Alzheimer’s Disease Case Study (Hypothetical Estimand)

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Background

Alzheimer's Disease (AD), the most common cause of dementia, is the biological process that begins with the appearance of a buildup of proteins in the form of amyloid plaques and neurofibrillary tangles in the brain. This causes brain cells to die over time and the brain to shrink.

Early symptoms of Alzheimer's disease include forgetting recent events or conversations. Over time, Alzheimer's disease leads to serious memory loss and affects a person's ability to do everyday tasks. In advanced stages, loss of brain function can cause dehydration, poor nutrition or infection. These complications can result in death.

There is no cure for AD but treatments to improve symptoms (symptomatic therapies) or slow the decline in thinking are available. Programs and services can help support people with the disease and their caregivers. The standard of care for Alzheimer's disease involves a multi-faceted approach, including diagnostic evaluation, medication management, and supportive care strategies focused on improving quality of life and slowing disease progression.

https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447

AD Phase 3 Trial

A sponsor company is currently running a phase 3 trial to investigate symptomatic therapy “A” to the standard of care in patients with Early Alzheimer's Disease. The primary outcome of interest is the 18-month change from baseline ADAS-Cog (Alzheimer's Disease Assessment Scale - Cognitive Subscale) score, a neuropsychological assessment widely used to evaluate cognitive impairment in individuals with Alzheimer's disease and related dementias. It is considered a "gold standard" in the field, particularly for assessing the effectiveness of anti-dementia treatments in clinical trials. ADAS-Cog scores:

- measures the severity of cognitive symptoms in Alzheimer's disease, focusing on memory, language, and praxis (motor planning),
- are obtained via a brief assessment, typically administered by a trained professional and scored based on a standard protocol, and
- range from 0-70 (or higher in some versions) with higher scores indicating greater cognitive impairment.

The trial is expected to be run for at least 18 months. At the end of the first year of the trial, another pharmaceutical company received regulatory approval for a disease modifying therapy for AD. As a result, the latter will be available to AD patients, including those that are currently enrolled in the study. As might be expected, some of the patients in the trial may decide to take this newly approved therapy. Moreover, some of them may do so but may remain in the AD trial, and some may actually discontinue their participation in the trial altogether. As there were no disease modifying therapies available at the initiation of the trial, the use of such during the trial was not foreseen.

Scientific Question of Interest

The sponsor clinical team is concerned about the situation and would like to assess the impact it may have not only on the AD trial, but also on the entire development program of their symptomatic therapy the new disease modifying therapy not been available. The clinical team considers this a meaningful estimand for internal decision making as they plan to context this beside a treatment policy estimand to get a sense of the impact the new therapy may have.

Case Study Prompts

- How would you communicate this clinical question to a non-statistical collaborator?
- Draw a causal diagram to communicate your problem with your collaborators
- How would you formally define this estimand in potential outcomes notation?
- What analysis method or model would you propose?
- How might the results of such an analysis look in a table?
- How would you go about communicating the relevant assumptions to collaborators?
- How would you interpret the results of such an analysis to a non-statistical collaborator?

When you're done, please email a picture of your results to iscb.causal.symposium@gmail.com and feel free to cc your team members to share the work.