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# Should the choice of the BOIN design parameter *p.tox* depend solely on the target DLT rate?

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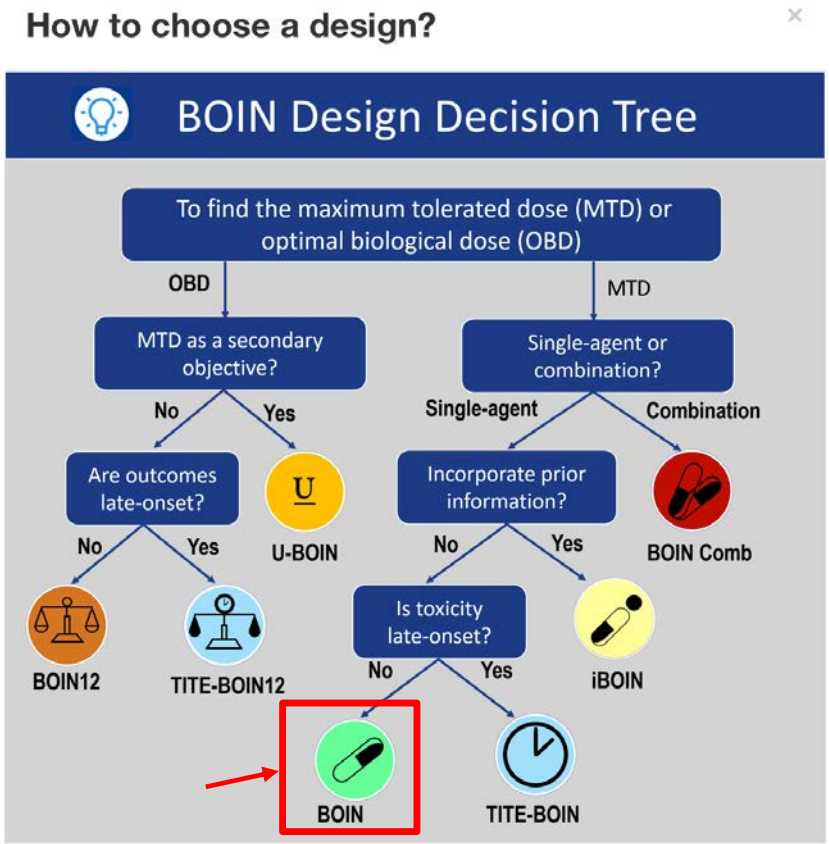
05/20/2024

https://doi.org/10.1101/2024.03.06.24303862

# BOIN Suite Designs


- https://trialdesign.org



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# BOIN Design

*Appl. Statist.* (2015)
**64**, *Part* 3, *pp.* 507–523

## Bayesian optimal interval designs for phase I clinical trials

Suyu Liu and Ying Yuan

*University of Texas MD Anderson Cancer Center, Houston, USA*

[Received April 2014. Revised August 2014]

**Summary.** In phase I trials, effectively treating patients and minimizing the chance of exposing them to subtherapeutic and overly toxic doses are clinicians' top priority. Motived by this practical consideration, we propose Bayesian optimal interval (BOIN) designs to find the maximum tolerated dose and to minimize the probability of inappropriate dose assignments for patients. We show, both theoretically and numerically, that the BOIN design not only has superior finite and large sample properties but also can be easily implemented in a simple way similar to the traditional '3+3' design. Compared with the well-known continual reassessment method, the BOIN design yields comparable average performance to select the maximum tolerated dose but has a substantially lower risk of assigning patients to subtherapeutic and overly toxic doses. We apply the BOIN design to two cancer clinical trials.

*Keywords*: Bayesian adaptive design; Decision error; Dose finding; Maximum tolerated dose

Erratum published on 11Jan2022:

https://rss.onlinelibrary.wiley.com/doi/full/10.1111/rssc.12541

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# https://trialdesign.org




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# R package

## Package 'BOIN'

October 12, 2022

**Type** Package

**Title** Bayesian Optimal INterval (BOIN) Design for Single-Agent and Drug- Combination Phase I Clinical Trials

**Version** 2.7.2

**Date** 2021-01-19

**Author** Ying Yuan and Suyu Liu

**Maintainer** Ying Yuan <yyuan@mdanderson.org>

**Imports** Iso

**Description** The Bayesian optimal interval (BOIN) design is a novel phase I clinical trial design for finding the maximum tolerated dose (MTD). It can be used to design both single-agent and drug-combination trials. The BOIN design is motivated by the top priority and concern of clinicians when testing a new drug, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses. The prominent advantage of the BOIN design is that it achieves simplicity and superior performance at the same time. The BOIN design is algorithm-based and can be implemented in a simple way similar to the traditional 3+3 design. The BOIN design yields an average performance that is comparable to that of the continual reassessment method (CRM, one of the best model-based designs) in terms of selecting the MTD, but has a substantially lower risk of assigning patients to subtherapeutic or overly toxic doses. For tutorial, please check Yan et al. (2020) <doi:10.18637/jss.v094.i13>.

**License** GPL-2



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## Fit-For-Purpose Tools and Supporting Information:

| Disease Area | Submitter | Tool | Trial Component | Issuance Date and Supporting Information |
|---|---|---|---|---|
| Alzheimer's disease | The Coalition Against Major Diseases (CAMD) | Disease Model: Placebo/Disease Progression | Demographics, Drop-out | Issued June 12, 2013<br>• Determination Letter |
| Multiple | Janssen Pharmaceuticals and Novartis Pharmaceuticals | Statistical Method: MCP-Mod | Dose-Finding | Issued May 26, 2016<br>• Determination Letter<br>• Statistical Review<br>• Pharmacometric Review |
| Multiple | Ying Yuan, PhD<br><br>The University of Texas MD Anderson Cancer Center Department of Biostatistics | Statistical Method: Bayesian Optimal Interval (BOIN) design | Dose-Finding | Issued: December 10, 2021<br>• Determination Letter<br>• Statistical Review<br>• Publication Erratum |
| Multiple | Pfizer | Statistical Method: Empirically Based Bayesian Emax Models | Dose-Finding | Issued: August 5, 2022<br>• Determination Letter<br>• Multidisciplinary Review |

https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative



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# FFP




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# R package BOIN Design Parameters I

This package allows the user to pre-specify **target dose limiting toxicity (DLT) rate ($\phi$)** as well as the following 8 design parameters:

1. ***ncohort****: The total number of cohorts.*

2. ***cohortsize****: The cohort size.*

3. ***n.earlystop****: The early stopping parameter. If the number of patients treated at the current dose reaches n.earlystop, stop the trial early and select the MTD based on the observed data. The default value of n.earlystop = 100 essentially turns off this type of early stopping.*



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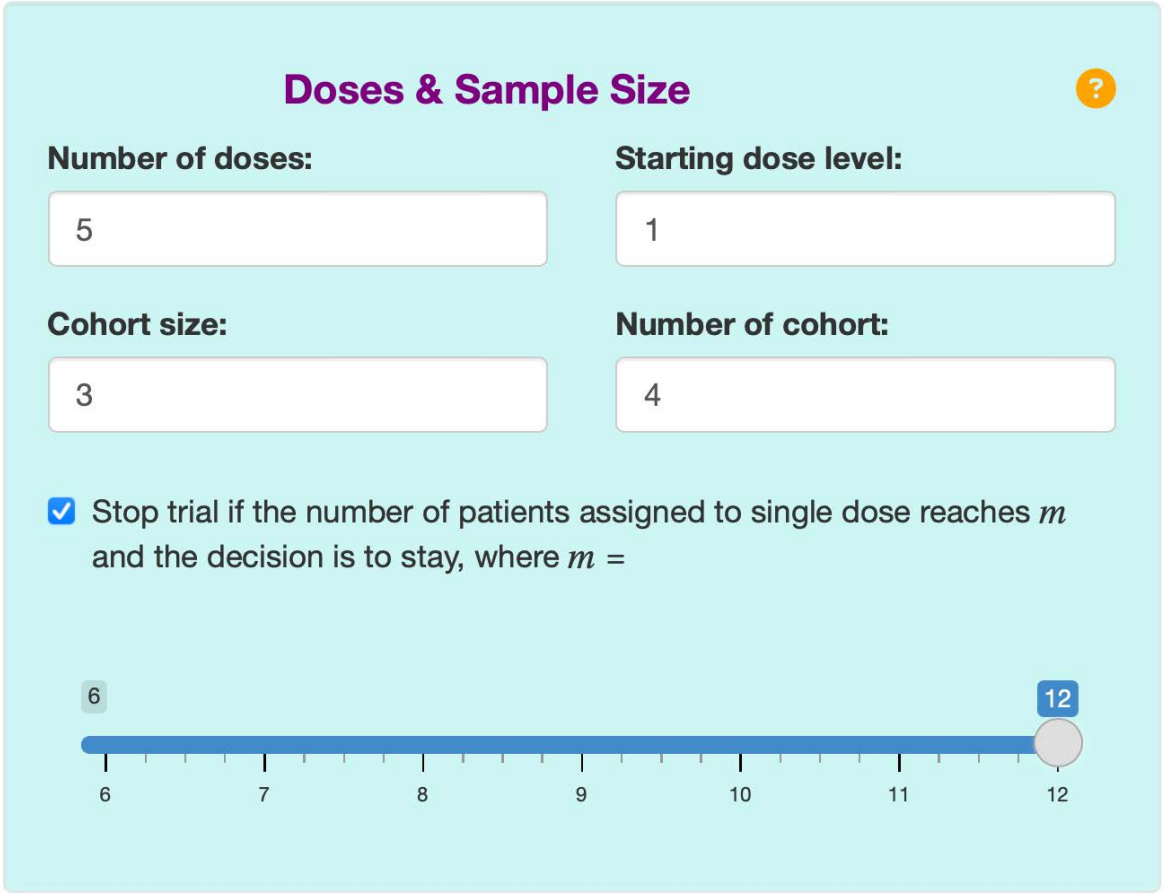
# https://trialdesign.org BOIN Parameters




- ***ncohort = 4***
- ***cohortsize = 3***
- ***n.earlystop = 12***



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# R package BOIN Design Parameters II

4. ***p.saf*** **($\phi_1$):** The highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that dose escalation should be made. The default value of *p.saf* = 0.6 * *target DLT rate*.

5. ***p.tox*** **($\phi_2$):** The lowest toxicity probability that is deemed overly toxic such that dose de- escalation is required. The default value of *p.tox* = 1.4 * *target DLT rate*.



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# https://trialdesign.org BOIN Parameters

**Target Probability**

**Target Toxicity Probability $\phi$ :**

0.25

☐ Use the default escalation and de-escalation boundaries (recommended).

The default boundaries are $\lambda_1$ =0.197 and $\lambda_2$ =0.298 for target toxicity probability 0.25

**Escalation boundary $\lambda_1$ :** 0.197

**De-escalation boundary $\lambda_2$ :** 0.298

The dose escalation/de-escalation boundaries correspond to the use of the following alternative hypotheses for minimizing the decision error of dose assignment: underdosing hypothesis $\phi_1$ =0.15 and overdosing hypothesis $\phi_2$ =0.35.

$$\lambda_d = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right\}}$$

$$\lambda_e = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}}$$

- ***p.saf = $\phi_1$ = 0.15***
- ***p.tox = $\phi_2$ = 0.35***



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# R package BOIN Design Parameters III

6. ***cutoff.eli***: The cutoff to eliminate the overly toxic dose for safety. We recommend the default value *cutoff.eli* = 0.95 for general use.
7. ***extrasafe***: Set *extrasafe* = TRUE to impose a stricter stopping rule.
8. ***offset***: A small positive number (between 0 and 0.5) to control how strict the stopping rule is when *extrasafe* = TRUE. A larger value leads to a stricter stopping rule. The default value *offset* = 0.05 generally works well.



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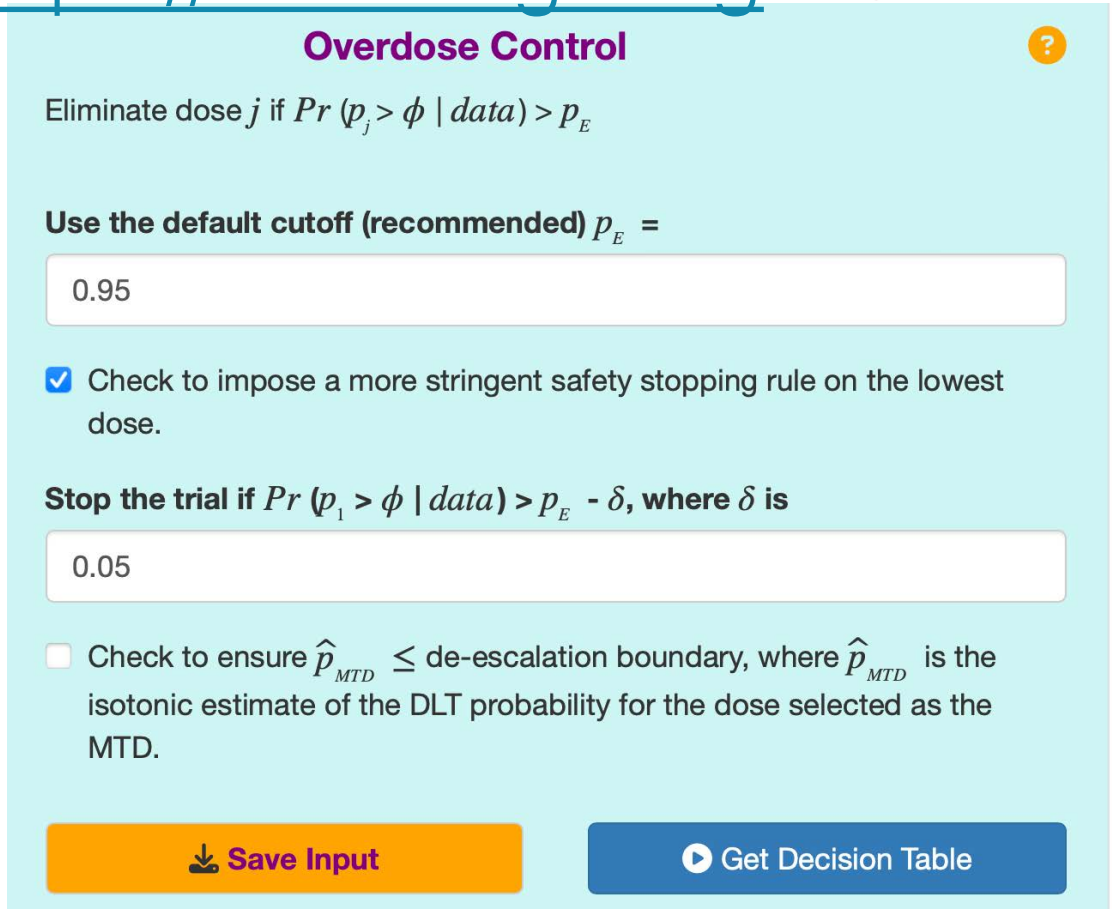
# https://trialdesign.org BOIN Parameters




- ***cutoff.eli* = 0.95**
- ***extrasafe* = TRUE**
- ***offset = 0.05***



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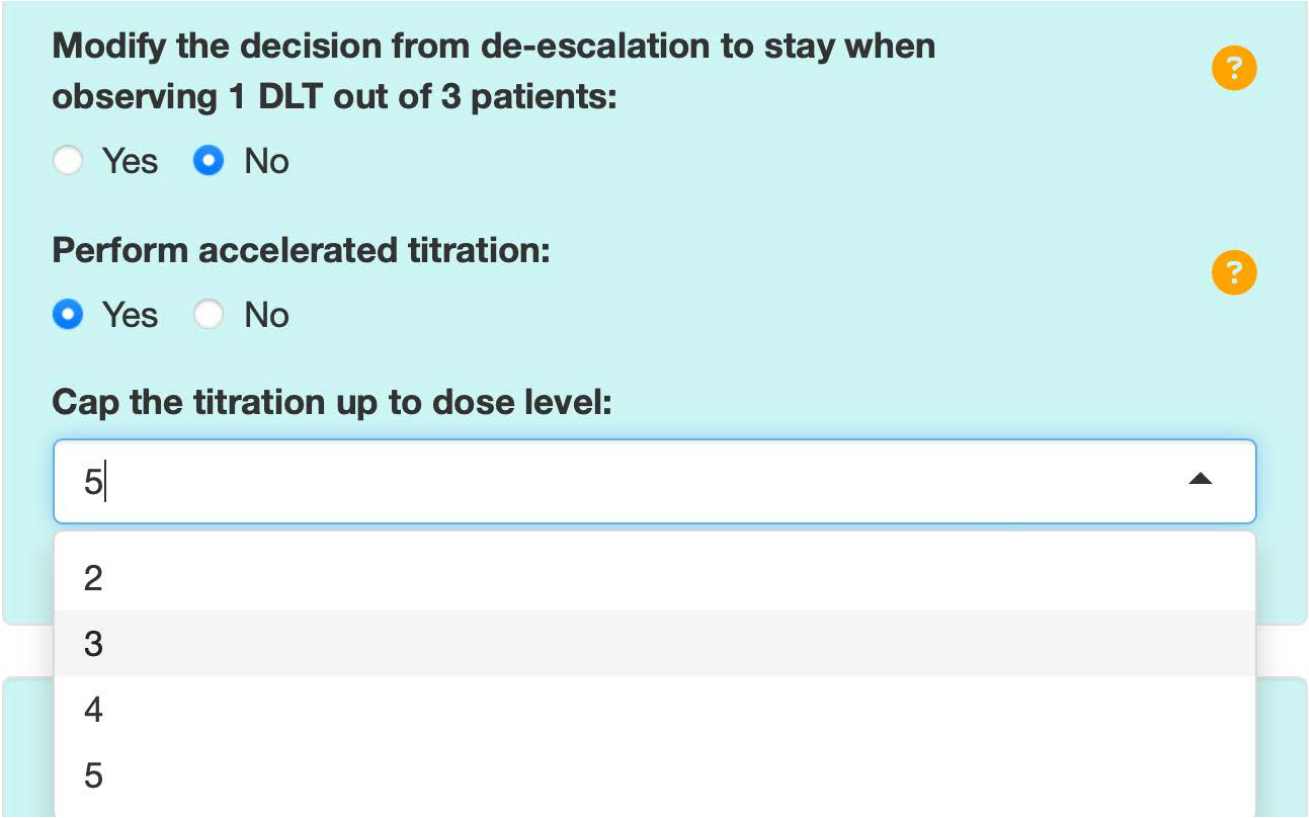
# https://trialdesign.org BOIN Parameters



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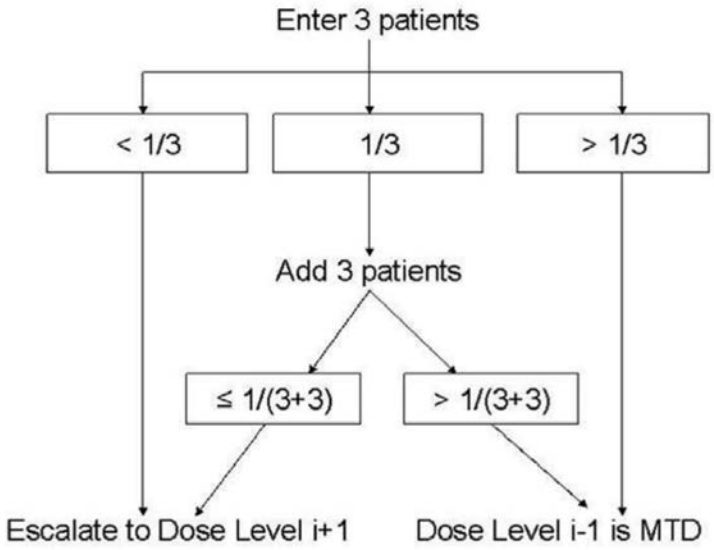
# 3 + 3 Design




Design Flow Chart | Decision Table

**Table 1: Dose escalation/de-escalation rule.**

Copy | CSV | Excel | Print

| | | | | |
|---|---|---|---|---|
| Number of evaluable patients treated | **3** | 4 | 5 | **6** |
| Escalate if # of DLT <= | **0** | 0 | 0 | **1** |
| Stay if # of DLT = | **1** | 1 | 1 | **NA** |
| De-escalate if # of DLT >= | **2** | 2 | 2 | **2** |
| Eliminate if # of DLT >= | **2** | 2 | 2 | **2** |

Note. # of DLT is the number of patients with at least 1 DLT.

https://doi.org/10.1016/j.conctc.2018.10.006



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# 3 + 3 Design

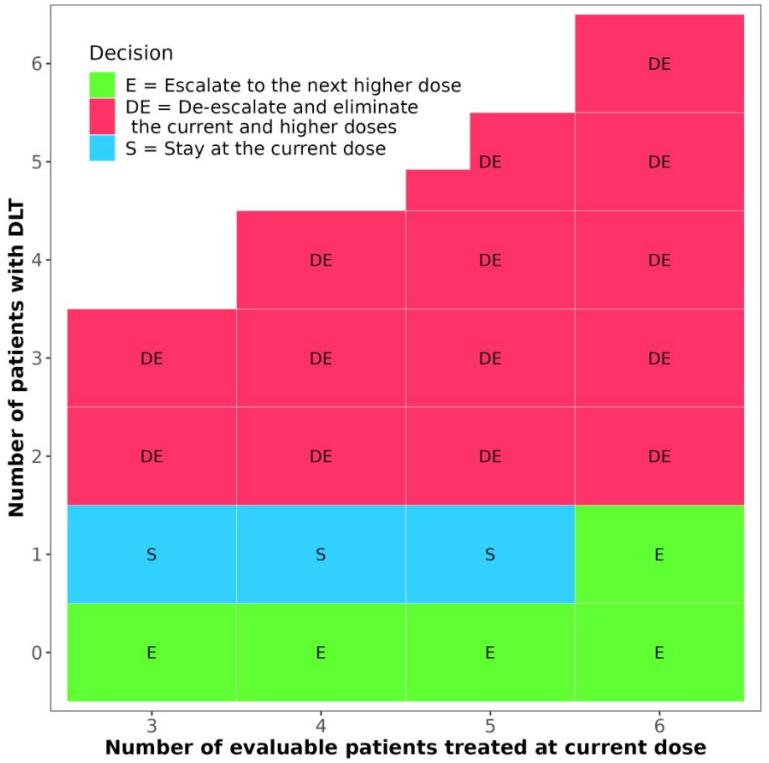
Design Flow Chart | Decision Table

**Table 1: Dose escalation/de-escalation rule.**

Copy | CSV | Excel | Print

| Number of evaluable patients treated | **3** | 4 | 5 | **6** |
|---|---|---|---|---|
| Escalate if # of DLT <= | **0** | 0 | 0 | **1** |
| Stay if # of DLT = | **1** | 1 | 1 | **NA** |
| De-escalate if # of DLT >= | **2** | 2 | 2 | **2** |
| Eliminate if # of DLT >= | **2** | 2 | 2 | **2** |

Note. # of DLT is the number of patients with at least 1 DLT.



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# 3 + 3 Design

**Appendix 1: Trial and Design Specifications**

| Parameter | Value |
|---|---|
| Number of doses | 5 |
| Starting dose | 1 |
| Max sample size | 6 |
| Cohort size | 3 |
| Stop trial if # patients assigned to single dose reaches | 6 |
| Use accelerated titration | FALSE |
| Target toxicity probability | 0.176 |
| Use the default alternatives to minimize decision errors | FALSE |
| Alternative (unacceptable high toxicity) for optimization | 0.9 |
| Alternative (unacceptable low toxicity) for optimization | 0.16 |
| Escalation boundary | 0.167 |
| De-escalation boundary | 0.559 |
| Eliminate dose threshold | 0.855 |
| Impose a more stringent safety stopping rule | FALSE |
| Require the isotonic estimate of the DLT probability for the dose selected as the MTD less than the de-escalation boundary | FALSE |
| Number of repetitions per scenario | 1000 |
| Random number generator seed | 6 |

```
> get.boundary(target=0.1761482, ncohort=10, cohortsize=3, n.earlystop = 6,
+              p.saf = 0.1582749, p.tox = 0.892814, cutoff.eli = 0.8548338,
+              extrasafe = F)
$lambda_e
[1] 0.1670842

$lambda_d
[1] 0.556843

$boundary_tab

Number of patients treated 3 6
Escalate if # of DLT <=    0 1
Deescalate if # of DLT >=  2 2
Eliminate if # of DLT >=   2 2

$full_boundary_tab

Number of patients treated  1  2 3 4 5 6
Escalate if # of DLT <=     0  0 0 0 0 1
Deescalate if # of DLT >=   1  2 2 2 2 2
Eliminate if # of DLT >=   NA NA 2 2 2 2

attr(,"class")
[1] "boin"
Warning message:
In get.boundary(target = 0.1761482, ncohort = 10, cohortsize = 3,  :
  the value of n.earlystop is too low to ensure good operating characteristic
s. Recommend n.earlystop = 9 to 18.
```



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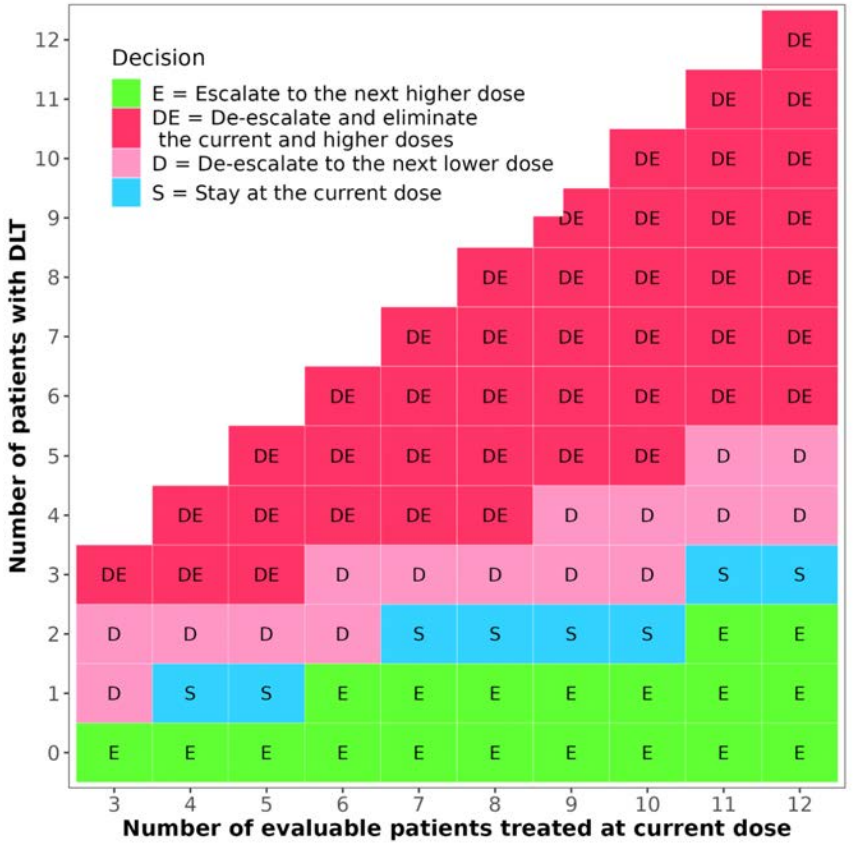
# BOIN Example

**Appendix 1: Trial and Design Specifications**

| Parameter | Value |
|---|---|
| Number of doses | 5 |
| Starting dose | 1 |
| Max sample size | 12 |
| Cohort size | 3 |
| Stop trial if # patients assigned to single dose reaches | 12 |
| Use accelerated titration | FALSE |
| Target toxicity probability | 0.25 |
| Use the default alternatives to minimize decision errors | FALSE |
| Alternative (unacceptable high toxicity) for optimization | 0.35 |
| Alternative (unacceptable low toxicity) for optimization | 0.15 |
| Escalation boundary | 0.197 |
| De-escalation boundary | 0.298 |
| Eliminate dose threshold | 0.95 |
| Impose a more stringent safety stopping rule | FALSE |
| Require the isotonic estimate of the DLT probability for the dose selected as the MTD less than the de-escalation boundary | FALSE |
| Number of repetitions per scenario | 1000 |
| Random number generator seed | 6 |



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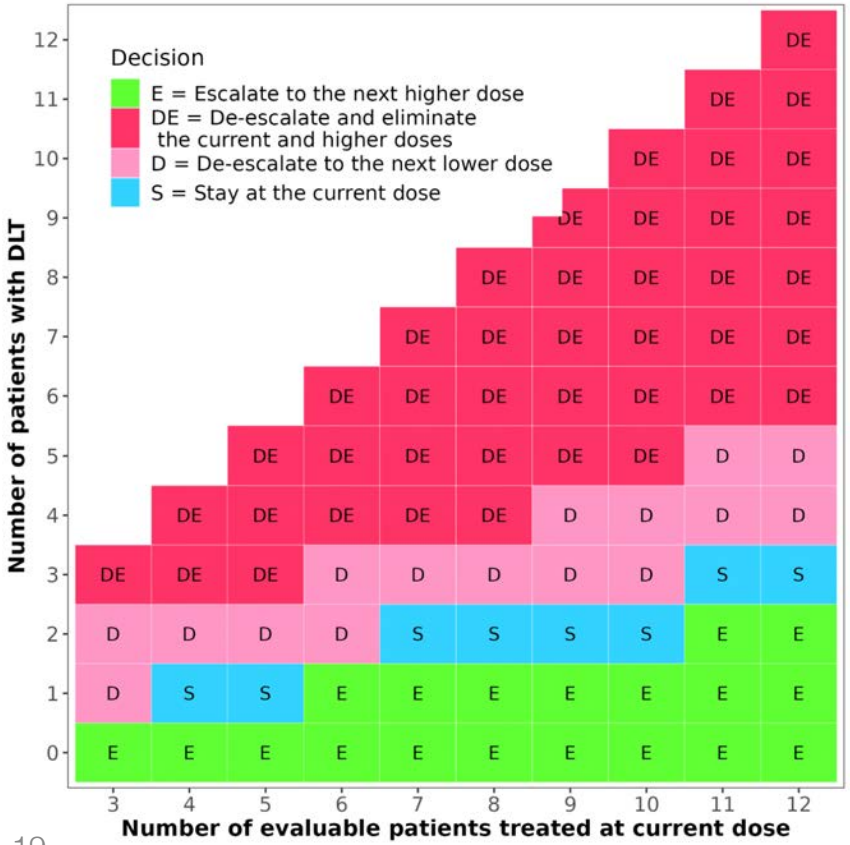
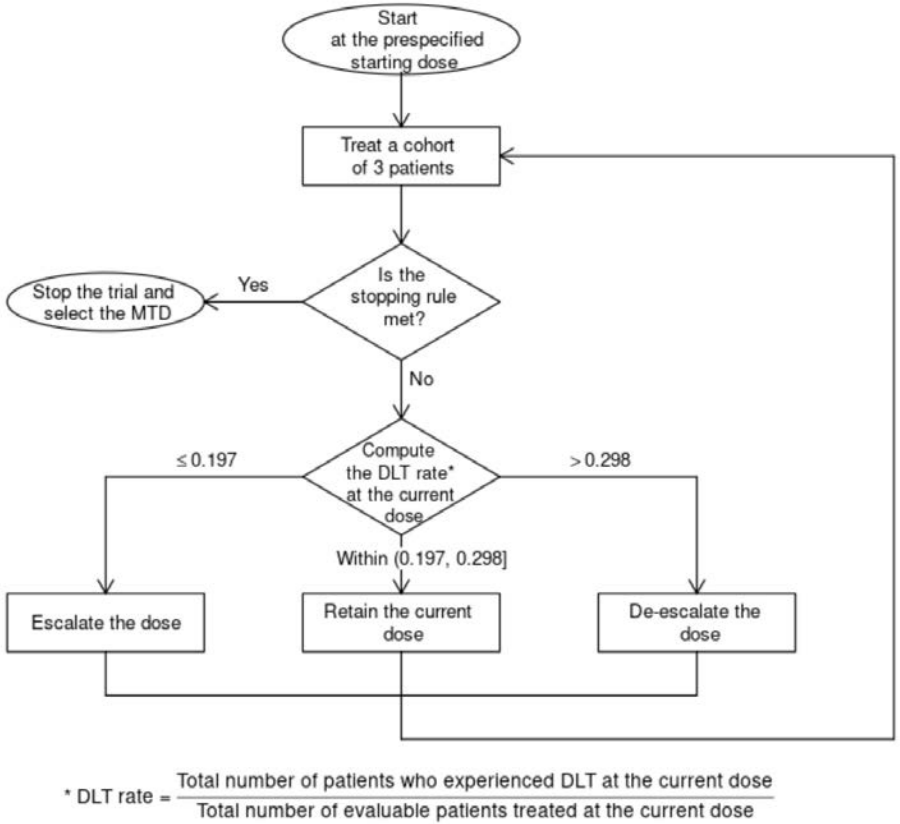
# BOIN Example




$$\text{* DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of evaluable patients treated at the current dose}}$$

# BOIN Example

**Table 1.** Dose escalation/de-escalation rule for the BOIN design

| | The number of evaluable patients treated at current dose | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Decision | **3** | 4 | 5 | **6** | 7 | 8 | **9** | 10 | 11 | **12** |
| Escalate if # of DLT <= | **0** | 0 | 0 | **1** | 1 | 1 | **1** | 1 | 2 | **2** |
| Stay if # of DLT = | **NA** | 1 | 1 | **NA** | 2 | 2 | **2** | 2 | 3 | **3** |
| De-escalate if # of DLT >= | **1** | 2 | 2 | **2** | 3 | 3 | **3** | 3 | 4 | **4** |
| Eliminate if # of DLT >= | **3** | 3 | 3 | **4** | 4 | 4 | **5** | 5 | 6 | **6** |

Note. “# of DLT” is the number of patients with at least 1 DLT.



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# Question

- As with other model-based dose-finding algorithms, the operating characteristics of a BOIN design are greatly affected by the choice of its design parameters.
- Although setting the BOIN design parameter *p.tox* = 1.4 * *target.DLT.rate* is recommended in almost all BOIN methodology articles and is the default value in the R package *BOIN*, it's unclear why the choice of p.tox should only depend on the target DLT rate and whether certain range of p.tox could produce the same BOIN boundary table.



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# Simulation Setup

- In this simulation study, following parameters will be varied one at a time, using R package *BOIN*, to explore each parameter's effect on the equivalence intervals of *p.saf* and *p.tox*:
  - 1) target DLT rate,
  - 2) *n.earlystop*,
  - 3) *cutoff.eli*,
  - 4) *cohortsize*
  - 5) *ncohort*.
- The 3+3 design boundary table will be used as a simple example to explore all equivalent sets of BOIN design parameters that can generate the same boundary table.



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# Simulation Setup

- All dose escalation/de-escalation boundary tables were calculated using the *get.bounddary()* function from R package *BOIN*
- *tryCatch()* function was used to handle *get.bounddary()* errors such as “the probability deemed safe cannot be higher than or too close to the target!”

- All *p.saf* and *p.tox* values that produce the same BOIN boundary table (*i.e.* the same *$boundary_tab* output) are considered equivalent.
- While the *$boundary_tab* output remain the same, the *$full_boundary_tab* outputs may be different.



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# Equivalent p.saf and p.tox under varying target DLT rates

Equivalent values of *p.saf* and *p.tox* were explored via uniform search under varying target DLT rates: *target* = 10%, 15%, 20%, 25%, 30%, 35%, or 40% and fixed values of following parameters :

- ncohort = 10
- cohortsize = 3
- n.earlystop = 12
- cutoff.eli = 95%
- extrasafe = FALSE

For each target DLT rate under evaluation, 100,000 pairs of *p.saf* and *p.tox* values were randomly drawn from the following uniform distributions :

- p.saf <- runif(1, min=0, max=target-0.0000001)
- p.tox <- runif(1, min=target+0.0000001, max=1)



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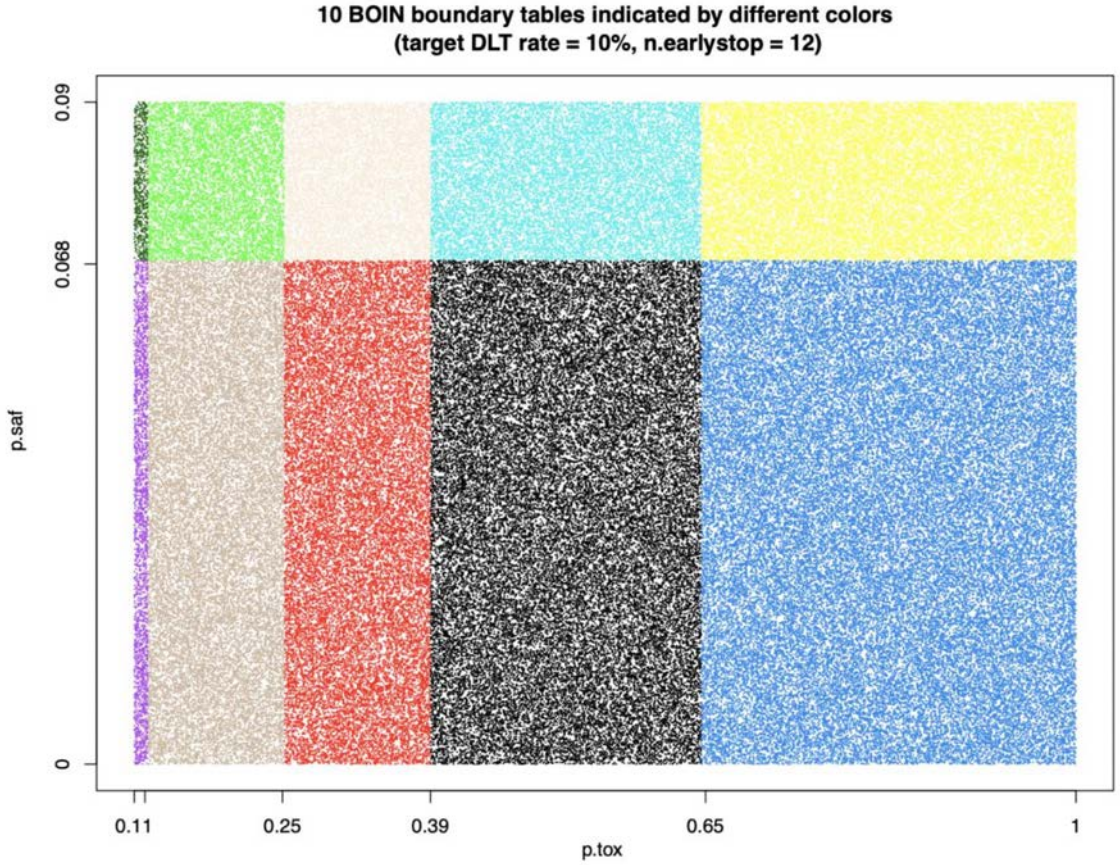


**Figure 2a:** equivalent intervals of *p.saf* and *p.tox* under target DLT rate = 10%, *cohortsize* = 3, *ncohort* = 10, *n.earlystop* = 12, *cutoff.eli* = 95%, and *extrasafe* = FALSE.



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```
> get.boundary(target=0.1, ncohort=10, cohortsize=3, n.earlystop = 12,
+              p.saf = 0.00001, p.tox = 0.123, cutoff.eli = 0.95,
+              extrasafe = F)
$lambda_e
[1] 0.01130893

$lambda_d
[1] 0.1111531

$boundary_tab

Number of patients treated 3 6 9 12
Escalate if # of DLT <=    0 0 0  0
Deescalate if # of DLT >=  1 1 2  2
Eliminate if # of DLT >=   2 2 3  3

$full_boundary_tab

Number of patients treated  1  2 3 4 5 6 7 8 9 10 11 12
Escalate if # of DLT <=     0  0 0 0 0 0 0 0 0  0  0  0
Deescalate if # of DLT >=   1  1 1 1 1 1 1 1 2  2  2  2
Eliminate if # of DLT >=   NA NA 2 2 2 2 2 3 3  3  3  3

attr(,"class")
[1] "boin"
```



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```
> get.boundary(target=0.1, ncohort=10, cohortsize=3, n.earlystop = 12,
+              p.saf = 0.067, p.tox = 0.14, cutoff.eli = 0.95,
+              extrasafe = F)
$lambda_e
[1] 0.08250041

$lambda_d
[1] 0.1190318

$boundary_tab

Number of patients treated 3 6 9 12
Escalate if # of DLT <=    0 0 0  0
Deescalate if # of DLT >=  1 1 2  2
Eliminate if # of DLT >=   2 2 3  3

$full_boundary_tab

Number of patients treated  1  2 3 4 5 6 7 8 9 10 11 12
Escalate if # of DLT <=     0  0 0 0 0 0 0 0 0  0  0  0
Deescalate if # of DLT >=   1  1 1 1 1 1 1 1 2  2  2  2
Eliminate if # of DLT >=   NA NA 2 2 2 2 2 3 3  3  3  3

attr(,"class")
[1] "boin"
```



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```
> get.boundary(target=0.1, ncohort=10, cohortsize=3, n.earlystop = 12,
+              p.saf = 0.067, p.tox = 0.25, cutoff.eli = 0.95,
+              extrasafe = F)
$lambda_e
[1] 0.08250041

$lambda_d
[1] 0.1659562

$boundary_tab

Number of patients treated 3 6 9 12
Escalate if # of DLT <=    0 0 0  0
Deescalate if # of DLT >=  1 1 2  2
Eliminate if # of DLT >=   2 2 3  3

$full_boundary_tab

Number of patients treated  1  2 3 4 5 6 7 8 9 10 11 12
Escalate if # of DLT <=     0  0 0 0 0 0 0 0 0  0  0  0
Deescalate if # of DLT >=   1  1 1 1 1 1 2 2 2  2  2  2
Eliminate if # of DLT >=   NA NA 2 2 2 2 2 3 3  3  3  3

attr(,"class")
[1] "boin"
```



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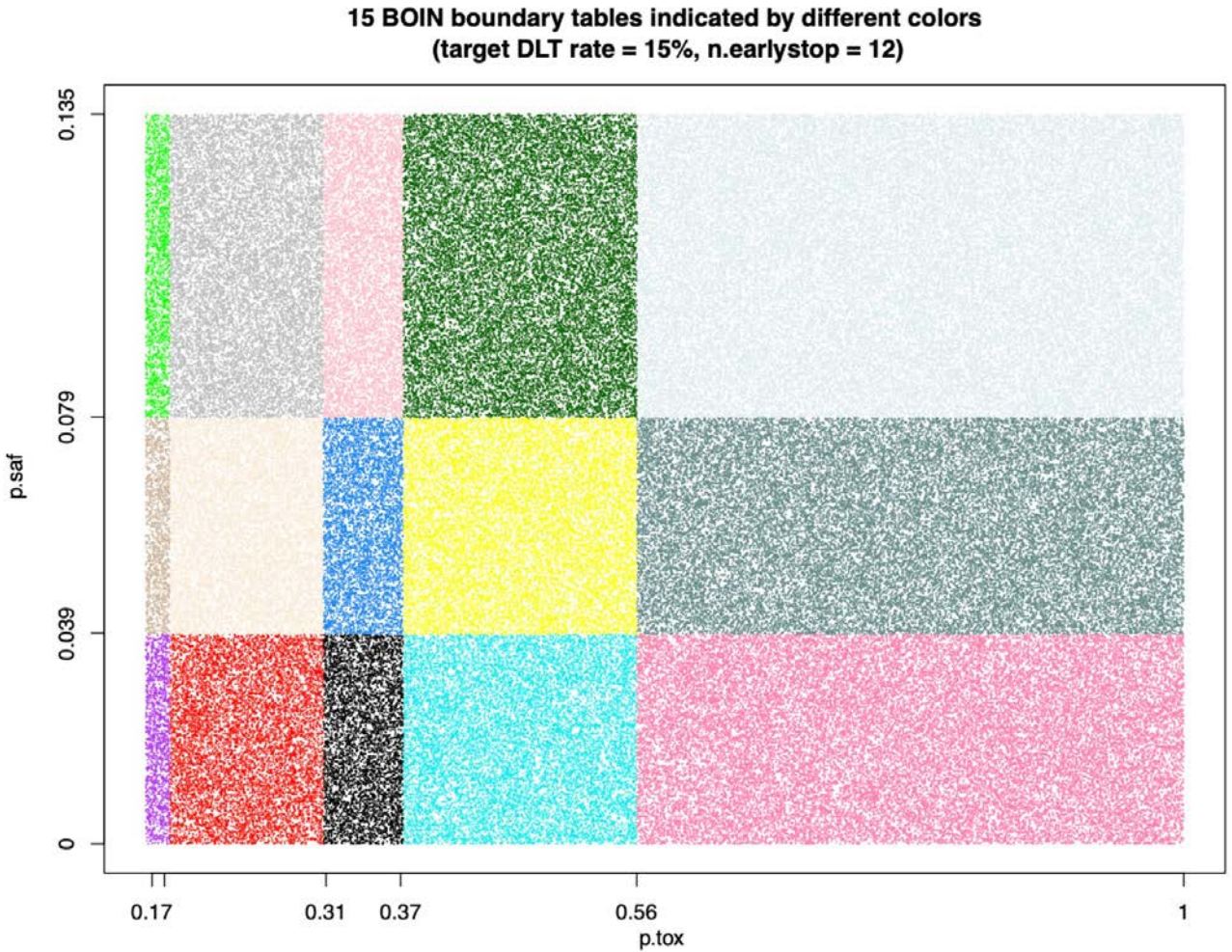




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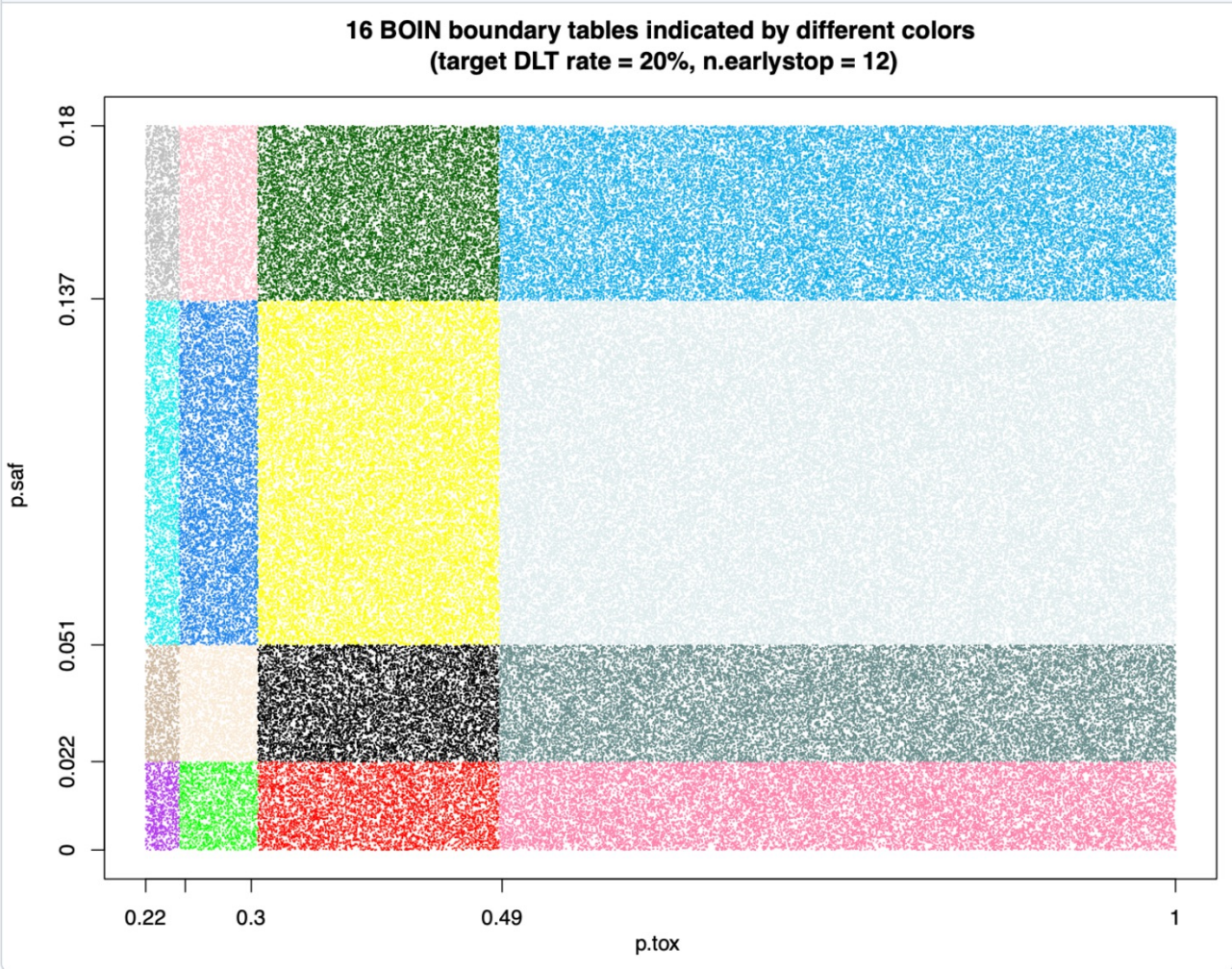




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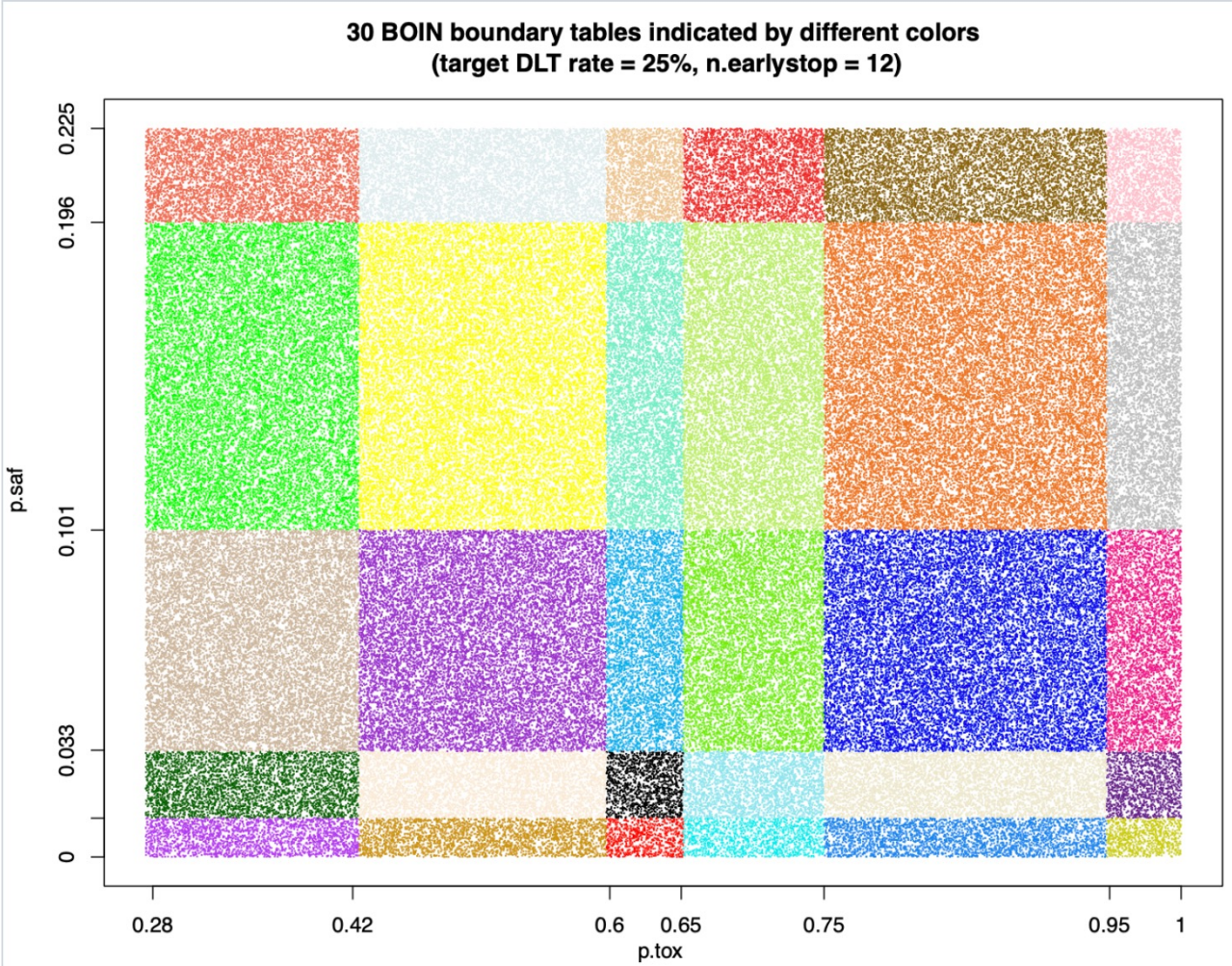




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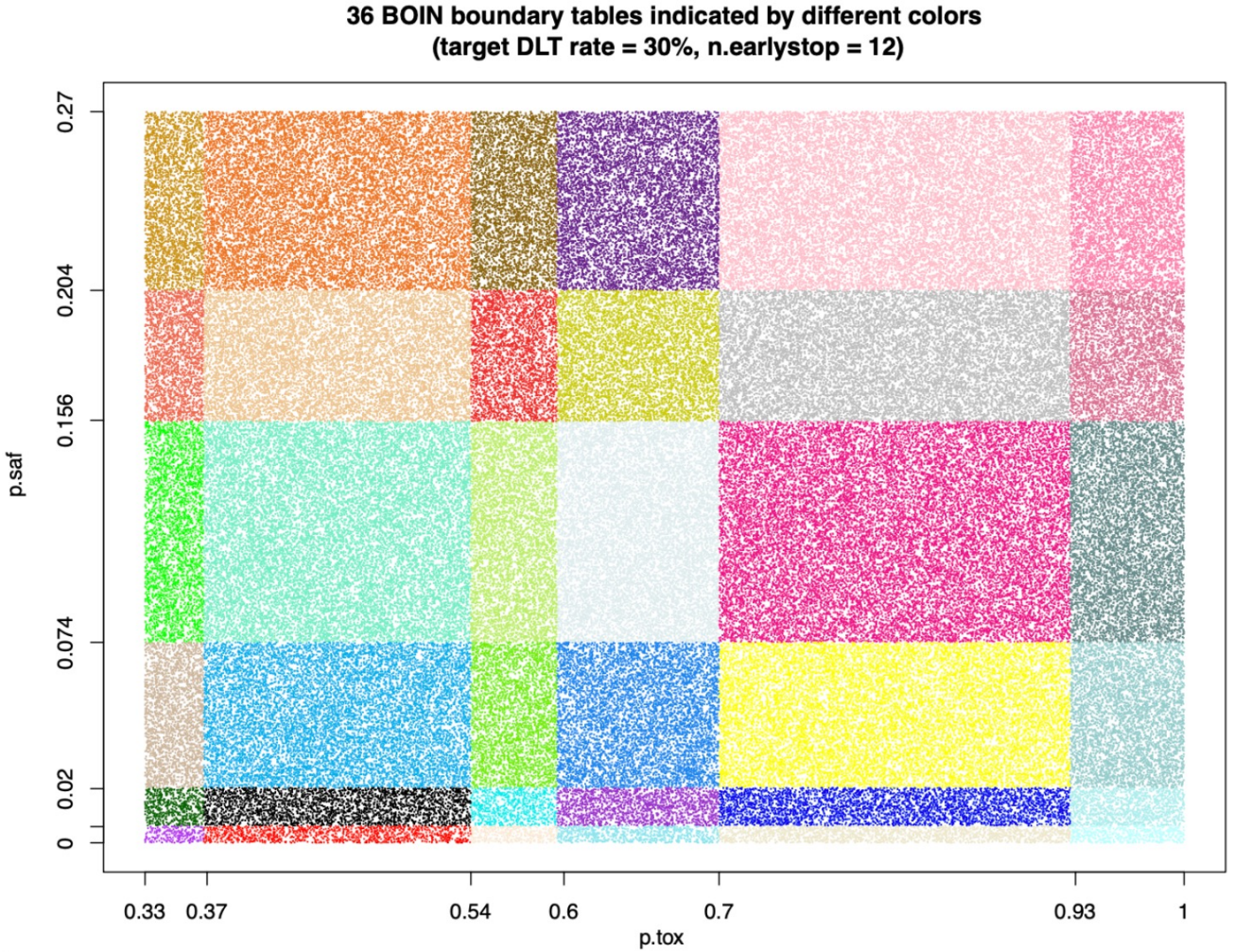




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# Equivalent p.saf and p.tox under varying n.earlystop

Equivalent values of p.saf and p.tox were explored via uniform search under varying n.earlystop = 15, 18, 21, 24, 27, or 30 and fixed values of following parameters:

- ncohort = 10
- cohortsize = 3
- target = 10% (target DLT rate)
- cutoff.eli = 95%
- extrasafe = FALSE

For each n.earlystop value, 100,000 pairs of p.saf and p.tox values were randomly drawn from the following uniform distributions:

- p.saf <- runif(1, min=0, max=target-0.0000001)
- p.tox <- runif(1, min=target+0.0000001, max=1)



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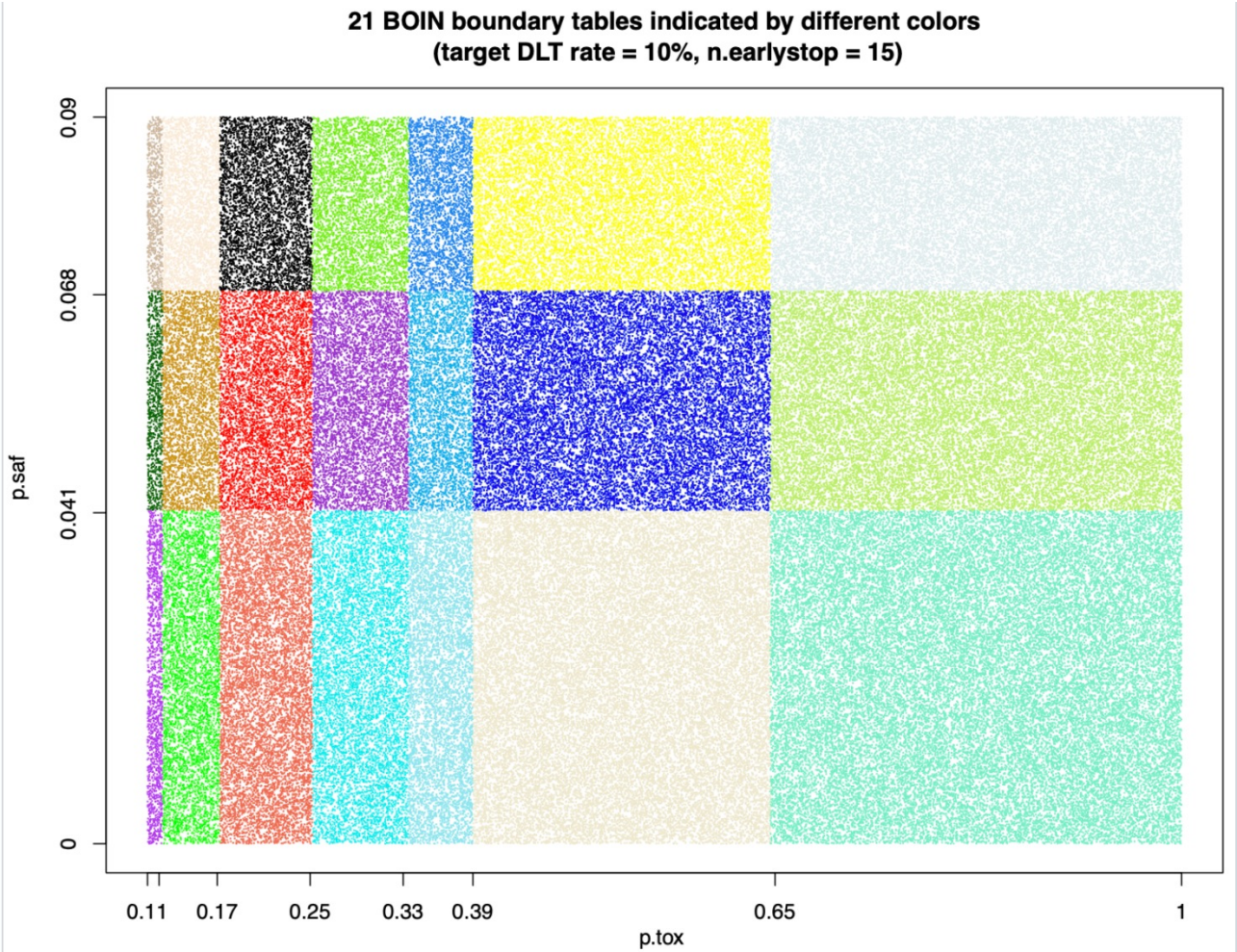




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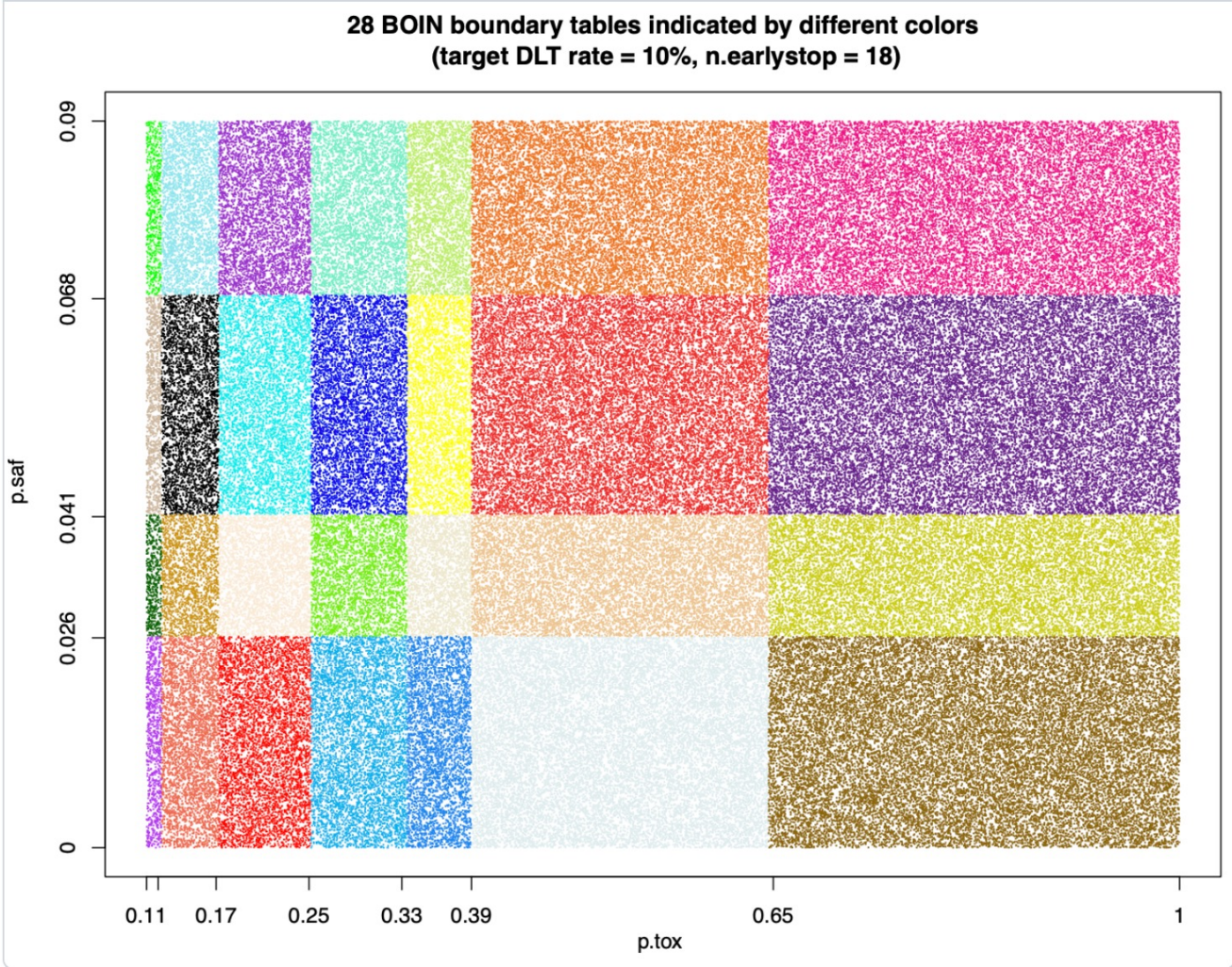




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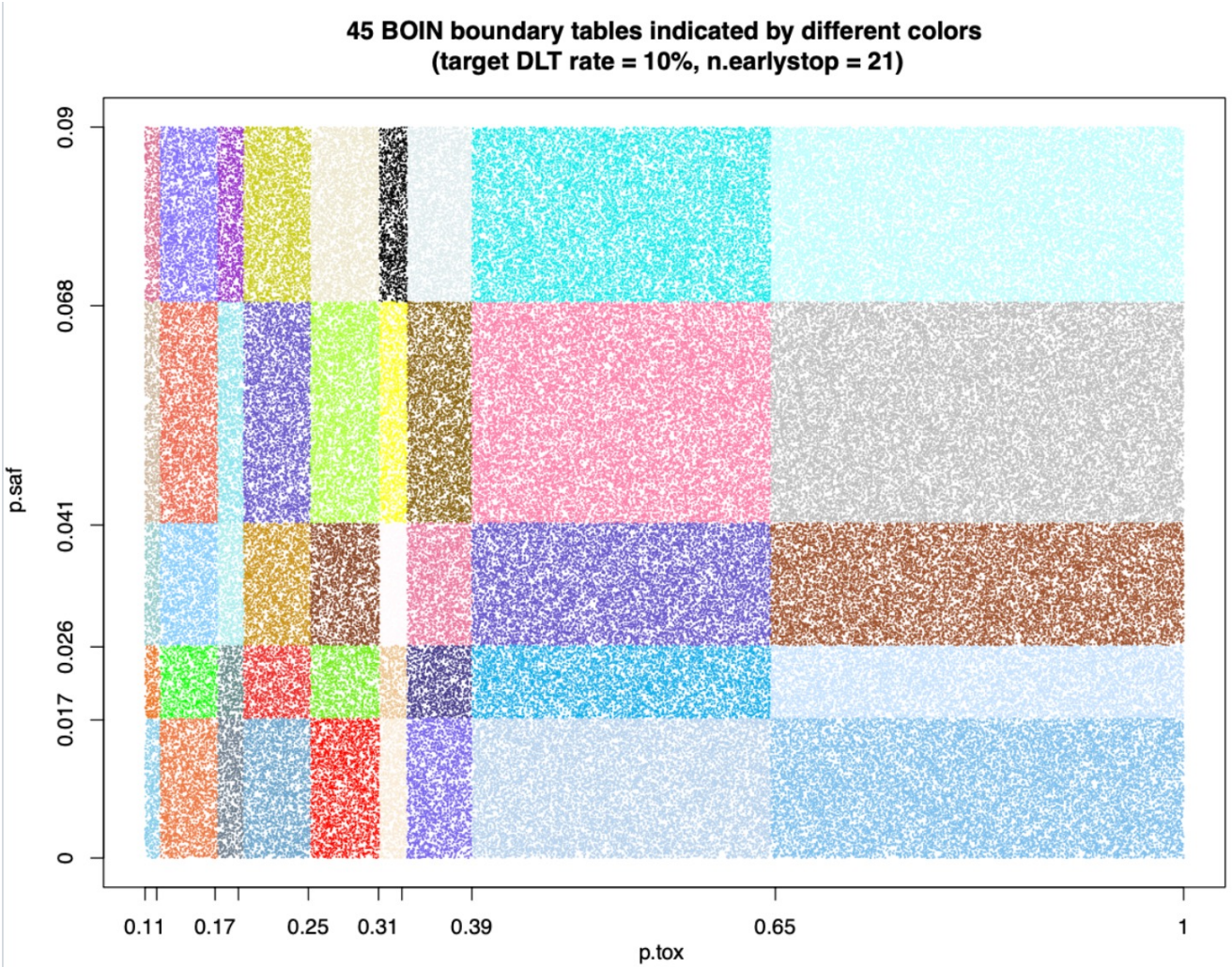




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# Equivalent p.saf and p.tox under varying cutoff.eli

Equivalent values of p.saf and p.tox were explored via uniform search under varying cutoff.eli = 70%, 80%, 90%, 97%, or 99% and fixed values of following design parameters:

- ncohort = 10
- cohortsize = 3
- target = 10% (target DLT rate)
- n.earlystop = 12
- extrasafe = FALSE

For each cutoff.eli value, 100,000 pairs of p.saf and p.tox values were randomly drawn from the uniform distributions described in the previous sections.



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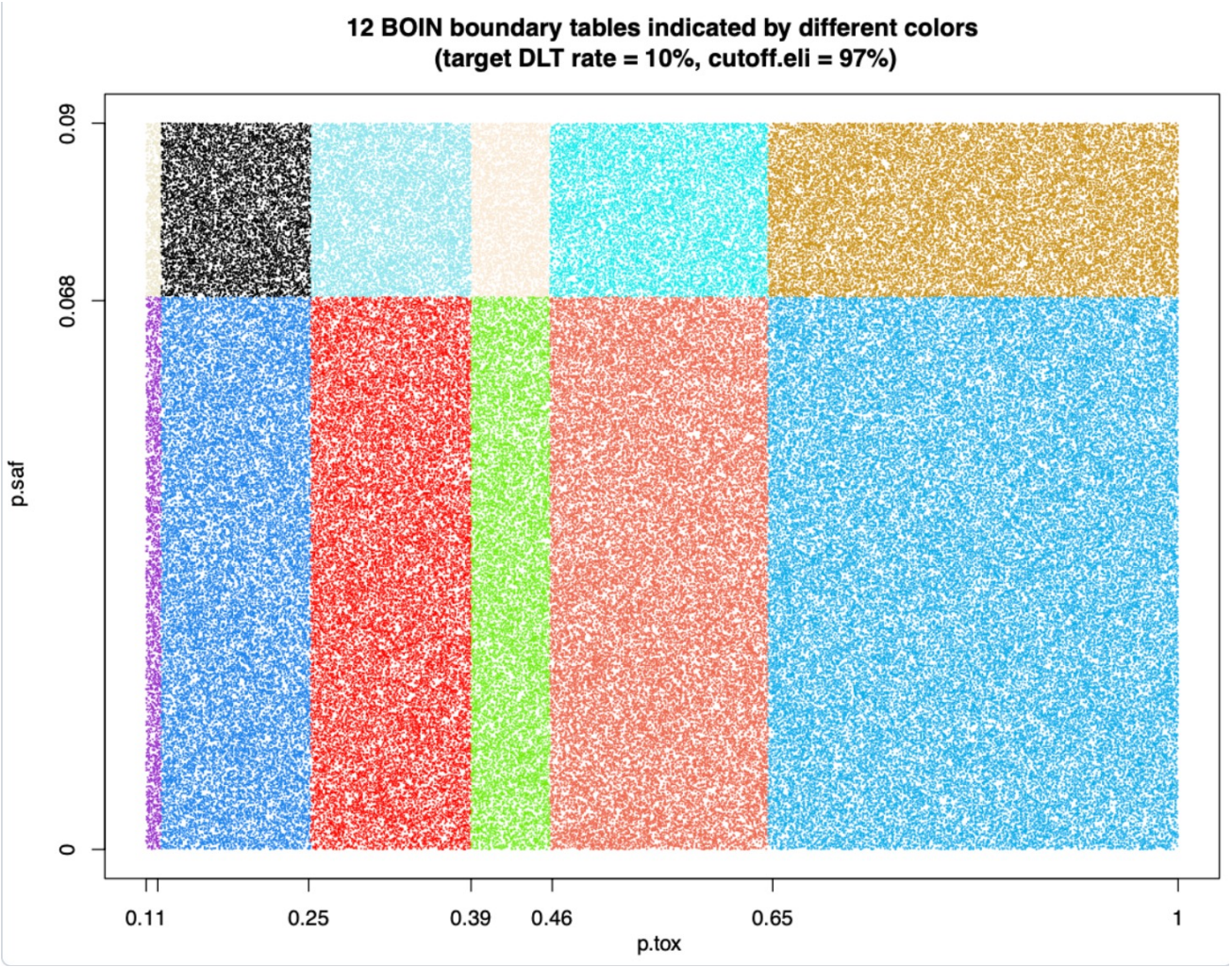




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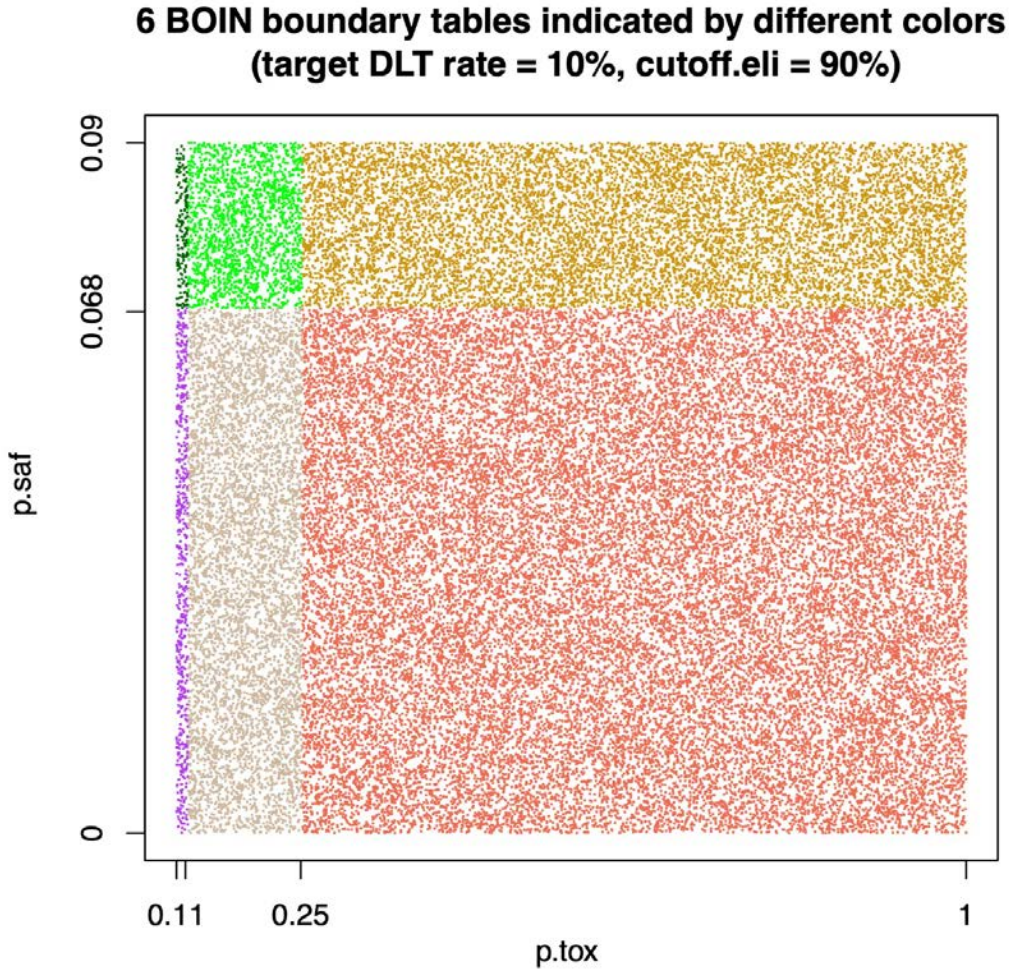




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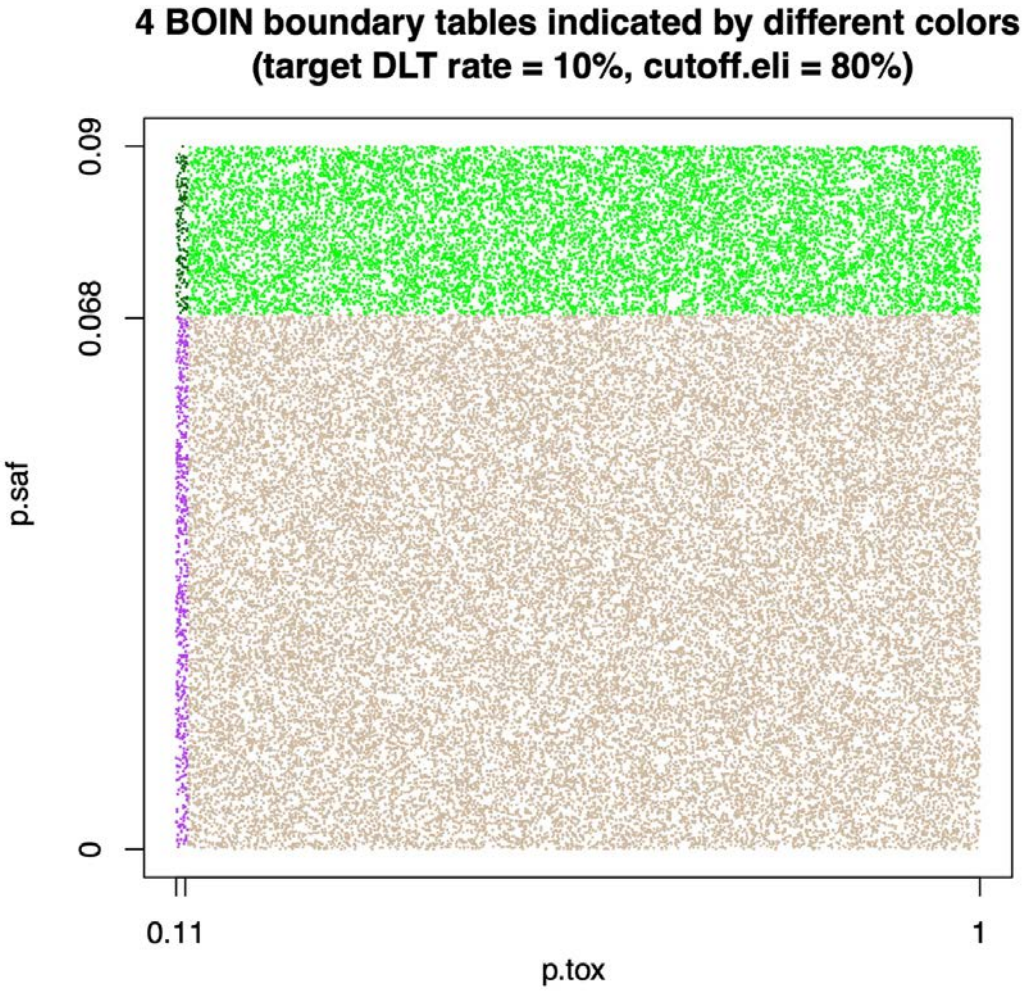




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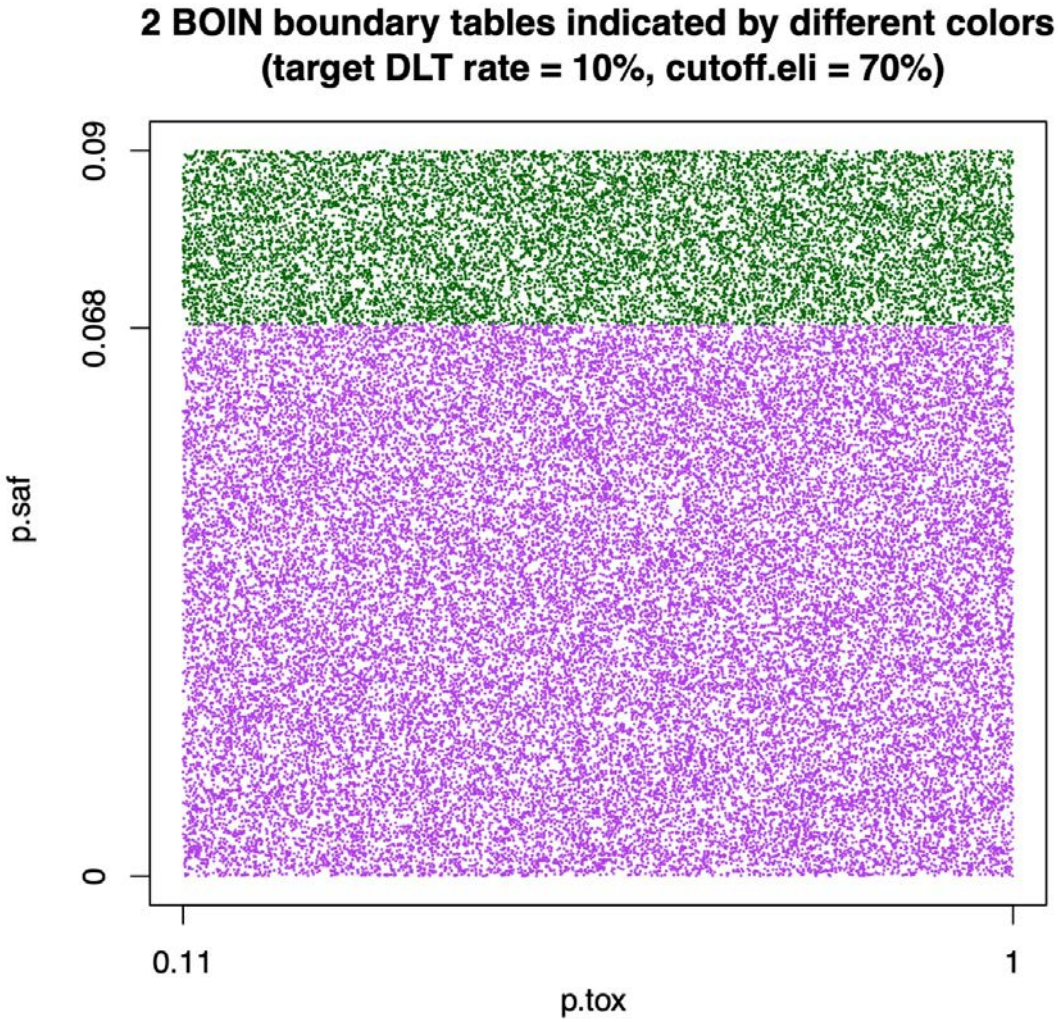




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# Equivalent p.saf and p.tox under varying cohortsize

Equivalent values of p.saf and p.tox were explored via uniform search under varying cohortsize = 4, 5,  6, 7, or 8 and fixed values of following design parameters:

- ncohort = 10
- cutoff.eli = 95%
- target = 10% (target DLT rate)
- n.earlystop = 12
- extrasafe = FALSE

For each cohortsize, 100,000 pairs of p.saf and p.tox values were randomly drawn from the uniform distributions described in the previous sections.



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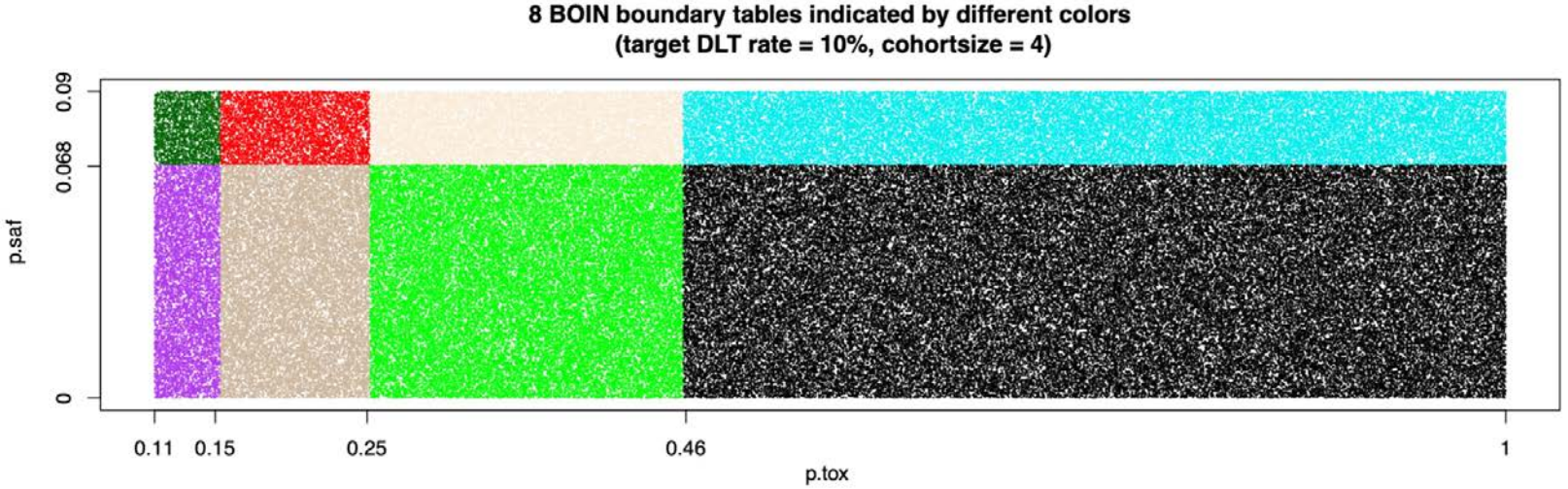


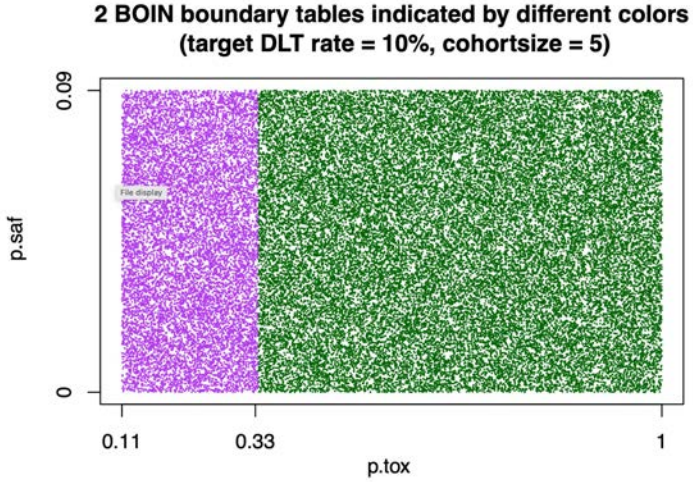


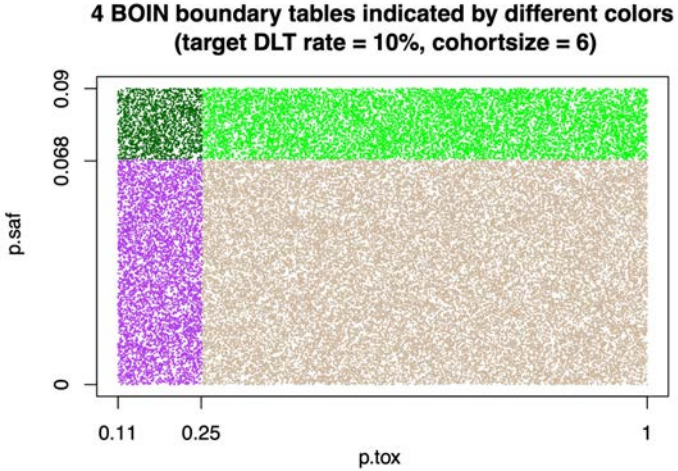




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# Equivalent p.saf and p.tox under varying ncohort

Equivalent values of p.saf and p.tox were explored via uniform search under varying ncohort = 5,  6, 7, 8, 9, 12, 20, 40, or and fixed values of following design parameters:

- target = 10% (target DLT rate)
- cohortsize = 3
- n.earlystop = 12
- cutoff.eli = 95%
- extrasafe = FALSE

For each ncohort value, 100,000 pairs of p.saf and p.tox values were randomly drawn from the uniform distributions described in the previous sections



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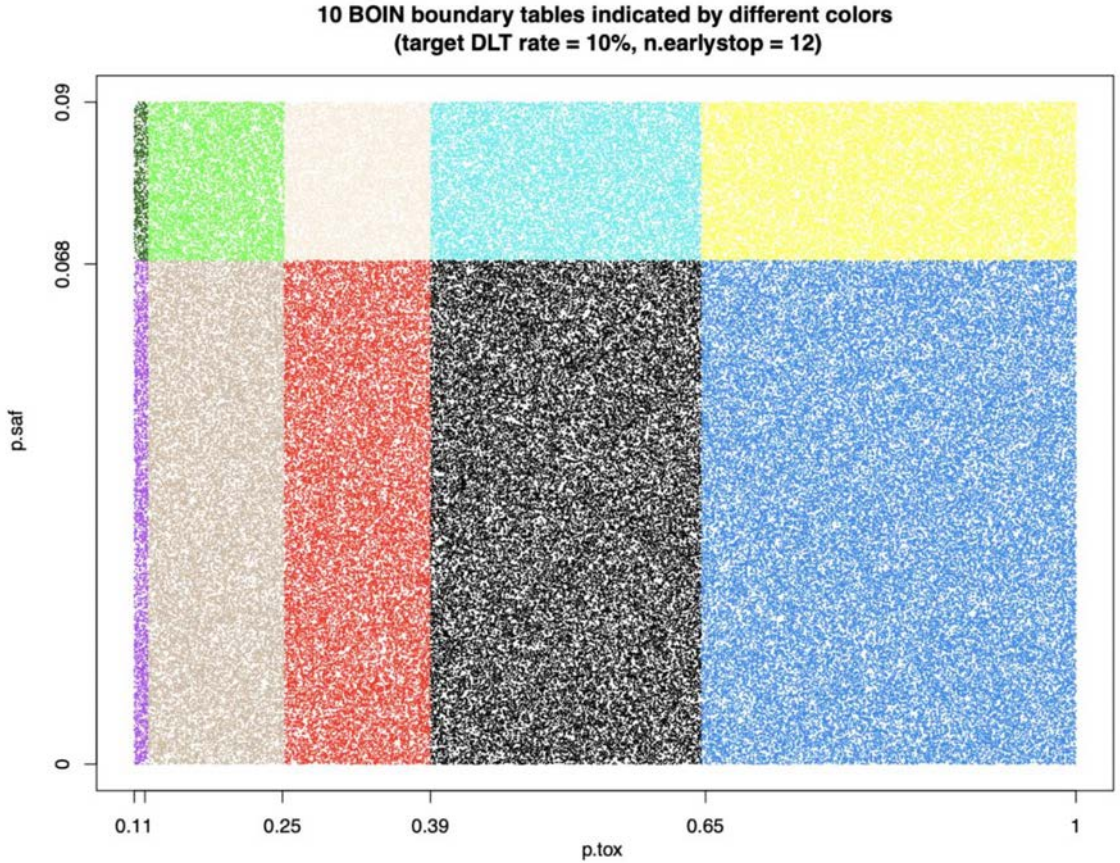


When target DLT rate = 10%, cohortsize = 3, n.earlystop = 12, cutoff.eli = 95%, and extrasafe = FALSE, there are the same 10 possible BOIN boundary tables, regardless of the choices of ncohort $\in$ {5, 6, 7, 8, 9, 10, 12, 20, 40, 100}.



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```
> get.boundary(target=0.1, ncohort=5, cohortsize=3, n.earlystop = 12,
+              p.saf = 0.068, p.tox = 0.14, cutoff.eli = 0.95,
+              extrasafe = F)
$lambda_e
[1] 0.08306706

$lambda_d
[1] 0.1190318

$boundary_tab

Number of patients treated 3 6 9 12
Escalate if # of DLT <=    0 0 0  0
Deescalate if # of DLT >=  1 1 2  2
Eliminate if # of DLT >=   2 2 3  3

$full_boundary_tab

Number of patients treated  1  2 3 4 5 6 7 8 9 10 11 12
Escalate if # of DLT <=     0  0 0 0 0 0 0 0 0  0  0  0
Deescalate if # of DLT >=   1  1 1 1 1 1 1 1 2  2  2  2
Eliminate if # of DLT >=   NA NA 2 2 2 2 2 3 3  3  3  3

attr(,"class")
[1] "boin"
```



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```
> get.boundary(target=0.1, ncohort=10000, cohortsize=3, n.earlystop = 12,
+              p.saf = 0.00001, p.tox = 0.14, cutoff.eli = 0.95,
+              extrasafe = F)
$lambda_e
[1] 0.01130893

$lambda_d
[1] 0.1190318

$boundary_tab

Number of patients treated 3 6 9 12
Escalate if # of DLT <=    0 0 0  0
Deescalate if # of DLT >=  1 1 2  2
Eliminate if # of DLT >=   2 2 3  3

$full_boundary_tab

Number of patients treated  1  2 3 4 5 6 7 8 9 10 11 12
Escalate if # of DLT <=     0  0 0 0 0 0 0 0 0  0  0  0
Deescalate if # of DLT >=   1  1 1 1 1 1 1 1 2  2  2  2
Eliminate if # of DLT >=   NA NA 2 2 2 2 2 3 3  3  3  3

attr(,"class")
[1] "boin"
```



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# BOIN parameters for generating the 3+3 boundary table

Equivalent values of BOIN design parameters were explored via uniform search under varying offset = 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, or 0.49 and fixed values of following design parameters:

- cohortsize = 3
- ncohort = 10
- n.earlystop = 6
- extrasafe = TRUE
- target <- runif(1,min=0,max=0.5)
- p.saf <- runif(1,min=0,max=target-0.0000001)
- p.tox <- runif(1,min=target+0.0000001,max=1)
- cutoff.eli <- runif(1,min=0,max=1)

All parameter sets of BOIN design capable of yielding the 3+3 boundary table are viewed as being equivalent.



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# 3 + 3 BOIN Design

A random search script was used to sample 8,127 sets of BOIN parameters that can generate the 3+3 design boundary table. These 8,127 sets of BOIN parameter values satisfy following conditions:

- $0.17 < target.DLT.rate < 0.30$
- $0.08 < p.saf < 0.26$
- $0.306 - 0.85 * target.DLT.rate < p.saf < 0.0002 + 0.9 * target.DLT.rate$
- $p.saf > 0.4295 - 2.11 * target.DLT.rate + 3.1171 * target.DLT.rate^2$



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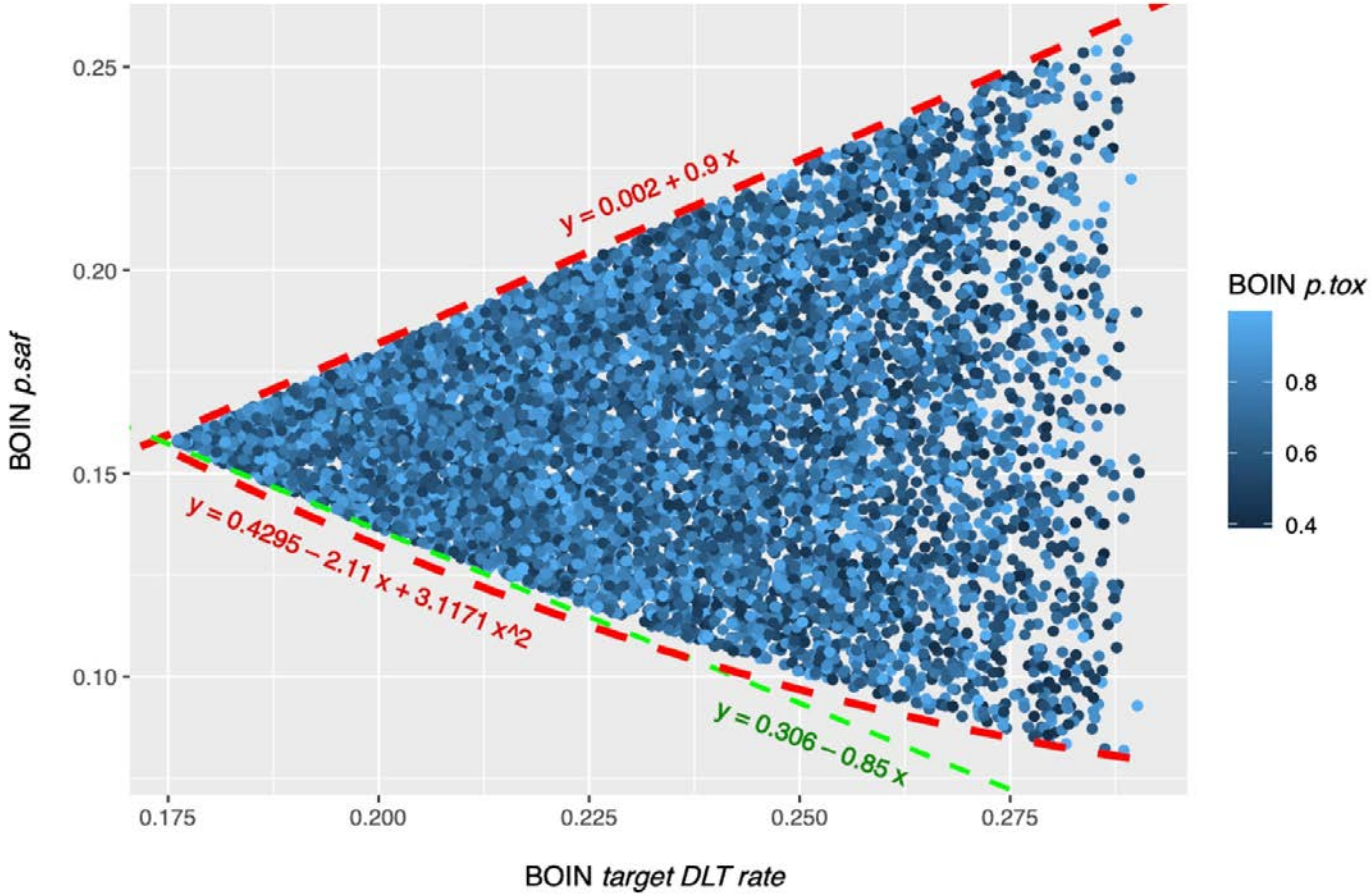
To generate the 3+3 design boundary table using BOIN designs:



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# 3 + 3 BOIN Design

- $0.17 < target.DLT.rate < 0.30$
- $0.08 < p.saf < 0.26$
- $0.38 < p.tox < 1$
- $0.725 - 1.2 * target.DLT.rate < p.tox < 1$



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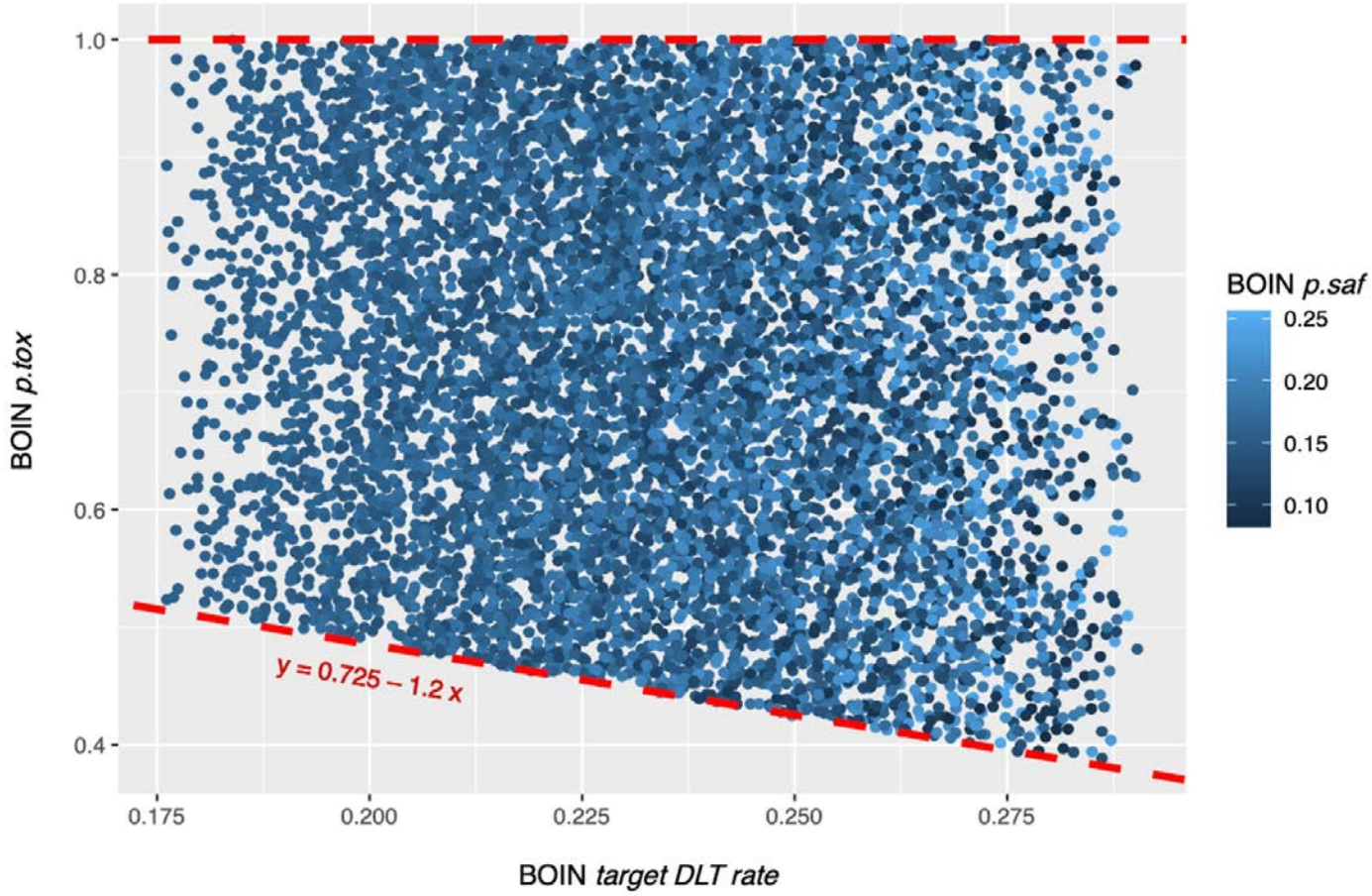
To generate the 3+3 design boundary table using BOIN designs:



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# 3 + 3 BOIN Design

- $0.17 < target.DLT.rate < 0.30$
- $0.08 < p.saf < 0.26$
- $0.38 < p.tox < 1$
- $0.66 < cutoff.eli < 0.89$
- $cutoff.eli > 1.085 - 1.1141 * target.DLT.rate - 1.1438 * target.DLT.rate^2$
- $cutoff.eli < 1.0215 - 0.00858 * target.DLT.rate - 4.11 * target.DLT.rate^2$



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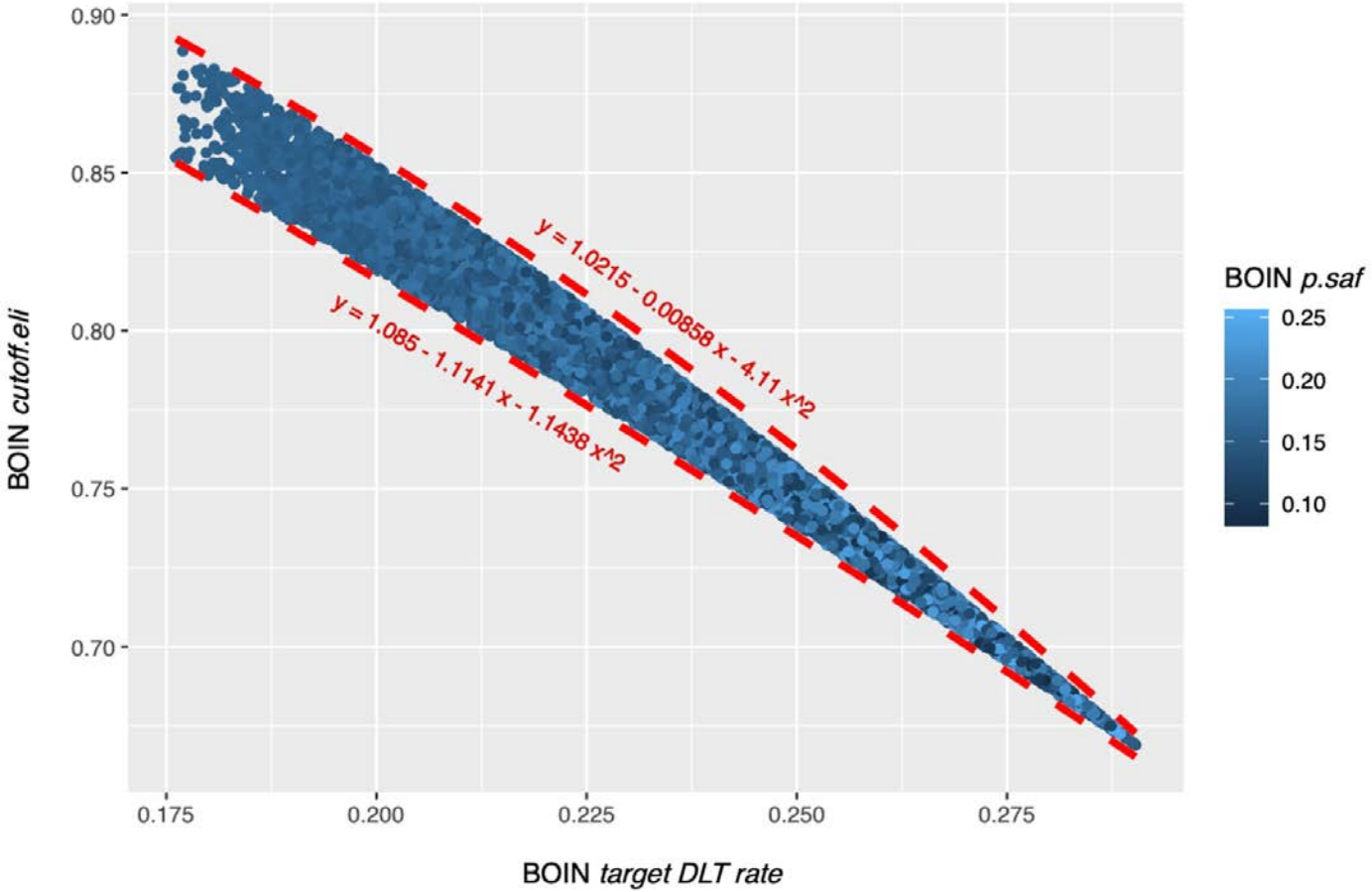
To generate the 3+3 design boundary table using BOIN designs:



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# Summary/Discussion:

- In addition to target DLT rate, equivalent intervals of *p.tox* also depend heavily on *cohortsize, cutoff.eli* and *n.earlystop*.
- Although *ncohort* is one of the required input parameter of *get.boundary()*, the choice of *ncohort* value has no effect on the calculation of BOIN boundary table. The main purpose of specifying *ncohort* is to terminate dose finding process when the sample size budget is reached.
- When the early stopping parameter *n.earlystop* is relatively small or the *cohortsize* value is not optimized via simulation, it might be better to use *p.tox* < 1.4 * *target.DLT.rate*, or try out different cohort sizes, or increase *n.earlystop*, whichever is both feasible and provides better operating characteristics.
  - When target DLT rate = 10%, *cohortsize* = 5, *ncohort* = 10, *n.earlystop* = 12, *cutoff.eli* = 95%, and *extrasafe* = FALSE, using *p.tox = 1.4 * target.DLT.rate* to calculate BOIN boundary table is equivalent to using *p.tox > 3 * target.DLT.rate*.



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# Summary/Discussion:

- While changing target DLT rate, *cohortsize,* and *n.earlystop* will affect the equivalent intervals for both *p.saf* and *p.tox*, increasing or decreasing *cutoff.eli* will only affect *p.tox* equivalent intervals.
- It appears that increasing *cutoff.eli* will add more equivalent interval boundary points from both side of *p.tox* = 0.5 but won't be able to narrow *p.tox* intervals that are either close to target DLT rate (plus a small margin) or close to 1.
- And *cutoff.eli* < 90% may need to be used with caution because the resulted equivalent interval of *p.saf* could be too wide for some pediatric trials.
  - when target DLT rate = 10%, *cohortsize* = 3, *ncohort* = 10, *n.earlystop* = 12, *cutoff.eli* = 80%, and *extrasafe* = FALSE, using *p.tox* = 1.4 * *target.DLT.rate* to calculate BOIN boundary table is equivalent to using any *p.tox* ∈ (12.3%, 99.9%), as long as p.saf values fall into one equivalent interval of *p.saf*.



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# Summary/Discussion:

- This research highlights the importance of interpreting the BOIN design parameter p.tox as a range of toxicity rates regarded as excessively toxic, as opposed to one pre-determined value reflecting the lowest toxicity probability deemed overly toxic.
- It's also essential to perform simulation studies to recognize comparable sets of BOIN design parameters capable of producing an identical boundary table.



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- All scripts and data produced are available online at https://github.com/ronglu-stanford/BOIN_p.tox_17Jan2024




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# ACKNOWLEDGEMENT


- **Funding Sources:** This work is partially supported by the Biostatistics Shared Resource (BSR) of the NIH-funded Stanford Cancer Institute (P30CA124435) and the Stanford Center for Clinical and Translational Research and Education (UL1- TR003142).




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Thank you for your attention!



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