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Vignette for ISCB mini symposium 1
"Causal Inference for Improved Clinical Collaborations: A Practicum"

Covariate adjustment in the ODYSSEY trial

by Tim Morris

The ODYSSEY trial was a randomized, parallel group, open-label, non-inferiority trial designed to compare two HIV treatment regimes in children. The ODYSSEY analysis was to be adjusted for three binary stratification covariates. This may be challenging because:

(1) interest was in the risk of virologic or clinical treatment failure at a landmark time (96 weeks after randomization);

(2) some censoring occurred before 96 weeks, so time to virological or clinical failure was recorded as a time-to-event (note: censoring is assumed not to affect the existence or value of the outcome);

(3) the aim was to demonstrate non-inferiority (with non-inferiority margin of 10 percentage points at 96 weeks).

The below questions are intended to facilitate discussion about the principal challenges and what approaches you might use to ensure you would robustly – and efficiently – estimate the difference in risks at 96 weeks. The principal focus is on covariate adjustment.

Remember, this is a randomized controlled trial, so you need to be able to unambiguously pre-specify your proposed analysis procedure.

If you are interested, the paper can be (open) accessed at

https://doi.org/10.1056/NEJMoa2108793

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Specific questions/suggestions:

- What is the unconditional estimand?
- How would you write the null hypothesis formally, making use of potential outcomes / counterfactuals?
- What challenges do you foresee in estimating this contrast?
- How would you estimate this contrast in subgroups?
- Draw a causal DAG, including stratification covariates, treatment and outcome.
- To estimate the unconditional estimands, should you adjust for covariates? Why/why not?
- Is there any further information you need to make progress? (If so, give yourselves a made-up answer, or, if time, look into the appendix of the paper where you can find additional information, e.g. in the consort diagram)
- What approach would you use for estimation? Can you come up with alternative reliable estimation strategies, whether less or more efficient?
- How would you graphically display the time-to-event over time (in addition to the landmark analysis at W96)?

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.