Estimands in klinischen Studien: was ist das und geht mich das was an?

CTU Lecture 03.04.2018

Sven Trelle
ICH E9(R1) – Statistical Principles for Clinical Trials
   — "Addendum … to focus on statistical principles related to estimands and sensitivity analysis."

ICH E6(R2) – GCP
   — Not mentioned at all

MEDLINE search "estimand*" → 112 hits (1998-2018)
   — Special issue in *Pharmaceutical Statistics*
   — Debate in *Statistics in Medicine*
Estimands are about the scientific questions we ask in a randomized clinical trial.
Why randomized-controlled trials

To enable causal statements about the effect(s) of health-care interventions
Causality!
Causality!
But which effects?
Context

Missing data, non-adherence, per-protocol population, lost to follow-up, cross-over, intercurrent events, intention-to-treat principle, post-randomization confounding
Context

? Missing data, non-adherence, per-protocol population, lost to follow-up, cross-over, intercurrent events, intention-to-treat principle, post-randomization confounding

💡 Quality-by-Design

↔ Reality

- Long-term trials
- Complexity
A hypothetical trial

P Patients with acute (unspecific) low back pain

I Physiotherapy: 6 weeks, 3 guided sessions per week, home exercises [rescue: opioid]

C Pain killer: 6 weeks, 2 x day [rescue: opioid]

O Pain at 6 weeks (Visual Analogue Scale), development of pain (daily with diary)
Participants

1. Fully adherent
2. Fully adherent for 3 weeks, than stopped
3. Completed 6 weeks but took only one dose/day
4. Completed 6 weeks but no home exercises
5. Switched to pain killer after 1st physiotherapy session

…
Patient flow
Classical approach

Intention-to-treat analysis (ITT)

— Analyse patients in the group they were randomized regardless of protocol deviations (including cross-overs)

→ Maintains randomization
Potential issues with ITT analysis

- May not answer/targeting the scientific question
- Postrandomization events may complicate interpretation of treatment effect
- Depending on type of analysis: potential selection bias
- More than one treatment effect can be described/estimated
The concept of estimands

Strategies for handling postrandomization events

Description of estimands
  — Participant population
  — Outcome(s)
  — How to handle postrandomization (intercurrent) events
  — Effect measure (population level; comparison)
Estimands

1. Treatment policy
2. Composite
3. Hypothetical
4. Principal stratum
5. While on treatment
Treatment policy example (ITT)

- **P**: All participants randomized
- **O**: Pain (VAS) at 6 weeks
- **E**: Not considered/taken into account
- **M**: Mean difference
2 Composite strategy

⚠️ Incorporate intercurrent event(s) in definition of outcome

Example ➔ Dichotomize pain into response/non-response
— Pain ↓ <50% OR
— Rescue medication OR
— Cross-over
Composite strategy example

P All participants randomized

O Pain ↓ >=50%, no rescue/cross-over, stop at 6 weeks

E Component of outcome

M Relative risk
3 Hypothetical strategy

⚠️ The treatment effect in a situation where the rescue, cross-over and stop had not been available

💡 By design often unethical
Hypothetical strategy example

P All participants randomized
O Pain (VAS) at 6 weeks
E Prohibit rescue/stop OR predict outcome data after intercurrent event (probably strong assumptions)
M Mean difference
4 Principal stratum

⚠️ Treatment effect in the (sub)group of participants where non-adherence and rescue/cross-over would not occur regardless of randomization

Example
— By design: run-in phase OR
— Subgroup identification by covariates
Principal stratum strategy example

- Participants randomized after completing an enrichment phase (e.g. placebo plus dummy physiotherapy)
- Pain (VAS) at 6 weeks
- Selected population (enrichment) plus covariate adjustment
- Mean difference
Adherence

Adherence very narrow: intake

Intervention might include stop or switches
5 While on treatment strategy

⚠️ Treatment effect before intercurrent event(s)

Example

— Use data only up to intercurrent event or end
— Pain diary e.g. repeated measures model
While on treatment strategy example

- **P**: Adherent patients up to rescue/cross-over or end
- **O**: Pain (VAS) at 6 weeks
- **E**: Subset of patients and data (assumptions/confounding!)
- **M**: Mean difference over all timepoints up to last observation
The protocol core
Structure and consistency

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit

Evidence

Need

Rationale

Background

Need

Rationale

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit

Need

Rationale

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit

Need

Rationale

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit

Need

Rationale

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit

Need

Rationale

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit

Need

Rationale

Aims

Outcome(s)

Assessment(s)

Analyses

Design

Eligibility

Interventions

Risk-benefit
Implications for planning

- Estimand of interest might determine design → teamwork
- Consistent protocol → teamwork
- Data to be collected at/after intercurrent event (motivation, reasons, covariates, …)
- Statistical methodology from causal modelling (observational data); naïve per-protocol/as-treated not appropriate
References