Estimation methods for estimands using the treatment policy strategy

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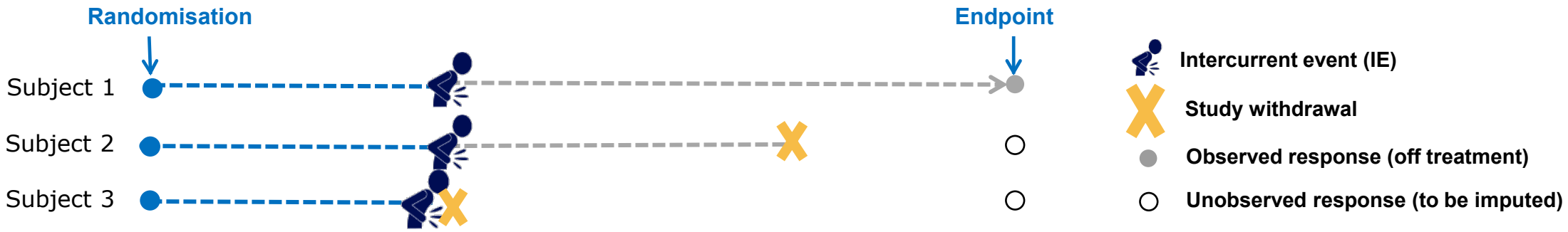
Adequate handling of missing data essential for estimation of treatment policy estimand



- Data after the intercurrent event is relevant for a treatment policy estimand
- Subjects withdrawing from the study prior to the collection of the endpoint create missing data
  - Even with best efforts, missing data are inevitable in most trials, particularly post-IE
- Standard MMRM models often do not adequately handle missing data
- Common models for imputing missing data in treatment policy setting
  - Reference-based multiple imputation, e.g., jump-to-reference, copy increments in reference, etc.
  - “Retrieved Dropout”

Imputation models for treatment policy estimands differ in clinical assumptions and statistical properties

	Retrieved dropout models	Reference-based multiple imputation
Assumptions	• Missing data after IE similar to observed data after IE within same study arm	• Missing data after IE similar to observed data from the reference group • Requires choice of clinical assumptions and their justification
Pros	• Negligible bias in realistic scenarios[1,2] • No assumptions about treatment effect	• Controls type I error rate[1] • No relevant standard error inflation[1]

Cons	• Issues when insufficient data after IE:
	  • inflated standard errors
	  • power loss
	  • difficult/impossible to fit
		• Assumptions about treatment effect for subjects with missing post-IE data
		• Deviations could cause bias

[1] Bell et al. https://arxiv.org/abs/2402.12850. [2] Drury et al. https://arxiv.org/abs/2308.10857

Discussion questions

1. When estimating a (primary) estimand that adopts a treatment policy strategy, would regulators accept an analysis approach that imputes the missing values using a reference-based imputation method if the assumptions of the imputation approach can be clinically justified?
2. If it is unclear which assumptions are appropriate for the missing data imputation, which principles should guide the selection of the imputation model, e.g., type I error rate control, conservative bias for the treatment effect estimate (i.e., underestimate the treatment effect), bias-variance trade-off, clinical plausibility?
   - What is the priority order of the listed criteria?
   - Are there other important criteria which are not listed?

Thank you