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INSIGHTS · CLINICAL DEVELOPMENT

Estimands in practice: choosing intercurrent event strategies

Applying ICH E9(R1) from protocol design to analysis, with worked examples and estimation choices.

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THE FRAMEWORK

An estimand states precisely what treatment effect the trial will estimate

1 · TREATMENT

The treatment condition of interest and the comparator, including any background or rescue therapy.

2 · POPULATION

The patients targeted by the clinical question, defined by eligibility criteria.

3 · VARIABLE

The endpoint measured for each patient, e.g. change in HbA1c at week 26.

4 · INTERCURRENT EVENTS

How each post-randomisation event that affects interpretation is handled.

5 · SUMMARY MEASURE

The population-level comparison: mean difference, odds ratio, hazard ratio.

Intercurrent events (ICEs) occur after treatment starts and change either the interpretation or the existence of the outcome: treatment discontinuation, rescue medication, treatment switching, surgery, death.

Why it matters: ICH E9(R1) asks sponsors to align objectives, estimand, design, estimator and sensitivity analyses, so the handling of ICEs is a design decision, not a missing-data afterthought.

ICH E9(R1) STRATEGIES

Five strategies for handling intercurrent events

Strategy	Question it answers	Typical use	Data and assumptions
Treatment policy	Effect of assigning treatment, regardless of whether the ICE occurs	Discontinuation or rescue in confirmatory efficacy trials	Keep collecting outcomes after the ICE (retrieved dropouts)
Hypothetical	Effect in a scenario where the ICE would not occur	Rescue medication in symptomatic trials; pandemic disruptions	Unobserved outcomes modelled, e.g. MMRM or MI under MAR
Composite variable	The ICE becomes part of the outcome definition	Death or treatment failure counted as non-response	ICE must be clinically an unfavourable outcome
While on treatment	Effect up to the time of the ICE	Symptom relief, palliative care, short-term outcomes	Outcomes up to the ICE; interpret alongside time on treatment
Principal stratum	Effect in the subgroup in which the ICE would (not) occur	Vaccine effect on severity among those infected	Strata are not observed; strong, explicit assumptions needed

Different ICEs in the same trial can be handled with different strategies, for example treatment policy for rescue therapy and composite for death.

MAKING THE CHOICE

A practical workflow for choosing strategies

1. **Start from the clinical question** and the decision it informs: regulatory approval, HTA, labelling or prescribing.
2. **List the likely ICEs** by treatment arm, with expected frequency from earlier trials.
3. **Pick a strategy per ICE** with clinicians, regulatory and HTA colleagues; document the reasoning.
4. **Design data collection to match**: treatment policy needs follow-up after discontinuation.
5. **Choose the estimator and its assumptions**, then sensitivity analyses that stress those assumptions.
6. **Write it into the protocol and SAP**, using the five attributes explicitly.

Questions to test each choice

- Is the scenario clinically meaningful? (hypothetical)
- Can we retain patients after the ICE? (treatment policy)
- Is the ICE truly a bad outcome? (composite)
- Do different stakeholders need different estimands?

Tip: agree the primary estimand with regulators at the end-of-phase 2 or scientific advice meeting; HTA bodies often prefer treatment policy.

APPLICATIONS

Worked examples across therapeutic areas

TYPE 2 DIABETES · HBA1C AT WEEK 26

ICE: rescue medication

Treatment policy estimates the effect as used in practice (rescue allowed), estimated with retrieved-dropout or reference-based imputation. **Hypothetical** estimates the effect without rescue, often via MMRM under MAR, and is common as a supplementary estimand.

ONCOLOGY · OVERALL SURVIVAL

ICE: crossover or subsequent therapy

Treatment policy is the usual primary estimand. HTA bodies may request a **hypothetical** estimand ("no crossover"), estimated with RPSFTM, IPCW or two-stage methods.

DEPRESSION · RESPONSE AT WEEK 8

ICE: discontinuation for adverse events

A **composite** strategy counts discontinuation for lack of efficacy or tolerability as non-response, reflecting benefit and tolerability together.

VACCINES · DISEASE SEVERITY

ICE: infection itself

Severity exists only in infected people, so a **principal stratum** estimand targets those who would be infected under either vaccine or placebo, with explicit assumptions.

Align estimators and sensitivity analyses with the estimand

ESTIMATORS

- **Treatment policy:** observed post-ICE data; retrieved-dropout MI; jump-to-reference or copy-reference MI
- **Hypothetical:** MMRM or MI under MAR; IPW; tipping-point analysis for MNAR
- **Composite:** responder or rank-based analyses
- **Sensitivity analyses** vary assumptions for the same estimand; **supplementary analyses** target a different estimand

REFERENCES

1. ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials. Step 4, November 2019.
2. Kahan BC, Hindley J, Edwards M, et al. The estimands framework: a primer on the ICH E9(R1) addendum. BMJ 2024;384:e076316.
3. Ratitch B, Bell J, Mallinckrodt C, et al. Choosing estimands in clinical trials: putting the ICH E9(R1) into practice. Ther Innov Regul Sci 2020;54:324–341.
4. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: reference-based multiple imputation. J Biopharm Stat 2013;23:1352–1371.
5. Mallinckrodt C, Molenberghs G, Lipkovich I, Ratitch B. Estimands, Estimators and Sensitivity Analysis in Clinical Trials. CRC Press, 2020.