An Introduction to the Estimand and Target Trial Emulation (TTE) Frameworks Q&A 22 April 2025

Link: At the Intersection of Estimands and Target Trial Emulation (TTE) for RWE

Answered Live (Edited)

1. **To Lauren: You mentioned that intercurrent events will be a topic of a webinar. Is this why intercurrent events were not shown under attributes of the estimand framework?**

Lauren: Good question! The different strategies for intercurrent events will change the estimand attributes in different ways. For example, the composite variable strategy changes the variable/endpoint attribute. The hypothetical strategy changes the treatment strategy. Principal stratification changes the target population. On treatment changes the treatment strategy and the follow-up period. Rather than being a separate attribute, I consider the intercurrent events to change the specified attributes in different ways.

Rachele: Lauren's points are salient, especially how decisions to monitor intercurrent events affect composite endpoints, such as those developed or chosen for consideration within the estimand framework. Indeed, five key attributes are typically considered: treatment, population, outcome variable, population-level summary, and handling intercurrent events. The emphasis here, however, is on how one 'handles' intercurrent events within the framework (i.e. presenting or treating intercurrent events as a separate or unspecified attribute). This has been discussed in the community as an emerging best practice, through a scientific and data transparency lens, within the estimand framework.

Juanjo: I agree with Lauren. In some cases, the attributes of the estimand can be used to implement the strategies chosen to deal with intercurrent events. While technically the intercurrent events and the handling strategies were not originally proposed to be an attribute of the estimand, in practice it's helpful to present them together with the attributes for the sake of clarity and transparency. Otherwise, readers have to 'infer' from the attributes the identified intercurrent events and the strategies selected to deal with them.

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2. Are there any methods for causal inference for adverse events and drug exposures in non-interventional studies?

Lauren: Great question! You can apply any of the proposed frameworks to answer these questions. For example, if you want to study adverse events, then you can define an estimand where the variable/endpoint/outcome is the adverse event/s of interest. If you are interested in drug exposures in non-interventional studies, then you can define an estimand where the treatment strategy involves exposure to that drug. We just need to be specific about the treatment strategy of interest (e.g. is it receiving at least one prescription for the drug, is it staying on the drug for a certain period, is it receiving a certain dose of drug, etc.). After defining the estimand for your question of interest, you can follow the remaining steps recommended for TTE, ICH E9(R1) or the Causal Roadmap to design your study.

Rachele: Just about any causal inference method or framework can be applied via non-interventional studies to evaluate causal mechanisms behind adverse events and drug exposures, so long as the adverse event/s of interest is/are specified in the study protocol. It will be important, however, to clarify and select appropriate comparator groups and conduct power calculations to achieve an appropriate effect size within your observational sample. The causal roadmap, for example, offers a structured way of doing this to obtain high-quality estimates of causal effects, as it requires studies to define or prespecify an observational dataset/s and assess the identifiability of the causal estimand from that observed data.

Juanjo: In the EU, it is not uncommon for the Pharmacovigilance Risk Assessment Committee (PRAC) to require a post-authorisation safety study (PASS) to better understand the potential risk of serious adverse events associated with exposure to medicines. Many of these studies are non-interventional and aim to compare the risk in the exposed compared to the unexposed. The frameworks Lauren mentioned help increase the causal interpretation of the results from such studies.

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Not Answered Live

3. Meta-analysis is an essential tool for analysing a set of very similar observational studies. Will using the same estimands across studies conducted by research centres be challenging?

Tuhin (**PHUSE webinar planning team**): Yes, using identical estimands across observational studies is highly challenging due to between-study heterogeneity in populations, outcome definitions, confounder adjustment, and intercurrent-event handling. Prospective harmonisation via the ICH E9(R1) estimand framework, which standardises population, endpoint, intercurrent-event strategies, and summary measures, can mitigate these challenges.

Rachele: This is an excellent point and question. While meta-analyses of observational studies are considered a strong form of RWE, applying the same estimands across multiple studies conducted unharmoniously and across heterogenous settings would be challenging. That is due to the likelihood of significant variation in study protocols used, population-level variables, the likelihood of specific intercurrent events, etc. However, meta-analyses are helpful to inform the development of new study protocols seeking to apply a causal inference framework to address a research or regulatory question focused on a given estimand or target outcome.

Lauren: Using the same estimands across studies conducted by different research centres is challenging. If different studies target different estimands, then it is not easy to define what causal estimand would be the target of a traditional meta-analysis based on those studies. Definition of a highly specific estimand (based on ICH E9(R1), TTE, or other frameworks) can be helpful for several reasons. First, if individual-level data on the same covariates, exposures and outcomes are available from the potential studies to be meta-analysed, then the estimand for the meta-analysis can be specified and directly targeted (see, for example, Dahabreh et al., 2020). Second, if each study that is a potential candidate for a meta-analysis specifies an estimand in a systematic fashion, it may help researchers decide which studies targeted similar enough estimands to consider collectively analysing their results (see, for example, Schnitzer et al., 2016). Third, estimand specification can help researchers understand reasons for heterogeneity in effects estimated in different studies and help investigators define an estimand in a new study based on whether they aim to confirm the results of the original study or provide evidence for a new question (e.g. the effect on a new target population).

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References

Dahabreh IJ, Petito LC, Robertson, SE, Hernán MA, Steingrimsson, JA. (2020). Toward Causally Interpretable Meta-analysis: Transporting Inferences from Multiple Randomized Trials to a New Target Population. Epidemiology 31(3): 334–344. DOI: 10.1097/EDE.0000000000001177

Schnitzer M, Steele R, Bally M, Shrier I. (2016). A Causal Inference Approach to Network Meta-Analysis. Journal of Causal Inference. 4(2): 20160014. https://doi.org/10.1515/jci-2016-0014

Juanjo: It may be challenging, especially if the studies included in the meta-analysis were designed for slightly different purposes and/or by different teams. However, when running a meta-analysis, consideration to the estimands is really important as a source of between-study heterogeneity. This is because different estimands imply different research questions and therefore we can expect different answers, i.e. different treatment effects.

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4. How can we better reward careful attention to methods and estimands in observational studies?

Tuhin (PHUSE webinar planning team):
·Registered Reports: Peer review and in-principle acceptance before data collection reward robust protocols and explicit estimands over 'positive' findings.
·Open Science Badges: Visible recognition for preregistration, data and materials sharing, and transparent methods incentivises careful planning and reporting.
·Funder & Institutional Mandates: Tie grant funding, promotion, and awards to prespecified analytic plans, clear estimand frameworks, and reproducibility standards to embed methodological rigour into career incentives.

Rachele: Incentives can certainly be built within the scientific community to ensure and reward careful attention to methods and estimands in observational studies. This can be in the form of regulatory guidance acknowledging the need for such careful attention and building protected time and space with regulators and other RWE end users for it to be given on a routine or required basis.

Lauren: I think that encouraging careful attention to methods and estimands in observational studies will necessitate a combination of reporting requirements (for example by journals and funding agencies) and ongoing training of investigators. I also like Tuhin's suggestions.

Juanjo: Consideration to estimands in non-interventional studies is becoming increasingly part of regulatory guidance. And adherence to guidance increases the chance of regulatory acceptance. Hopefully this will help embrace these methodologies.