Solutions for End-User Accessibility of Regulatory-Endorsed Quantitative Drug Development Tools

Jackson Burton[1], Daniela J. Conrado[1], Timothy Nicholas[2], Danny Chen[2], Julie Stone[3], Vikram Sinha[3], Brian Willis[4], Neva Coello[5], Wenping Wang[5], Volker D. Kern[1], Stephen P. Arnerić[1], Klaus Romero[1]; on behalf of the Critical Path for Alzheimer's Disease (CPAD) Consortium

[1]Critical Path Institute, Tucson, AZ; [2]Pfizer, Groton, CT, USA; [3]Merck & Co. Inc., North Wales, PA, USA; [4]Eli Lilly and Company, Indianapolis, IN, USA; [5]Novartis Pharmaceutical Corporation, Cambridge, MA, USA

Objectives

- The Critical Path for Alzheimer's Disease (CPAD) consortium is a public-private partnership which previously developed a regulatory-endorsed (FDA [Ref. 1], EMA [Ref. 2]) clinical trial simulation tool (CTS) for mild-to-moderate Alzheimer disease (AD), using integrated clinical data from several legacy studies.
- Despite public availability of the AD CTS and other quantitative drug development tools [Ref. 3], adoption of these tools by drug developers requires several considerations:
  - The necessity for the tools to be concurrent with emerging data-based scientific insights
  - Challenges with needing statistical and programming expertise to use the tools
  - The use of open access platforms to host the tools
  - Demands for computing power to run clinical trial simulations
- This effort aims to develop generalizable solutions to the above considerations using the AD CTS as a case study.

Methods

Addressing consideration 1:

- The original CPAD database used to develop the AD CTS received additional patient-level data and required aggregation:
  - Clinical Trial Data Interchange Standards Consortium (CDISC) standards utilized for data standardization
  - Judicious data curation strategy developed to integrate the data
- Insights gained from the additional data warranted statistical modifications to the underlying model:
  - Generalized logistic function to update generalized linear model
  - Genetic *APOE*-ε4 genetic status to be accounted for as a continuous additive allele effect
  - Effects of concomitant medication included

Addressing consideration 2:

- Development of user friendly interface is warranted to provide broad access to the tool without the need for technical skillsets
  - The Rshiny package was utilized to develop a fully functioning graphical user interface (GUI) for the updated tool

Addressing consideration 3:

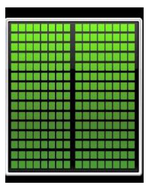
- The open access shinyapps.io domain was utilized to host the GUI, allowing for multiple user access

Addressing consideration 4:

- The updated tool computes multiple independent trial simulations and is well suited for computational parallelization using a multi-CPU core or single GPU (graphical processing unit) approach (**Figure 1**)
  - Both CPU and GPU computing platforms are being developing through strategic collaboration

Figure 1: CPU and GPU comparison

CPU:
- 'powerful' cores
- ~4-48 cores



GPU:
- 'basic' cores
- ~ 500-1,000 cores

Results

Results for consideration 1:

- The additional patient level clinical data was mapped to CDISC standards and aggregated into the CPAD database (**Table 1**)

Table 1: Summary of expanded CPAD 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 diagnosis	2.07	2.46
Mean baseline ADAS-cog11	23.4	24.0
Info on number of *APOE*-ε4 alleles	1486	1895
Concomitant medication info	2483	3271

- The underlying model to the CTS AD tool was updated (**Table 2**):
  - Disease progression model better accounts for nonlinear progression in AD
  - Rate covariate for genetic risk shows additive allele effect
  - Addition of rate covariate for concomitant mediation use shows significantly faster progression for those *on* AD medication

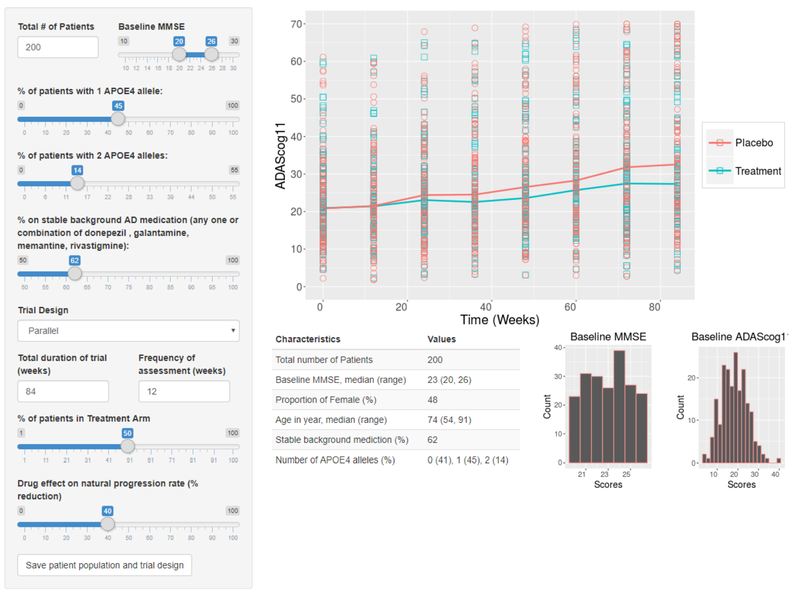
Table 2: Model modifications to updated AD CTS tool

Model Component	Form in original AD CTS tool	Form in updated AD CTS tool
Disease progression model	$g(\theta_{ijk}) = \eta_{ij} + \alpha_{ij} t_{ijk}$	$\theta_{ij} = \frac{S_{0ij}}{[S_{0ij}{}^{\beta} + (1 - S_{0ij}{}^{\beta})]^{1/\beta}}$
Rate covariate for genetic risk (*ApoE4* alleles)	$\lambda_{APO1} I(ApoE = 1) + \lambda_{APO2} I(ApoE = 2)$	$1 + \lambda_{APO}(ApoE - 0.72)$
Rate covariate for concomitant medication use	-	$1 + \lambda_{Comed(no\ AD\ medication)}$

Results for consideration 2 & 3:

- A graphical user interface (GUI) was developed (**Figure 2**) using Rshiny. Users can:
  - Generate patient populations enriched for baseline severity, sex, age, *APOE*-ε4 genetics, and stable medication use
  - Simulate parallel and delayed-start clinical trial designs Perform power calculations to detect disease modifying effects between treatment groups
  - Apply statistical testing using confidence interval used to replace computationally expensive approximated p-values
- Publicly available at cpath.shinyapps.io/adctsgui/

Figure 2: AD CTS graphical user interface

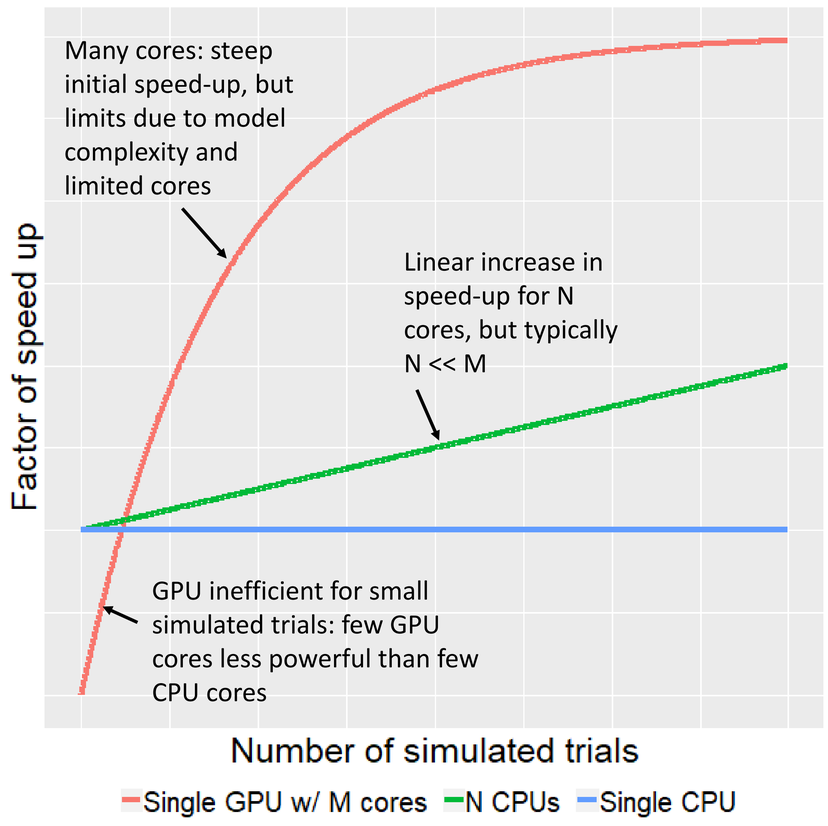


Results (continued)

Preliminary analysis for consideration 4:

- Through strategic collaboration, high performance computing platforms are being developed that:
  - Will allow users to access CPU and GPU architecture for optimal speed-ups
  - Are extremely low cost
  - Are seamless, requiring no additional programming or expertise
- Preliminary analysis shows expected trends for CPU and GPU speed ups for trial simulations using the AD CTS tool

Figure 3: Schematic illustrating trends in speeds up attained with various high performance computing platforms



Envisioned Outcome

Several milestones are being targeted:

- Completion of a thorough beta-testing period for the GUI
- Implementation of high performance computing platform
- Development of supporting documentation for utilizing the GUI, including access, use of high performance computing platforms, and report generation

The continuation of these efforts will provide powerful and practical tools to support critical decision making in drug development for a variety of disease areas.

References

1. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM508857.pdf
2. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/10/WC500151309.pdf
3. Conrado DJ, et al. Dopamine Transporter Neuroimaging as an Enrichment Biomarker in Early Parkinson's Disease Clinical Trials: A Disease Progression Modeling Analysis. Clin Transl Sci. 2018;11(1):63–70.

Acknowledgments: This work was supported by a grant the Arizona Alzheimer's Consortium and, in part, by grant number 1U18FD005320 from the U.S. Food and Drug Administration's Critical Path Public Private Partnerships Grant, and members including: AbbVie Inc., Alzheimer's Association, Alzheimer's Disease Discovery Foundation, Alzheimer's Research UK, Biogen, Boehringer Ingelheim Pharmaceuticals Inc., CHDI Foundation, Eisai, Eli Lilly and Company, F. Hoffmann La Roche, Johnson & Johnson Pharmaceutical Research & Development LLC., Merck Sharp & Dohme Corp., Novartis Pharmaceuticals Corporation, Pfizer Inc., Takeda Pharmaceuticals, and UsAgainstAlzheimer's.