Clinical Trial Simulator for Pre-Dementia and the Role of Hippocampal Volume Neuroimaging

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Daniela Conrado, Associate Director
Quantitative Medicine, Critical Path Institute
NOT UNCOMMON IN AD TRIALS

Disease Worsening

-Time

“Fast Progressor”

“Slow/No Progressor”

AD = Alzheimer disease
THE NEED IN AD: WHY NOW?

• There is an increased focus on evaluating drug candidates at earlier disease stages

• Selection of patients in trials of early AD is challenging due to patient heterogeneity

AD = Alzheimer disease
ACTUAL DATA: MCI ADNI-1 + ADNI-2

Baseline FreeSurfer ICV-HV

ICV-HV = intracranial volume-adjusted hippocampal volume
FreeSurfer™ = an algorithm for calculating ICV-HV
7.46 cm³ = median of the ICV-HV in dataset
OUR SOLUTION

Model-Based Drug Development Tool for Pre-dementia

A clinical trial simulator
Based on a disease progression model
THE DISEASE PROGRESSION MODEL

Input
Studies
ADNI-1
ADNI-2
InDDEEx

Several other studies are being pursued.

Disease Progression Model
ICV-HV
CDR-SB at baseline
Longitudinal CDR-SB
Sex
Age
APOE genotype
MMSE
Amyloid-beta imaging
Dropout
Concomitant AD medication

Output
Understanding of progression
Trajectory
Rate
Predictors

Web Clinical Trial Simulator

www.c-path.org/cpad
Trajectory of CDR-SB scores over time was described by a generalized logistic model (mixed-effects beta regression)

CDR-SB = clinical dementia rating scale sum of boxes
HIPPOCAMPAL VOLUME PREDICTS PROGRESSION

A 1-cm³ decrease in baseline ICV-HV is associated with more than 50% increase in CDR-SB progression rate

ICV-HV = intracranial volume-adjusted hippocampal volume
CDR-SB = Clinical Dementia Rating Scale Sum-of-Boxes

*Illustrative cut-off
HIPPOCAMPAL VOLUME-BASED ENRICHMENT REDUCES TRIAL SIZE

~26% and ~55% reduction of sample size with baseline ICV-HV <84.1<sup>th</sup> and <50<sup>th</sup> percentile

Clinical trial with:
- No enrichment
- Only ICV-HV<97.7th (+2SD) subjects
- Only ICV-HV<84.1th (+1SD) subjects
- Only ICV-HV<50th (median) subjects

Monte-Carlo Simulation Assumptions:
- 24-month placebo-controlled parallel group trials
- Drug effect of 50% reduction in the progression rate
- Dropout model
- Power was calculated as the proportion of trials for which the effect of treatment on progression rate was beneficial with a two-tailed P-value < 0.05.

ICV-HV = intracranial volume-adjusted hippocampal volume
SD = standard deviation of the distribution of ICV-HV values at baseline
OTHER PREDICTORS OF DISEASE PROGRESSION

Monte-Carlo Simulation Assumptions:
- 24-month placebo-controlled parallel group trials
- Drug effect of 50% reduction in the progression rate
- Dropout model
- Power was calculated as the proportion of trials for which the effect of treatment on progression rate was beneficial with a two-tailed $P$-value < 0.05.

$APoE-e4 = \text{apolipoprotein E-encoding gene } \varepsilon4 \text{ allele}$

MMSE = mini-mental state examination

ICV-HV = intracranial volume-adjusted hippocampal volume
USER-FRIENDLY CLINICAL TRIAL SIMULATOR

Hippocampal Neuroimaging-Informed Amnestic MCI Clinical Trial Simulator
Simulate clinical trials on patients with amnestic mild cognitive impairment

By Daniela Conrado (Model and App Developer) and Jackson Burton (App Developer) on behalf of the Critical Path for Alzheimer’s Disease (CPAD) consortium. E-mail DConrado@c-path.org with questions or comments.

Already available to members!
CONSIDERATIONS

- Patients have clinical impairment consistent with Stage 3 of the Alzheimer disease continuum

- This work supports the use of varying enrichment approaches
FUTURE ACTIONS

- Continue the pursuit of clinical trial data in early AD
- Describe other components besides natural disease progression:
  - Placebo response profile
  - Drug effect, including concomitant medications
  - Dropout pattern of clinical trials
Letter of support for Model-based CT enrichment tool for CTs in aMCI

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Executive Director

evaluating enrichment strategies, over a varied range of assumptions and trial design options. Current approaches for sample size estimation, based on literature metadata of the estimated standard deviation for the clinical endpoint and the expected effect size, do not account for differences in clinical and demographic characteristics of the enrolled trial population, disease worsening profile over time, and the different levels of variability (e.g., between-study, between-subject, and residual variability). The current version of the model accounts for the contribution of the aforementioned aspects and is
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- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute on Aging (NIA)
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- National Institutes of Health (NIH)

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- UsAgainstAlzheimer’s Network
- Alzheimer’s Research UK
- Alzheimer’s Drug Discovery Foundation
- CHDI Foundation
Thank you!

DConrado@C-Path.Org