Does Randomization protect against bias? What can be done to improve the level of clinical evidence of effectiveness

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IDeAI - EU funded project

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.

IDeAI-Coordinator: Ralf-Dieter Hilgers

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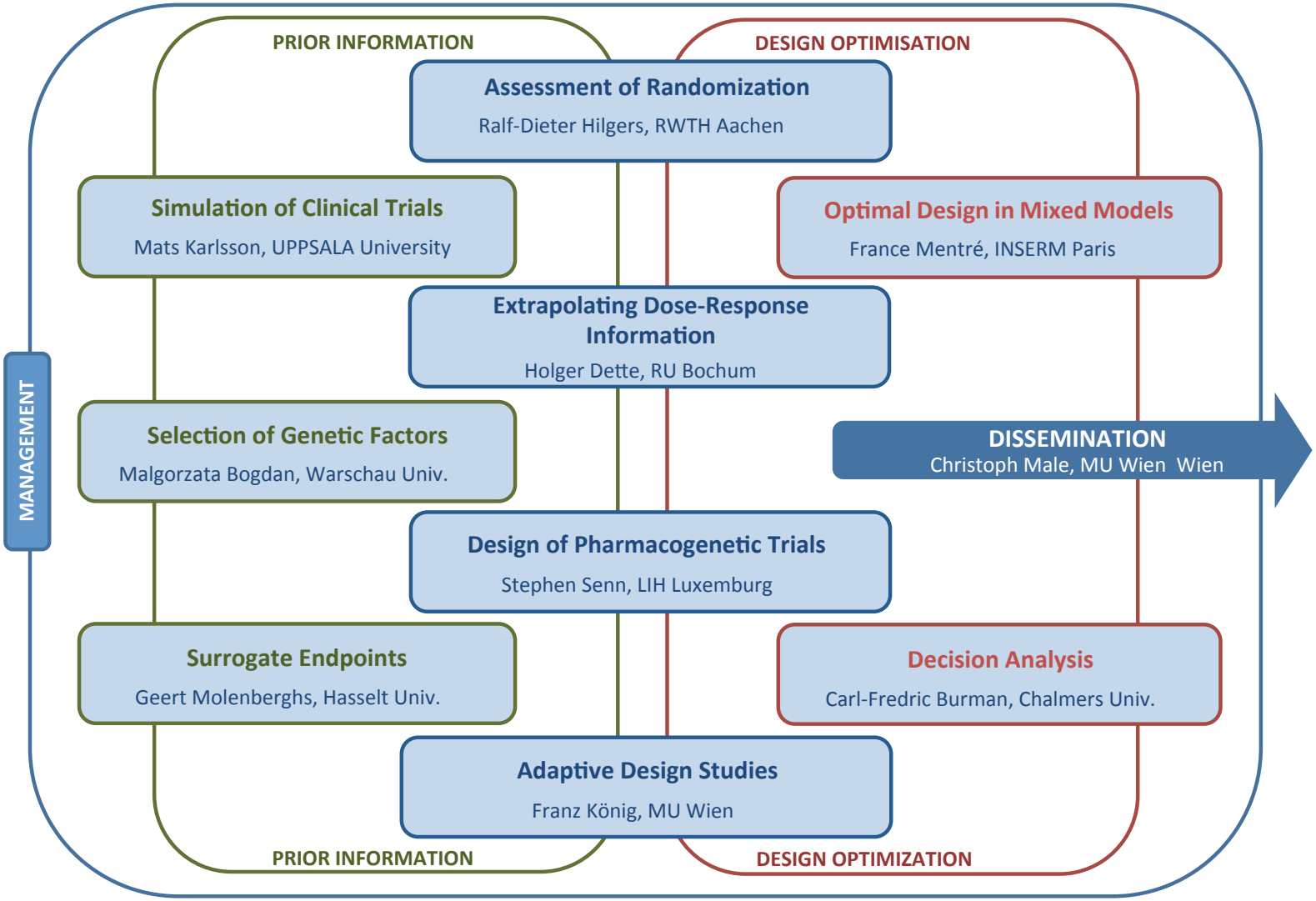
Structure of the IDeAI Project



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Motivation - Level of Evidence - Bias

(FDA, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, 1998): Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions.

(ICH E9): 2.3.3 Randomization: In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

Does Randomisation do a good job?

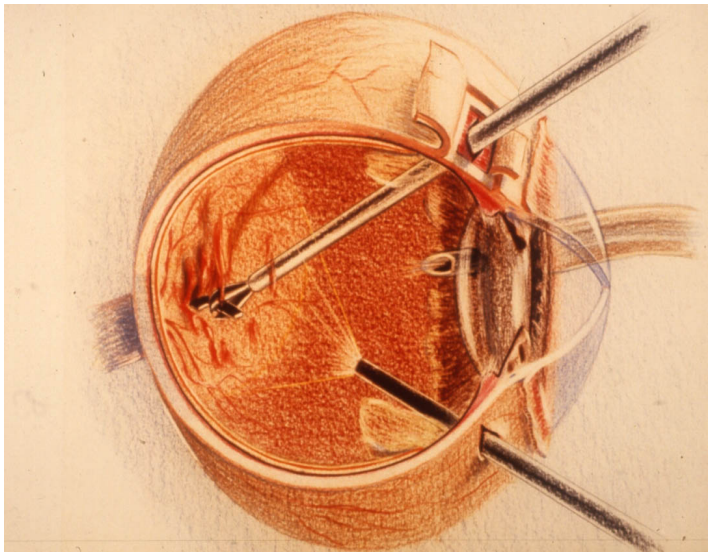
SPR-Study: Multicenter, randomized (open label), prospective clinical trial comparing scleral buckling (SB) versus primary vitrectomy (PPV) in rhegmatogenous retinal detachment of medium complexity, change in BCVA

Surgeon no 12 (n = 36)

- SB $-1.046(0.711)$, PPV $-0.390(0.662)$
  Welch t-test: $p = 0.0071$
- LR test for treatment: 5.59 ($p = 0.0179$).
- LR test for selection bias: 0.007 ($p = 0.9338$).

Surgeon no 13 (n = 34)

- SB $-0.707(0.622)$, PPV $-0.680(1.048)$
  Welch t-test: $p = 0.9278$
- LR test for treatment: 1.27 ($p = 0.2593$).
- LR test for selection bias: 3.577 ($p = 0.0586$).



(Heimann, 2007)
(Kennes, 2015)

Study Design in Practice

- no randomization procedure performs best with all criteria
  - Rosenberger (2016), Atkinson (2014)
- no recommendation to give scientific arguments for the choice of randomization procedure
  - ICH Guidelines
  - CONSORT Statement
- 21 out of 63 Orphan drug legislations involve open label studies (Joppi, 2013)

Objective

1. present a framework for assessment of the impact of bias (both, selection and chronological) on the type-I-error probability for a given randomization procedure
2. stimulate a scientific discussion of the appropriate choice of the randomization procedure
3. understanding the properties of randomization procedures in practical settings

Clinical Scenario Evaluation (CSE)

(Benda, 2011)

2. CSE - Objective

Objective of CSE-Randomization

select a randomization procedure based on scientific arguments with respect to the practical setting, by showing the influence of bias on the study results

Assumptions of CSE-Randomization

focus on the magnitude of the selection bias effect η and the time trend θ based on reasonable assumptions

- time trend as a synonym for chronological bias
- practical experience
- reporting standard is weak, no recommendation to report on the randomization list or randomization procedure

3.2 CSE - Options

Options of CSE-Randomization

- **various randomization procedures and their parameter settings**

3.2 CSE - Options: Randomization Procedures

Fixed sample procedures, no adaptive randomization procedures.

- **CR** Complete randomization is accomplished by tossing a fair coin, so the probability that patient i will receive treatment 1 is always $\frac{1}{2}$
- **RAR** Random Allocation rule, fix total sample size N. Randomize so that half the patients receive treatment 1
- **PBR** (Permuted Block Randomization) Implementation of RAR within B Blocks of size $b_s, 1 \leq s \leq B$
- **BSD(a)** (Big Stick design) CR allow for imbalance within a limit a
- **MP(a)** (Maximal Procedure) allow for imbalance within a limit (a) but force terminal balance at the end, resulting sequences are set to be equiprobable
- **EBC(p)** (Efrons Biased Coin) flip a biased coin (p) in favour of the treatment which is allocated less frequently

. . .etc.

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3.3 CSE - Metric: type-I-error probability

Choose a measure which reflects the impact of bias on the results of the trial with respect to the randomization procedure:

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.

Metric of CSE randomization

- $\rightarrow$ **empirical type-I-error rate**

Evaluation Methods of CSE - Randomization

use a specific design, e.g. two arm parallel group with continuous endpoint, to analyse the impact of various randomization procedures with respect to the study settings (bias specifications) on the study results e.g. type-I-error probability

- model
  - two arm parallel group with continuous endpoint (Kennes, 2011), (Langer, 2014)
  - multiarm parallel group with continuous endpoint (Tasche, 2016)
  - two arm parallel group with time to event endpoint (Rückbeil, 2015)
- bias specification
  - selection bias (Kennes, 2011), (Tamm, 2011), (Rückbeil, 2015), (Tasche, 2016)
  - chronological bias (Tamm, 2014)

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4. CSE - Evaluation: Statistical Model (1)

two arm parallel group design, continuous endpoint

Aim: test the hypotheses $H_0 : \mu_E = \mu_C$ vs. $H_1 : \mu_E \neq \mu_C$

Model for two arm parallel group design with continuous endpoint

$$Y_i = \mu_E T_i + \mu_C(1 - T_i) + \tau_i + \epsilon_i, \quad 1 \leq i \leq N_E + N_C$$

- allocation

$$T_i = \begin{cases} 1 & \text{if patient } i \text{ is allocated to group } E \\ 0 & \text{if patient } i \text{ is allocated to group } C \end{cases}$$

- μ_j expected response under treatment $j = C, E$
- τ_i denotes the fixed unobserved "bias" effect acting on the response of patient i
- errors ϵ_i iid $\mathcal{N}(0, \sigma^2)$

4. CSE - Evaluation: Selection Bias Model (1)

two arm parallel group trial continuous endpoint

Biasing policy according to convergence strategy

$$\tau_i = \begin{cases} \eta & \text{if } n_E(i-1) < n_C(i-1) \\ 0 & \text{if } n_E(i-1) = n_C(i-1) \\ -\eta & \text{if } n_E(i-1) > n_C(i-1) \end{cases}$$

- η proportional to effect size δ
- $\tau_i = \eta \ [\text{sign}(\ n_E(i-1) - n_C(i-1)\ )]$
- $n_j(i)$: assignments to treatment j after i allocations

(Proschan 1994)
(Kennes 2011)

4. CSE - Evaluation: Examples Selection Bias

Random Sequence	Response (expected response for treatment difference)	Selection Bias
ECECCE	$\frac{1}{3}\left[(0)-(-\eta)+(0)-(-\eta)-(0)+(\eta)\right]$	η
EEECCC	$\frac{1}{3}\left[(0)+(-\eta)+(-\eta)-(-\eta)-(-\eta)-(-\eta)\right]$	$\frac{\eta}{3}$
ECECEC	$\frac{1}{3}\left[(0)-(-\eta)+(0)-(-\eta)+(0)-(-\eta)\right]$	η
ECCC	$(0)-\frac{1}{3}\left[(-\eta)+(\eta)+(\eta)\right]$	0

4. CSE - Evaluation: Statistical Test for Model (1)

two arm parallel group trial continuous endpoint

Aim: test the hypotheses $H_0 : \mu_E = \mu_C$ vs. $H_1 : \mu_E \neq \mu_C$

use t-Test (under misspecification)

$$S = \frac{\sqrt{\frac{N_E N_C}{N_E+N_C}}\,(\tilde{y}_E - \tilde{y}_C)}{\frac{1}{N_E+N_C-2}\left(\sum_{i=1}^{N} T_i(y_i - \tilde{y}_E)^2 + \sum_{i=1}^{N}(1-T_i)(y_i - \tilde{y}_C)^2\right)} \sim t_{N_E+N_C-2,\vartheta,\lambda}$$

where $\tilde{y}_E = \frac{1}{N_E}\sum_{i=1}^{N} y_i T_i$; $\tilde{y}_C = \frac{1}{N_C}\sum_{i=1}^{N} y_i(1-T_i)$; $N = N_E + N_C$

4. CSE - Evaluation: Statistical Test for Model (1)

Theorem: Under $H_0 : \mu_E = \mu_C$ the type-I-error probability for the two arm parallel group normal model (under misspecification) for the allocation sequence $\mathbf{T} = (T_1, \ldots, T_{N_E+N_C})$ is

$$P\left(|S| > t_{N_E+N_C-2}(1-\alpha/2)\middle|\mathbf{T}\right)$$
$$= F_{N-2,\vartheta,\lambda}\left(t_{N_E+N_C-2}(\alpha/2)\right) + 1 - F_{N_E+N_C-2,\vartheta,\lambda}\left(t_{N_E+N_C-2}(1-\alpha/2)\right).$$

$F_{N_E+N_C-2,\vartheta,\lambda}$ denotes the distribution function of the doubly non-central t-distribution with $N_E + N_C - 2$ degrees of freedom and parameters

$$\vartheta = \frac{1}{\sigma}\sqrt{\frac{N_E N_C}{N_E + N_C}}\,(\tilde{\tau}_E - \tilde{\tau}_C) \quad \lambda = \frac{1}{\sigma^2}\left[\sum_{i=1}^{N}\tau_i^2 - N_E\tilde{\tau}_E^2 - N_C\tilde{\tau}_C^2\right]$$

where $\tilde{\tau}_E = \frac{1}{N_E}\sum_{i=1}^{N}\tau_i T_i$; $\quad \tilde{\tau}_C = \frac{1}{N_C}\sum_{i=1}^{N}\tau_i(1-T_i)$

6. CSE - (general) Result: Selection Bias

with PBR, the empirical type-I-error is elevated compared to 5%

- ... with smaller blocksize (Tamm, 2012; Kennes, 2011)
- ... with smaller blocksize and misclassification of patients performance (Tamm, 2012)
- ... with smaller blocksize in multiarm trials (Tasche, 2016)
- ... with smaller blocksize in time to event trials (Rückbeil, 2015)

empirical type-I-error elevation is reduced compared to 5%

- ... with a randomization list, which is too long
- ... with multicenter trial, where biasing policies in centers are in opposite directions
- ... with number of arms in multiarm trials (Tasche, 2016)

6. CSE - Result: Selection Bias

Empirical type-I-error probability of a two sided t-test

N	$\delta(N)$	BSD (2)	CR	EBCD ($\frac{2}{3}$)	MP(2)	PBR(4)	RAR
8	2.381	0.064	0.058	0.089	0.118	0.141	0.102
20	1.325	0.075	0.054	0.093	0.129	0.177	0.082
32	1.024	0.083	0.055	0.097	0.137	0.188	0.072
40	0.909	0.088	0.053	0.100	0.140	0.195	0.071

- $N_E = N_C, N_E + N_C = N$
- $\delta(N) : \alpha = 0.05, 1 - \beta = 0.8$
- selection bias effect $\eta = \frac{\delta(N)}{2}$

using R with 100 000 replications

6. CSE - (general) Result: Selection Bias

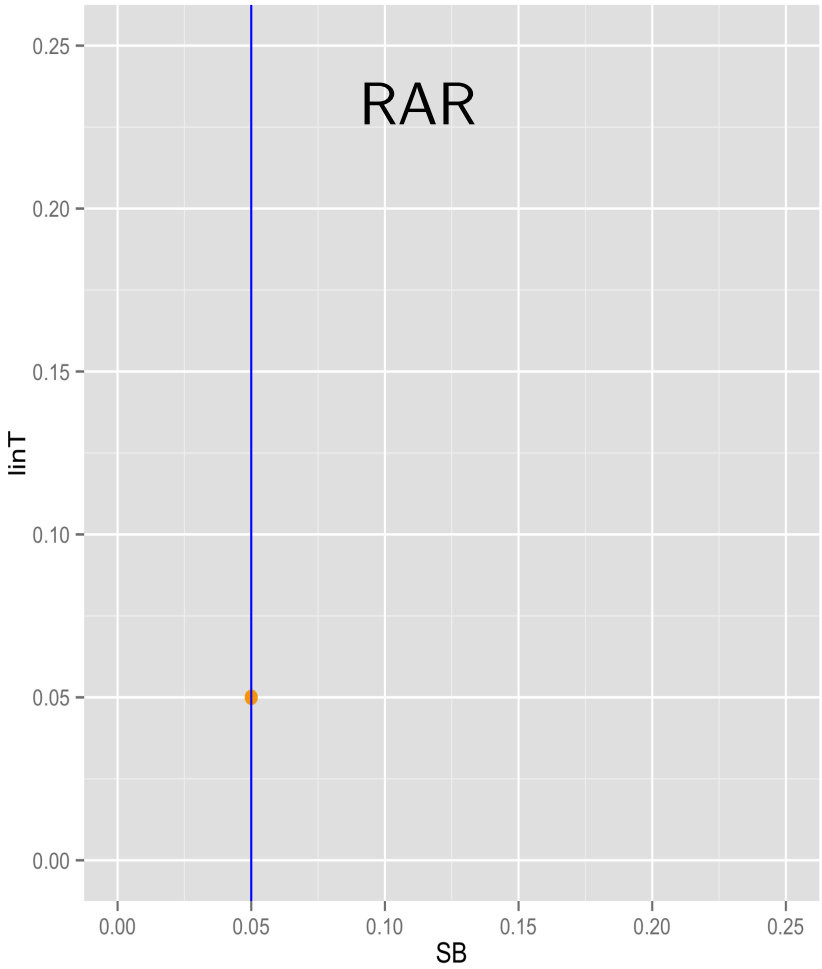
Rückbeil (2015) investigated RAR, PBR (2,4,8), MP (2,3) and BSD(2,3) for $N = 200$:

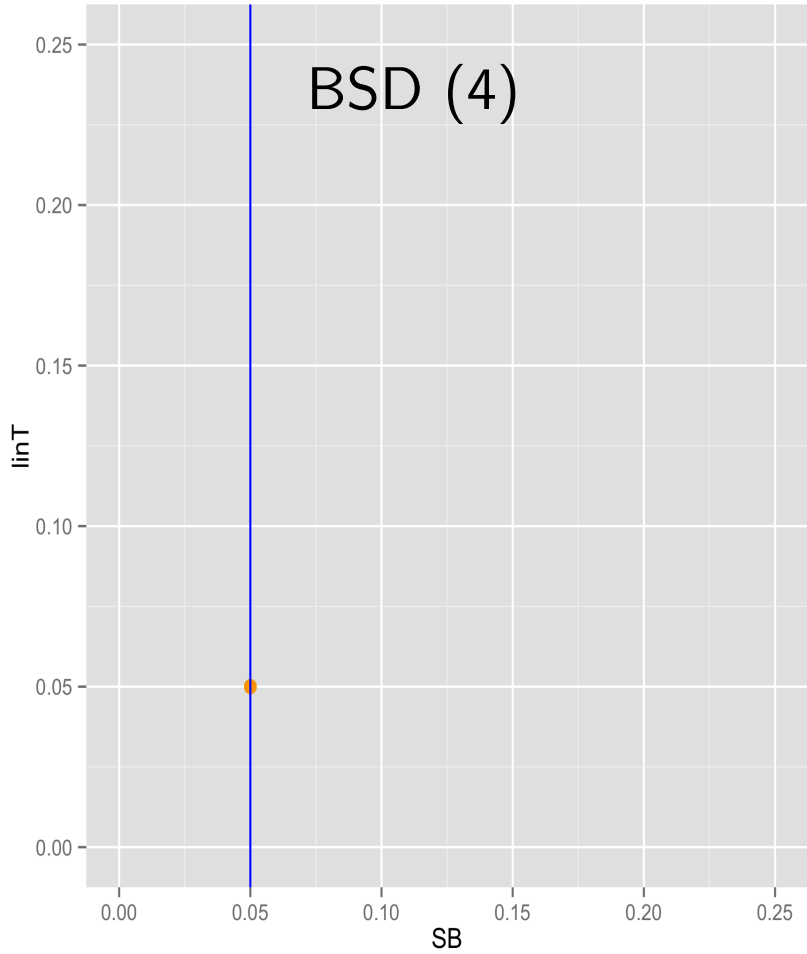
- empirical type-I-error increases with smaller blocksize under PBR
- RAR performed better than BSD(3)
- MP (2,3) are as good or even better than PBR(8)
- further research necessary to derive realistic selection bias effects here

(Rückbeil, 2015)

6. CSE - Result: Selection Bias (N=96)

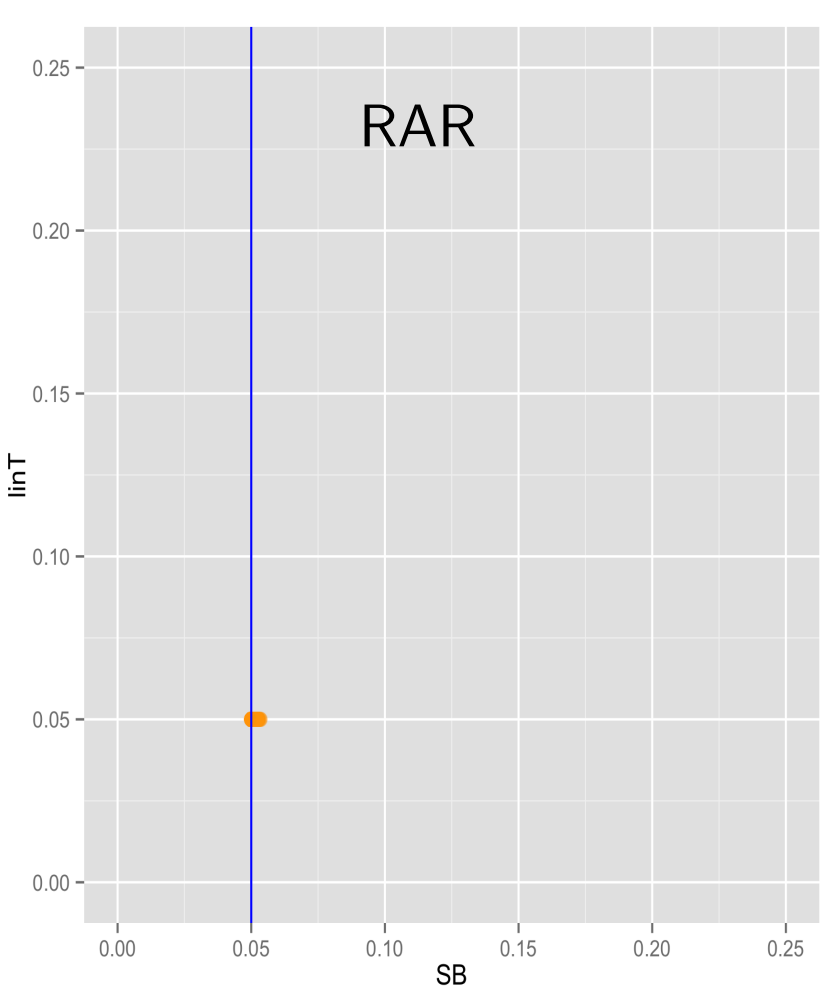
setting: $N_E = N_C = 48, \eta = 0.0 \times \delta; \theta = 0$

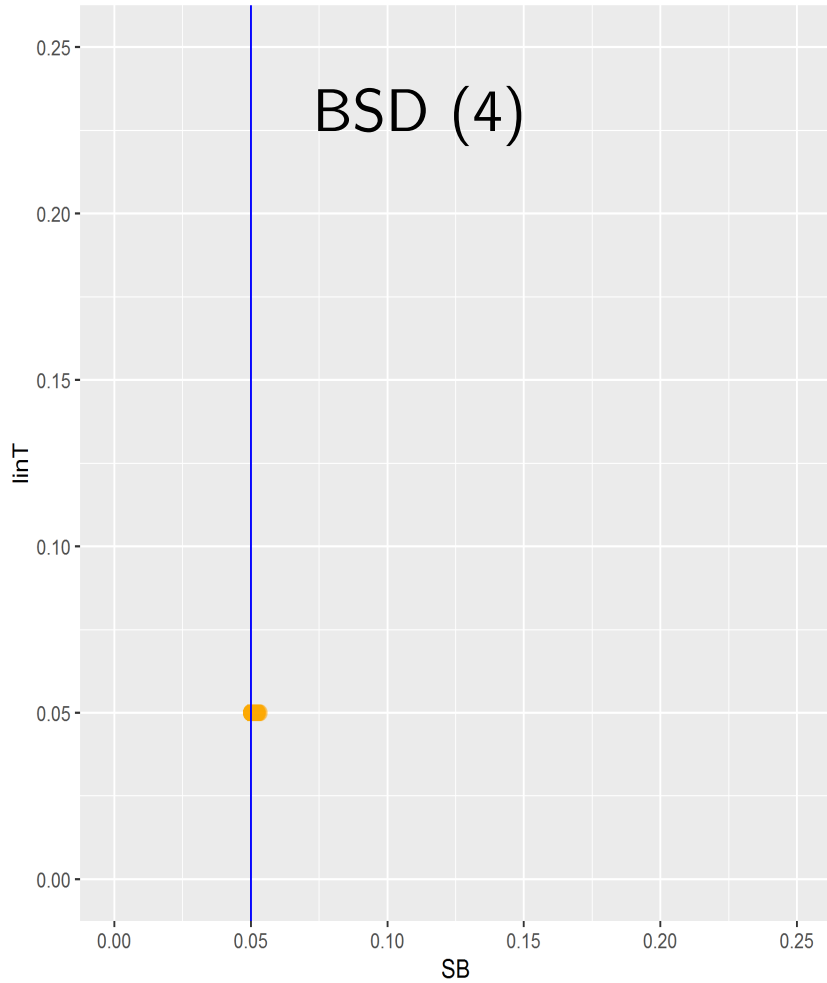




6. CSE - Result: Selection Bias (N=96)

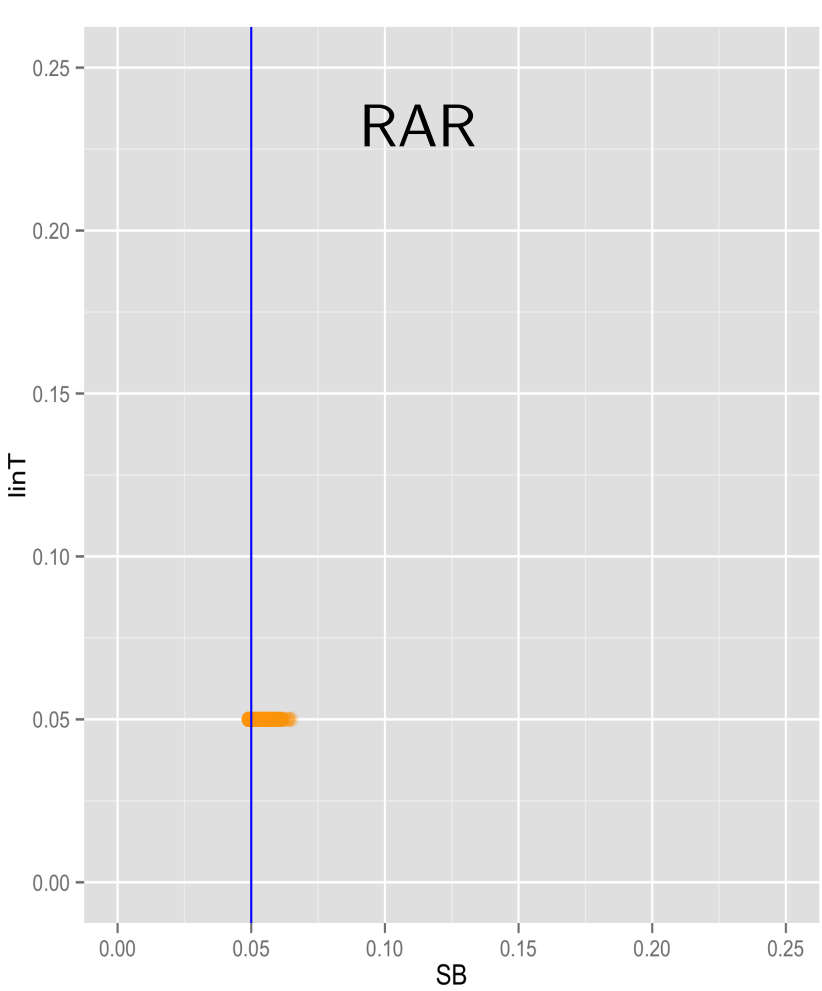
setting: $N_E = N_C = 48, \eta = 0.1 \times \delta;\ \theta = 0$

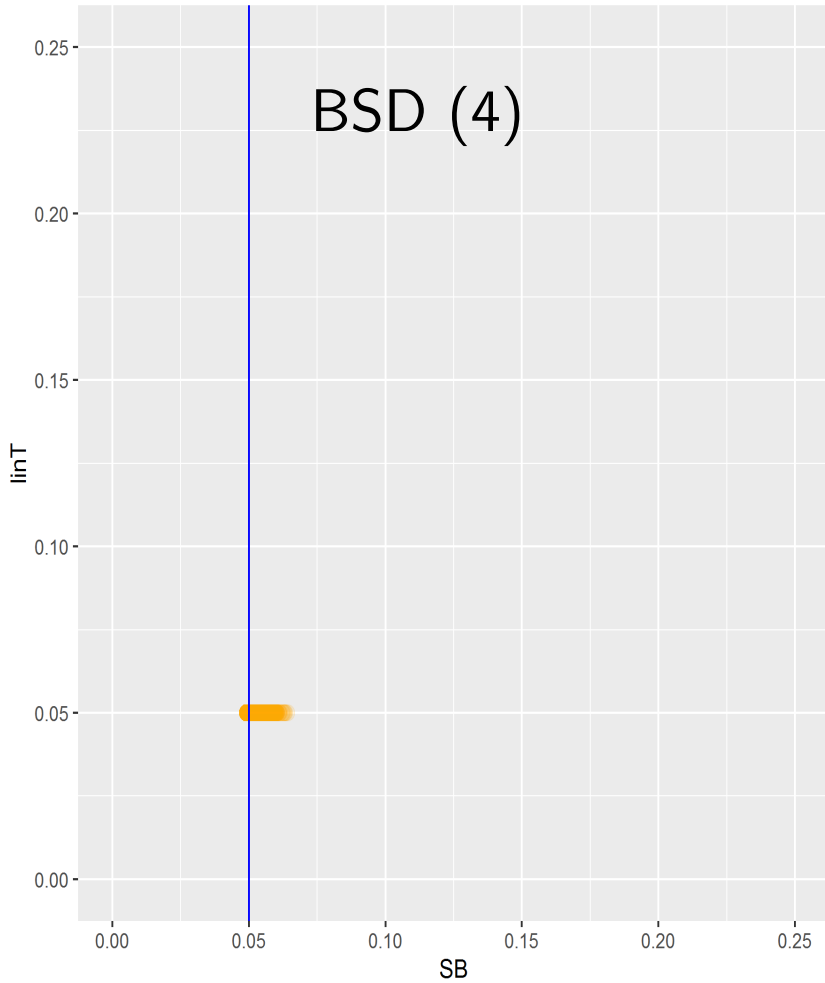




6. CSE - Result: Selection Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0.2 \times \delta;\ \theta = 0$





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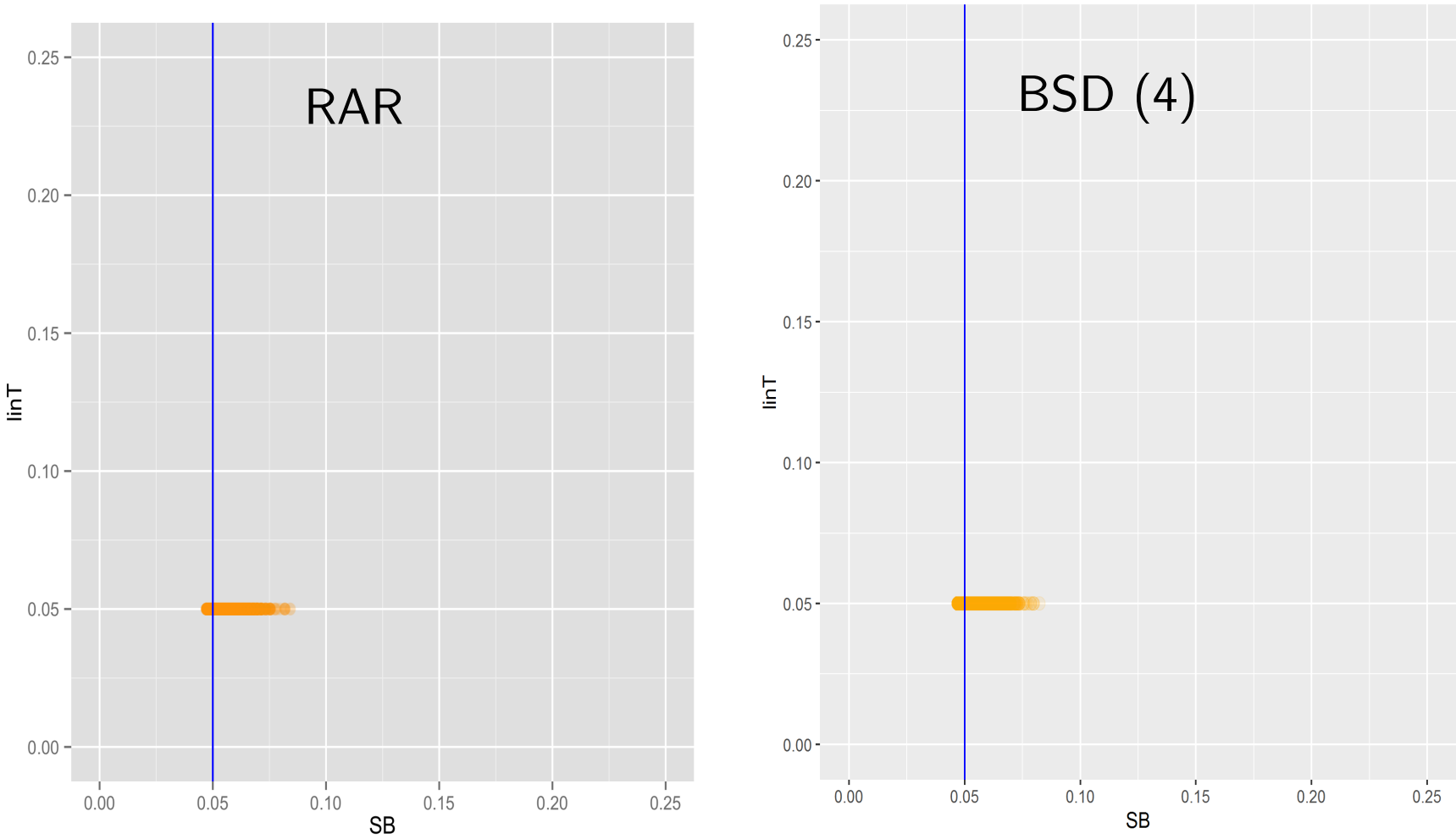
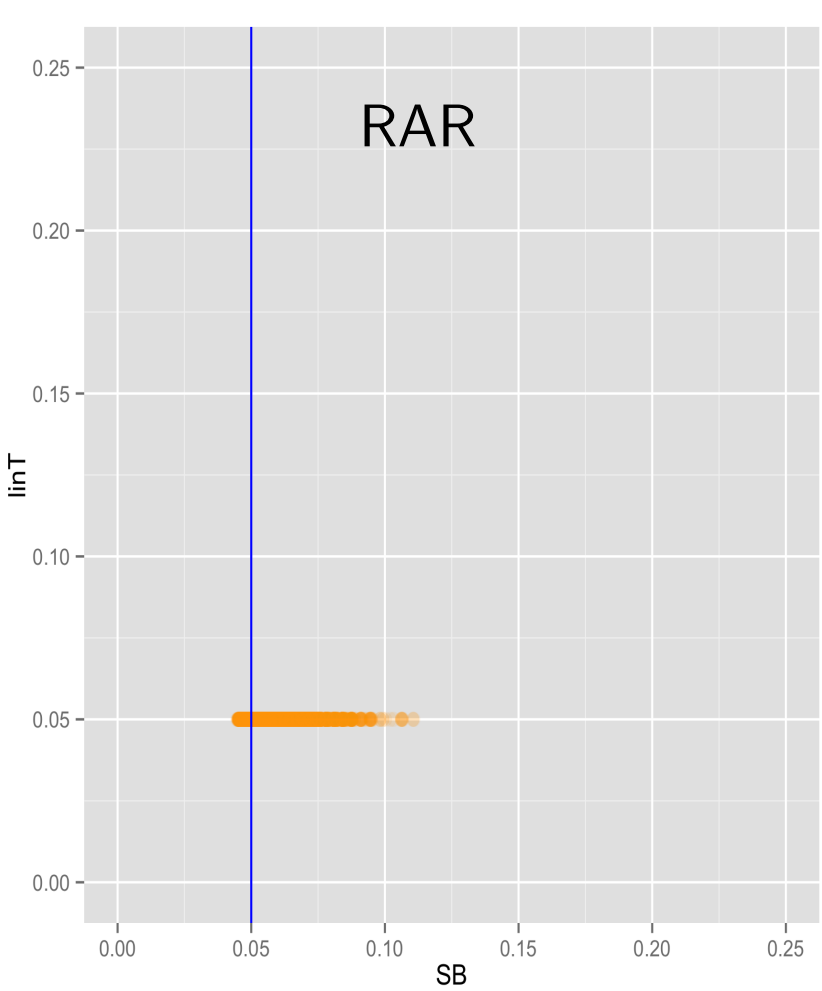
6. CSE - Result: Selection Bias (N=96)

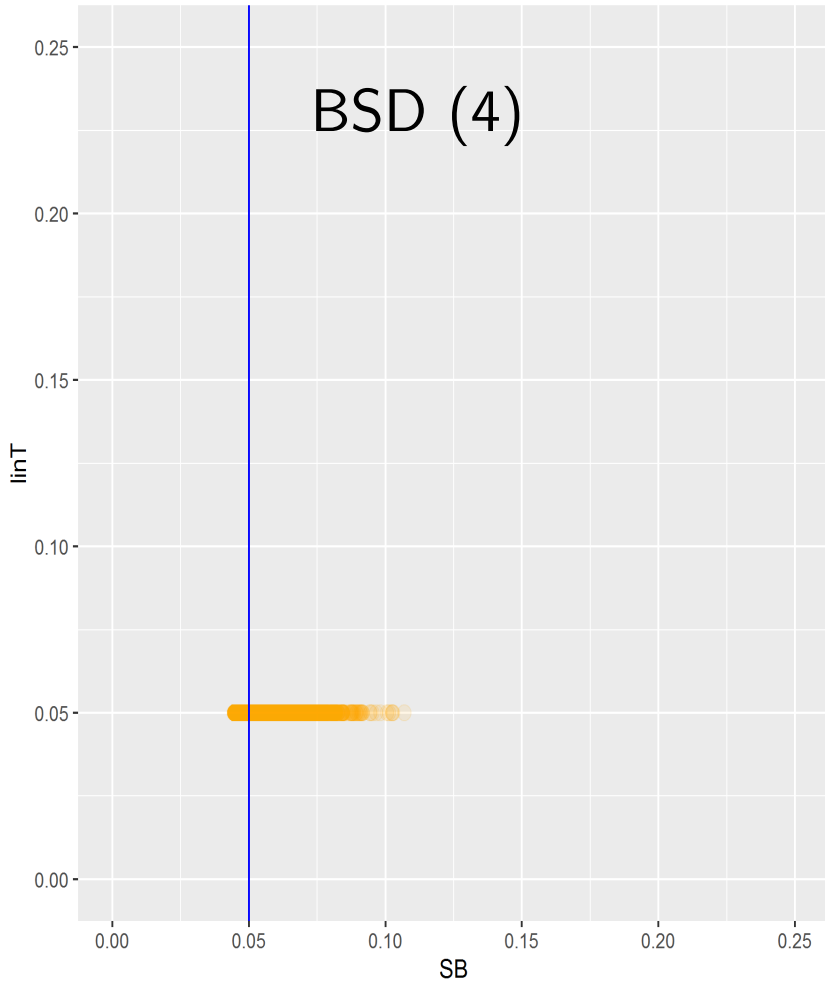
setting: $N_E = N_C = 48, \eta = 0.3 \times \delta;\ \theta = 0$



6. CSE - Result: Selection Bias (N=96)

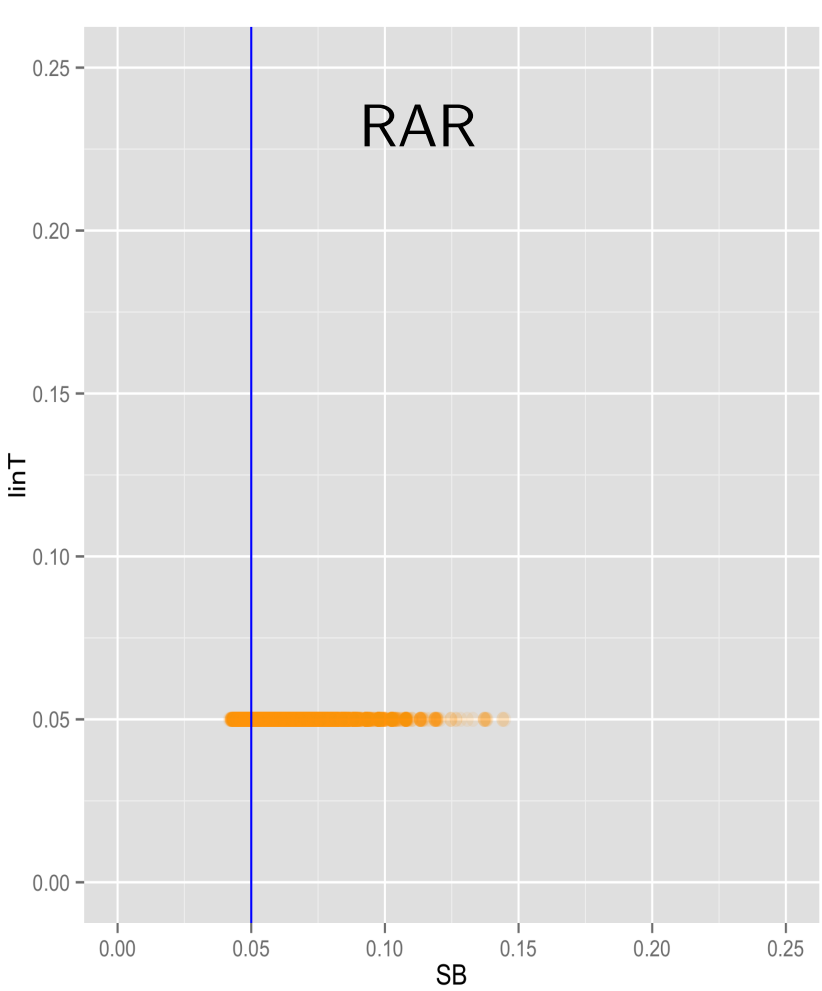
setting: $N_E = N_C = 48, \eta = 0.4 \times \delta; \theta = 0.8$

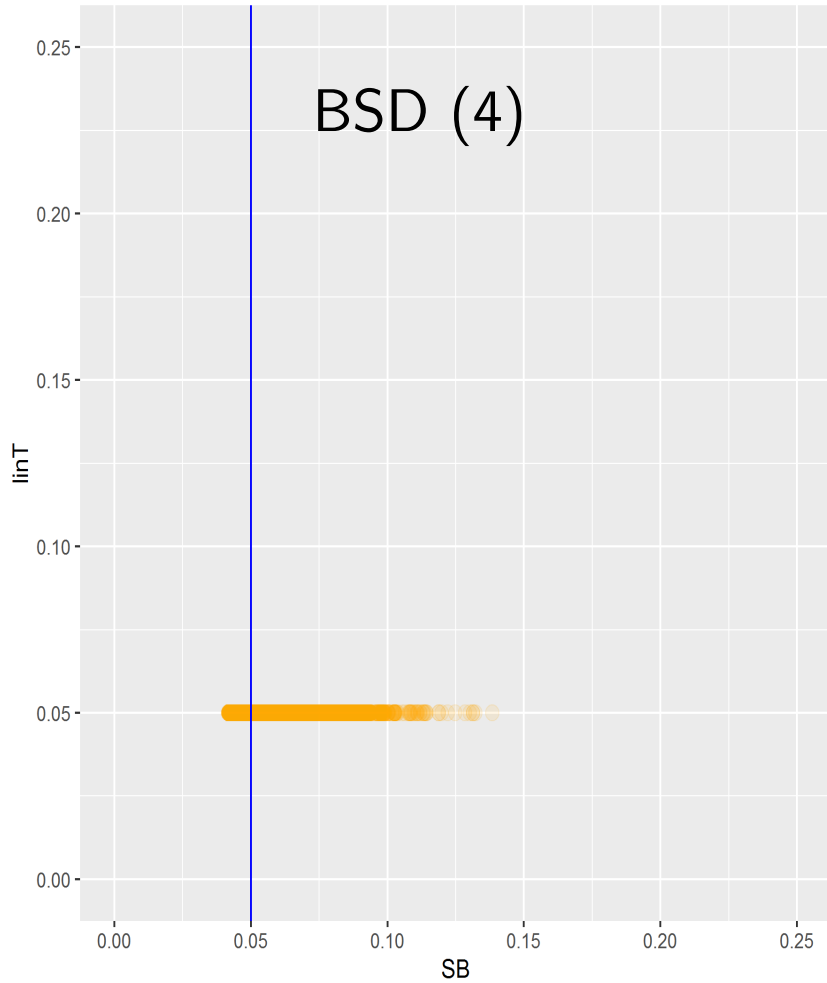




6. CSE - Result: Selection Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0.5 \times \delta; \theta = 0$





4. CSE - Evaluation: Time Trend Bias Model

two arm parallel group trial continuous endpoint

Biasing policy according to convergence strategy

$$\tau_i = \theta \times \begin{cases} \frac{i}{N_E+N_C} & \text{linear time trend} \\ \mathbb{1}_{i \geq S}(i) & \text{stepwise trend} \\ \log(\frac{i}{N_E+N_C}) & \text{log trend} \end{cases}$$

- θ proportional to variance
- other functions are possible
- long recruitment time in rare diseases, (EMA, 2006)
  - changes in population characteristics
  - learning effect in therapy / surgical experience (Hopper, 2007)
  - change in diagnosis (FDA, 2011), etc.
- special form of accidental bias, when considering a time-heterogeneous covariate *(Tamm, 2014)*

4. CSE - Evaluation: Example Linear Time Trend

Random Sequence	Response (expected response for treatment difference)	Time Trend Bias
ECECCE	$\frac{1}{3}\left[(\theta) - (2\theta) + (3\theta) - (4\theta) - (5\theta) + (6\theta)\right]$	$-\frac{1}{3}\theta$
EEECCC	$\frac{1}{3}\left[(\theta) + (2\theta) + (3\theta) - (4\theta) - (5\theta) - (6\theta)\right]$	-3θ
ECECEC	$\frac{1}{3}\left[(\theta) - (2\theta) + (3\theta) - (4\theta) + (5\theta) - (6\theta)\right]$	$-\theta$
ECCC	$(\theta) - \frac{1}{3}\left[(2\theta) + (3\theta) + (4\theta)\right]$	-2θ

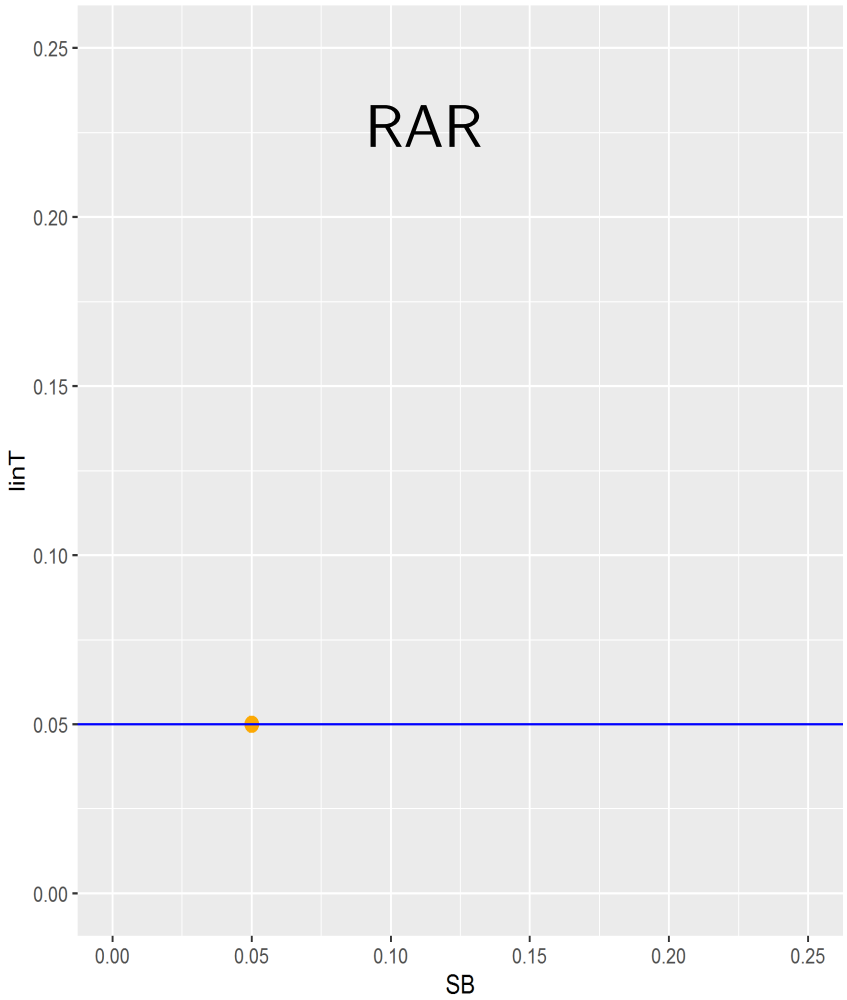
6. CSE - (general) Result: Time Trend Bias

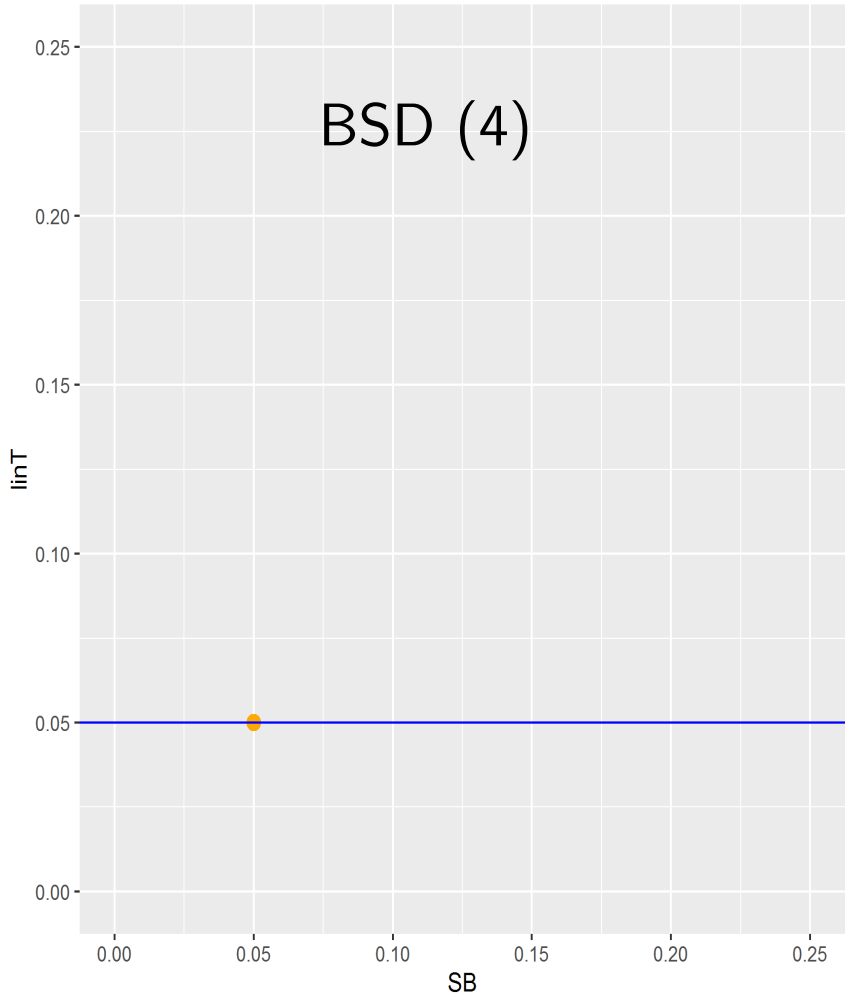
Tamm (2014) investigated PBR and found

- large block sizes affect the empirical type-I-error rate toward conservative test decisions.
- medium block sizes are preferable because they already restrict chronological bias to an acceptable extent
- that block length should be include in the statistical analysis
- that possible time trends can be evaluated by using the graphical methods suggested by Altman and Royston

6. CSE - Result: Linear Time Trend Bias (N=96)

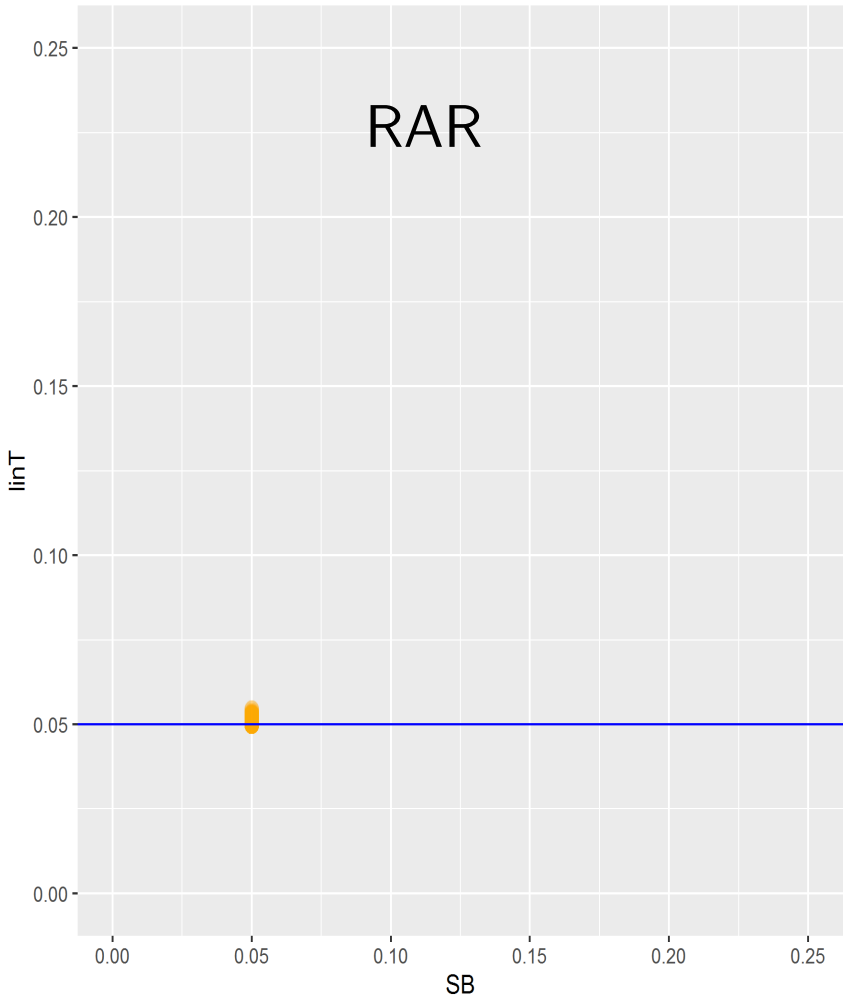
setting: $N_E = N_C = 48, \eta = 0; \theta = 0.0 \times \sigma$

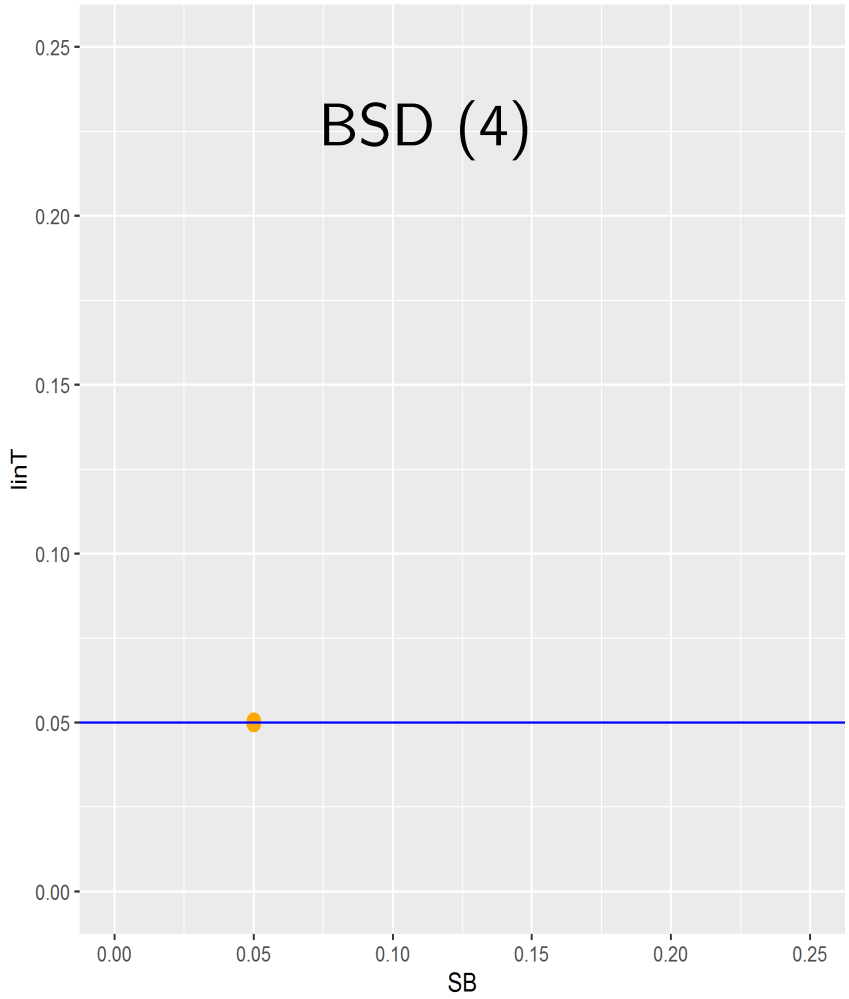




6. CSE - Result: Linear Time Trend Bias (N=96)

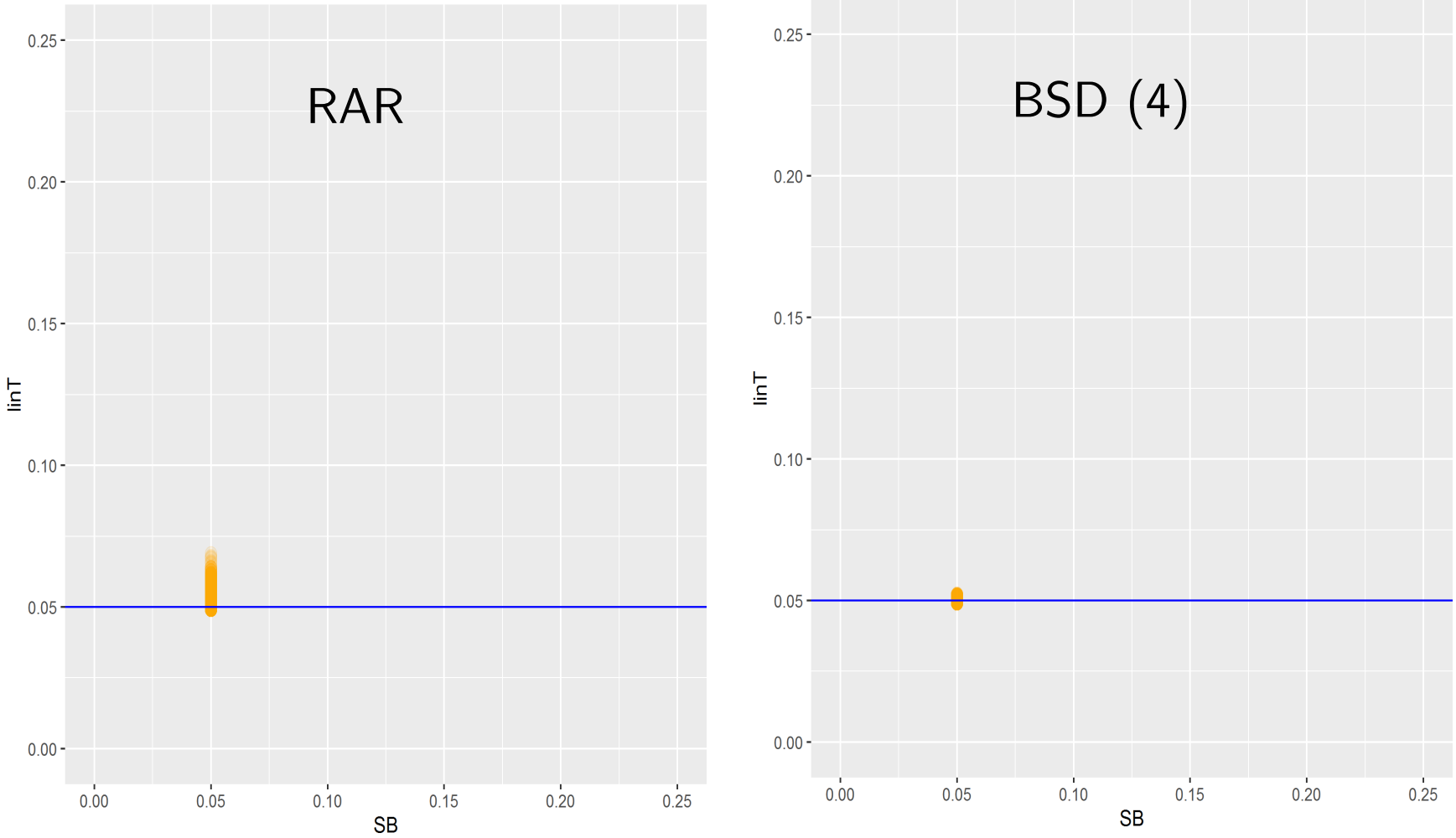
setting: $N_E = N_C = 48, \eta = 0; \theta = 0.2 \times \sigma$





6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 0.4 \times \sigma$



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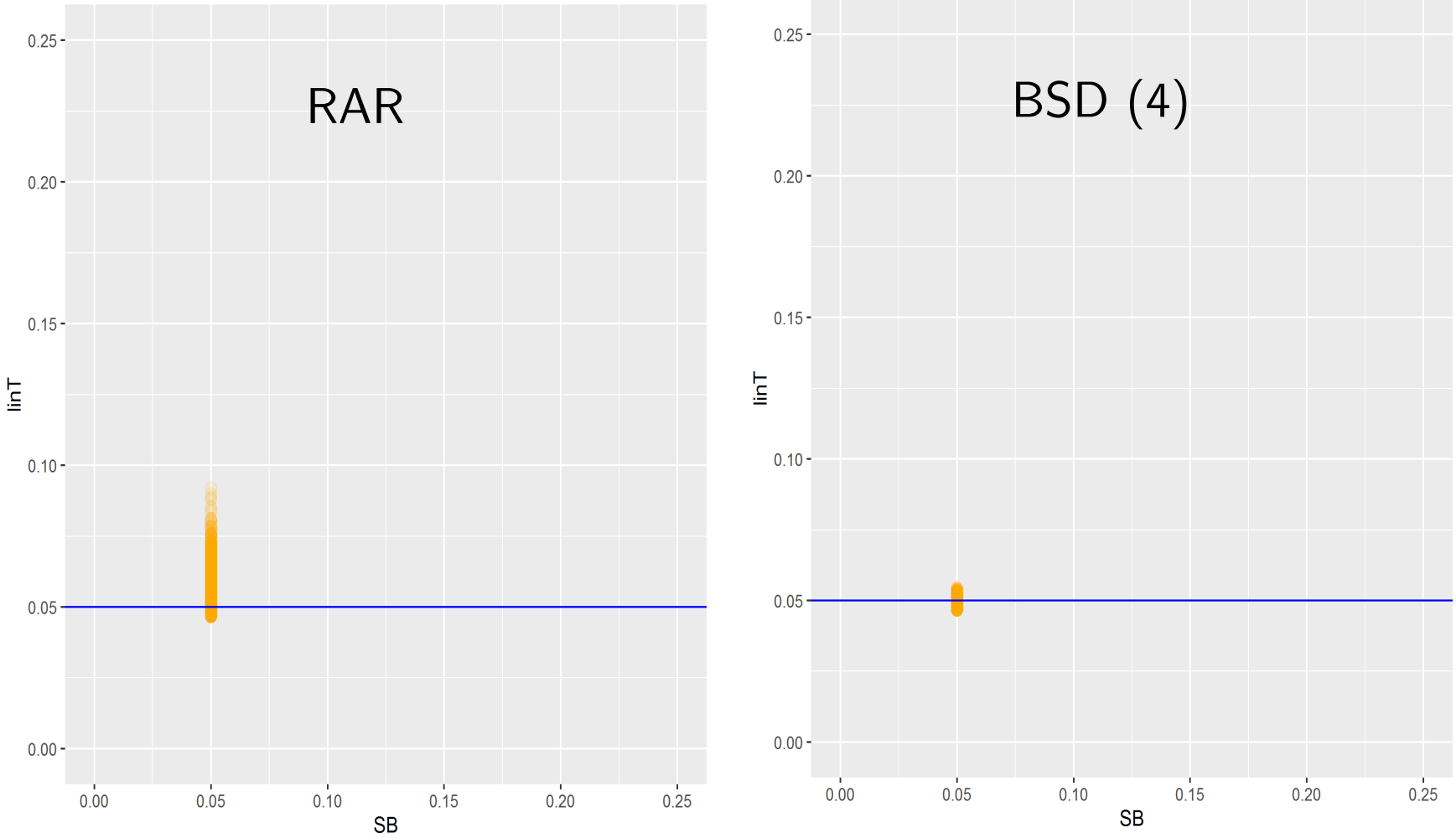
6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 0.6 \times \sigma$



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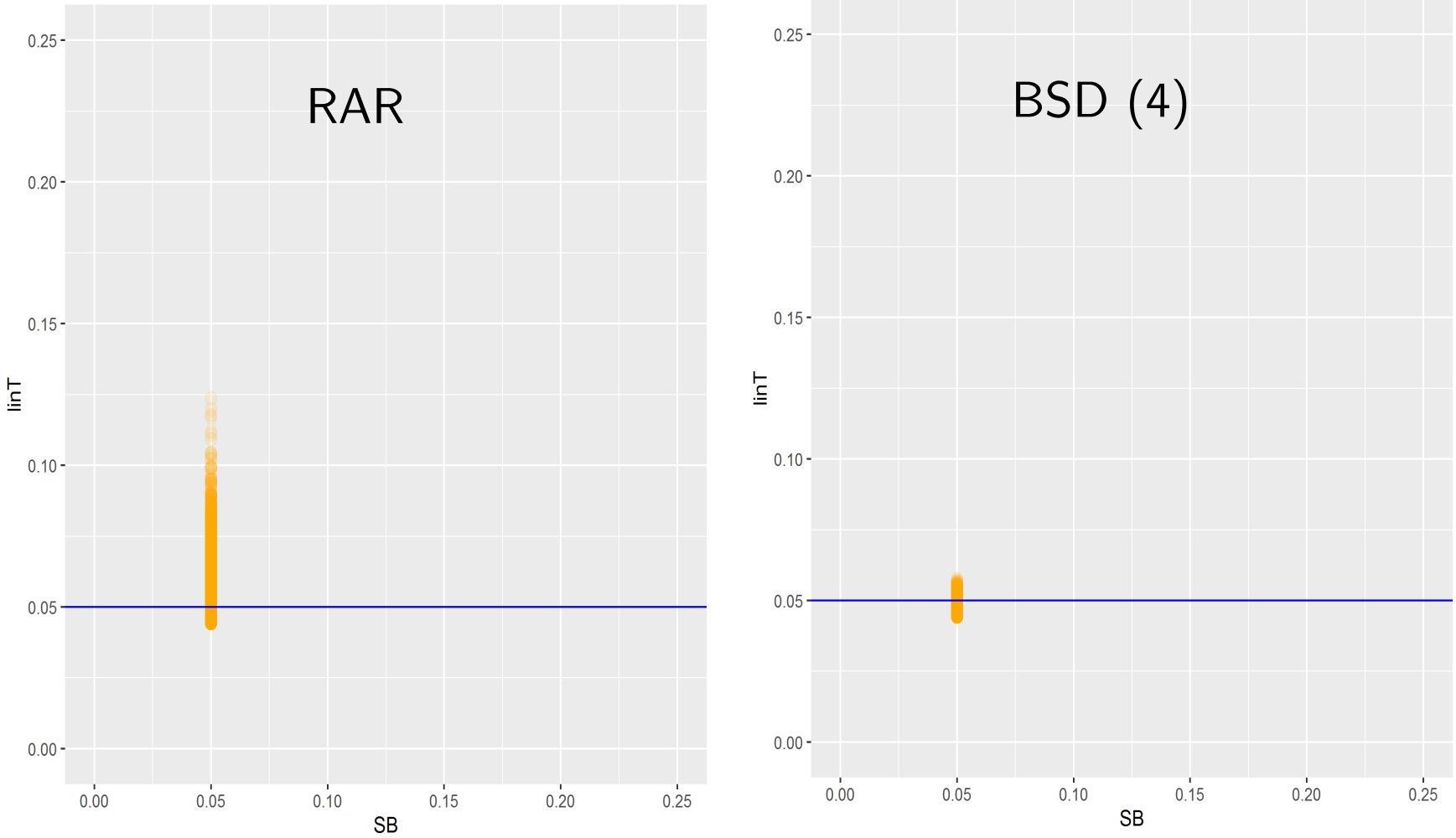
6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 0.8 \times \sigma$



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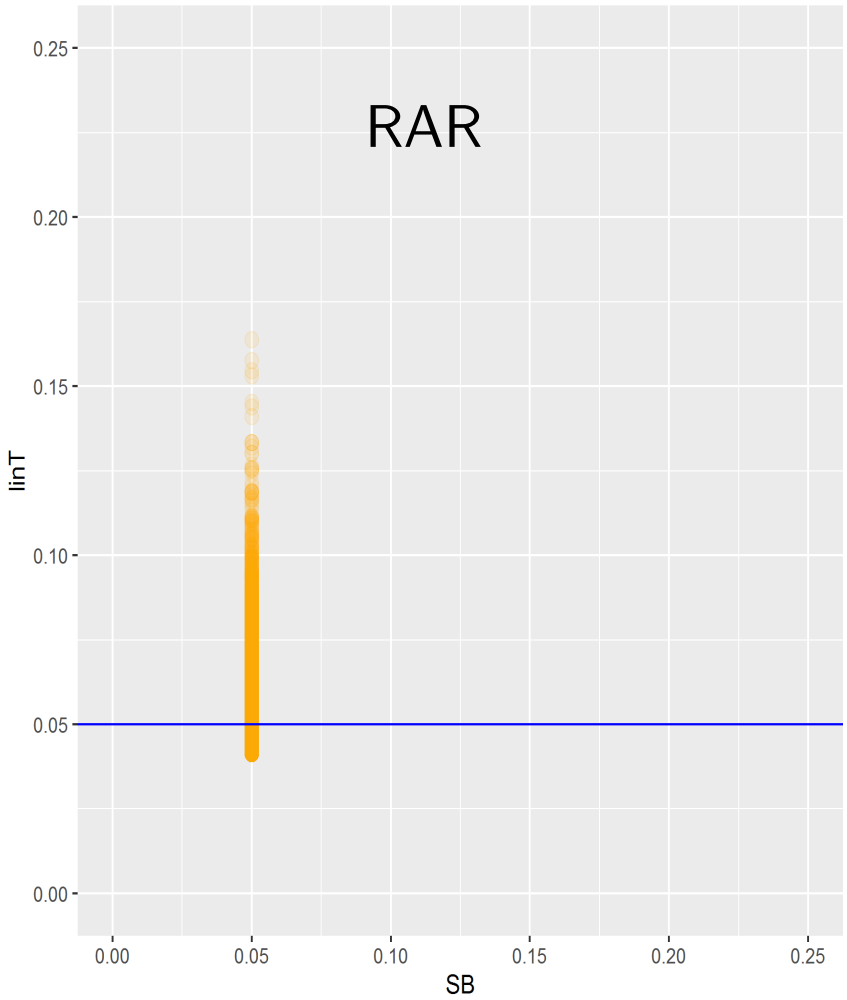
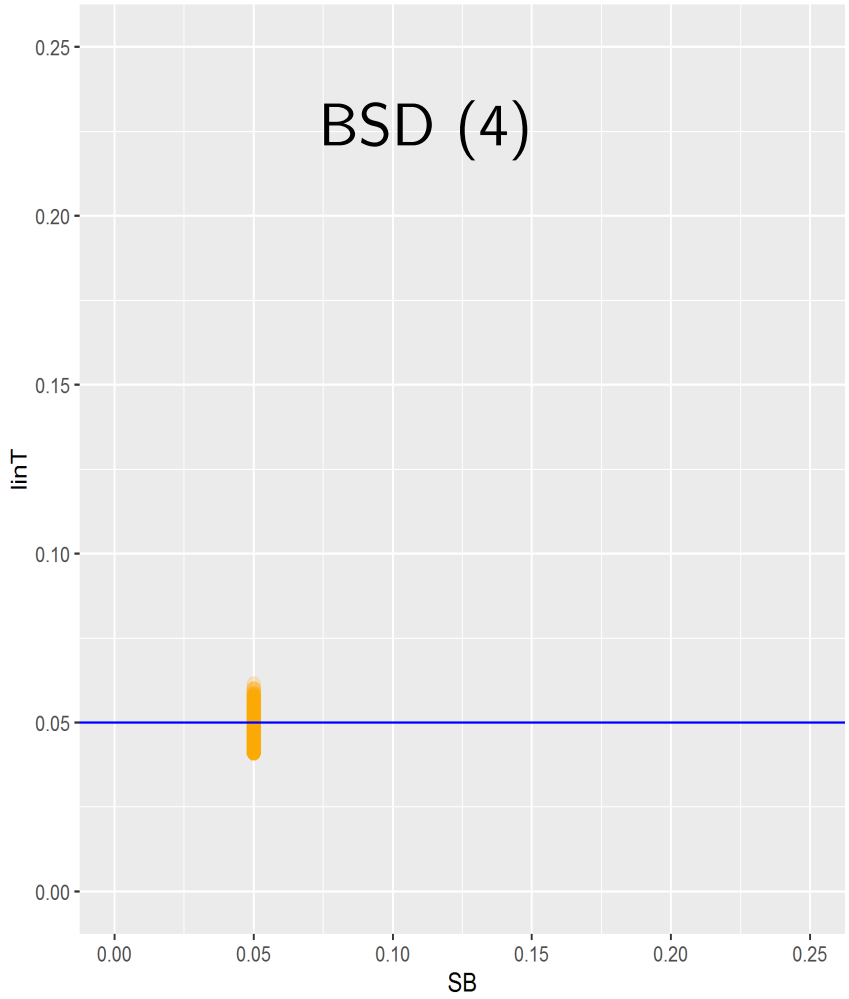
6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 1.0 \times \sigma$





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4. CSE - Evaluation: Joint Additive Bias Model (2)

two arm parallel group trial continuous endpoint

Joint Additive Bias

$$\tau_i = \underbrace{\theta \frac{i}{N_E + N_C}}_{\text{time trend}} + \underbrace{\eta \ [\text{sign}(\ n_E(i-1) - n_C(i-1)\ )]}_{\text{selection bias}}$$

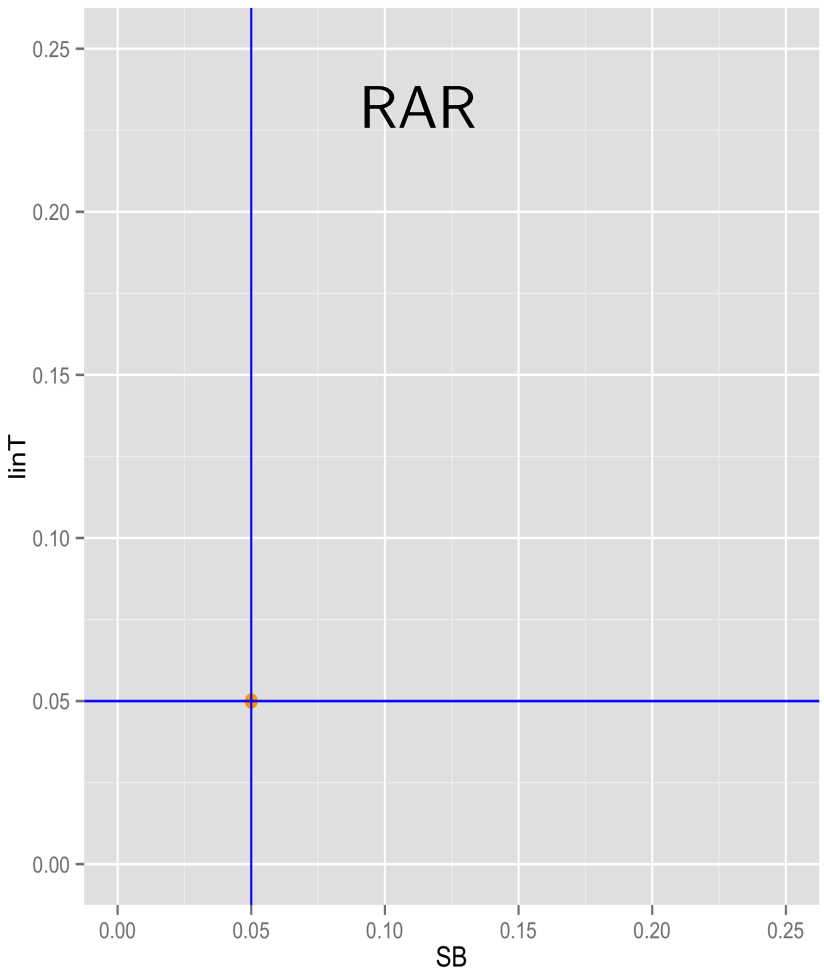
- weighted additive (selection and chronological) bias model
- weights via definition of θ and η
- multiplicative could also be done
- different shape of time trend can be incorporated (Tamm, 2014)
- relaxed version of bias policy (non strict decision, random η)

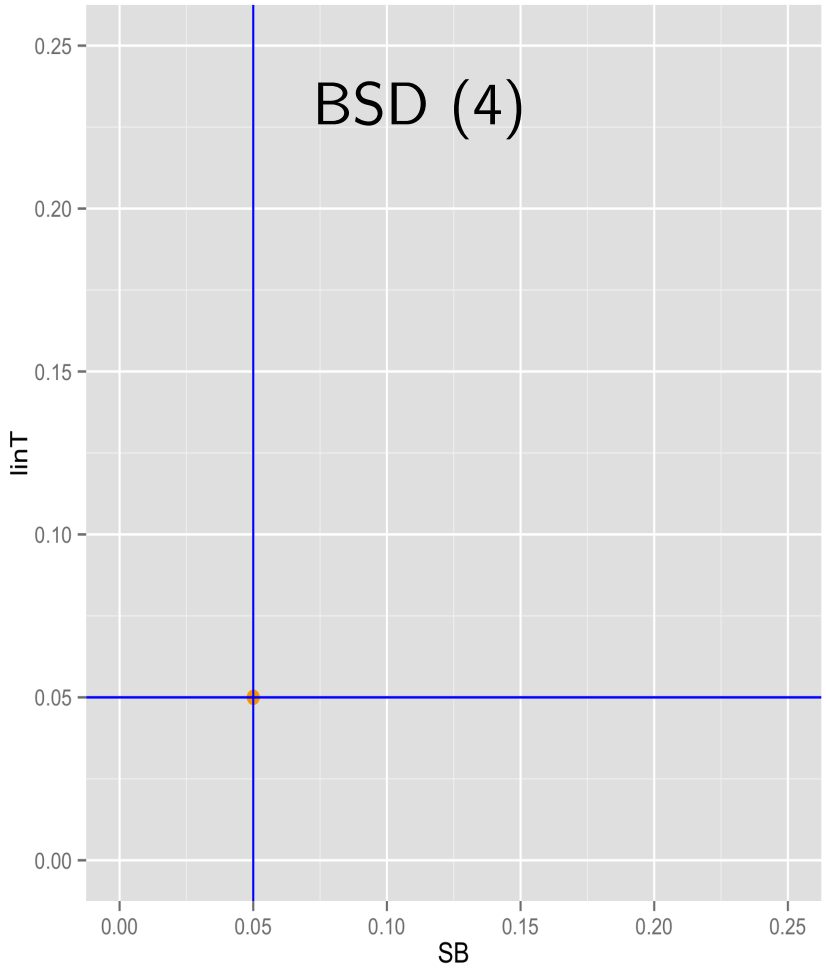
4. CSE - Evaluation: Examples Joint Additive Bias

Random Sequence	Response (expected response for treatment difference)	Joint Bias
ECECCE	$\frac{1}{3}\left[(\theta) - (-\eta + 2\theta) + (3\theta) - (-\eta + 4\theta) - (5\theta) + (\eta + 6\theta)\right]$	$\eta - \frac{\theta}{3}$
EEECCC	$\frac{1}{3}\left[(\theta) + (-\eta + 2\theta) + (-\eta + 3\theta) - (-\eta + 4\theta) - (-\eta + 5\theta) - (-\eta + 6\theta)\right]$	$\frac{\eta}{3} - 3\theta$
ECECEC	$\frac{1}{3}\left[(\theta) - (-\eta + 2\theta) + (3\theta) - (-\eta + 4\theta) + (5\theta) - (-\eta + 6\theta)\right]$	$\eta - \theta$
ECCC	$(\theta) - \frac{1}{3}\left[(-\eta + 2\theta) + (\eta + 3\theta) + (\eta + 4\theta)\right]$	2θ

6. CSE - Result: both Biases for (N=96)

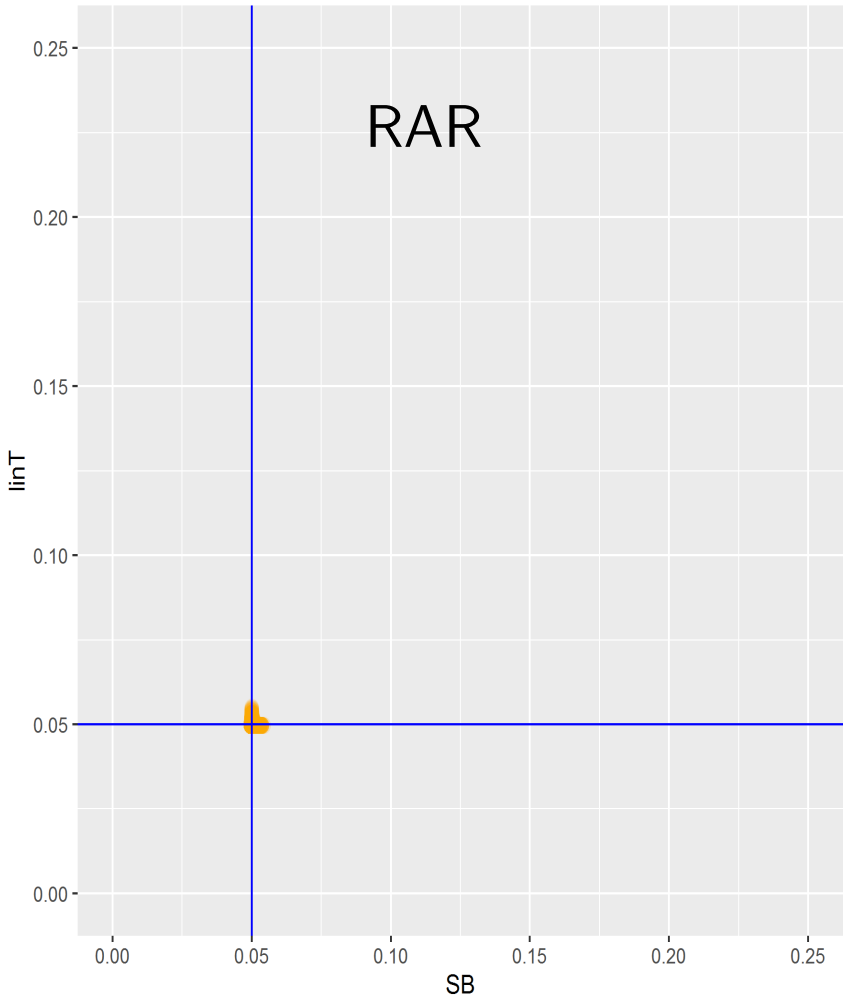
setting: $N_E = N_C = 48, \eta = 0.0 \times$effectsize (δ), $\theta = 0.0 \times \sigma$

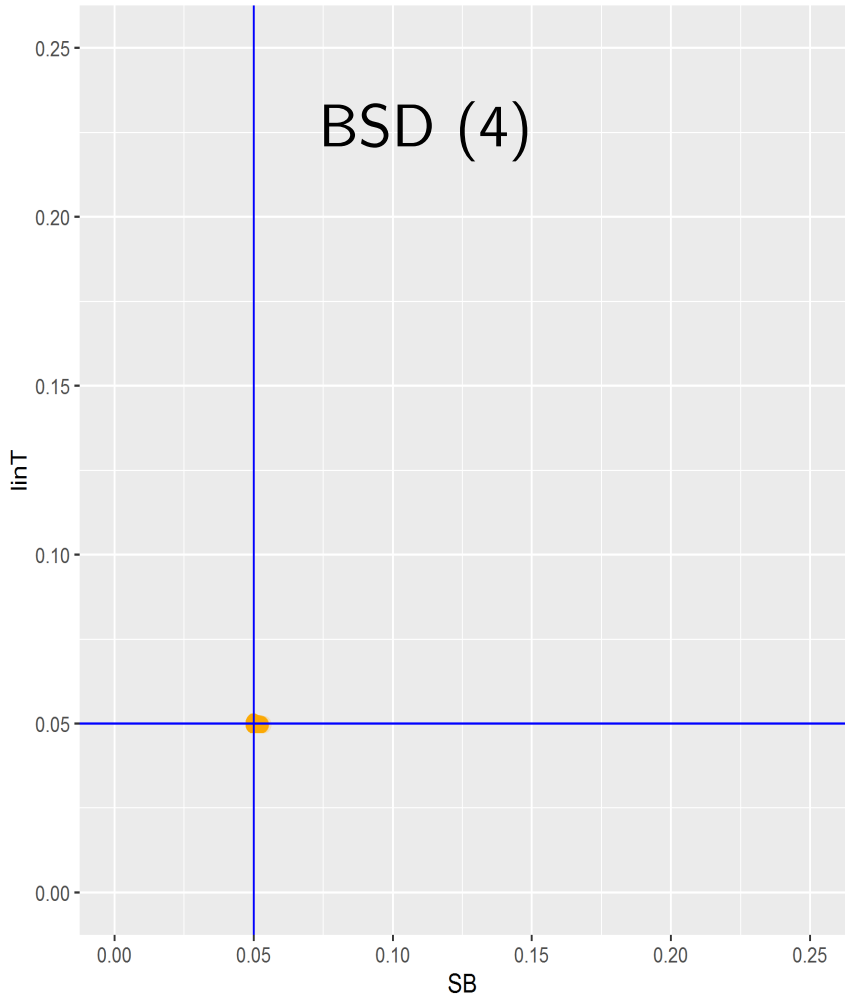




6. CSE - Result: both Biases for (N=96)

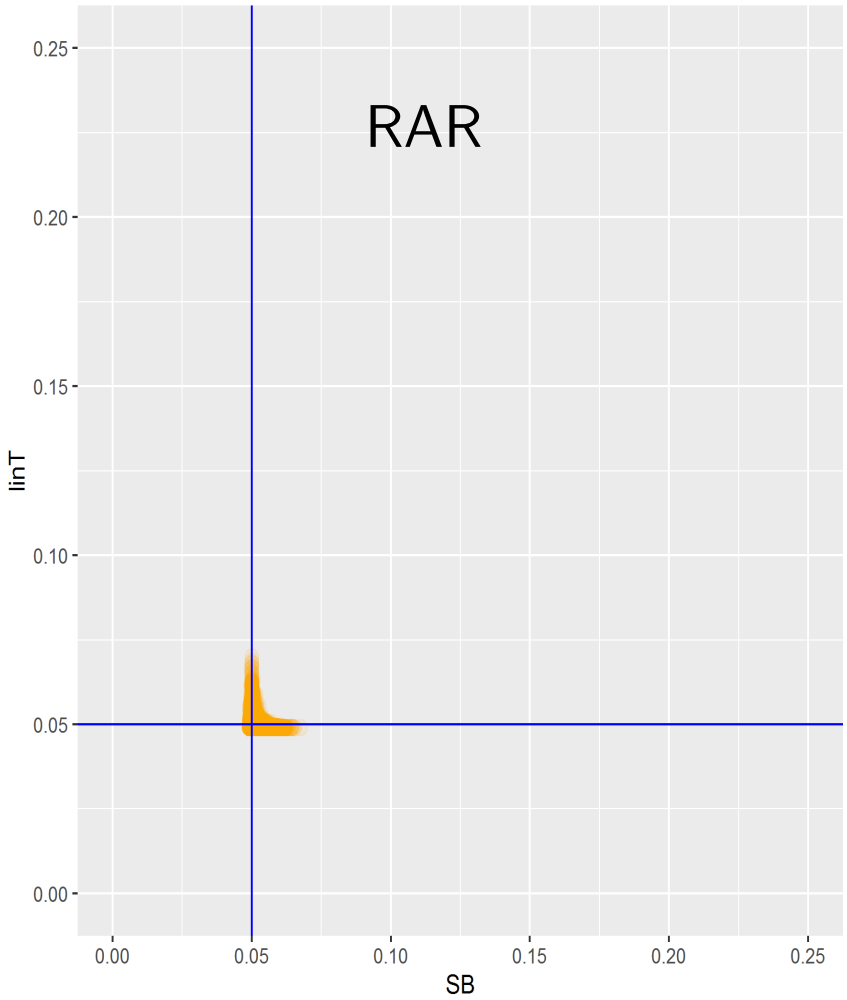
setting: $N_E = N_C = 48, \eta = 0.1 \times \delta, \theta = 0.2 \times \sigma$

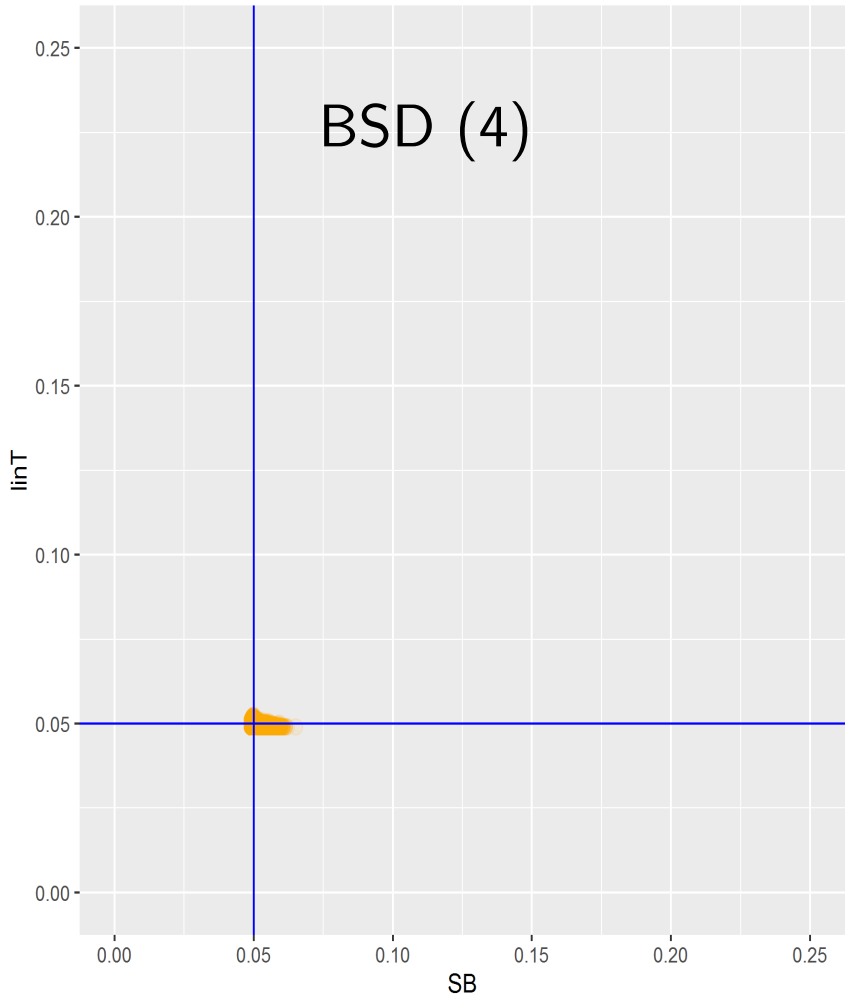




6. CSE - Result: both Biases for (N=96)

setting: $N_E = N_C = 48, \eta = 0.2 \times \delta, \theta = 0.4 \times \sigma$





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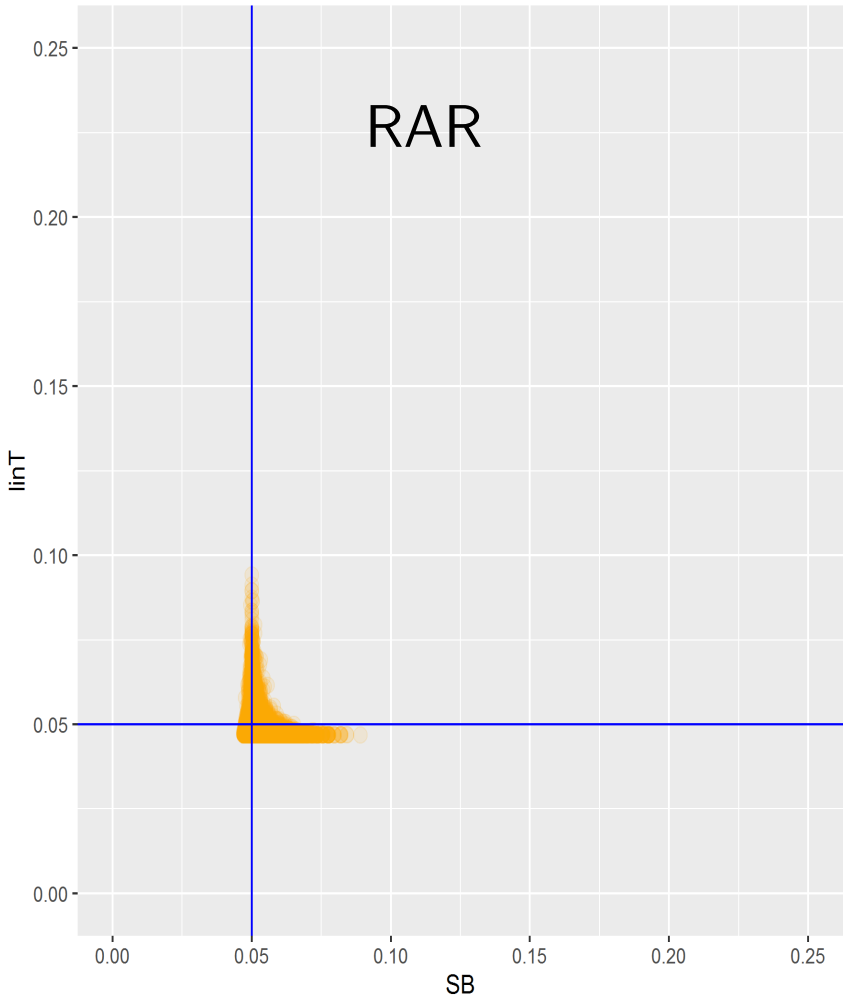
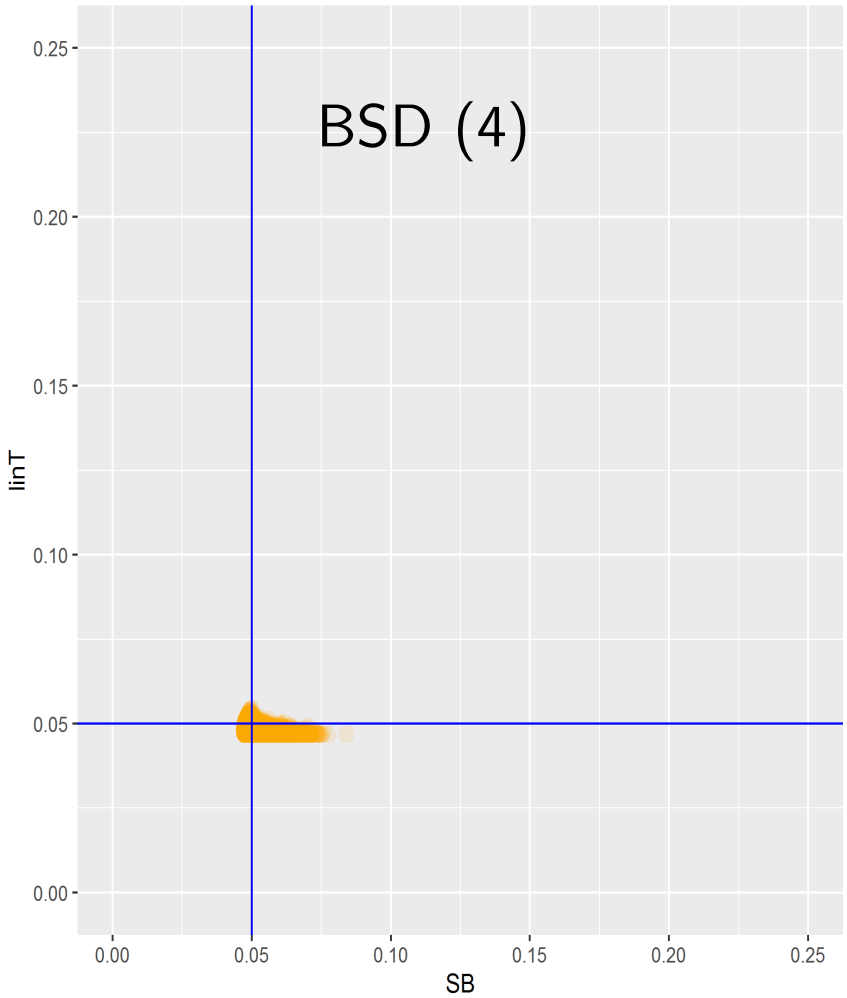
6. CSE - Result: both Biases for (N=96)

setting: $N_E = N_C = 48, \eta = 0.3 \times \delta, \theta = 0.6 \times \sigma$





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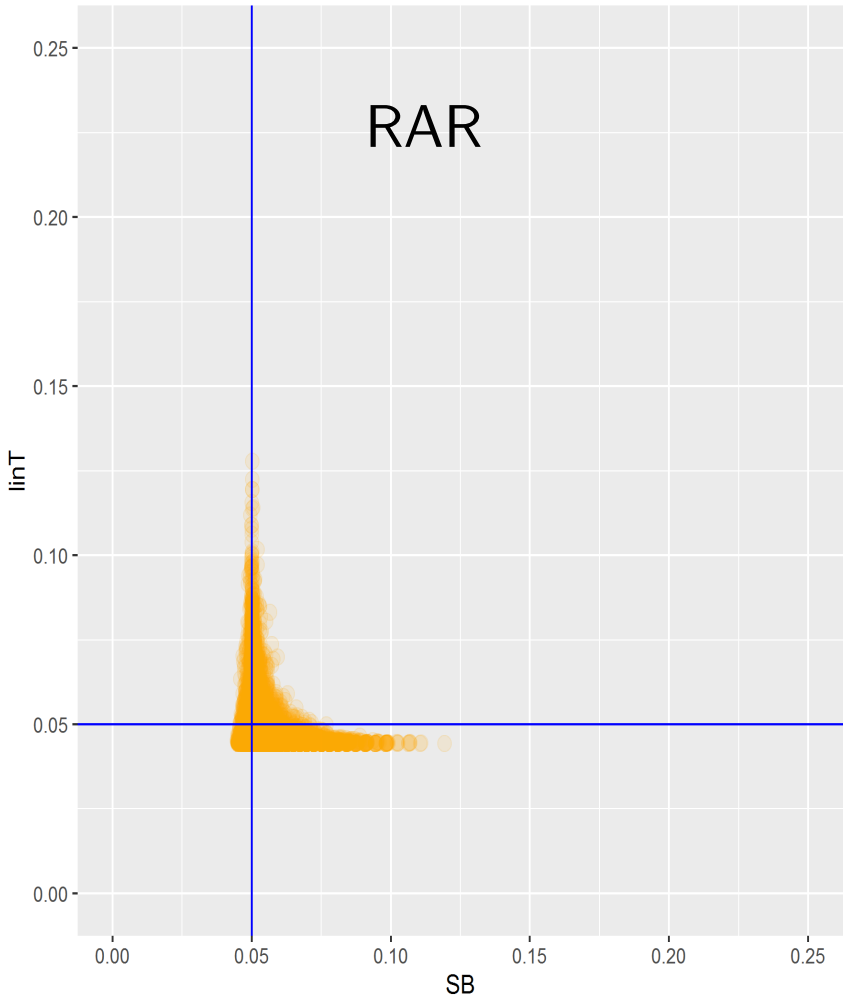
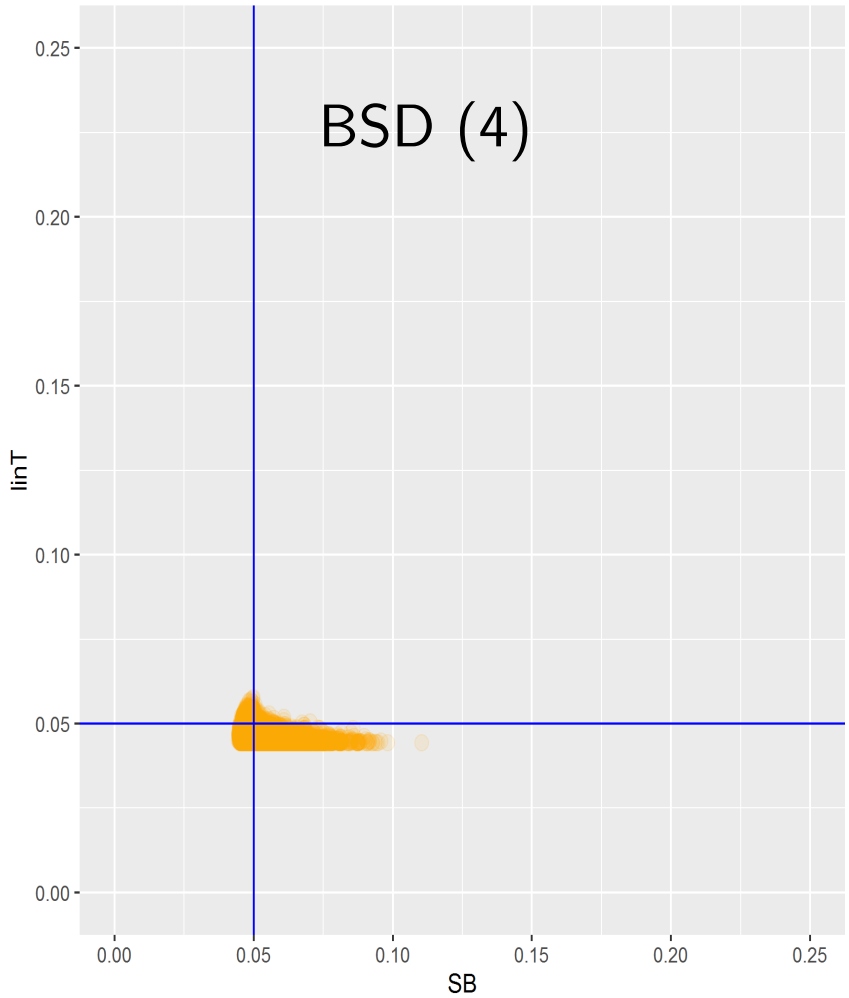
6. CSE - Result: both Biases for (N=96)

setting: $N_E = N_C = 48, \eta = 0.4 \times \delta, \theta = 0.8 \times \sigma$





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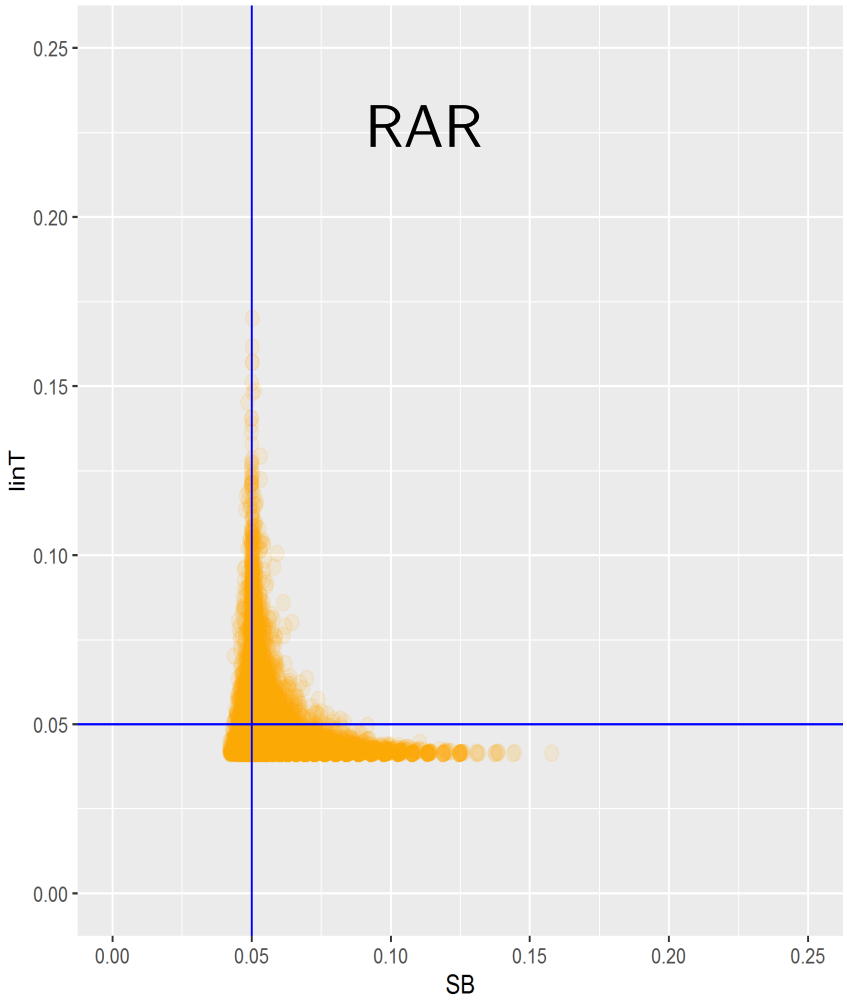
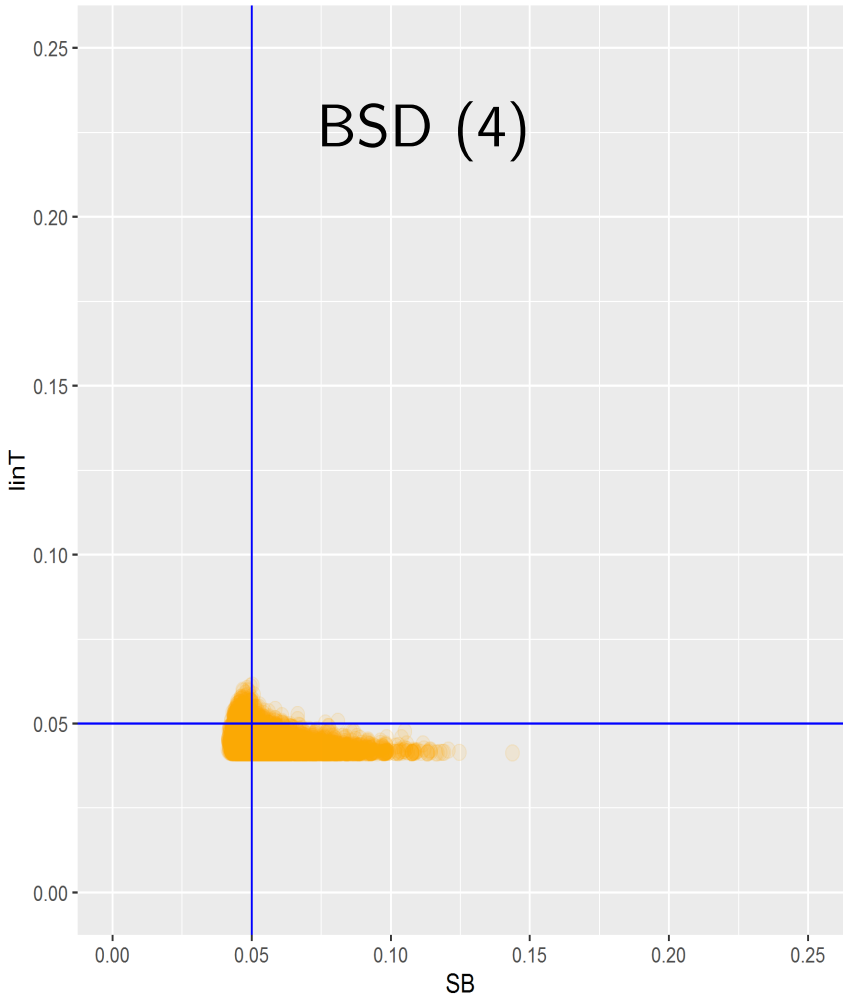
6. CSE - Result: both Biases for (N=96)

setting: $N_E = N_C = 48, \eta = 0.5 \times \delta, \theta = 1.0 \times \sigma$





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5. CSE - Software: randomizeR

. . . will use randomizeR, to conduct the evaluation and report the findings

current status of randomizeR

- implemented randomization procedures: `CR`, `RAR`, `PBR`, `RPBR`, `HADA`, `MP`, `BSD`, `UD`, `TBD`, `EBC`, `GBC`, `CD`, `BBC`

$\Rightarrow$ generating / saving a randomization sequence as `.csv` file

- implemented assessment criteria: `selBias`, `chronBias`, `corGuess`, `imbal`, `setPower`, `combineBias`

$\Rightarrow$ assessment and comparison of randomization procedures possible

in progress\next steps

- assessment of linked criteria, randomization tests, time to event model, multiarm model
- bias corrected test
- development of a shiny app

7. CSE - Discussion

- among other it is shown, that non of the randomization procedures perform uniformly best.
- practical restrictions, like balancing, risk of selection bias, risk of time trend bias may affect the choice of a randomization procedure.
- the choice the magnitude of η and θ have to be discussed within the practical context.
- time trend may be reasonable based on geographically wide distributed population, learning curves etc.
- at least a minimum effect (related to the clinical important effect size) should be assumed
- discussion of theses topics may help to understand the selection a randomization procedure within the particular/practical study settings

7. CSE - Discussion - Clinical implication

- ignoring the influence of selection bias may affect the test decision, by means of type-I-error rate probability
- the effect may be, that conservative or anticonservative test decisions occure

Conclusion

- presented a framework for scientific evaluation of randomization procedures in the presence of bias, to be included in trial documents
- understand that the treatment effect could be hidden by bias, which may result from a randomization sequence
- software to do assessment is available, R package *(randomizeR)*

- start understanding effects with time to event data *(Rückbeil, 2015)*
- start understanding effects with multifactorial designs *(Tasche, 2016)*
- start understanding the effect of missing values on the test decision based on randomization test

- no yet completely developed a bias corrected test *(Kennes, 2015)*

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Developments - A brief History

- **Randomization Procedures**: Rosenberger WF, Lachin JM (2016) Randomization in Clinical Trials. Wiley, New Jersey.

Selection Bias	**Chronlogical Bias**
Blackwell & Hodges (1957)	Altman & Royston (1998)
Proschan (1994)	Rosenkranz (2011)
Kennes, Cramer, Hilgers &Heussen (2011)	Tamm & Hilgers (2014)
Tamm, Cramer, Kennes & Heussen (2011)	
Langer (2014)	
Rückbeil (2015)	
Kennes, Rosenberger & Hilgers (2015)	
Tasche (2016)	

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- Kennes, L. N. (2012). The impact of selection bias on test decisions in randomized clinical trials *Master Thesis Mathematics RWTH Aachen*
- Kennes, L. N., Rosenberger William F., Hilgers, R.-D., (2015). Inference for blocked randomization under a selection bias model *Biometrics* 2015; **71**:y 979?984. doi.org/10.1111/biom.12334.
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- Rückbeil M. The impact of selection bias on test decisions in survival analysis *Master Thesis, RWTH Aachen University, Germany*, 2015
- Tasche A. Selection Bias bei mehr als zwei Behandlungsgruppen *Studienarbeit, RWTH Aachen University, Germany*, 2016
- Tamm M, Cramer E, Kennes LN, Heussen N Influence of Selection Bias on the Test Decision - A Simulation Study *Methods of Information in Medicine* 2012; **51**:138-143. DOI: 10.3414/ME11-01-0043.
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