Estimands in pharmacometrics – being precise about what we estimate

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Summary

- Precisely defining what we intend to estimate is important for anyone estimating (including pharmacometricians)

- The ICH E9 addendum on estimands provides a useful framework for doing this

- Case Example: a proof-of-concept study with missed doses due to the COVID pandemic

WHAT before HOW

ICH E9 addendum proposes a new framework to define estimands

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

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- Estimand = What to estimate

- Emphasizes "what to estimate" before "how to estimate"

- Focus of ICH E9 addendum on treatment effect estimates in confirmatory trials

- Being clear about what to estimate is also relevant for pharmacometricians

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The five attributes to specify an estimand

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

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- Treatment(s)
- Population
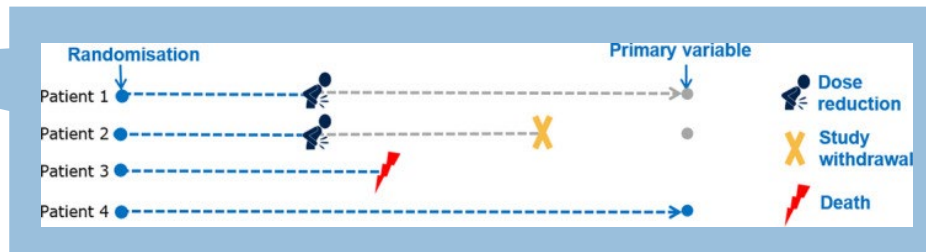- Variable
- Strategy to handle intercurrent events not already covered in other attributes
- Population-level summary

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Intercurrent events affect interpretation or existence of measurements of interest

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

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The strategies to handle intercurrent events

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

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- Treatment policy strategy
  = regardless of whether IE occurred
- Hypothetical strategies
  = if IE had not occurred
- While on treatment strategies
- Composite variable strategies
- Principal stratum strategies

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What's in it for the pharmacometrician?

- More clarity on what we are estimating

- Common language with statisticians and clinicians

- Facilitates discussion about why estimates are different (is the WHAT or the HOW different?)

- Pharmacometric methods might offer ways of estimating (=how) for estimands (=what) that are hard to estimate otherwise

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Case example: a PoC study with potentially missed doses

- This is based on theoretical considerations around a PoC study in diabetic macular edema
- Three monthly doses (injections) scheduled. Some doses might be missed due to unforeseen circumstances not related to patient health or drug response (e.g. a global pandemic)

Scheduled dosing

Month 0 | Month 1 | Month 2 | Month 3 Readout
Time

Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient ...

Actual / observed dosing

Month 0 | Month 1 | Month 2 | Month 3 Readout
Time

Patient 1 — Doses as scheduled
Patient 2 — Doses as scheduled
Patient 3 — Missed last dose
Patient 4 — Missed 2/3 doses
Patient 5 — Missed intermediate dose
Patient ...
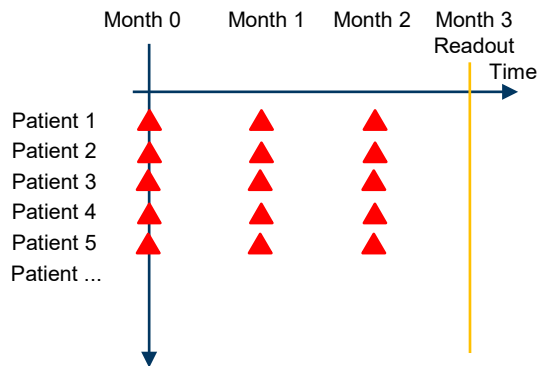
▲ = dose   △ = missed dose

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What are treatment policy vs hypothetical estimands?

- Consider the intercurrent event of missed doses (could be missing doses intermittently or discontinuing treatment at some timepoint)

- **Treatment policy estimand** is ...
  What is the effect of assigning treatment – regardless of whether doses were actually taken as scheduled or not.
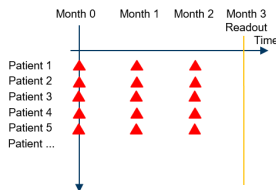
- **Hypothetical estimand** is ...
  What is the effect of the treatment – if it were taken according to the prescribed schedule.

Why would you use treatment policy vs. hypothetical?

- Treatment policy allows a causal effect estimate without additional assumptions (if randomized and no missing data).
  - Note, that this is the causal effect of assigning the treatment, not of taking the treatment.

- Hypothetical to assess full potential of regimen
  - Here, the hypothetical situation without the intercurrent event (i.e. no missed doses due to the ongoing pandemic) is hopefully relevant for the later real world use case
  - One can argue that "what if doses were taken" is more relevant in a "learning" setting than in a "confirming" setting
  - → method effectiveness (Sheiner)

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Hypothetical estimand for the case example

Scheduled dosing

Actual / observed dosing

Patient 1	Doses as scheduled
Patient 2	Missed last dose
Patient 3	Missed 2/3 doses
Patient 4	Missed intermediate dose
Patient 5	
Patient ...	

Hypothetical response

control

active
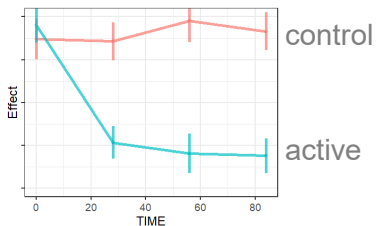
Observed response

control

active
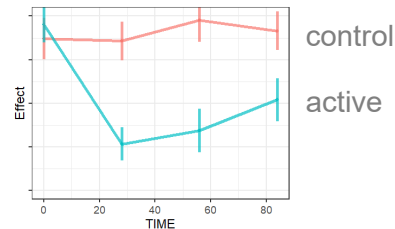
PMX analyses often target a hypothetical estimand

- Hypothetical is what we often do in PMX
  - **Estimate the model taking actual dosing into account (i.e. the dosing records)**
  - **Then simulate from population model with scheduled (hypothetical) dosing**

- Allows for extrapolation to different doses or regimens

- Here, the intercurrent event was independent of patient health / drug response. Otherwise, beware of confounding.

- To simulate treatment policy estimands, one needs to either
  - Simulate using actual dosing & posthoc estimates for observed subjects, or
  - Implement a dosing/compliance model

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References

- Akacha, M., Bartels, C., Bornkamp, B., Bretz, F., Coello, N., Dumortier, T., Looby, M., Sander, O., Schmidli, H., Steimer, J.-L., Vong, C. (2021). Estimands—What they are and why they are important for pharmacometricians. CPT: Pharmacometrics & Systems Pharmacology, 10(4), 279.

- ICH E9 addendum on estimands [link]. 2020.

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Thank you