Target trial emulation to leverage randomized trial data

investigate alternative questions of interest in late-stage development of monoclonal antibodies in Alzheimer's disease

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What does this mean for the AD community?

- A clinical trial is conceived to answer a single question of interest
- Alternative question of interest may arise after primary study read-out
- Alter the primary estimand's attributes making the intent-to-treat estimator not relevant

Conclusions

Trial emulation reduces bias in the estimation of the alternative question of interest based on the study data
Trial emulation should not be limited to observational data, as it is:
- an analysis strategy that dominates per-protocol analyses
- an efficient approach to de-risking next clinical trials

Background

Target trial emulation, a method to draw causal conclusions from observational data (Hernan, JAMA 2022), can be applied to clinical trial data. Phase III randomized clinical trials (RCT) evaluating experimental molecules are designed to address a pre-specified question for registration purposes. In case of high attrition, incomplete observance or dose adaptation, leveraging the large amount of data collected to consider counterfactual situations becomes crucial: what would have happened in absence of attrition, perfect observance or in a real-life population.

Objective

We propose to use trial emulations to address these alternative causal questions enhancing the RCT intent-to-treat (ITT) analysis. We illustrate our strategy with a post-hoc analysis of RCTs in Alzheimer's disease (AD) aligning definitions for exposure and inclusion criteria to those of a competing trial.

Methodology

Building an emulated clinical trial

- Participants were randomized to control or study drug at baseline, a_0
- Exposure of study drug: 36 weeks up-titration period, A_{36}, followed by 80 weeks at the full dose
- Clinical outcome measures after 116 weeks, Y_{116}

Alternative clinical question of interest

What is the treatment effect while on full dose?
Did up-titration period impacted outcomes?
What treatment effect on early disease stage?

Counterfactuals

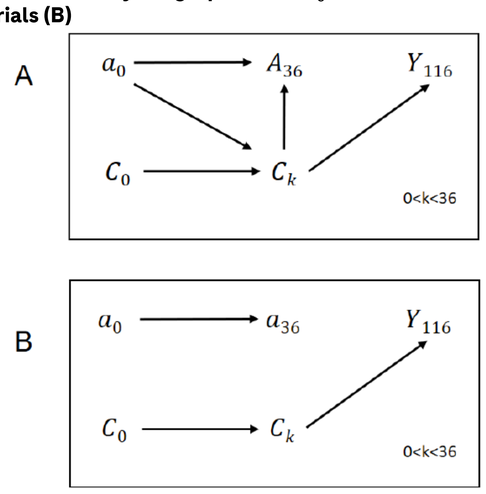
1. No study withdrawals before the end of up-titration period, week 36
2. Optimal dose schedule: all participants escalated successfully to full dose at week 36
3. Optimal dose and early disease stage at baseline

Building an estimator

Marginal structural model in longitudinal change in clinical outcome
Inverse probability weighting method
Propensity score derived using an extensive list of baseline, C_0, and post-baseline confounders, C_k :

$$Pr[A_{36} = a|C_0, C_k]$$

Figure 1. Directed acyclic graph under H_0 for our AD case study (A) and for target trials (B)



Results

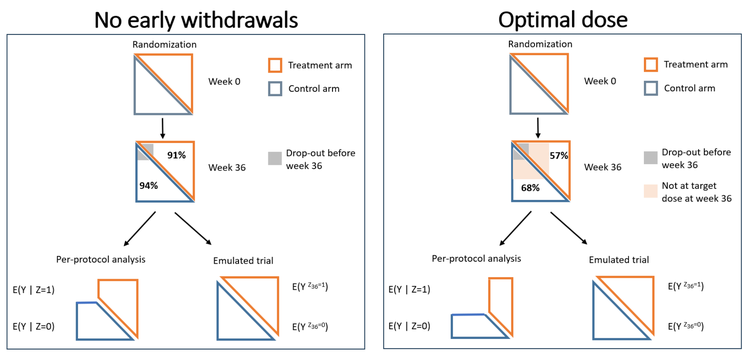
The studies comprised 1959 participants in the intent-to-treat population.

At week 36, 1805 participants were still on treatment including 906 (91%) participants in the experimental arm and 899 (94%) in the control arm, see Figure 2. The main reason for withdrawal study drug before week 36 was participant's decision in both the experimental and the control arm. In the experimental arm, the second most frequently reported reason for withdrawal was adverse events.

At week 36, 1224 participants (62% of the ITT population) were exposed to the target dose including 571 (57%) participants in the experimental arm and 653 (68%) in the control arm, see Figure 2. The main reasons for not being at target dose were adverse events and covid-19 pandemic related causes.

At week 36, a total of 905 participants (46% of the ITT population) met inclusion criteria restricted to early disease stage and were exposed to the target dose at week 36, including 410 (41%) participants in the experimental arm and 495 (68%) in the control arm, not shown in Figure 2.

Figure 2. Analysis strategies of counterfactual outcomes

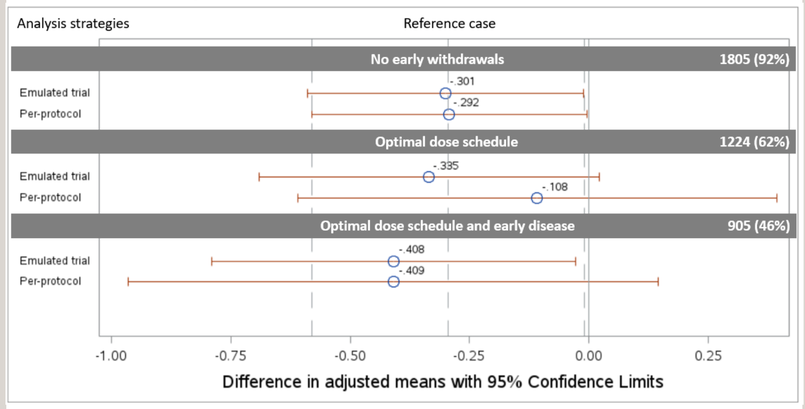


After Figure 1.1, page 12, in Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.

Emulated trial estimator showed increased precision compared to per-protocol analysis and confirmed the primary analysis results

The change from baseline to week 116 in CDR-SB derived from the emulated trial was similar to the estimation from the ITT analysis (-0.30 and -0.29 points respectively). In two out of three counterfactual scenarios, optimal dose schedule and optimal dose schedule on early disease stage, the emulated trial estimator showed improved precision compared to the per-protocol analysis.

Figure 3. Target trials and per-protocol estimations of adjusted mean difference of change from baseline to week 116 in the clinical primary outcome



Discussion

While phase III RCTs are designed to address a single clinical question of interest, target trial emulation using RCT data offers a methodologically robust alternative to post-hoc analyses for investigating alternative clinical questions and informing the design of future trials.

Table 1. Randomized controlled trials and emulated target trials insights

Estimand attributes	Randomized controlled trials	Emulated target trial
Objectives	Pre-specified question described in the statistical analysis plan	Post-hoc analysis, revisit the trial's initial assumptions
Population	Participants who meet the inclusion criteria	Closer to real world, embracing diversity, sub-group of interest
Treatment	Protocol mandated exposure	Alternative exposure of interest, compliers, defiers
Variable of interest	Validated endpoint for registration	Broader definition of response: composite endpoint, quality of life
Population-level Summary	Average treatment effect	Average treatment effect, Average treatment on the treated, Average treatment on the control
Intercurrent events	Treatment policy	Hypothetical, Composite variable

Conclusion

Target trial emulation was described as an approach using observational data to mimic or emulate the design of a randomized controlled trial (RCT) - the 'target' trial - to estimate the effect the trial would have had if conducted.
In this work, we applied this strategy on RCT data to inform post-hoc analysis on alternative questions of interest. We showed that emulating target trials using RCT data provides a methodologically robust alternative to post-hoc analyses.
We demonstrated that well informed marginal structural models enhanced the estimation of these alternative estimands.
Our application stands out for its innovative approach, bridging insights from past pivotal trials to inform future ones and address emerging alternative clinical questions of interest.
As the clinical research community continues to explore innovative approaches to maximize the utility of existing datasets, our analysis strategy contributes to the evolving landscape of evidence synthesis and clinical inquiry.

More on estimands implementation?

Check the Statisticians in Pharma Industry (PSI) Webinar: Estimands framework in action, the Alzheimer's disease case; 02 July 2024
With Rachid Abbas, Angeliki Thanasopoulou, Marcel Wolbers

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Disclosures

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