Integrated Design and Analysis of Clinical Trials in Small Population Group (The IDeAI Project)

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IDeAI - Objective

Integrated DEsign and AnaLysis of small population group trials aims to refine the statistical methodology for clinical trials in small population groups by strictly following the concept of an improved integration of design, conduct and analysis of clinical trials from various perspectives.

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EMA issues and interest - IDeAI project(s)

EMA interest	IDeAI - Workpackages
	WP3: Extrapolating Dose-Response Information (*Holger Dette*) WP 4: Adaptive Design Studies (*Franz König*)
	WP 9: Decision Analysis (*Carl Fredrik Burman*)
	WP 6: Design of Pharmacogenetic Trials (*Stephen Senn*)
	WP 7: Simulation of Clinical Trials (*Mats Karlsson*) WP 5: Optimal Design in Mixed Models (*France Mentré*)
	WP 10: Surrogate Endpoints (*Geert Molenberghs*) WP 2: Assessment of Randomization (*Ralf-Dieter Hilgers*)

EMA issues and interest - IDeAI project(s)

EMA interest	IDeAI - Workpackages
Extrapolation Standards of evidence	WP3: Extrapolating Dose-Response Information (*Holger Dette*) WP 4: Adaptive Design Studies (*Franz König*)
Data-driven decision-making	WP 9: Decision Analysis (*Carl Fredrik Burman*)
Understanding value of research	WP 6: Design of Pharmacogenetic Trials (*Stephen Senn*)
Multidisciplinary simulations	WP 7: Simulation of Clinical Trials (*Mats Karlsson*) WP 5: Optimal Design in Mixed Models (*France Mentré*)
Effects, bias randomisation	WP 10: Surrogate Endpoints (*Geert Molenberghs*) WP 2: Assessment of Randomization (*Ralf-Dieter Hilgers*)

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Randomization in Orphan Drug Approval

ICH E9: *The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or inference.*

- 21 out of 63 Orphan drug marketing authorizations involve open label studies (Joppi, 2013)
- no recommendation to give scientific arguments for selection of randomization procedure
- no uniform performance of randomization procedures

Assessment - Selection Bias

Table: Empirical type 1 error probability of a two sided t-test with $2n$; $\alpha = 0.05$, $\beta = 0.2$ and selection bias effect $\eta = \frac{\delta(2n)}{2}$

2n	$\delta(2n)$	CR	RAR	PBR(4)	BSD (2)
8	2.381	0.058	0.102	0.141	0.064
20	1.325	0.054	0.082	0.177	0.075
32	1.024	0.055	0.072	0.188	0.083
40	0.909	0.053	0.071	0.195	0.088

using R with 100 000 replications

Framework for Evaluation of Randomization Procedure

Objective . . . to select a randomization procedure with respect to the clinical study restrictions by showing the influence of bias on the study results

Assumptions . . . will focus on the magnitude of the selection bias effect η and the time trend θ based on specific clincal situation

Options . . . will take into account various randomization procedures

Metrics . . . will belong to the size of the test

Evaluation Methods / Software . . . will use the software tool randomizR and write a report on the findings

Decision . . . will decide on a suitable randomization procedure and the test to evaluate the data.

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Assessment - Comparison RAR and BSD(2) (N=12)

Figure: RAR

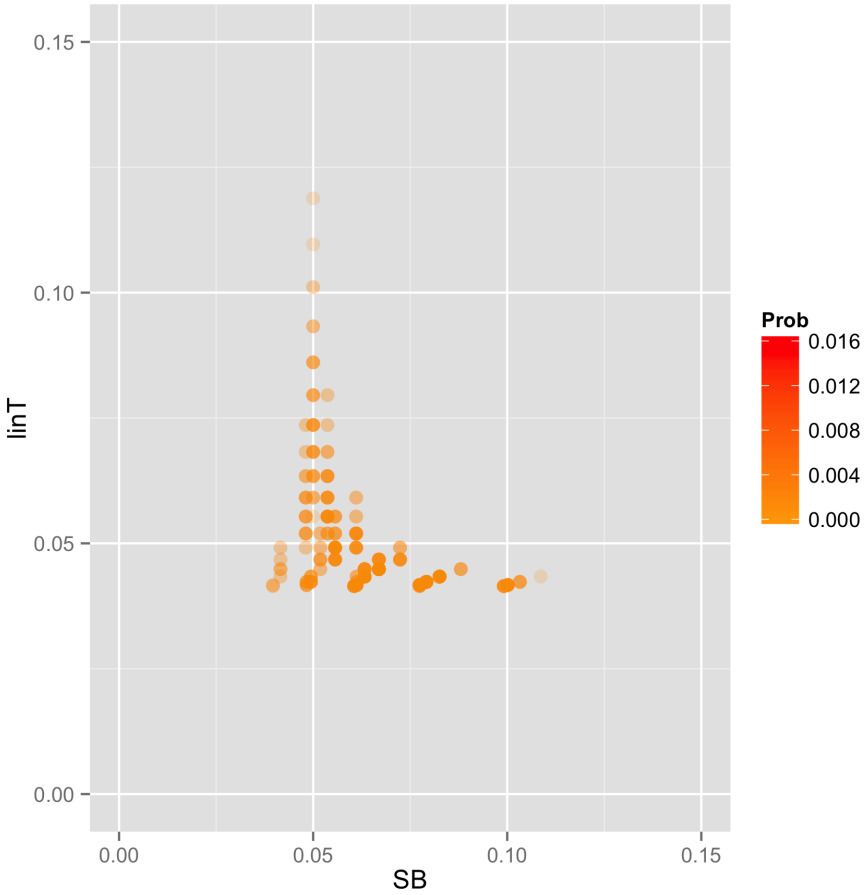
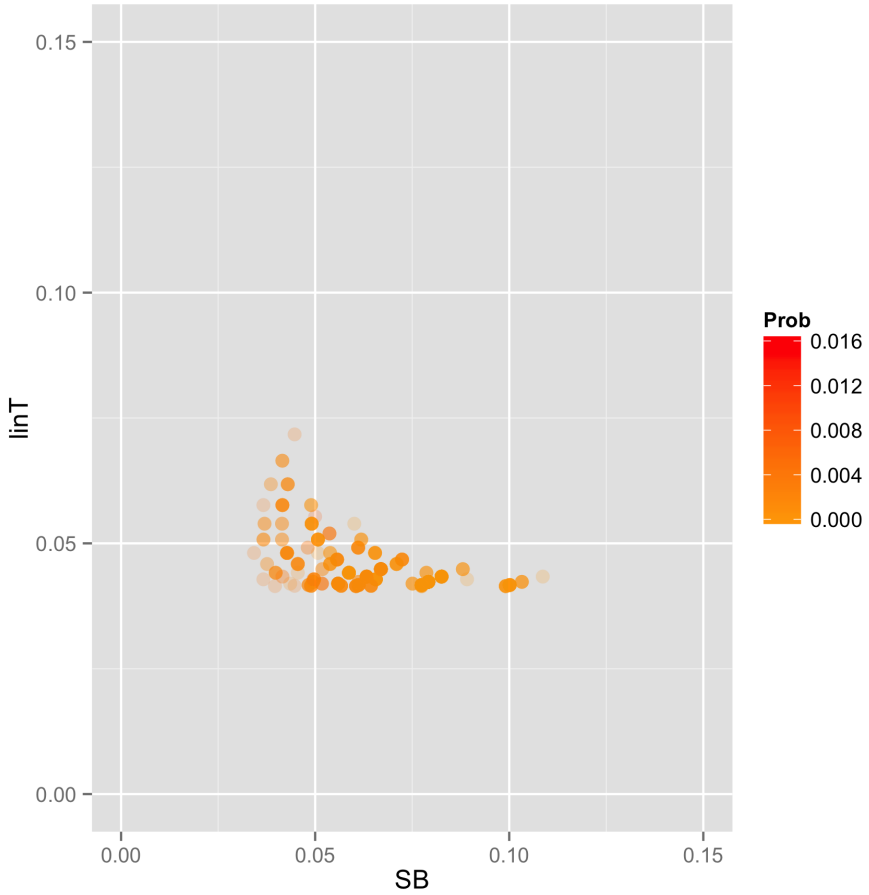


Figure: BSD(2)



setting: $n_A = n_B = 6, \eta = \frac{\delta(12)}{4} = 0.45, \lambda = \sigma = 1$

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Conclusion - WP2 Research

- understand that the treatment effect could be hidden by bias caused by the randomization procedure
- proposed a framework for scientific evaluation of randomization procedures with respect to bias for continuous and time to event data
- the evaluation should end up in a randomization report attached to the trial documents
- we released an R package *(randomizeR)* at CRAN as toolbox
- we are currently working on clear decision criteria within a comprehensive comparison study
- we published an (approximative) selection bias corrected test
- start working with randomization based inference, e.g. how to handle missing data, impact of selection bias and time trend

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