

Enhancing Pharmacometric Analyses with Estimand framework and Causal inference

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Motivation / Background

- We aim at enhancing the strength of claims that can be made based on pharmacometric analyses by relating them to the estimand framework and causal Inference.
- The ICH E9 (R1) guidance [1] and the related estimand framework [2] propose to clearly define and separate the clinical question of interest formulated as estimand from the estimation method. With that it becomes important to assess the validity of the estimation method and the assumptions that must be made.
- When going beyond intention to treat analyses that can rely on randomization, causal inference [3] is usually used to discuss the validity of estimation methods for the estimand of interest.
- The handling of inter-current events is of particular importance, since these events that occur post-randomization may affect the estimand of interest and consequently a valid estimation approach(es).
- In pharmacometrics, mixed effects models are routinely used to analyze longitudinal clinical trial data.
- Pharmacometrics modelling is lacking a formal framework to discuss assumptions, and it is rarely discussed as method for causal inference.

Methods and Settings

- We position non-linear mixed effects modeling and simulation (NLME M&S) in the context of causal inference as standardization method for longitudinal data in presence of confounders [4-7].
- Standardization is a well-known method in causal inference to correct for confounding by analyzing and combining results from groups of similar patients.
- Via a simulation study we evaluate the potential and limitations of NLME M&S to correct for confounding that may occur as result of post-randomization intercurrent events (IE).
- The focus is on studies in which intercurrent events related to either efficacy or tolerability may lead to deviations from the assigned treatment schedule, and on hypothetical estimands of the efficacy at the end of the trial assuming adherence to a given treatment regimen.
- Assumptions are visualized in a causal diagram (DAG, direct acyclic graph).
- From the causal diagram, conditional independence assumptions are summarized either adjusting on the individual parameters or on earlier outcomes. With either of the conditional independency assumptions fulfilled, unbiased estimates can be obtained.
- Simulation-estimation illustrates the appropriateness and robustness of NLME M&S to estimate the hypothetical estimands

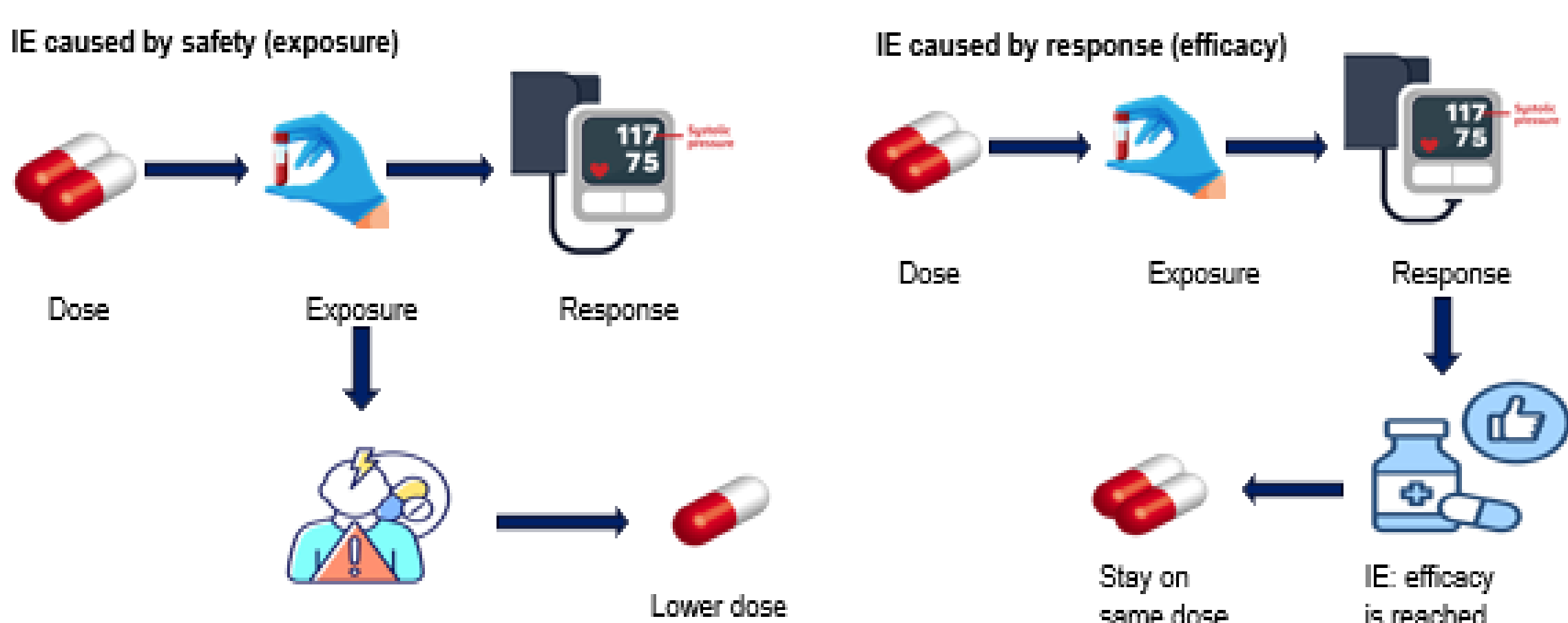


Figure 1: Sometimes we need to go beyond ITT using randomization: Trial that starts with a high dose. Patients may end up lowering dose (=intercurrent event) due to off-target tolerability. One question of interest: What would have been efficacy or safety, if patients would have started at lower dose?

Summary & Conclusion

- The estimand framework may be used to express the objective of pharmacometric analyses to clearly distinguish between the quantity to be estimated, i.e. the estimand (in line with the clinical question of interest) and the estimation method.
- Causal inference approach(es) are then used to discuss the validity of pharmacometrics (NLME) estimation methods for the estimand of interest.
- Conditioning/Adjusting on individual parameters (random effects) can correct for confounding in settings explored, corresponds to PMX NLME modeling and simulation.
- Using longitudinal data and introducing pharmacokinetics (PK) as mediator helps to correct for confounding.

Simulation set-up

- Phase 2b study of drug candidate for patients with high blood pressure:
- 7 dose levels (0, 25, 50, 100, 200, 400, 800mg)
 - 3 treatment arms, randomized starting dose level 2, 3, or 6
 - Individual up-titration until desired response is reached, except
 - Safety event → reduce dose level by 1
 - Completion of 5 treatment cycles

Steps to define a hypothetical estimand

Step 1: Defining Hypothetical estimands of interest: e.g., start at dose level 2 and escalate at each dose up to the highest dose level.

Step 2: Develop a DAG to represent the assumptions made

DAG, visualizes which factors affect response and helps to discuss data-generation process:

- Treatment confounding feedback because R_1 will determine D_2 , and
- Subsequent responses, R_1 and R_2 , are correlated due to their dependence on individual characteristics θ , e.g., baseline renal impairment or individual parameters.

Step 3: Chose approach to estimate estimand, eg “standardization”

Standardization for adjustment:

- Stratifying by individual characteristics θ ,
- Estimate the $D_2 \rightarrow R_2$ relationship in each group separately,
- Then average over the different strata

Step 4: PKPD model to estimate the estimand of interest via standardization

$$\begin{aligned} P(R_2^{D_2=d_2} = r_2) &= \sum_{\phi} (R_2^{D_2=d_2} = r_2 | \phi = \phi) * P(\phi = \phi) \\ &= \sum_{\phi} (R_2^{D_2=d_2} = r_2 | D_2 = d_2, \phi = \phi) * P(\phi = \phi) \\ &= \sum_{\phi} \underbrace{P(R_2 = r_2 | D_2 = d_2, \phi = \phi)}_{\text{Conditional outcome model as a function of dose and individual characteristics}} * \underbrace{P(\phi = \phi)}_{\text{Distribution of individual characteristics}} \end{aligned}$$

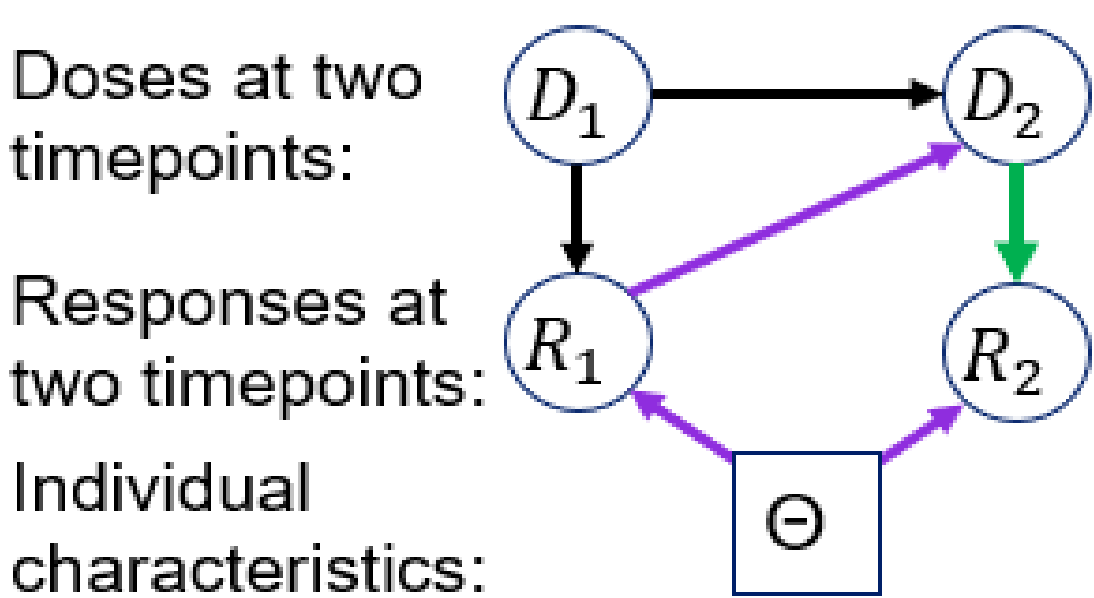


Figure 2: Simple DAG, Decision on D_2 is based on R_1

- A typical pharmacometrics NLME model estimates these terms!
- NLME modeling & simulation is a special implementation of standardization!

NLME M&S can provide unbiased estimates in many settings

Intercurrent Event	Efficacy data	Unbiased estimate
Exposure ¹ (safety)	Rich	Yes!
	At end of study	Yes!
Efficacy	Rich	Yes!
	At end of study (Cross-sectional)	No → unobserved confounding, diagnostics to detect inappropriate adjustment

¹ Exposure is a measure of drug concentration, usually in plasma

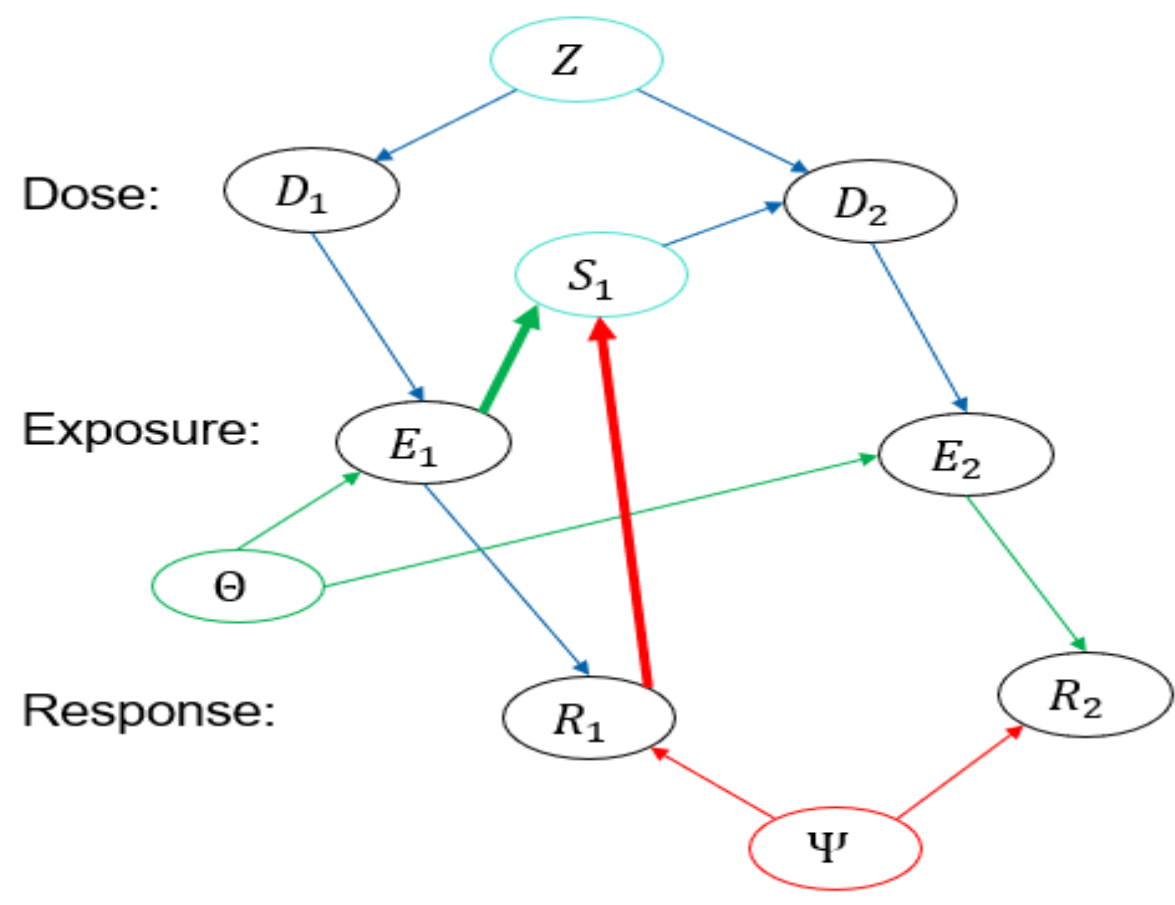


Figure 3: More complex DAG where exposure induces tolerability issues. Z denotes Randomization, S refers to an IE

References

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