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.

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.

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).

Table 1. Studies currently integrated in the database

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Contributor</th>
<th>Type of Study</th>
<th>Number of MCI Subjects (Trial Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNI-1</td>
<td>ADNI</td>
<td>Observational</td>
<td>305 (400)</td>
</tr>
<tr>
<td>ADNI-2</td>
<td>ADNI</td>
<td>Observational</td>
<td>122 (163)</td>
</tr>
<tr>
<td>InDDEx (control arm)</td>
<td>Novartis</td>
<td>Clinical trial</td>
<td>394 (510)</td>
</tr>
</tbody>
</table>

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

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

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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