A Case Study of Statistical Randomized Clinical Trial (RCT) Design in Drug Development: Aducanumab in Alzheimer's Disease

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July 15, 2022

On June 7, 2021, the US Food & Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) announced the accelerated approval of aducanumab, a monoclonal antibody targeting amyloid, in the treatment of Alzheimer's Disease. This decision was made in the face of two confirmatory clinical trials that had been terminated for futility, a negative opinion from the CDER Office of Biostatistics, and an overwhelmingly negative recommendation (0 yes, 10 no, 1 abstention) from the Peripheral and Central Nervous System (PCNS) Advisory Committee that reviewed the evidence (Dr. Emerson was a member of that Advisory Committee).

This module presents a statistical perspective on clinical trial design issues that adversely impacted the available evidence; on problems with data analyses that were presented to the committee; and on the arguments put forth as justification for accelerated approval using a surrogate endpoint that had not been validated. The goal of this module is to examine how different choices in the drug development process might have prevented, or at least mitigated, the controversies in the approval process. In particular, this module will cover:

- the important role that screening pilot studies play in drug discovery and how the results of screening studies can best inform the design of confirmatory RCT (both in terms of powering the study and monitoring safety),
- the appropriate choice and implementation of sequential sampling in clinical trial designs (with particular emphasis on futility boundaries for longitudinal primary endpoints),
- the special problems that arise when time-varying treatment effects are of concern (as might exist due to either treatment mechanism of action or changing RCT conditions),
- the interpretation of discordant RCT results (under both presumptions of a null or an alternative hypothesis),
- the dangers of conditioning on post-randomization variables (with particular focus on nonadherence or changes in concomitant therapies), and
- the proper validation of surrogate endpoints that might be used in drug approval.

SCHEDULE (timings other than break are approximate)

8:30	Background: Brief regulatory history of aducanumab in Alzheimer's Disease
8:45	Screening trials in drug discovery Dose 1b dose ranging study
9:15	Phase 3 trial design Patient eligibility Dosing / safety considerations Primary endpoint Sequential testing
10:00	Break
10:30	Protocol amendments: Modification of dose Handling potential time varying treatment effect
11:00	Termination of RCT and analysis of discordant results
11:30	Surrogate outcomes

Zoom link: https://washington.zoom.us/j/93085804125

FURTHER READING

Aducanumab:

1. Phase 1b trial publication:
   Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016 Aug 31;537(7618):50-6. PubMed.

2. Nov 6, 2020 FDA Peripheral and Central Nervous System Advisory Committee (PCNSAC) Meeting Event Materials
   https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-meeting#event-materials

   a. Briefing Document (combined Sponsor and FDA)
      https://www.fda.gov/media/143502/download

   b. Pre-recorded Sponsor presentation slides, transcript and AC presentation
      Slides : https://www.fda.gov/media/143506/download
      Transcript: https://www.fda.gov/media/143507/download

   c. Pre-recorded FDA presentation slides, transcript
      Slides : https://www.fda.gov/media/143504/download
      Transcript: https://www.fda.gov/media/143505/download

   d. Nov 6, 2020 PCNS AC Meeting
      Sponsor slides : https://www.fda.gov/media/143577/download
      FDA slides : https://www.fda.gov/media/143576/download
      Transcript : https://www.fda.gov/media/145691/download

3. *JAMA* Viewpoint from some PCNSAC members
   Alexander GC, Emerson S, Kesselheim A. Evaluation of aducanumab for Alzheimer's disease: Scientific evidence and regulatory review involving efficacy, safety, and futility. *Journal of the American Medical Association* (2021 Published online March 30, 2021. doi:10.1001/jama.2021.3854)
   https://jamanetwork.com/journals/jama/article-abstract/2778191

4. FDA memo re decision
   https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease

5. *NEJM* perspective from some PCNSAC members
   Alexander GC, Knopman DS, Emerson SS, Ovbiagele B, Kryscio RJ, Perlmutter JS, Kesselheim AS. Revisiting FDA approval of aducanumab. *New England Journal of Medicine* 2021 Jul 28. doi: 10.1056/NEJMp2110468.
   https://www.nejm.org/doi/full/10.1056/NEJMp2110468

6. Phase 3 trials publication
   Budd Haeberlein S, 1, Aisen PS, etal. J Prev Alz Dis 2022;2(9):197-210
   Published online March 18, 2022, http://dx.doi.org/10.14283/jpad.2022.30
   https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb

RCT methodology

1. Screening trials in drug discovery (1.5 hour recorded lecture)
   http://RCTdesign.org/Learning_May2011Course.html

2. Introduction to adaptive sequential trial design from a 2010 1 day short course at CDRH
   http://RCTdesign.org/Learning_Nov2010Course.html

3. Reprints / Technical reports
   a. Frequentist evaluation of RCT designs:
      http://RCTdesign.org/TechReports/SIMfreqeval.pdf

   b. Bayesian evaluation of RCT designs:
      http://RCTdesign.org/TechReports/SIMbayeseval.pdf

   c. Issues with stochastic curtailment:
      http://RCTdesign.org/TechReports/BEPcurtail.pdf

   d. Efficient adaptive sample size re-estimation
      http://RCTdesign.org/TechReports/SIMcommentarymehtapocock.pdf
      http://RCTdesign.org/TechReports/SIMefficientadaptive.pdf

   e. Inference after adaptive RCTs
      http://RCTdesign.org/TechReports/BCSAdaptiveInference.pdf

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