA) in September of 2008, in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution (Washington, DC, USA). The coalition is based on the value of sharing precompetitive patient level data from the control arms from legacy clinical trials, and transforming those data into generalizable and shareable knowledge in the form of drug development tools for AD and PD [5,6]. As of May of 2011, CAMD has 20 members (14 pharmaceutical companies and seven patient groups), joined by the US FDA, the European Medicines Agency (EMA), the National Institute of Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS). The current manuscript describes the framework of CAMD and the current status of each of the working groups. The general workflow for each of the subgroups is described in [Figure 1](#).

### Sharing precompetitive data (data standards and database development)

#### ■ Data standards & integration workgroup background & formation

As a key component of CAMD, the necessary standardization and development of a pooled database of clinical trials data was tackled by a dedicated workgroup. Existing standards set by the Clinical Data Interchange Standards Consortium (CDISC) were used, and new ones were created wherever current standards did not yet exist. CDISC is a non-profit organization whose mission is to develop platform-independent, vendor-neutral and freely available data standards that enable information system interoperability.

Consensus was reached on how best to share the patient-level control arm data from CAMD-member companies, in order to develop an AD precompetitive data repository. It was agreed that the repository would align with the CDISC Study Data Tabulation Model (SDTM) industry data standard, since pharmaceutical companies will align with this in submissions to the FDA, as the foundation for standardized clinical content.

Thus, sponsors would also be able to utilize these standards for multiple prospective collection of information.

#### ■ Data standards & integration workgroup process

This group worked with others in CAMD (particularly modeling and simulation) to better understand the needs for standard data elements to fulfill CAMD's mission. The initial focus was on the Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog). A comparison of relevant case report forms (CRFs), including the Alzheimer's Disease Neuroimaging Initiative, highlighted the different implementations used by each sponsor. Differences included the number and order of questions and the level of detail captured. With this in mind, the draft SDTM standard would show how to supply all the various items and sub-items.

This same approach was also used for the alignment of the Mini-Mental State Exam (MMSE) and Auditory Verbal Learning Test scales in CDISC SDTM.

#### ■ Standards drafting process

Through periodic interactions, the group aligned the scales utilizing CDISC spreadsheet templates, in order to define the database table structure with the associated terminology. Each scale domain was reviewed by the CDISC Submission Data Standards Team.

### ■ Company use of draft standards for the Coalition Against Major Diseases database

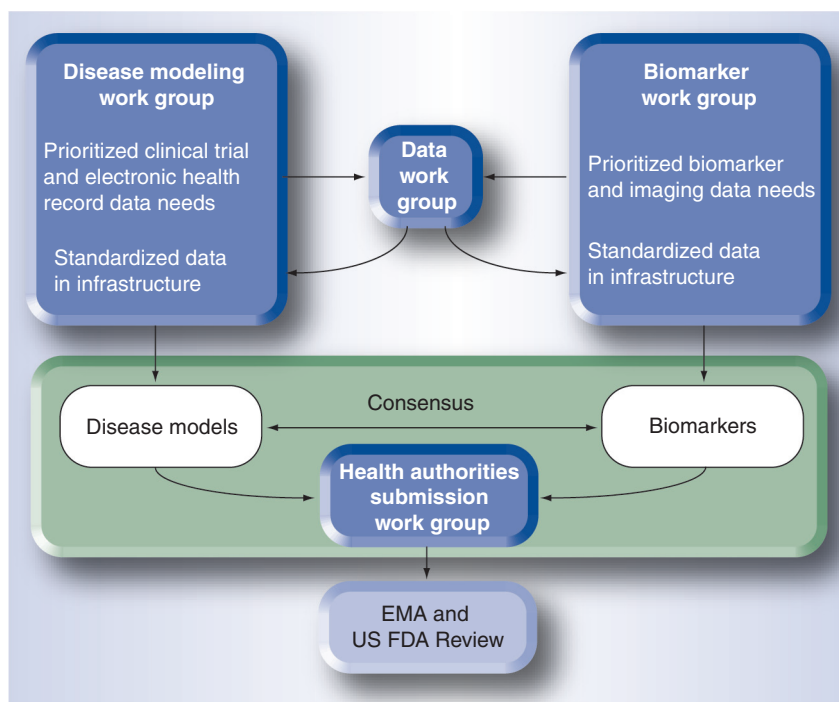
The next step involved the CAMD sponsors mapping their respective studies from their source database structure to the CDISC SDTM data domain. The mapping process involved each company progressing through a learning curve on the standards. Mapping of the legacy data to the new standards involved programming to restructure the source data to meet the SDTM domain structures and also include the SDTM-approved terminology for data values. The effort took an average of 2 months per sponsor to complete.

### ■ Development of the Coalition Against Major Diseases data repository

The CAMD chose Ephibian, an organization based in Tucson (AZ, USA), as the PostgreSQL database and user interface developer based on demonstrated experience and proximity to the CAMD headquarters at the Critical Path Institute. Open-source SDTM-based validation software was integrated in the system to automatically validate incoming data. Each validation report was reviewed for SDTM compliance and fitness for the database. Data sets were either approved to the production database, or sent back for corrections to the supplier. Currently, the database houses data on approximately 4000 patients from ten clinical trials supplied by seven pharmaceutical companies. The group is currently in the process of transforming data from clinical studies from academic sources for future inclusion in the CAMD database as well.

### ■ The Clinical Data Interchange Standards Consortium Alzheimer's disease data implementation guide development

The CDISC SDTM standard is the result of more than a decade of consensus building through three SDTM versions by a dedicated CDISC SDTM made up of 27 volunteers representing various stakeholders from pharmaceutical companies, regulatory agencies and clinical research. More recently, CDISC has expanded its scope to include producing efficacy standards for disease-specific areas. Based on this and the growing interest from industry and government in expanding the SDTM standard, it was decided that the CAMD AD effort should be used as a test case for creating a disease-specific user guide supplement. This supplemental user guide shows how to structure data and apply controlled terminology in a standard SDTM



**Figure 1.** General description of the workflow within the Coalition Against Major Diseases work groups.

format for ADAS-cog, MMSE, Auditory Verbal Learning Test, volumetric MRI brain measurements, MRI device and protocol properties, as well as genotype tests and various biomarker laboratories of interest to the Alzheimer's clinical community. These Alzheimer's standards will be made publicly available on the CDISC website [102].

### Development of a quantitative disease-progression model

The modeling and simulation workgroups objectives are to bring drug sponsors, regulators and advocacy groups together to build these types of drug development tools. In the specific cases of PD and AD – given the complex nature of the underlying disease, uncertainty in differential diagnosis and the need to understand the clinical outcomes that are typically used for registration – a ‘top-down’ approach is being used, which initially focuses on the registration end points, taking into account pharmacogenetic and other patient-specific factors.

As such the initial goals of this group for AD are to:

- Develop a longitudinal model for cognition
- Develop a simulation tool for use in trials in mild-to-moderate AD patients

- Create a submission package to support qualification by the EMA and FDA following the new processes that have been outlined
- Introduce a publicly available simulation tool and training materials

Modeling and simulation work for CAMD is being prosecuted in a staged manner, consisting of the following activities:

- Completion of a quantitative disease progression and drug-effect model, including model fitting to three available data sets: Alzheimer's Disease Neuroimaging Initiative, literature and CAMD data (described later);
- Model validation to the satisfaction of key stakeholders, including posterior predictive checks and plausibility of parameter estimates, as well as with external validation;
- Identification of a range of hypothesized valid drug effects to be considered, modifying the structure of the drug effect component of the model to accommodate these hypotheses;
- Identification of a set of candidate clinical trials possible for use in neurodegenerative trials and their associated primary analyses;
- Simulation of clinical trial data sets based on: the established model, the hypothesized drug effects and the candidate trial designs, using a range of feasible sample sizes;
- Application of the associated analysis methodologies to the simulated data sets, and computation of operating characteristics based on the variation in these analysis results across simulated trial data sets.

#### ▪ Data sources for Coalition Against Major Diseases modeling and simulation

**The Alzheimer's Disease Neuroimaging Initiative**  
The data set available from the Alzheimer's Disease Neuroimaging Initiative database [103] contained 817 subjects consisting of 229 normal, 402 mild cognitive impairment (MCI) and 186 AD patients described in the proceeding sections (Table 1).

#### Publicly available literature

The literature was searched by Ito *et al.* [7] and selected according to the approach suggested at the 'Quality of Reporting of Meta-analysis' (QUOROM) conference [8]. A systematic search of public data sources (Medline, Embase, NICE and Summary for Basis of Approvals at the FDA)

was conducted from 1990 to 2008. Key search terms included acetylcholinesterase inhibitor names (donepezil, galantamine, rivastigmine and tacrine), trial end points (e.g., ADAS-cog, MMSE and CIBIC), and clinical trial design descriptions (e.g., double-blind and randomized). The specifics for this selection process have been described in previous publications (reviewed in [7]).

#### Coalition Against Major Diseases database

The CAMD database will be incorporated, which includes patient-level data from more than 3000 participants in control arms from clinical trials for AD provided by member companies. The updated model fitted to the expanded data will be used for trial simulation work following an appropriate validation process. It is anticipated that a model substantively similar to the current draft version described here will eventually be selected.

#### ▪ The model

##### Mean structure

The model takes into account baseline, change in cognition as a function of time, time-dependent placebo effects and various types of drug effects (symptomatic and disease modifying).

The current version of the model employs random subject-level effects on the 'natural progression' parameters (i.e., intercept and rate of decline). Consequently, observations from the same individual are modeled as correlated and (consistent with observed data) modeled variances increase over time.

Covariates to be tested in the model include *APOE4* status, gender, age, as well as baseline MMSE and ADAS-cog. Imaging and cerebrospinal fluid (CSF) biomarker covariates will be explored, dependent on data availability and assay variability.

Patients lost to follow-up will be modeled using a constant (exponential) hazard, with hazard rate estimated from historical data.

The model will be estimated using Bayesian Markov Chain Monte Carlo methodology, using diffuse priors [104]. Informative priors may be used for some nuisance parameters if this is deemed necessary for computational convergence.

Data obtained from the literature sources will provide estimates of treatment effects for currently available agents. The limitation of this type of data is that trends in subpopulations cannot be observed. The model submitted will

include external validation on a data set that includes active treatment (not in the current CAMD database).

Model evaluation will include at least the following elements:

- Posterior prediction intervals plotted with actual data superimposed (i.e., posterior predictive checks and visual predictive checks);
- Plausibility and comparison of certain parameter estimates including: the slope of ‘natural decline’; the marginal variance of observations at 12 weeks and 18 months; and the effect of donepezil 10 mg daily for 12 weeks;
- Distributional assumptions to be checked using QQ plots and residual-versus-fitted scatter-plots.

Further external validation to include random selection of one or two studies is also planned.

#### ▪ Identification of trial design characteristics of interest

A set of candidate clinical trial designs of interest that reflect designs required at various stages of drug development have been identified in consultation with colleagues representing statistics, clinical pharmacology, clinical and pharmacometrics both from CAMD members, FDA and EMA. Designs will be compared with respect to power (probability of a significant result for at least one dose after multiplicity adjustment), required study duration, impact of sampling times and expected sample size will be among the operating characteristics examined.

#### ▪ Clinical trial simulation tool

The ultimate deliverable from this exercise is a documented publicly available simulation package, allowing the user to simulate patient-level data according to various trial designs of interest.

Data obtained from literature sources will provide estimates of treatment effects for currently available agents. The limitation of this type of data is that trends in subpopulations cannot be observed. The model submitted will include external validation on a data set that includes active treatment (not in the current CAMD database).

### Evaluation of prognostic biomarkers of conversion from early Alzheimer’s & Parkinson’s disease

#### ▪ Context of Alzheimer’s disease biomarker

Early detection of AD is thought to offer the best opportunity for effective intervention; however,

**Table 1. Alzheimer’s Disease Neuroimaging Initiative demographic characteristics.**

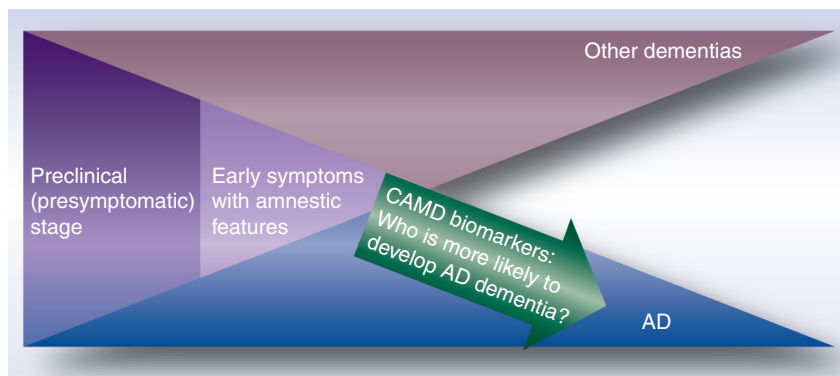
	AD	MCI	Normal controls
Patients (n)	186 <sup>†</sup>	402	229
Age (years)	75.3 ± 7.6	74.8 ± 7.4	75.9 ± 5.0
Female (%)	47.3	35.6	48.0
Baseline ADAS-cog	18.7 ± 6.3	11.5 ± 4.4	6.2 ± 2.9
Baseline MMSE	23.3 ± 2.0	27.0 ± 1.8	29.1 ± 1.0
Education (years)	14.7 ± 3.2	15.7 ± 3.0	16.0 ± 2.9
<b>ApoE4 status</b>			
ε4 noncarrier (%)	63 (33.9)	187 (46.5)	186 (73.4)
ε2, ε2 (%)	0	0	2 (0.9)
ε2, ε3 (%)	5 (2.7)	17 (4.2)	31 (13.5)
ε3, ε3 (%)	58 (31.2)	170 (42.3)	135 (59.0)
ε4 carrier (%)	123 (66.1)	215 (53.5)	61 (26.6)
ε2, ε4 (%)	4 (2.1)	11 (2.7)	3 (1.3)
ε3, ε4 (%)	83 (44.6)	157 (39.1)	53 (23.1)
ε4, ε4 (%)	36 (19.4)	47 (11.7)	5 (2.2)
<b>Race (%)</b>			
American-Indian or Alaskan native	0	1 (0.2)	0
Asian	2 (1.1)	9 (2.2)	3 (1.3)
Black or African American	8 (4.3)	15 (3.7)	16 (7.0)
White	174 (93.5)	376 (93.5)	210 (91.7)
More than one race	2 (1.1)	1 (0.2)	0

<sup>†</sup>Mild = 171, moderate = 13, severe = 1 and NA = 1.  
AD: Alzheimer’s disease; ADAS-cog: Alzheimer Disease Assessment Scale-Cognitive; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Exam.

trials in this area have proven problematic, requiring significant resources and time, with no beneficial treatments found without the uniform use of biomarkers [1]. The major AD biomarkers can be now classed as either brain imaging studies, mainly MRI or biofluid assays, chiefly CSF [9]. AD protein misfolding is measured by decreased CSF amyloid β (Aβ) and increased tau, while the cell loss is driven by neurodegeneration observed in hippocampal atrophy [9]. CSF and MRI markers were chosen by the biomarker group as having enough pathological and longitudinal clinical evidence to support regulatory qualification as prognostic biomarkers of conversion from MCI to AD dementia, to be used for clinical trial recruitment to more clearly specify the AD target population, by excluding non-AD causes for memory loss, as illustrated in **Figure 2**. As shown, the proposed context is for prognosis of conversion to be used as a trial-enrichment tool during drug development, not diagnosis or prediction of progression.

For both CSF and MRI markers [10,11], there is now a large volume of literature supporting their use to predict conversion from MCI to





**Figure 2. Proposed context of use for the Alzheimer's disease biomarkers as a trial enrichment tool.**

AD: Alzheimer's disease; CAMD: Coalition Against Major Diseases.

AD, with at least 80% sensitivity and specificity and, importantly for sponsors and trial patients, within a practical 2-year time period. These findings moved the AD field from the Petersen [12] clinical-only criteria of MCI to the current clinical-plus-biomarker approach [13]. Thus, baseline CSF levels of  $A\beta_{1-42}$ , tau and hippocampal volume by MRI are proposed as prognostic markers of the likelihood that patients with episodic memory deficit will convert from amnesia to frank dementia of the AD type during the course of early-stage clinical trials in AD. Such 2-year trials, which apply these biomarkers for subject inclusion, could increase the certainty of decline to dementia stage, allowing a clearer evaluation of the efficacy of putative treatments.

■ **Context of the Parkinson's disease biomarker**

Similar to AD, PD has been defined on clinical presentation and symptoms, but efficient drug development for early disease stages requires the accurate identification of candidate subjects for trials evaluating potentially disease-modifying treatments. However, the existing clinical-based inclusion criteria for PD trials have not provided the necessary specificity and sensitivity [14]. Trials in early PD for disease-modifying candidates face the risk of enrolling non-PD subjects, identified on clinical features alone. Demonstrating robust efficacy of novel treatments in trials including a component of non-PD subjects would require larger samples and longer follow-up than studies with a similarly impaired but more uniform group of accurately identified idiopathic PD subjects [15]. Dopamine deficits on SPECT mirror

parkinsonism pathology, and thus enable exclusion of the nondopaminergic etiology [16]. While SPECT cannot make a PD diagnosis, it gives increased certitude at an early stage that the patient will likely convert to PD. Therefore, similarly to AD, the proposed context of use for SPECT in PD is to increase the certitude of subject enrollment in clinical trials at an early PD stage, defined as patients presenting with one or more motor signs of PD when combined with loss of dopamine transporter in SPECT.

Again, the proposed context is for the prognosis of conversion to be used as a trial-enrichment tool during drug development, not diagnosis or prediction of progression.

■ **Regulatory implications**

Tools examined from CAMD's data, modeling and biomarker groups will have full efficacy thanks to the FDA's and EMA's qualification processes [105,106]. The AD biomarkers are in advanced discussion with EMA, while both EMA and FDA have examined the AD model research plan. PD plans are currently being developed.

**Conclusion**

The qualification of biomarkers and the regulatory evaluation of modeling and simulation tools are expected to make the drug development process more efficient. CAMD provides the framework for the adoption of an integrated drug development process, which incorporates modeling and simulation tools as well as biomarkers that provide useful and significant insights into the nature of neurodegenerative diseases and their response to pharmacological interventions.

**Future perspective**

The coalition is expected to increase membership and potentially undertake projects in other therapeutic areas.

Modeling and simulation tools are expected to be continuously evolving, and as such, the CAMD's modeling and simulation tools are expected to be expanded to include earlier stages of disease (i.e., MCI).

The biomarker effort will continue to identify candidate biomarkers for additional contexts of use, potentially expanding the role of new predictive biomarkers, which can complement the current proposed prognosis biomarkers.

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