Rima Izem, PhD

Statistical Methodology

PSI Annual Meeting

June 17th 2026

The Good, The Bad, and The Ugly when leveraging external (real-world) data to the trial

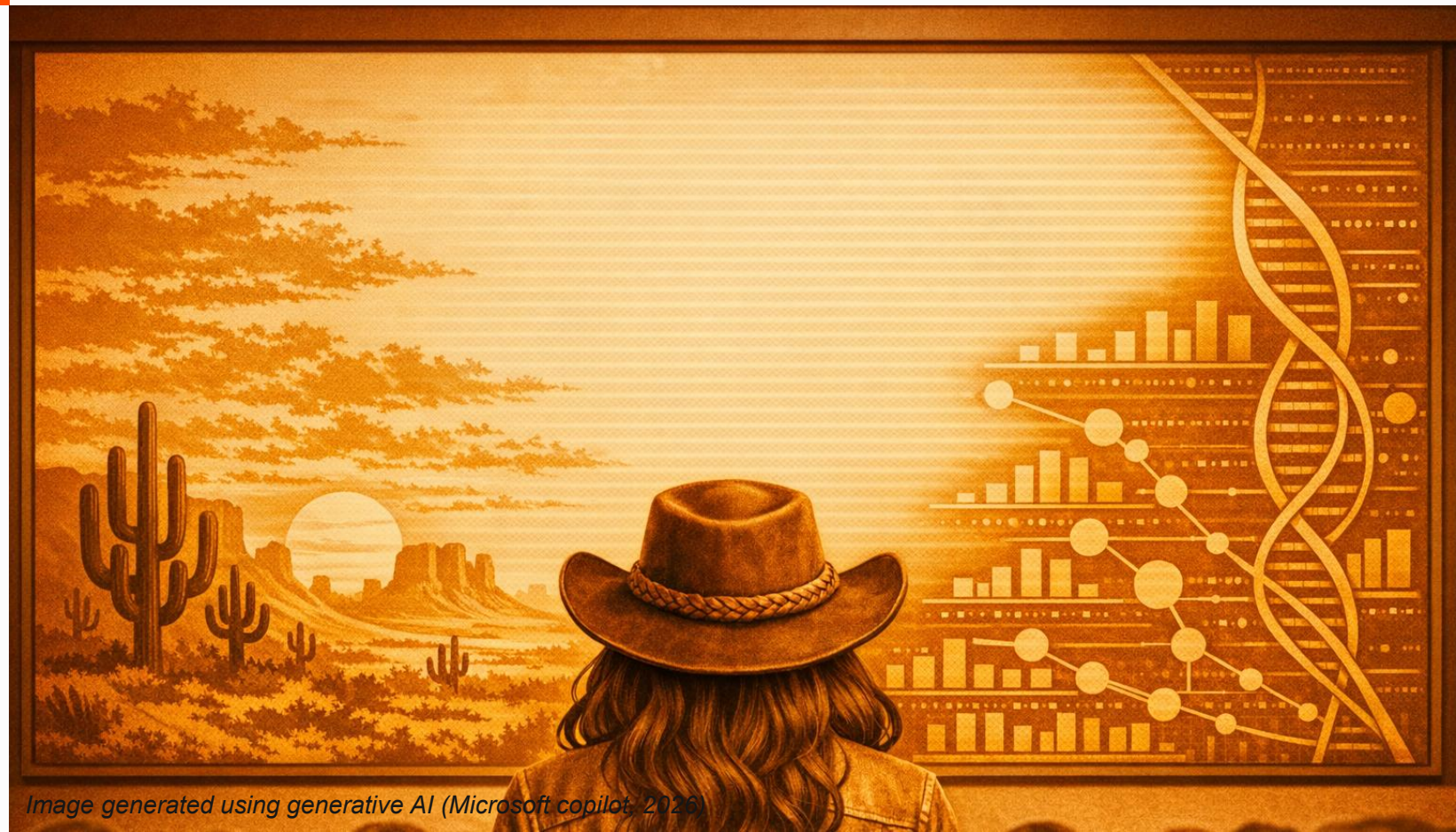
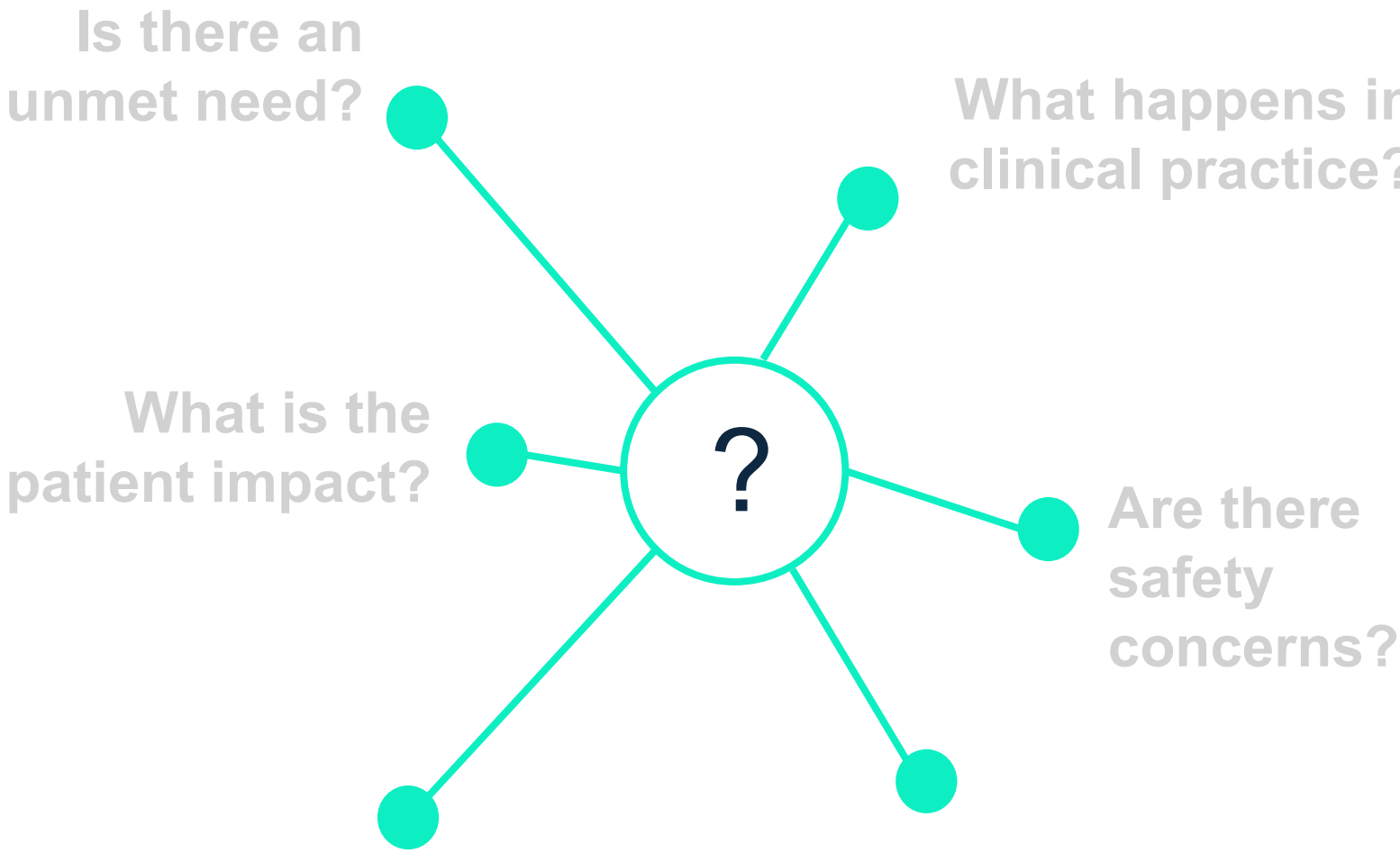


Image generated using generative AI (Microsoft copilot, 2026)

NOVARTIS



Real-world data can help answer key questions

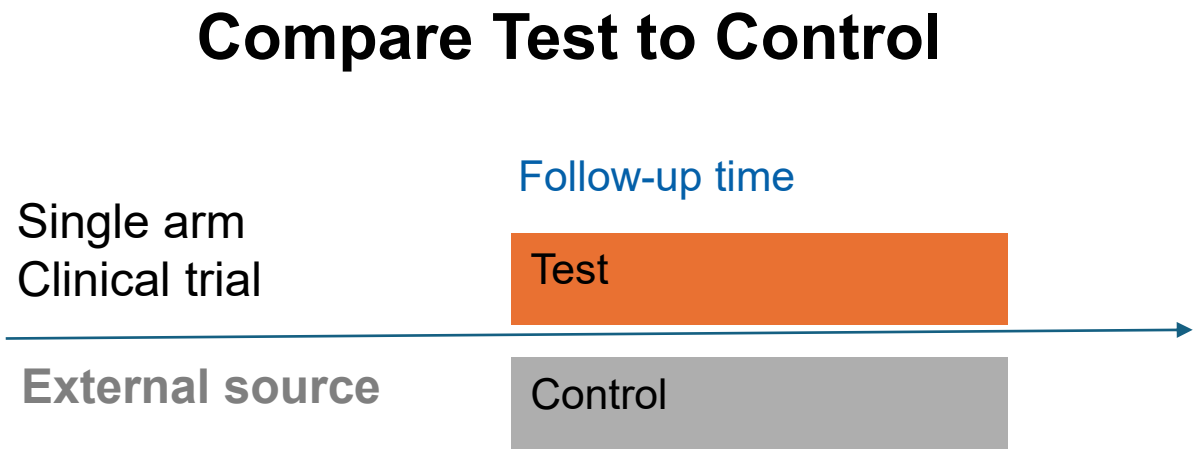
Scope of this presentation

- **External** to the clinical trial, the latter being the main source of evidence (internal, regulatory, health technology assessment)
- **Data** from **relevant** and **reliable** natural history studies and/or other real-world data sources
- **Purpose** fill a knowledge gap in efficacy or effectiveness, including but not limited to primary evidence of efficacy
- **Methods** (design & analysis) in observational research, causal inference, and/or evidence synthesis

Agenda

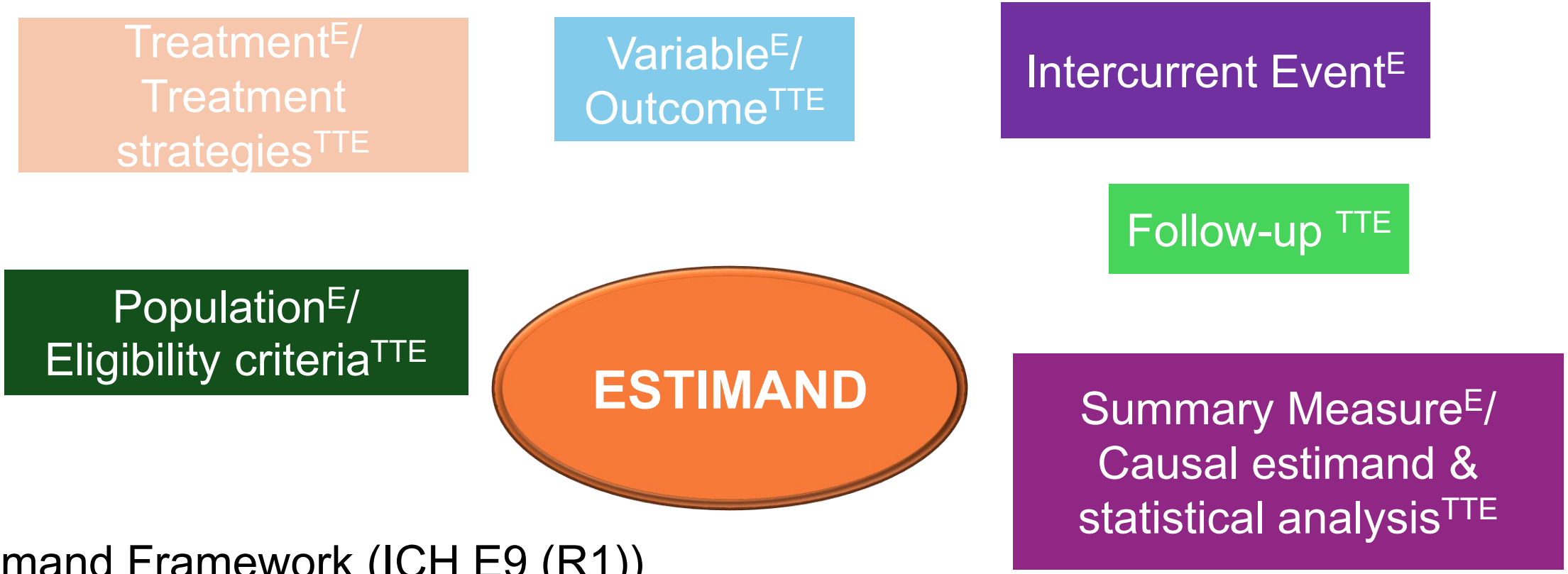
- The good
- The bad
- The ugly

- The interesting



The good: clear scientific objectives

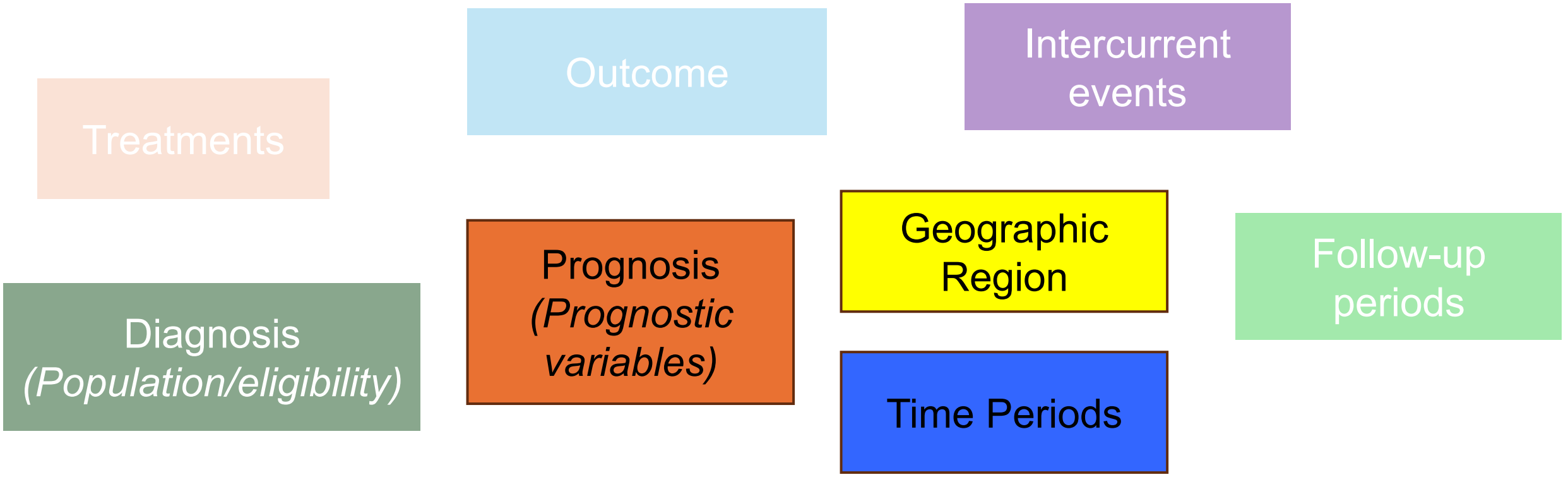
What is the estimand? What *simple* RCT can target it?



E: Estimand Framework (ICH E9 (R1))
TTE: Target Trial Emulation (Hernan and Robins 2016)
Combining E & TTE (Hampson et al 2024) and/or using both (EMA, 2024)

The good: relevant and reliable data

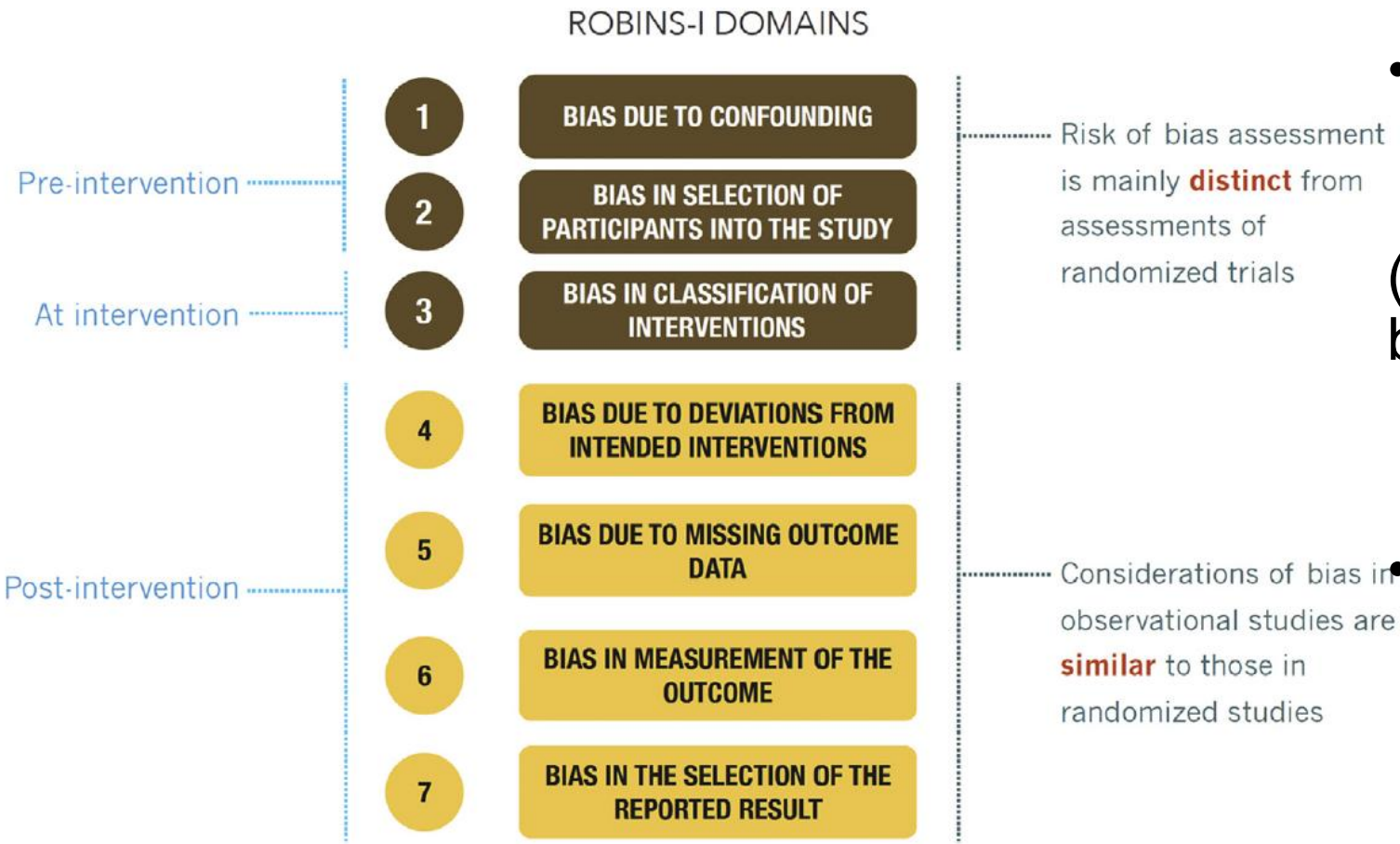
How ***comparable*** is the external control to the trial?



Source: Table 1 domains for assessing comparability of data (US FDA, 2023)

The good: manageable sources of bias

What are the different sources or bias?



- **confounding,** or failure to account for a common cause of treatment and outcome

(e.g., frailty (external control) at baseline> single arm)

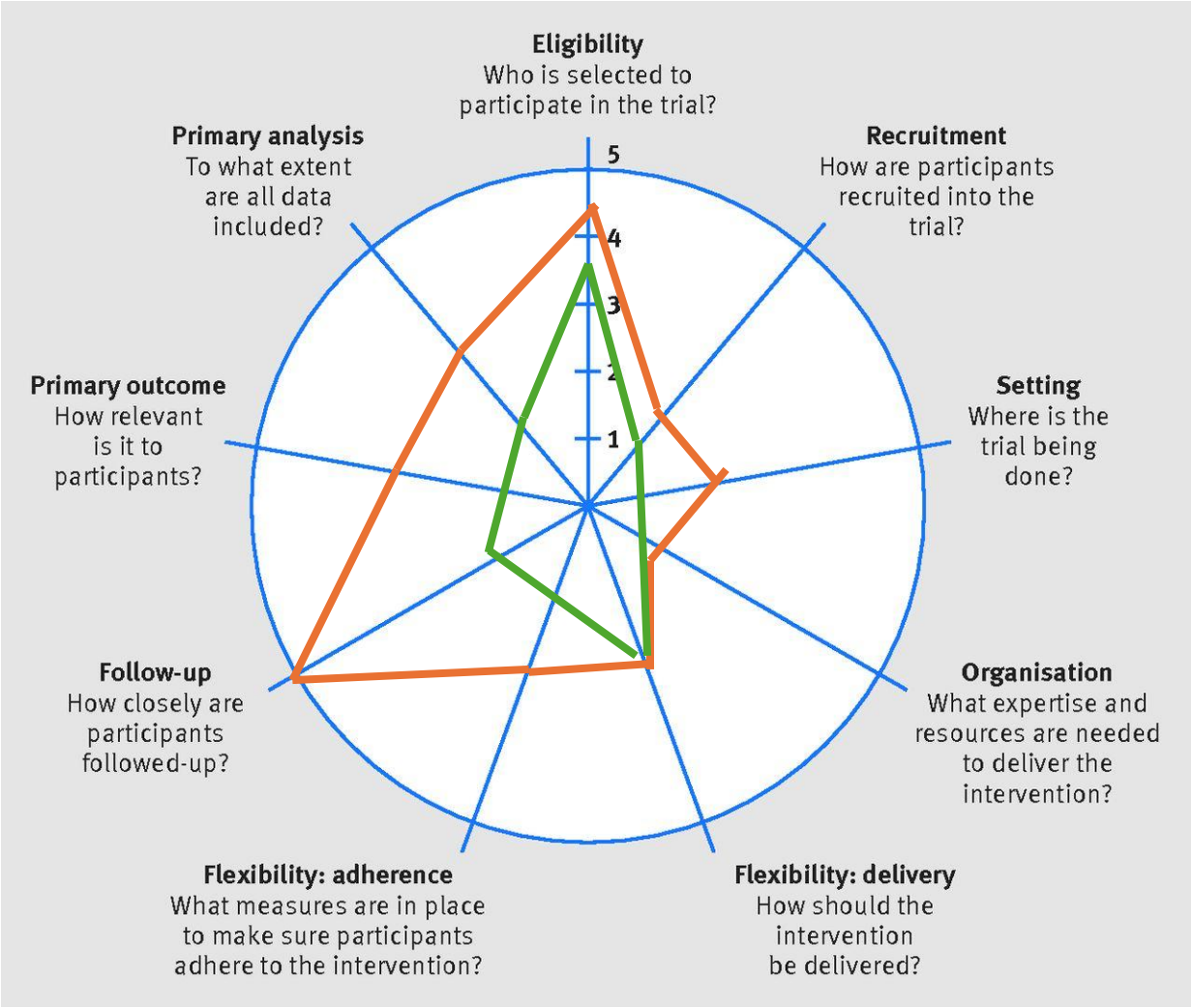
- **selection,** erroneously conditioning on a common effect of treatment and outcome (e.g., immortal time in single arm)

Robins's I domains (Sterne J A et al. (2016), similar considerations in Burger et al (2021)

The good: manageable sources of bias

What are the expected differences with RWD?

The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel. Loudon et al (2015)

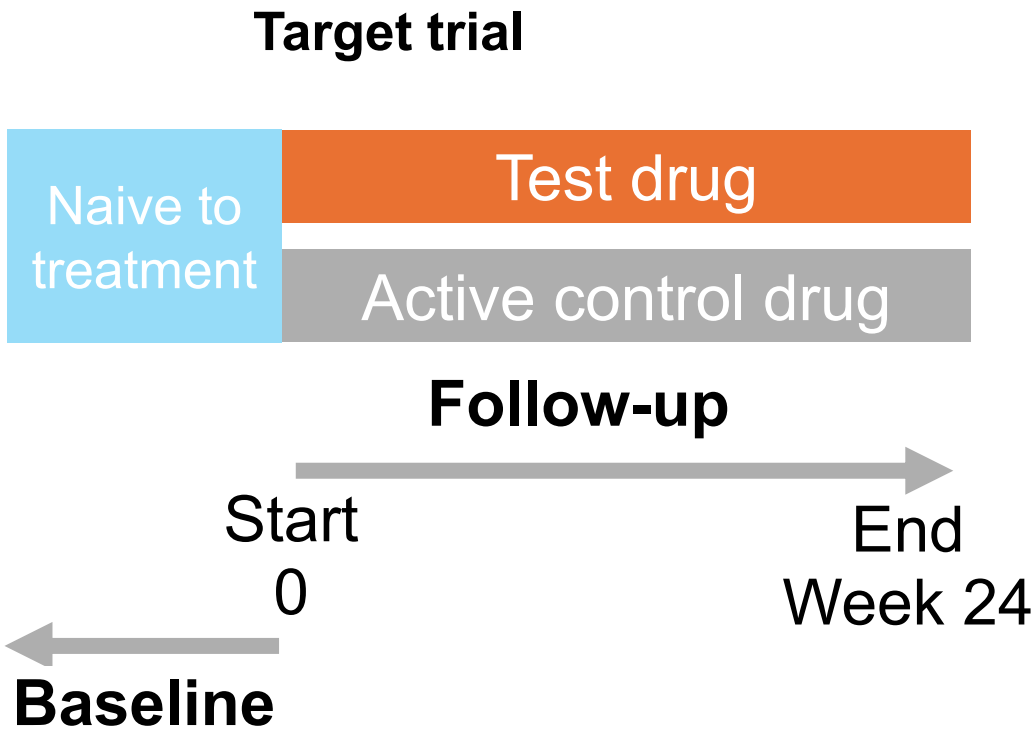


Natural history study

Single arm trial

The good: mitigate expected biases

How well can you emulate the target trial?

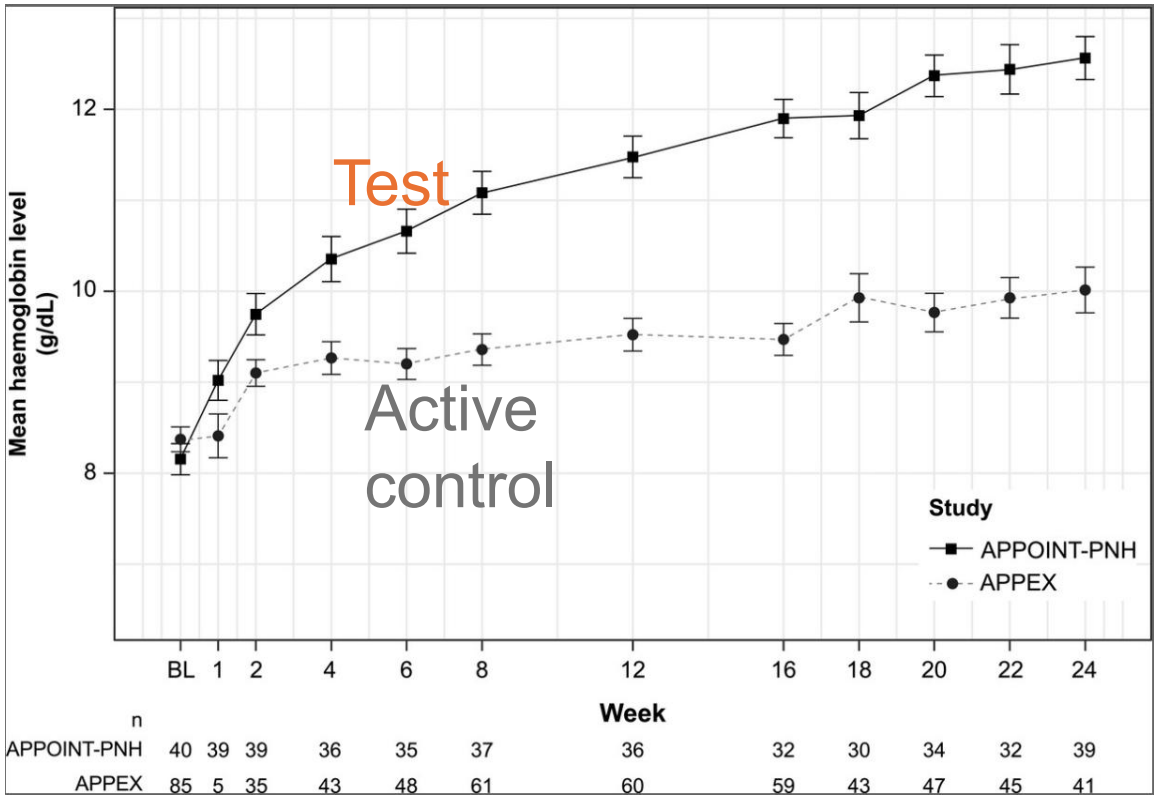


Sources of bias	Mitigation (design and analysis)
Selection of patients Confounding	- Clear time-0 - Filter external data based on baseline period characteristics - Identify prognostic factors & adjust using causal inference methods
Assessment schedule	Sensitivity analyses (different visit-windows definitions)

Source: Holt et al (2025)

The good: assess and stress-test results

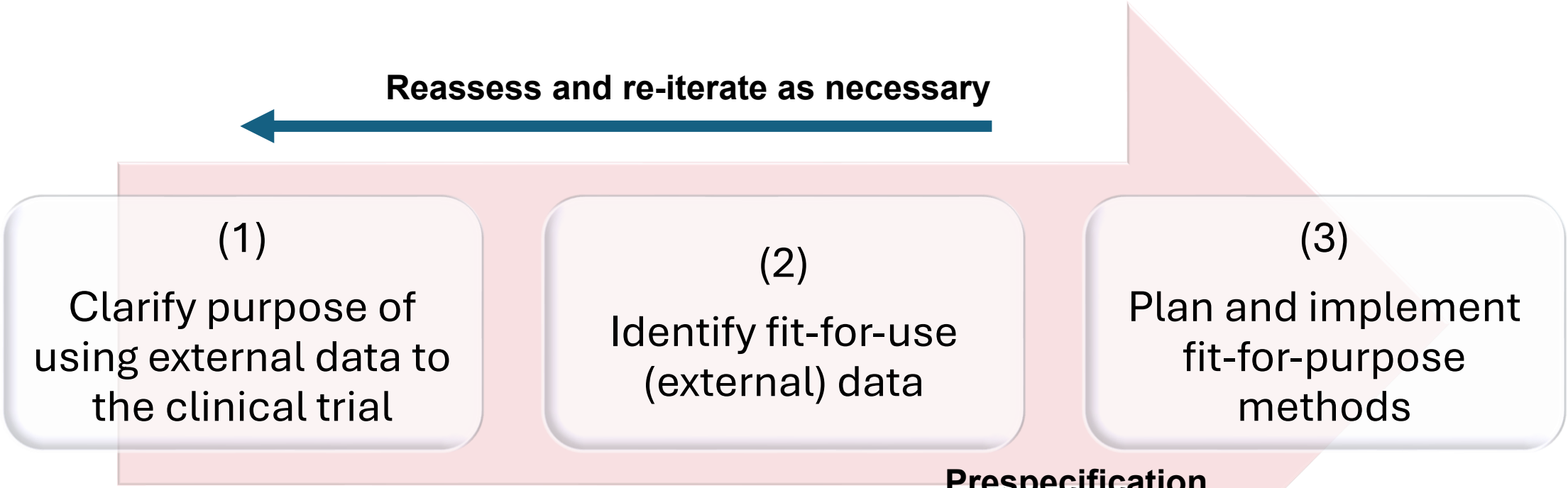
How plausible are your assumptions? When do results hold?



Source: Holt et al (2025)

Other examples and case studies (EMA, 2025)

The good: in summary



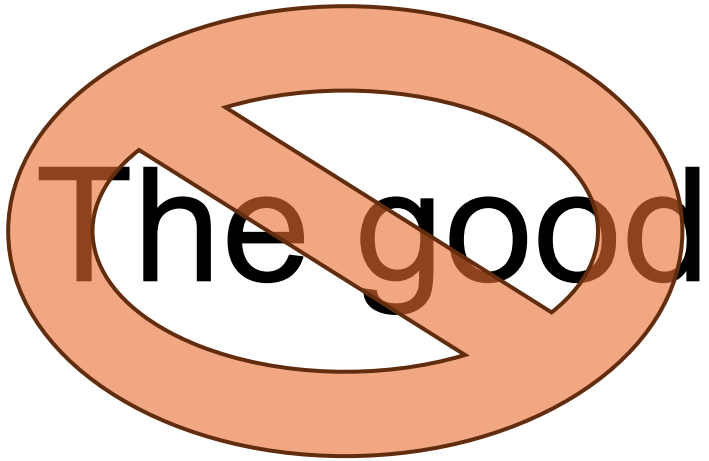
The Estimand Framework
The Target Trial

Comparative table
Robins I tool,
Precis-Tool

Target trial emulation
Causal inference methods
(assumption, estimation, quantitative bias analysis)

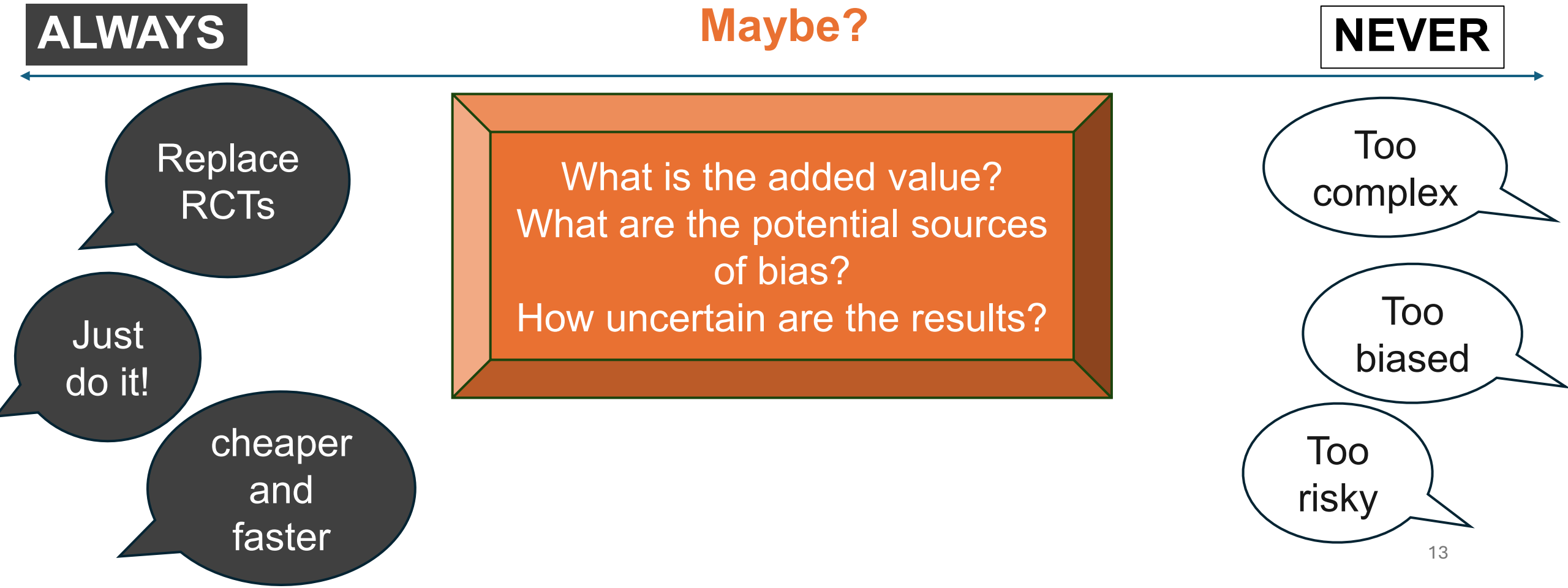
Similar workflows (Desai et al, 2024), Polito et al (2024), Dahabreh et al (2024)

The bad

The bad = 

Some case studies:
Izem, R., et al. (2022)
Mishra-Kalyani, P. S. et al (2022)

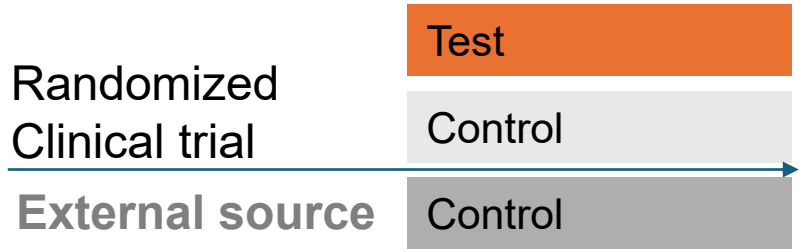
The ugly: extreme views about RWD/RWE



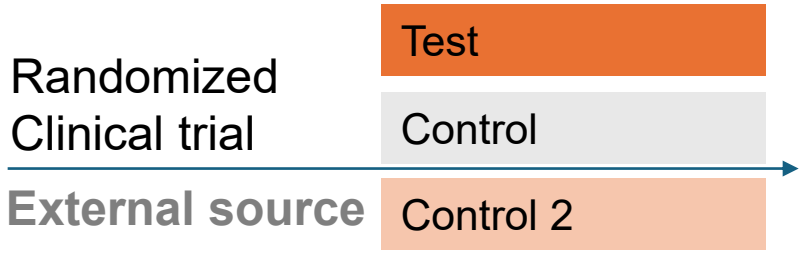
The interesting: hybrid approaches

Compare Test to Control (efficacy or safety)

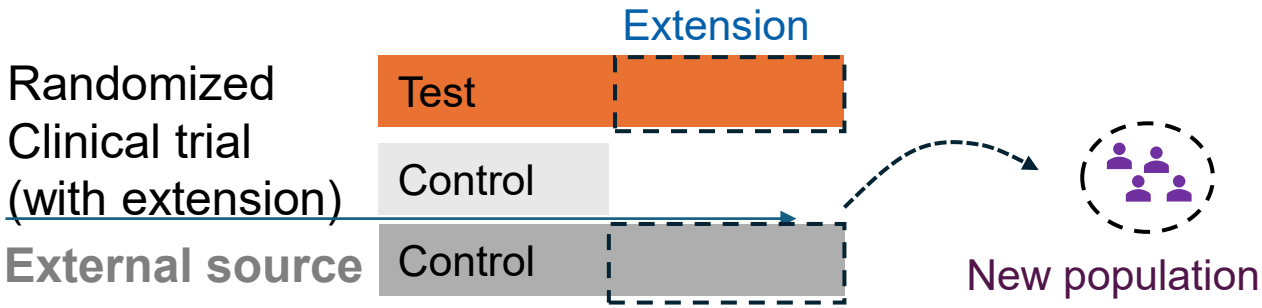
Power comparison of Test to Control



Compare Test to Control 2



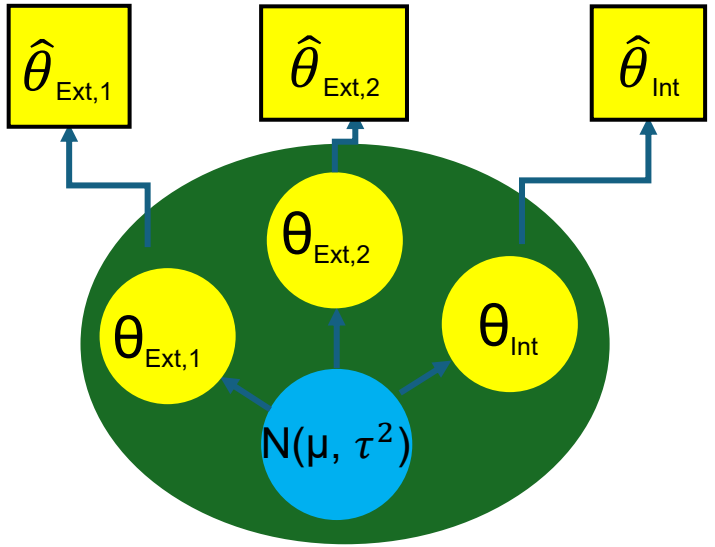
Compare Test to Control for a long-term outcome and/or new population



Hampson, and Izem (2023)

The interesting: evidence synthesis

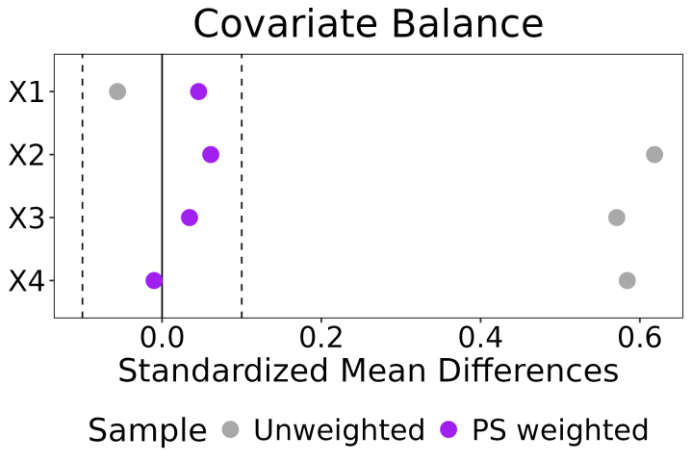
Bayesian dynamic borrowing
penalize outcome dissimilarity
(e.g., via robust MAP priors)



MAP = Meta-Analytic Predictive

+

Causal inference methods that increase baseline similarity
(e.g., IPW, AIPW)



IPW = Inverse probability weighting
AIPW = Augmented inverse probability weighting

Zhu, Izem et al (2026) (Review of methods by ASA Biopharm working group)

References

- Burger HU, Gerlinger C, Harbron C, et al. The use of external controls: To what extent can it currently be recommended?Pharmaceutical Statistics. 2021;20:1002–1016. https://doi.org/10.1002/pst.2120
- Dahabreh IJ, Bibbins-Domingo K. Causal Inference About the Effects of Interventions From Observational Studies in Medical Journals. *JAMA.* 2024;331(21):1845–1853. doi:10.1001/jama.2024.7741
- Desai RJ, Wang SV, Kattinakere Sreedhara S, et al. (2024) Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center. *British Medical Journal*, 384, e076460
- Holt, Matthew, et al. "Effectiveness of Iptacopan Versus C5 Inhibitors in Complement Inhibitor-Naive Patients With Paroxysmal Nocturnal Haemoglobinuria." EJHaem 6.3 (2025): e270055.
- Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016 Apr 15;183(8):758-64.
- Hampson, L. V., Chu, J., Zia, A., Zhang, J., Hsu, W. C., Parzynski, C. S., ... & Degtyarev, E. (2024). Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial. *Statistics in Biopharmaceutical Research*, *16*(1), 1-10.
- Hampson, Lisa V., and Rima Izem. "Innovative hybrid designs and analytical approaches leveraging real-world data and clinical trial data." *Real-World Evidence in Medical Product Development* (2023): 211-232.
- Izem, R., Buenconsejo, J., Davi, R., Luan, J. J., Tracy, L., & Gamalo, M. (2022). Real-world data as external controls: practical experience from notable marketing applications of new therapies. *Therapeutic Innovation & Regulatory Science*, *56*(5), 704-716.
- Loudon, K., Treweek, S., Sullivan, F., Donnan, P., Thorpe, K. E., & Zwarenstein, M. (2015). The PRECIS-2 tool: designing trials that are fit for purpose. *bmj*, *350*.
- Mishra-Kalyani, P. S., Kordestani, L. A., Rivera, D. R., Singh, H., Ibrahim, A., DeClaro, R. A., ... & Beaver, J. A. (2022). External control arms in oncology: current use and future directions. *Annals of Oncology*, *33*(4), 376-383.
- Polito L, Liang Q, Pal N, et al. (2024). Applying the estimand and target trial frameworks to external control analyses using observational data: a case study in the solid tumor setting. Frontiers in Pharmacology, 15, doi: 10.3389/fphar.2024.1223858
- Sterne, Jonathan AC, et al. "ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions." bmj 355 (2016).
- Zu, K, Izem, R, et al (2026) https://doi.org/10.48550/arXiv.2605.03282

References (continued)

- Regulatory material
- (EMA, 2025b) Workshop on the use of external controls for evidence generation in regulatory decision-making
- (MHRA, 2025) Draft guideline on the use of external control arms based on real-world data to support regulatory decisions
- (EMA, 2024) Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence - Scientific guideline
- (US FDA, 2023) Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products | FDA

Thank you!

Questions?

NOVARTIS