UNIVERSITÄT BERN

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

CTU Lecture 03.04.2018

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Mention

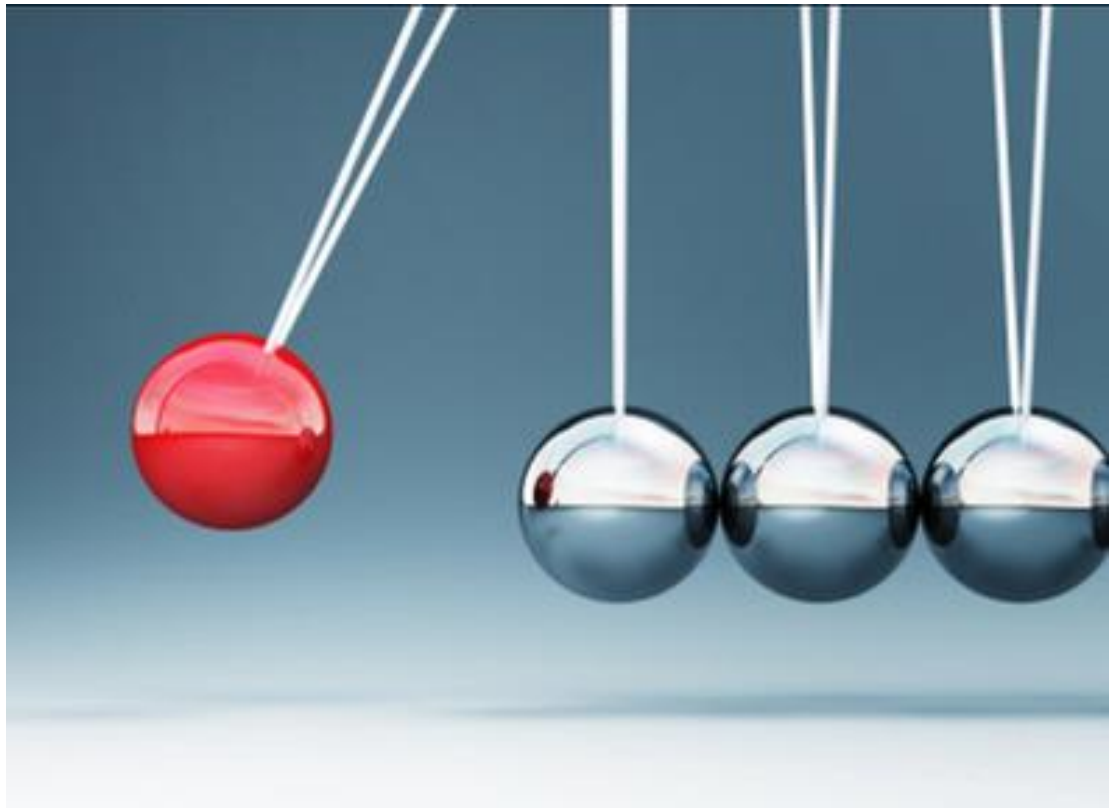
- ICH E9(R1) – Statistical Principl[illegible]or Clinical Trials
  - "Addendum … to focus on stat[illegible]al principles related to estimands and sensitivity analy[illegible]…"
- ICH E6(R2) – GCP
  - Not mentioned at all
- MEDLINE search "estimand*" → 112 hits (1998-2018)
  - Special issue in *Pharmaceutic[illegible]tistics*
  - 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

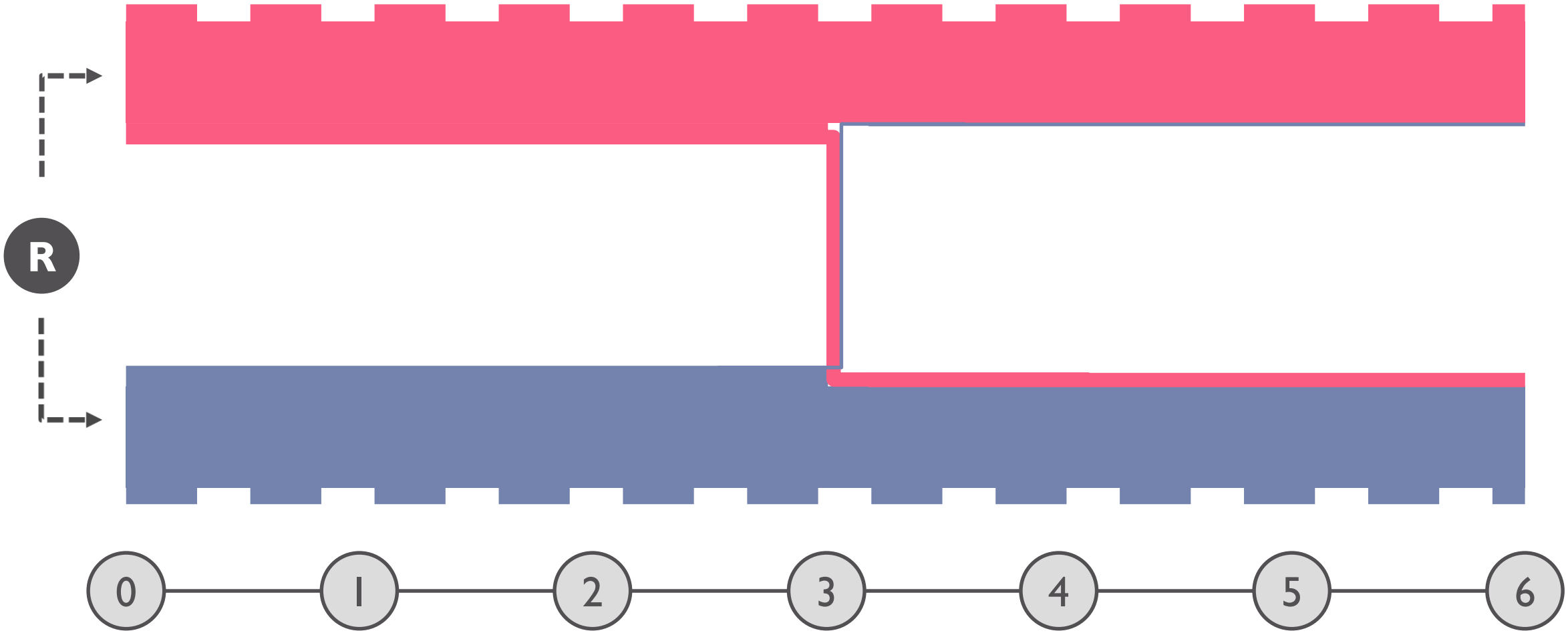
A hypothetical trial

- **P** Patients with acute (unspecific) low back pain
- **I** Physiotherapy: 6 weeks, 3 guided sessions per week, home exercises [rescue: opiod]
- **C** Pain killer: 6 weeks, 2 x day [rescue: opiod]
- **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
n. …

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 **p**opulation
  - **O**utcome(s)
  - How to handle postrandomization (intercurrent) **e**vents
  - Effect **m**easure (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

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

Adherence

- Adherence very narrow: intake
- Intervention might include stop or switches

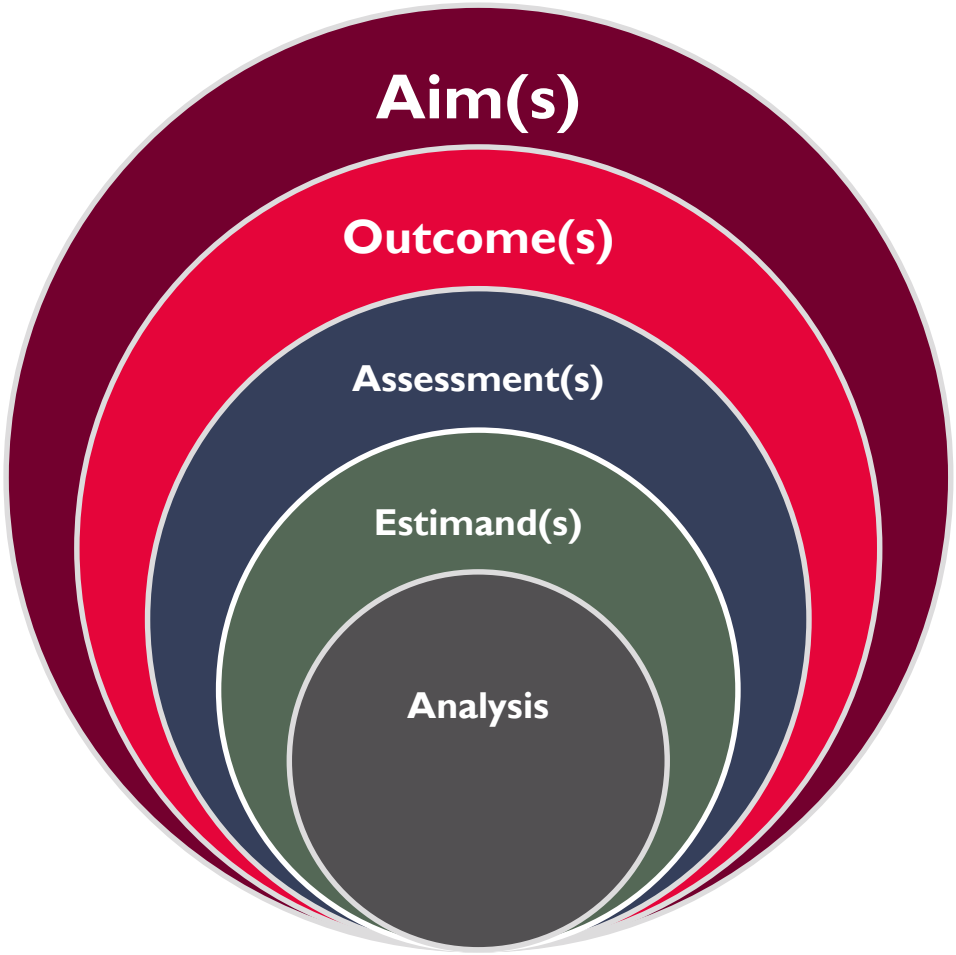
5 While on treatment strategy

- Treatment effect before intercurrent event(s)
- Example
  - Use data only up to intercurrent event or end
  - Pain diary e.g. repeated measures model

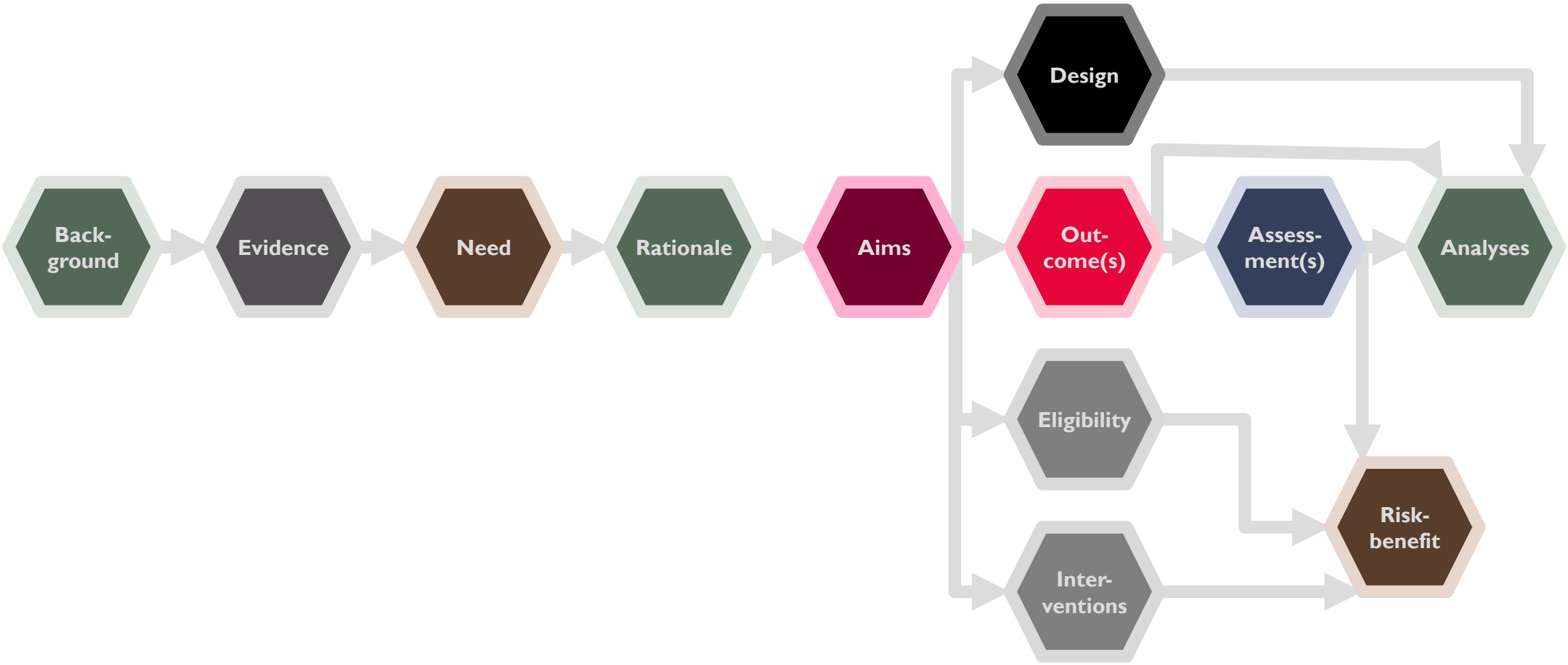
While on treatment strategy example

- **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



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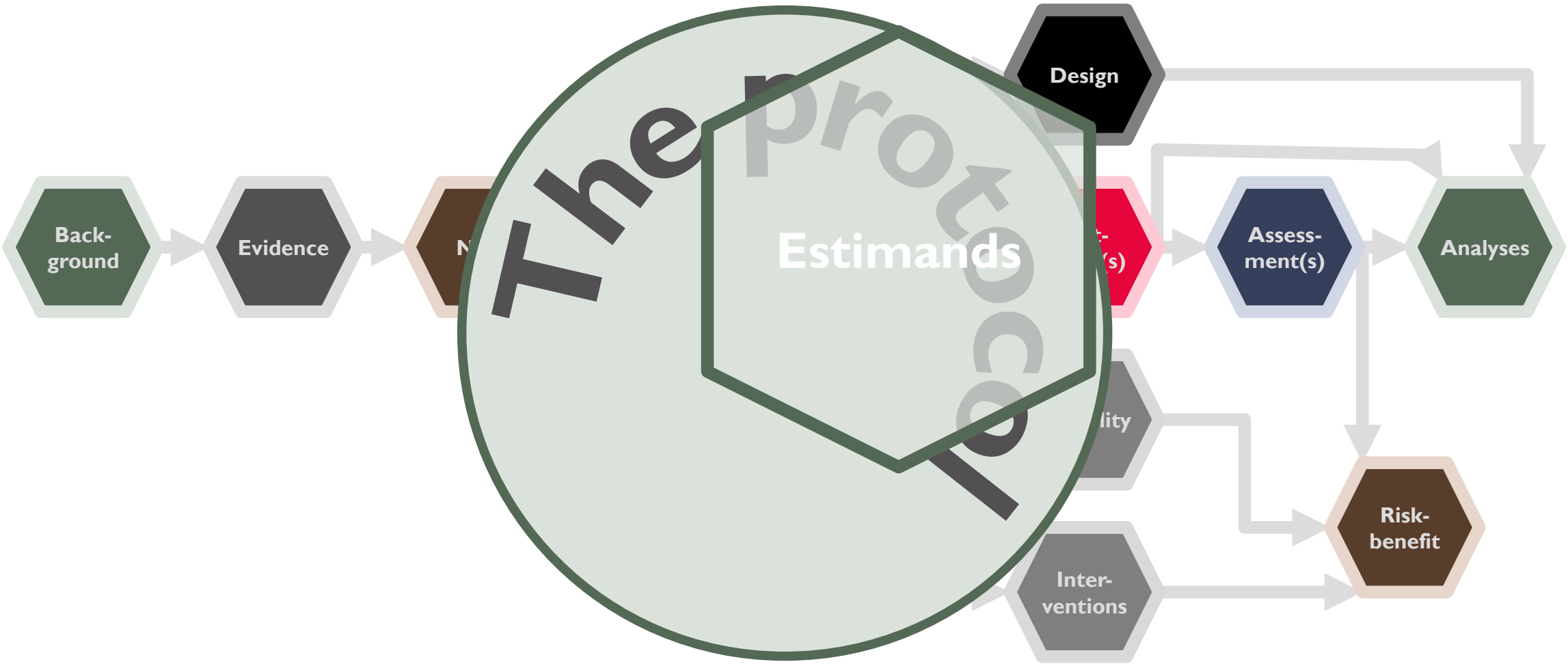

Implications for planning

- 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

- ICH Harmonised Guideline E9(R1). Estimands and Sensitivity Analysis in Clinical Trials. 2017. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf
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