Does the Level of Evidence depend on Randomization?

Ralf-Dieter Hilgers
Nicole Heussen, Diane Uschner

Department of Medical Statistics, RWTH Aachen University

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Study Design in Practice

- What the theory tells us:
  - no randomization procedure performs best with all criteria
- What applied scientist mostly feel:
  - scepticism to randomization
  - do not well understand randomization principle
  - select a procedure by opinion or software availability
- What the literature mirrors:
  - no training in randomization
  - no recommendation to give scientific arguments for the choice of randomization procedure, neither ICH Guidelines nor CONSORT
- What regulators want:
  - show impact of bias on the test decison (ICH E9)
  - analyses lead to consistent findings, e.g. thoughtfully constructed sensitivity analysis (ICH E9 (R1) Add)

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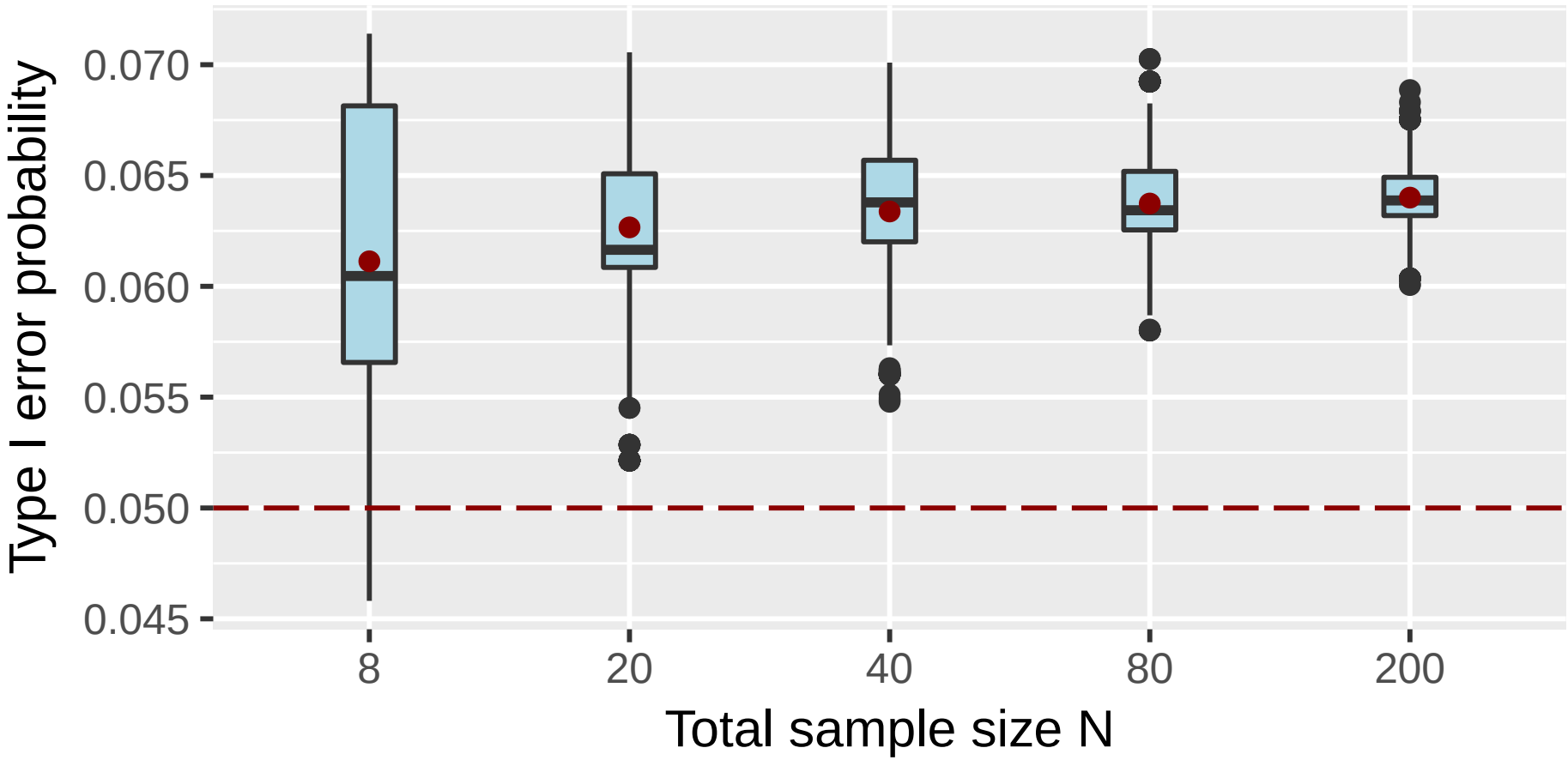
Problem with Randomization to avoid Bias

Randomzation Procedure: PBR(4), selection bias effect $\eta = 0.25 \times \delta$



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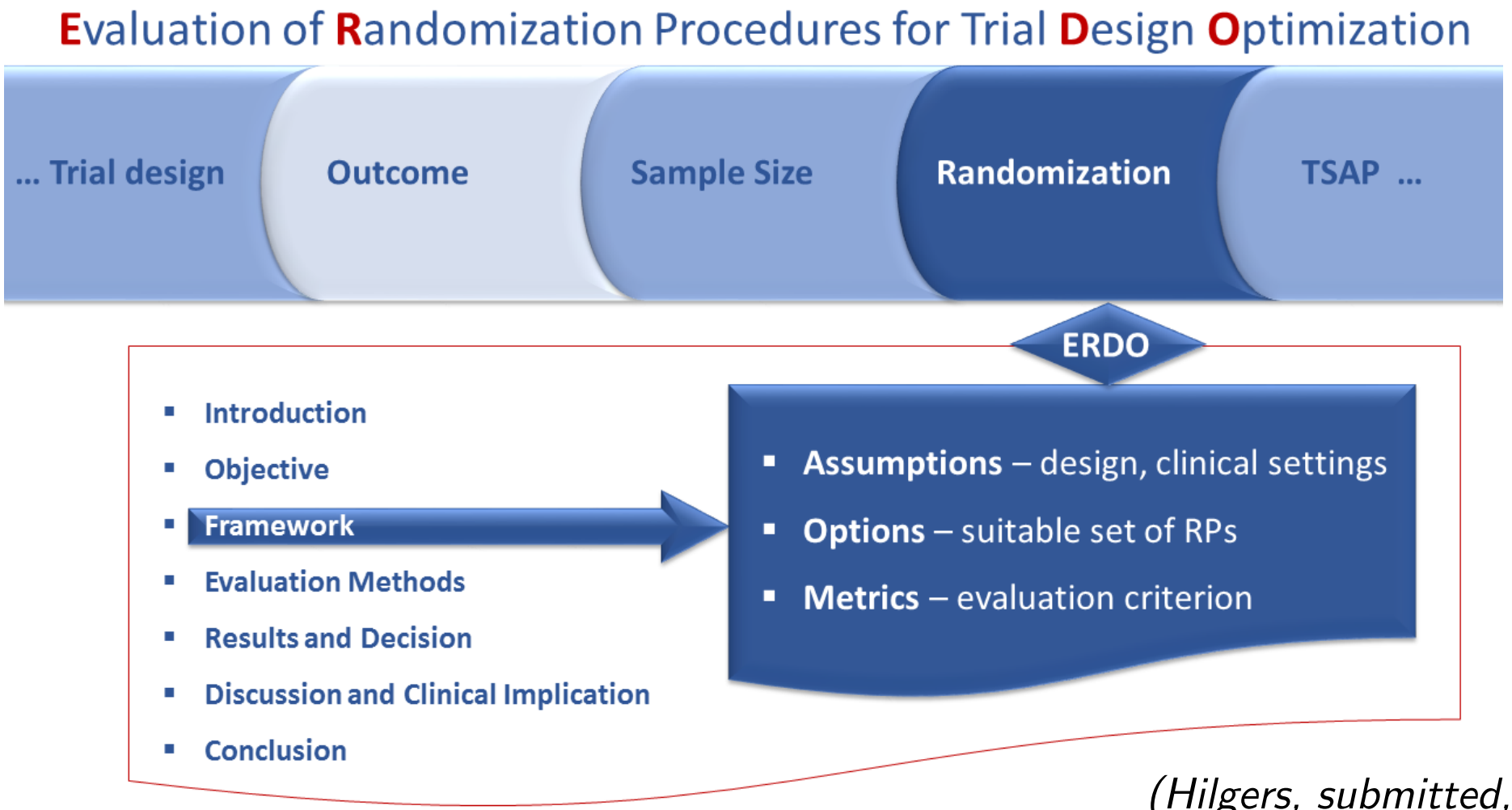
Recommended Assessment Procedures



(Hilgers, submitted, Benda, 2011)

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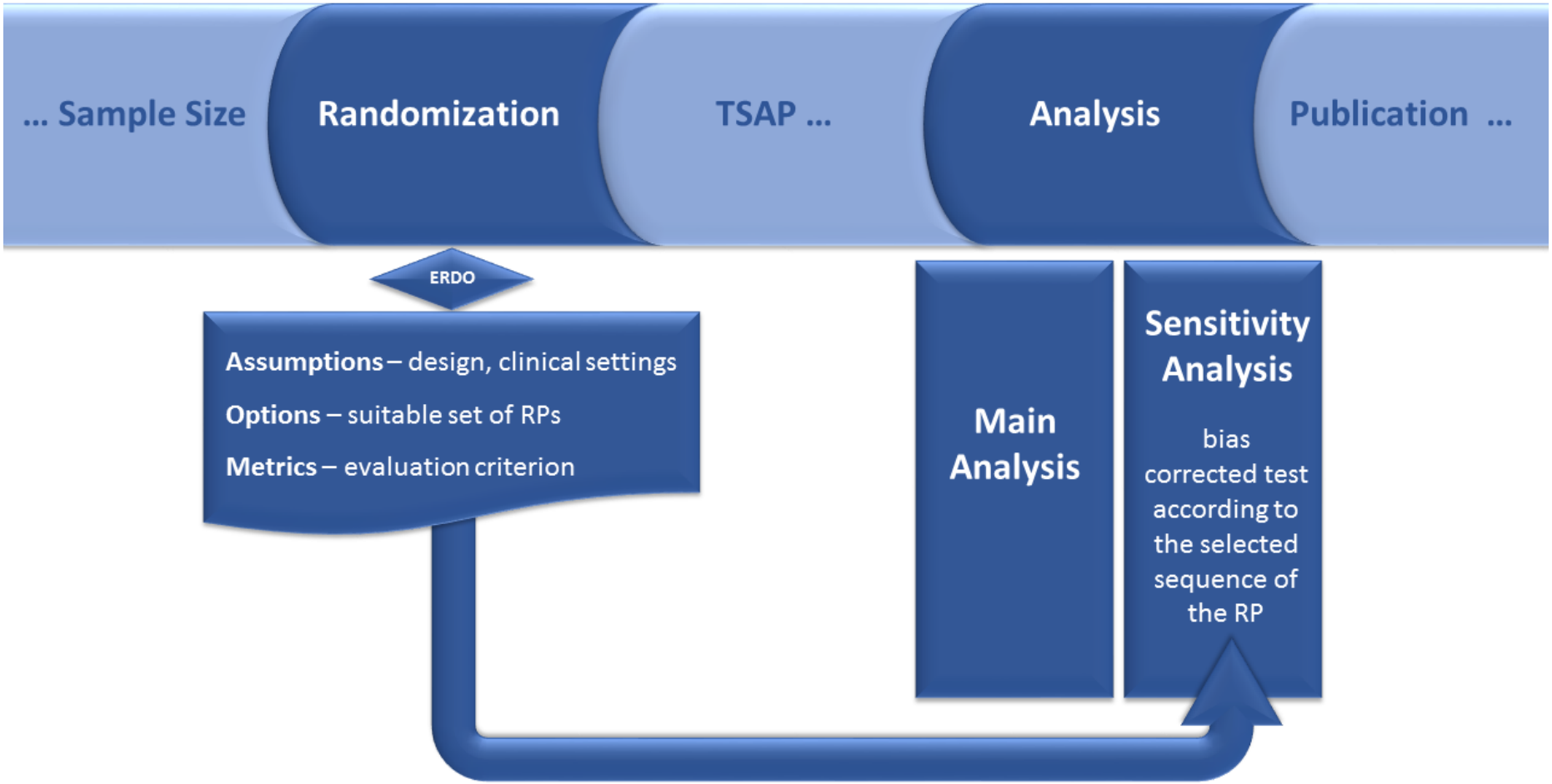
Recommended Analysis Procedure



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Developments

- treatment effect could be hidden by bias depending on randomization sequence *(Kennes 2011, Tamm 2011, Langer 2014)*
- *ERDO* framework for scientific evaluation of randomization procedures *(Hilgers, submitted)*
- *randomizeR* to assess randomization procedures *(Uschner 2017, accepted)*
- time to event model *(Rückbeil 2017, accepted)*
- understanding effects in multifactorial designs *(Tasche 2016)*
- bias corrected test *(Kennes 2015)*

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Conclusion

- Level of Evidence in terms of preserving the type I error probability is affected by selection and time trend bias
- the effect may be that conservative or anticonservative test decisions occure
- in the context of rare diseases or orphan drugs, this implies the risk to overlook an effective treatment

preserve the **Level of Evidence** with the . . .

- **proposed procedure (ERDO) and toolbox (randomizeR) to assess randomization procedures**
- **proposed sensitivity analysis procedure to reflect estimands in the presence of selection and time trend bias**

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