

# Causal Inference in Clinical Trials

EMA Methodology Working Party

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*Acknowledging input from industry colleagues*

# Causal Inference Methods in Randomized Controlled Trials: Why at all?

- In RCTs, situations occur where the evaluation of the treatment effect no longer occurs under *strict randomization*, making RCTs akin to observational studies
  - **Reasons:** Intercurrent events (ICE), responder only analysis, unbalanced subgroups, long-term follow-up analyses – *post baseline events*
  - **Consequence:** traditional methods may not result in properly answering the scientific question of interest (e.g. treatment switching)
- **Causal inference**<sup>[1]</sup>, using the **counterfactual outcome** framework<sup>[2]</sup>, aims to evaluate the **causal effects** in presence of potential **confounders**, while being **explicit on required assumptions** to identify the causally defined estimand and to promote the utilization of sensitivity analyses.
- By directly targeting the treatment effect, e.g. average treatment effect (ATE)<sup>[1]</sup> **efficiency gains can be obtained** by using single or doubly robust methodology<sup>[3,4]</sup>

# Opportunities in analyzing RCT data

In line with **estimand framework** of ICH E9 (R1) [5-6], following the principles of *trial objective - estimand - estimator - estimate* and *sensitivity analyses*, causal inference methodology explicitly specifies the causal **estimand in counterfactual outcomes**

## RCT data

Estimands & Intercurrent Events (ICEs)

- ☐ **ICEs** (e.g., treatment switching) using causal inference techniques [7,8,9]
- ☐ **Explicitly defined** estimator for causal estimand (e.g. ATE, cATE<sup>[1]</sup>, non-collapsibility<sup>[10]</sup>)
- ☐ **Adjusting for baseline covariates** [3,12-14]
- ☐ **Sensitivity analyses**<sup>[15]</sup>

*Application areas go beyond RCT data and include **RWE** data and **biomarker** data too*

# Next steps + Discussion

- **Acceptability** of the use of the causal inference methodology to address scientific questions of interest, relevant for regulatory interactions to increase quality of decision-making
  - *Randomization (and tacit assumptions)* versus explicit assumptions<sup>[16]</sup>
  - Specification of **estimands** using **counterfactual outcomes** for the population summary metric
  - **Estimation of treatment effects** using causal inference methodology, including single robust, doubly-robust and extensions to account for longitudinal data

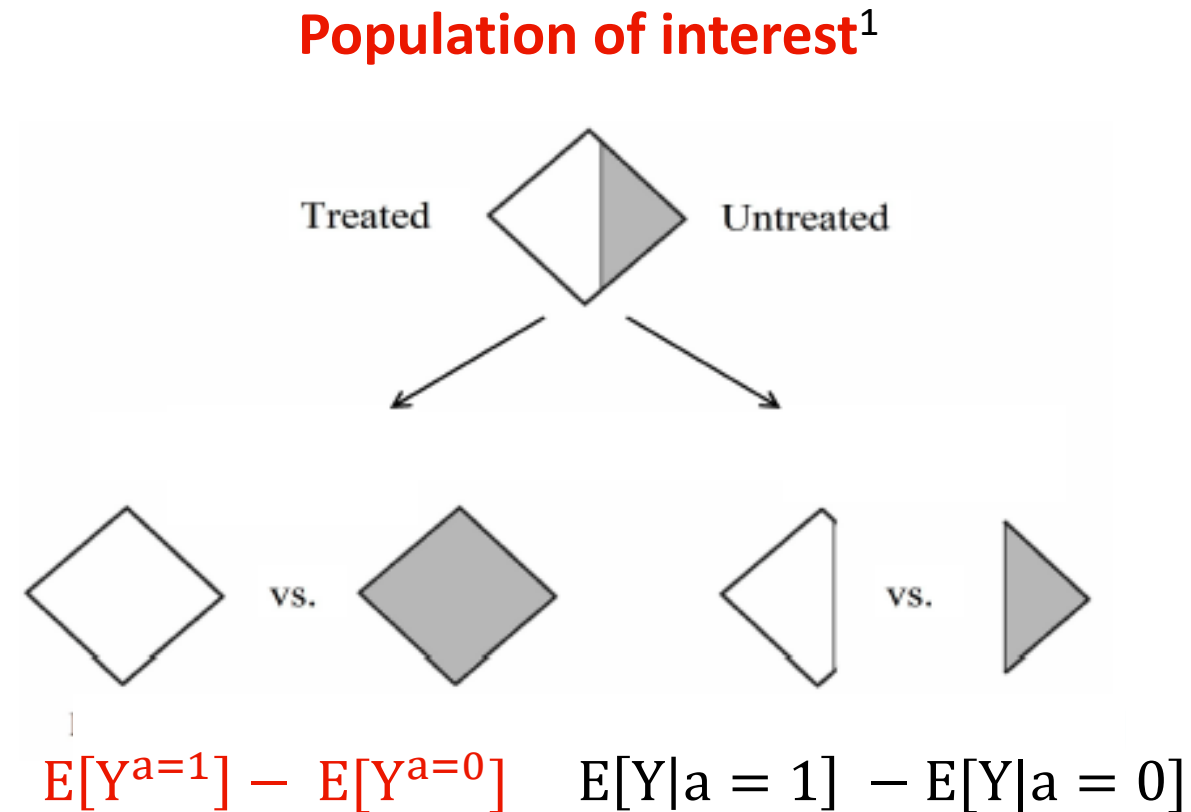
# References

- [1] Hernan & Robins (2024). What If. Retrieved via [https://www.hsph.harvard.edu/miguel-hernan/wp-content/uploads/sites/1268/2024/04/hernanrobins\\_WhatIf\\_26apr24.pdf](https://www.hsph.harvard.edu/miguel-hernan/wp-content/uploads/sites/1268/2024/04/hernanrobins_WhatIf_26apr24.pdf)
- [2] Rubin, D. Causal inference using Potential Outcomes. Journal of the American Statistical Association. 2005, 100, 322-331.
- [3] Ye, T., Shao, J., Yi, Y., & Zhao, Q. (2022). Toward Better Practice of Covariate Adjustment in Analyzing Randomized Clinical Trials. Journal of the American Statistical Association, 118(544), 2370–2382. <https://doi.org/10.1080/01621459.2022.2049278>
- [4] FDA guidance on covariate adjustment. <https://www.fda.gov/media/148910/download#:~:text=Covariate%20adjustment%20leads%20to%20efficiency,with%20the%20outcome%20of%20interest.>
- [5] CHMP on ICH e9 r1 [https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf)
- [6] ICH E9 (R1) [https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF\\_0.pdf](https://database.ich.org/sites/default/files/E9%28R1%29%20Training%20Material%20-%20PDF_0.pdf)
- [7] Olarte Parra C, Daniel RM, Bartlett JW. Hypothetical Estimands in Clinical Trials: A Unification of Causal Inference and Missing Data Methods. Stat Biopharm Res. 2022 Jul 6;15(2):421-432. <https://doi.org/10.1080/19466315.2022.2081599>
- [8] Michiels H, Sotto C, Vandebosch A, Vansteelandt S. A novel estimand to adjust for rescue treatment in randomized clinical trials. Stat Med. 2021 Apr;40(9):2257-2271. <https://doi.org/10.1002/sim.8901>
- [9] Gruber, S., Phillips, R. V., Lee, H., Ho, M., Concato, J., & van der Laan, M. J. (2023). Targeted Learning: Toward a Future Informed by Real-World Evidence. Statistics in Biopharmaceutical Research, 16(1), 11–25. <https://doi.org/10.1080/19466315.2023.2182356>
- [10] Wei, J., Xu, J., Bornkamp, B., Lin, R., Tian, H., Xi, D., ... Roychoudhury, S. (2024). Conditional and Unconditional Treatment Effects in Randomized Clinical Trials: Estimands, Estimation, and Interpretation. *Statistics in Biopharmaceutical Research*, 1–11. <https://doi.org/10.1080/19466315.2023.2292774>
- [11] Daniel R, Zhang J, Farewell D. Making apples from oranges: Comparing noncollapsible effect estimators and their standard errors after adjustment for different covariate sets. *Biometrical Journal*. 2021; 63: 528–557. <https://doi.org/10.1002/bimj.201900297>
- [12] Williams N, Rosenblum M, Díaz I. Optimising precision and power by machine learning in randomised trials with ordinal and time-to-event outcomes with an application to COVID-19. J R Stat Soc Ser A Stat Soc. 2022 Sep 23;10.1111/rssa.12915. doi: 10.1111/rssa.12915. Epub ahead of print. PMID: 36246572; PMCID: PMC9539267.
- [13] Van Lancker K, Bretz F, Dukes O. Covariate adjustment in randomized controlled trials: General concepts and practical considerations. Clinical Trials. 2024;0(0). doi:10.1177/17407745241251568
- [14] Schuler, Megan S., and Sherri Rose. Targeted Maximum Likelihood Estimation for Causal Inference in Observational Studies. American Journal of Epidemiology (2017),185 (1): 65–73. <https://doi.org/10.1093/aje/kww165>.
- [15] Tyler J. VanderWeele, Peng Ding. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med.2017;167:268-274. <https://doi.org/10.7326/M16-2607>
- [16] Dang LE, Gruber S, Lee H, Dahabreh IJ, Stuart EA, Williamson BD, Wyss R, Díaz I, Ghosh D, Kiciman E, Alemayehu D, Hoffman KL, Vossen CY, Huml RA, Ravn H, Kvist K, Pratley R, Shih MC, Pennello G, Martin D, Waddy SP, Barr CE, Akacha M, Buse JB, van der Laan M, Petersen M. A causal roadmap for generating high-quality real-world evidence. J Clin Transl Sci. 2023 Sep 22;7(1):e212. doi: 10.1017/cts.2023.635.
- [17] Hampson, L. V., Chu, J., Zia, A., Zhang, J., Hsu, W. C., Parzynski, C. S., ... Degtyarev, E. (2023). 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. <https://doi.org/10.1080/19466315.2023.2190931>
- [18] Gilbert PB, Fong Y, Hejazi NS, Kenny A, Huang Y, Carone M, Benkeser D, Follmann D. Four statistical frameworks for assessing an immune correlate of protection (surrogate endpoint) from a randomized, controlled, vaccine efficacy trial. Vaccine. 2024 Apr 2;42(9):2181-2190.
- [19] Vansteelandt S, Linder M, Vandenberghe S, Steen J, Madsen J. Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding. Stat Med. 2019 Oct 30;38(24):4828-4840. doi: 10.1002/sim.8336. Epub 2019 Aug 14.

**BACK -UP**

# Causal Inference?

- **Causal inference** is a discipline within statistics which aims to evaluate the **causal effect of treatment** (intervention) in presence of potential **confounders** while being **explicit on required assumptions**
- **Counterfactual** (or potential) outcome framework<sup>[1]</sup> to define the estimand of interest, and hence compare treated and untreated *populations*
- Flexible, and in principle not bound by specific models, not limited by data source (e.g. RCT, RWE) <sup>[16]</sup>



<sup>1</sup> Adapted from Fig. 1.1 from Hernan & Robins (2024) *What If.* <sup>[1]</sup>

# Relevant application areas

In line with **estimand framework** of ECH E9 (R1) <sup>[3-4]</sup>, following the principles of *trial objective - estimand - estimator - estimate* and *sensitivity analyses*, causal inference methodology explicitly specifies the causal **estimand in counterfactual outcomes**

## RCT data

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- ❑ **Adjusting for baseline covariates** <sup>[3,12-14]</sup>
- ❑ **Sensitivity** analysis<sup>[15]</sup>

## Observational data

(RWE, registry...)

- ❑ Analyzing **non-randomized or OL trials**: LTE, registries, RWE DB
- ❑ **Augmenting** single-arm trials (SAT) and RCT with external control data<sup>[17]</sup>
- ❑ Generalizing RCT results with RWE<sup>[14]</sup>
- ❑ Quantitative bias analysis and sensitivity analyses<sup>[12,15]</sup>

## Biomarker data

Exposure-Response  
Surrogate Markers

- ❑ Addressing potential bias in Exposure-Response evaluations <sup>[18]</sup>
- ❑ Proportion of treatment effect mediated through the biomarkers or other mediators <sup>[19]</sup>