Universal Performance Measures and the Minimax Allocation Procedure

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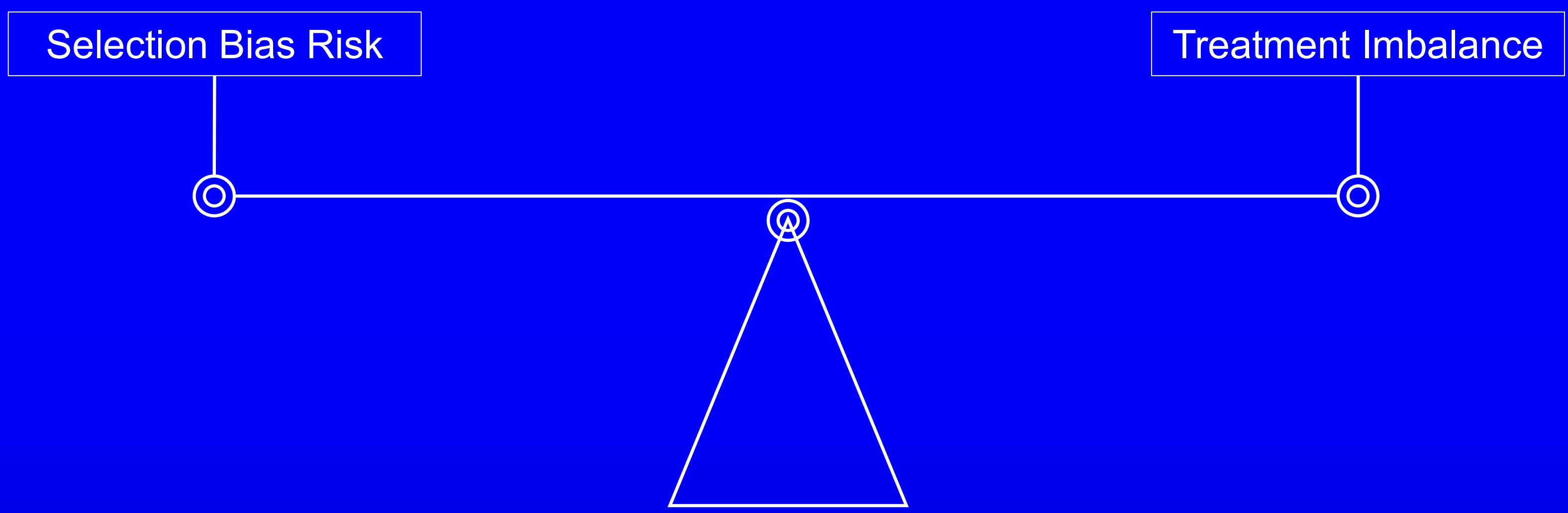
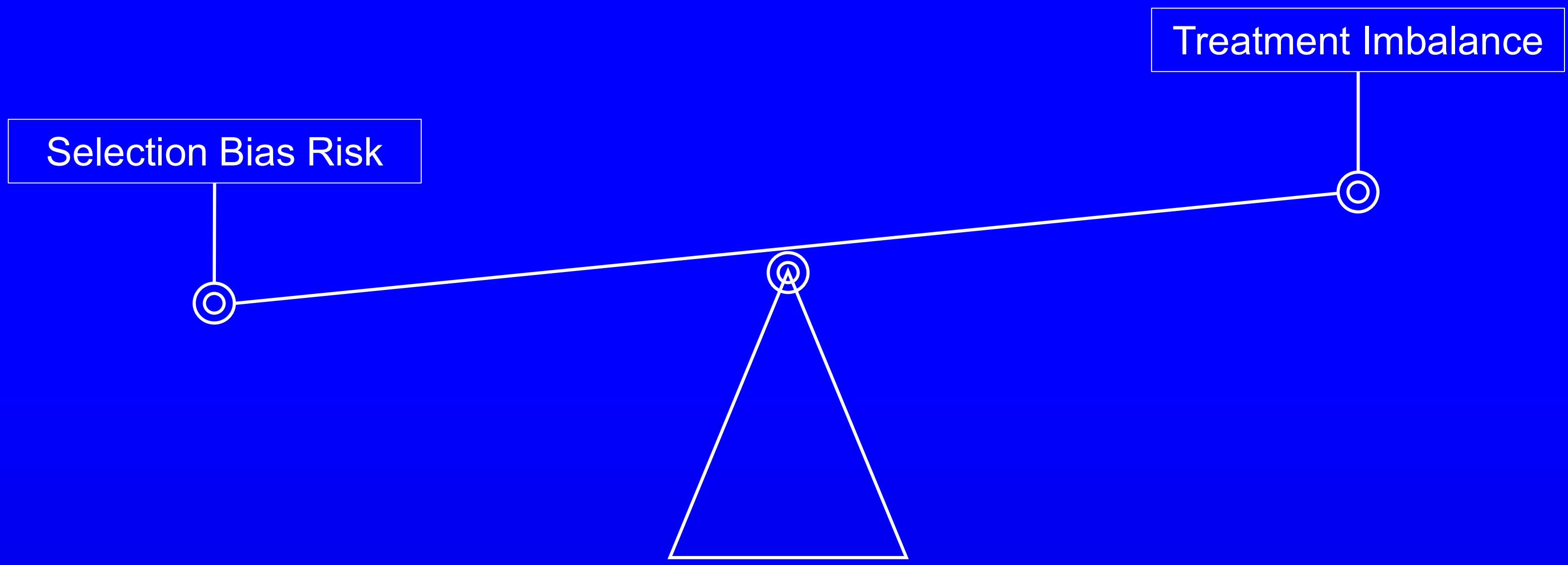
Randomization Working Group, June 23, 2026

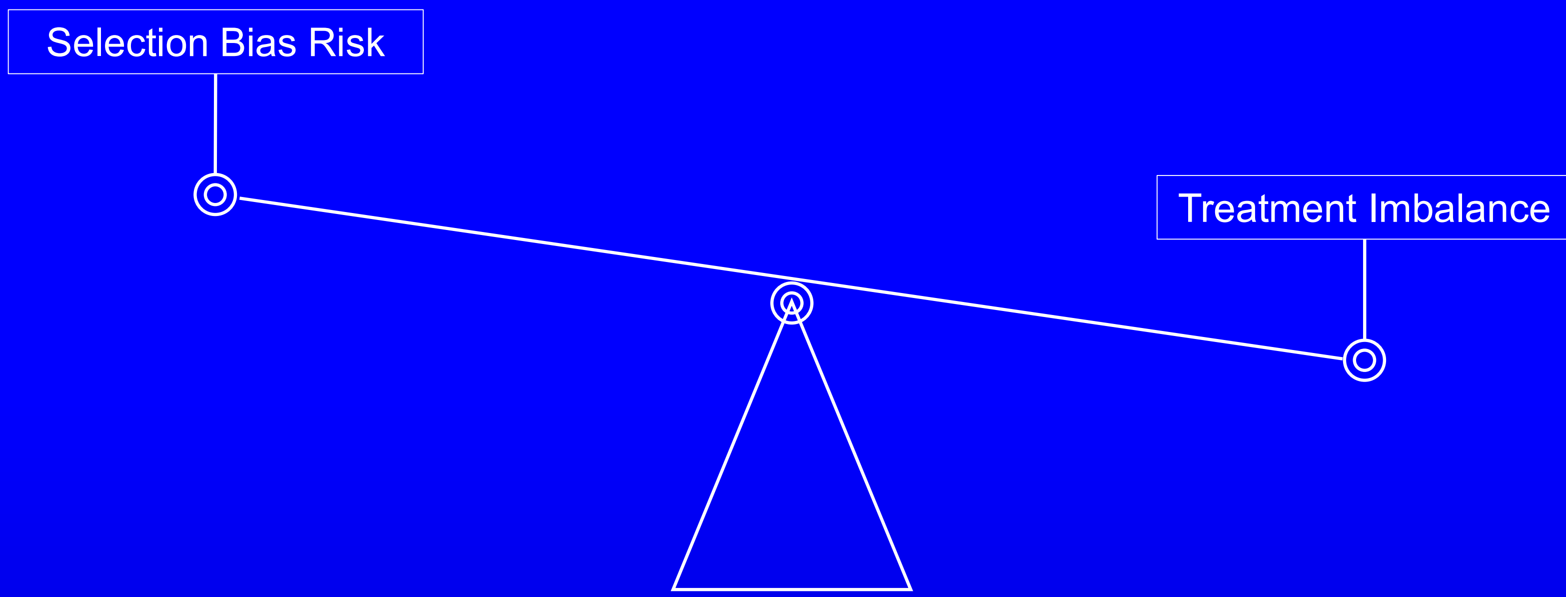
Objectives for Randomization



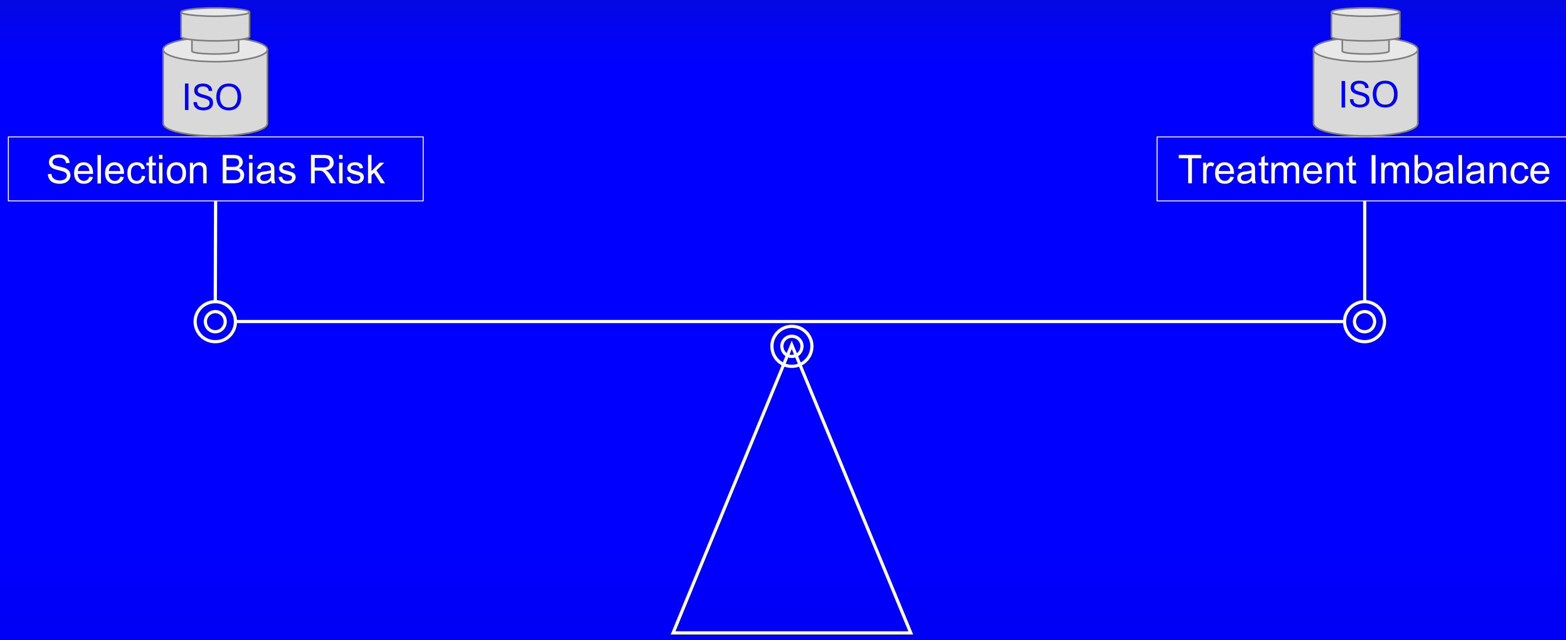
Competing Objectives



Competing Objectives



Measures for Treatment Imbalance and Selection Bias Risk

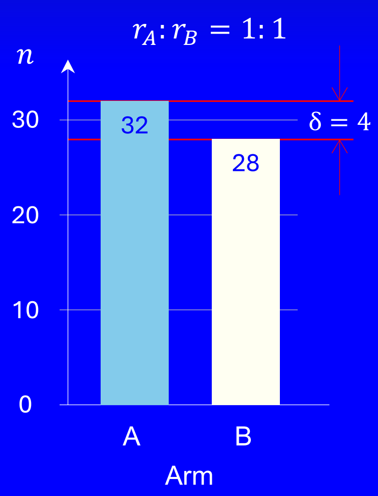


Advantages and Disadvantages of Block Randomization

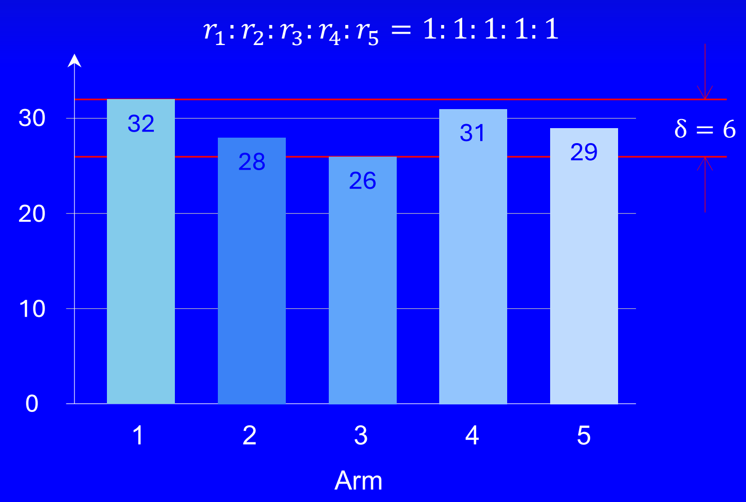
- ✓ Fixed treatment imbalance control by the block size.
  Beats Efron's Biased Coin Design, Wei's Urn Design, Mass-weighted Urn Design.
- ✓ Applicable to two- and multi-arm trials with equal or unequal allocations.
  Beats Big Stick Design, Ehrenfest Urn Design, Biased Coin Design with Imbalance Tolerance
- ✓ Easy for implementation.
  Beats Maximal Procedure, Brick Tunnel Design.
- ❖ Vulnerable to selection bias due to high allocation predictability.
  Beaten by ALL restricted randomization designs.

Randomization Designs Beyond Permuted Block

Treatment Imbalance for Equal Allocation



Range of assignments : $\delta = 4$

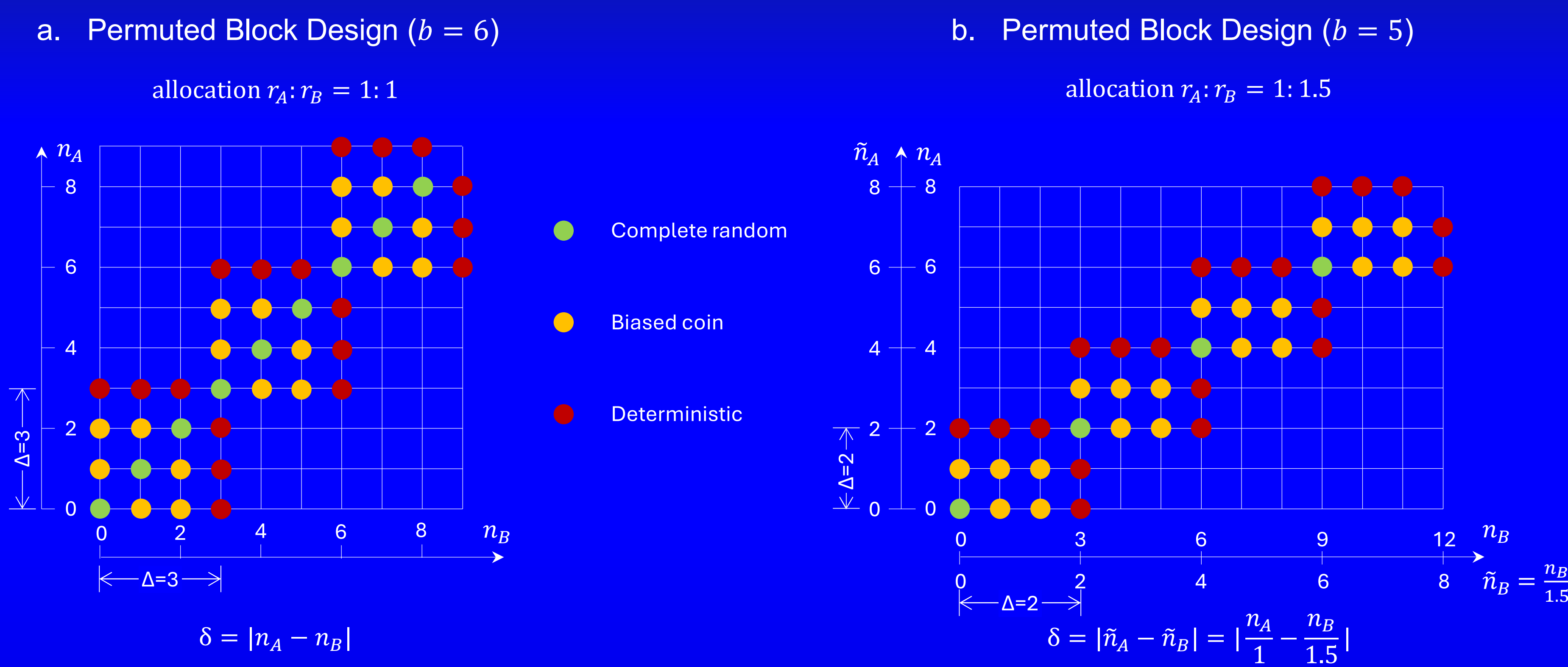


Range of assignments : $\delta = 6$

Treatment Imbalance for trials with equal allocation = Range of assignments

$$\delta = max(n_j) - min(n_j)$$

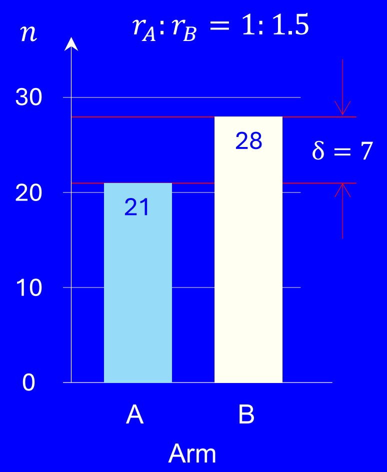
Treatment Imbalance for Unequal Allocation



Treatment Imbalance = Allocation-adjusted assignment difference between the two arms

Treatment Imbalance for Two-arm Unequal Allocation

Raw Assignments

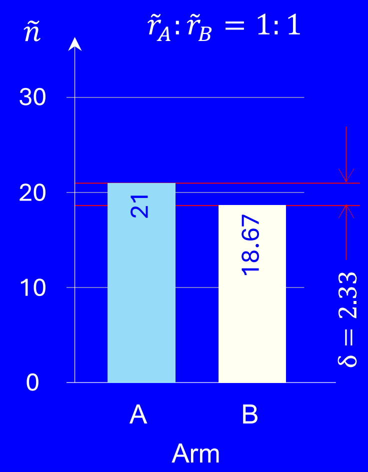


Allocation adjustment
converts
Unequal Allocation
to
Equal Allocation

$$\tilde{n}_A = \frac{n_A}{r_A}, \quad \tilde{n}_B = \frac{n_B}{r_B}$$

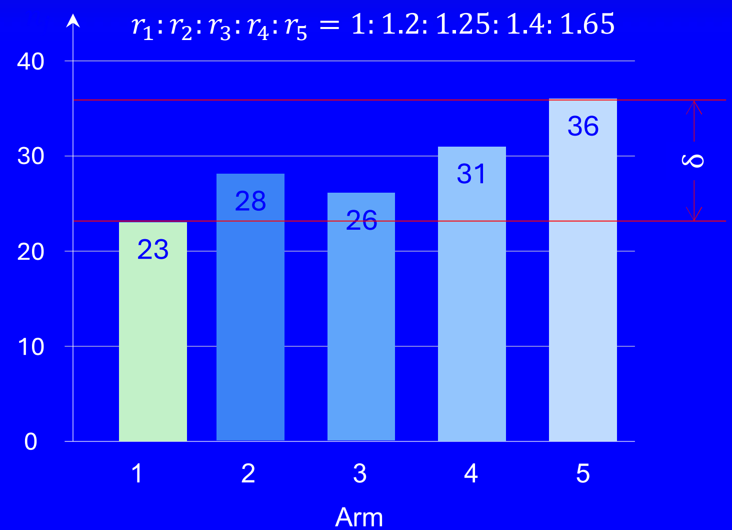
$$\delta = |\tilde{n}_A - \tilde{n}_B|$$

Allocation-Adjusted Assignments



Treatment Imbalance for Multi-arm Unequal Allocations

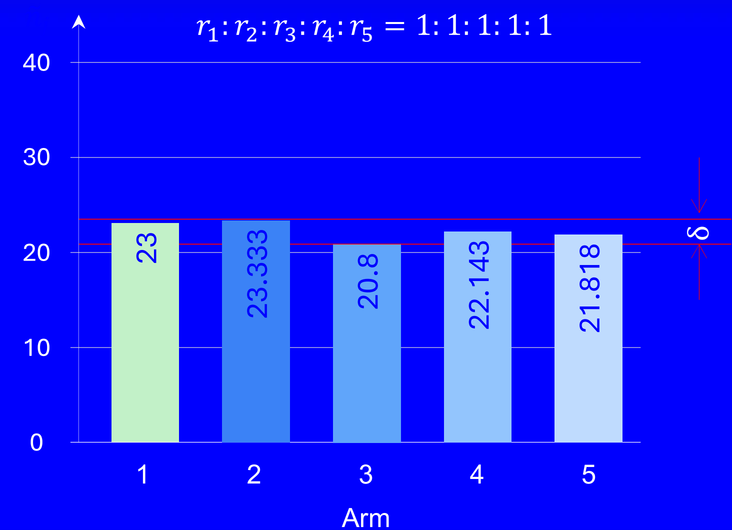
Raw Assignments



Allocation adjustment
$\tilde{n}_j = n_j / r_j$

Treatment imbalance
$\delta = max(\tilde{n}_j) - min(\tilde{n}_j)$

Allocation-Adjusted Assignments



Range $\delta = 2.53$

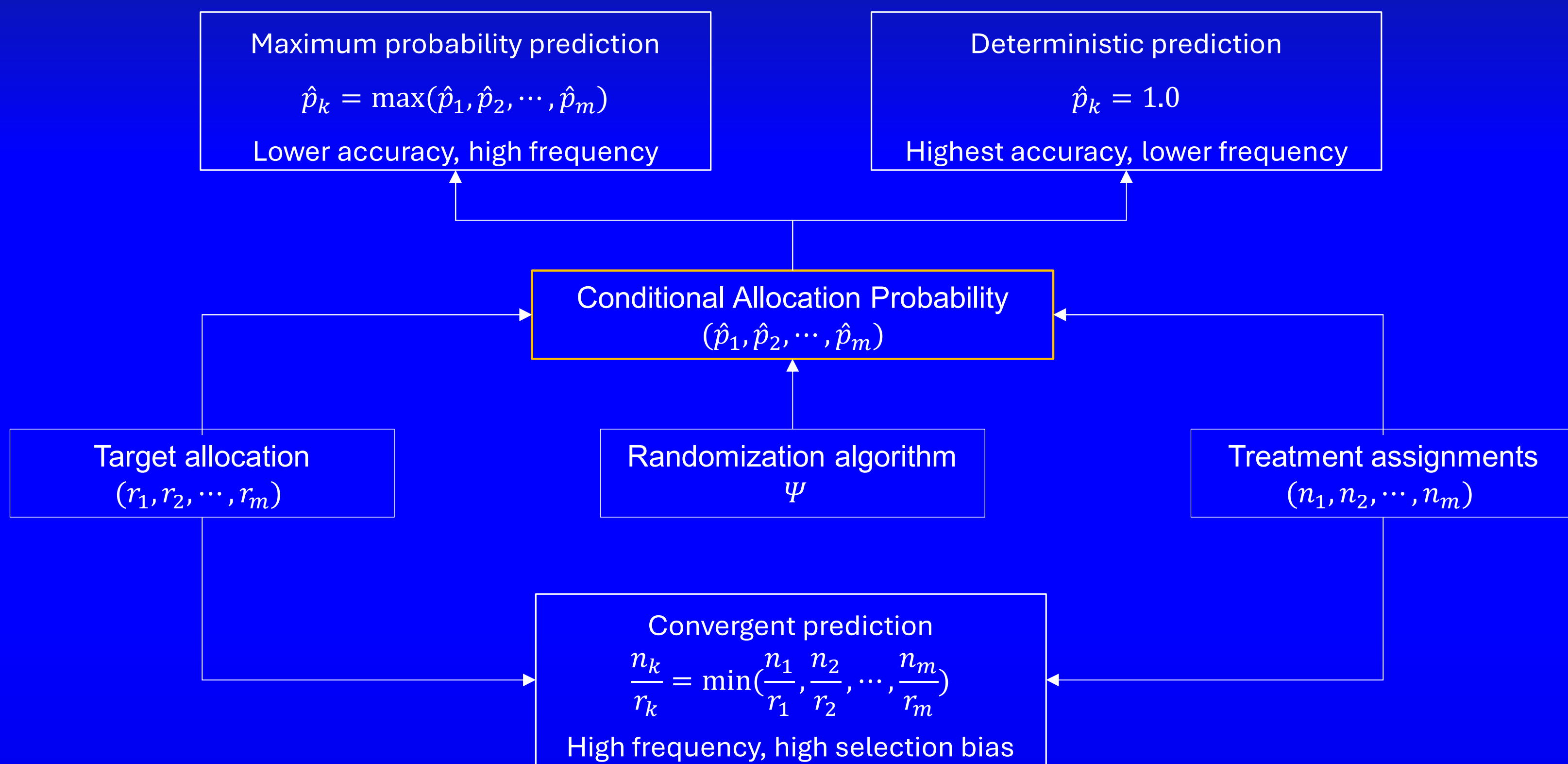
Universal Measure for Treatment Imbalance

Treatment imbalance = range of allocation-adjusted treatment assignments

$$\delta = max(n_j/r_j) - min(n_j/r_j)$$

Allocation Scenario	Two-arm Equal	Two-arm Unequal	Multi-arm Equal	Multi-arm Unequal	Multi-arm Irrational
Target allocation	1 : 1	1 : 1.5	1 : 1 : 1	1 : 2 : 3	$1 : \sqrt{2} : \sqrt{3}$
Treatment Assignments	12, 10	9, 16	7, 8, 9	11, 17, 25	12, 15, 19
Allocation-adjusted assignments	**12**, **10**	**9**, **10.67**	**7**, 8, **9**	**11**, 8.5, **8.33**	**12**, **10.61**, 10.97
Treatment imbalance	2	1.67	2	2.67	1.39

Allocation Randomness and Prediction Strategies



[1]: Blackwell, D, Hodges, JL. Design for the Control of Selection Bias. *Ann Math Stat*. 1957; 28(2), 449–460.

Definition of Selection Bias Risk

$$SBR = E\left[\sum_{j=1\sim m} v_j \left(\frac{\hat{p}_j - p_j}{1 - p_j}\right)\right]$$

p_j: target allocation probability for arm j.

$\hat{p}_j$: conditional allocation probability for arm j = prediction accuracy.

v_j: frequency of prediction under the specific strategy.

SBR : selection bias risk

Example #1:
Using complete randomization, $\hat{p}_j \equiv p_j (j = 1,2,\cdots,m)$. Therefore, $SBR = 0$.

Example #2:
Two-arm equal allocation trial, using permuted block design with block size 2, and deterministic prediction.
Assignments in odd places have $\hat{p}_A = \hat{p}_B = 0.5$; assignments in even places have $\hat{p}_A = 1$ or $\hat{p}_B = 1$. Therefore, $SBR = 0.5$

Example #3: Two-arm Trial with1:2 allocation Using PBD (b=6)

Block	Allocation	$\hat{p}_A$	$\frac{n_A}{r_A} - \frac{n_B}{r_B}$	Maximum Probability	Deterministic Prediction	Convergent Prediction
1	AABBBB	1/3,1/5,0,0,0,0	0,1,2,1.5,1,0.5	BBBBBB	OOBBBB	OBBBBB
2	ABABBB	1/3,1/5,1/4,0,0,0	0,1,0.5,1.5,1,0.5	BBBBBB	OOOBBB	OBBBBB
3	ABBABB	1/3,1/5,1/4,1/3,0,0	0,1,0.5,0,1,0.5	BBBBBB	OOOOBB	OBBOBB
4	ABBBAB	1/3,1/5,1/4,1/3,1/2,0	0,1,0.5,0,-0.5,0.5	BBBBOB	OOOOOB	OBBOAB
5	ABBBBA	1/3,1/5,1/4,1/3,1/2,1	0,1,0.5,0,-0.5,-1	BBBBOA	OOOOOA	OBBOAA
6	BAABBB	1/3,2/5,1/4,0,0,0	0,-0.5,0.5,1.5,1,0.5	BBBBBB	OOOBBB	OABBBB
7	BABABB	1/3,2/5,1/4,1/3,0,0	0,-0.5,0.5,0,1,0.5	BBBBBB	OOOOBB	OABOBB
8	BABBAB	1/3,2/5,1/4,1/3,1/2,0	0,-0.5,0.5,0,-0.5,0.5	BBBBOB	OOOOOB	OABOAB
9	BABBBA	1/3,2/5,1/4,1/3,1/2,1	0,-0.5,0.5,0,-0.5,-1	BBBBOA	OOOOOA	OABOAA
10	BBAABB	1/3,2/5,1/2,1/3,0,0	0,-0.5,-1,0,-0.5,0.5	BBOBBB	OOOOBB	OAAOBB
11	BBABAB	1/3,2/5,1/2,1/3,1/2,0	0,-0.5,-1,0,-0.5,0.5	BBOBOB	OOOOOB	OAAOAB
12	BBABBA	1/3,2/5,1/2,1/3,1/2,1	0,-0.5,-1,0,-0.5,-1	BBOBOA	OOOOOA	OAAOAA
13	BBBAAB	1/3,2/5,1/2,2/3,1/2,0	0,-0.5,-1,-1.5,-0.5,0.5	BBOAOB	OOOOOB	OAAAAB
14	BBBABA	1/3,2/5,1/2,2/3,1/2,1	0,-0.5,-1,-1.5,-0.5,-1	BBOAOA	OOOOOA	OAAAAA
15	BBBBAA	1/3,2/5,1/2,2/3,1,1	0,-0.5,-1,-1.5,-2,-1	BBOAAA	OOOOAA	OAAAAA

A, B: Correct prediction A, B: Incorrect prediction O: No prediction

Example #3: Two-arm Trial with1:2 allocation Using PBD (b=6)

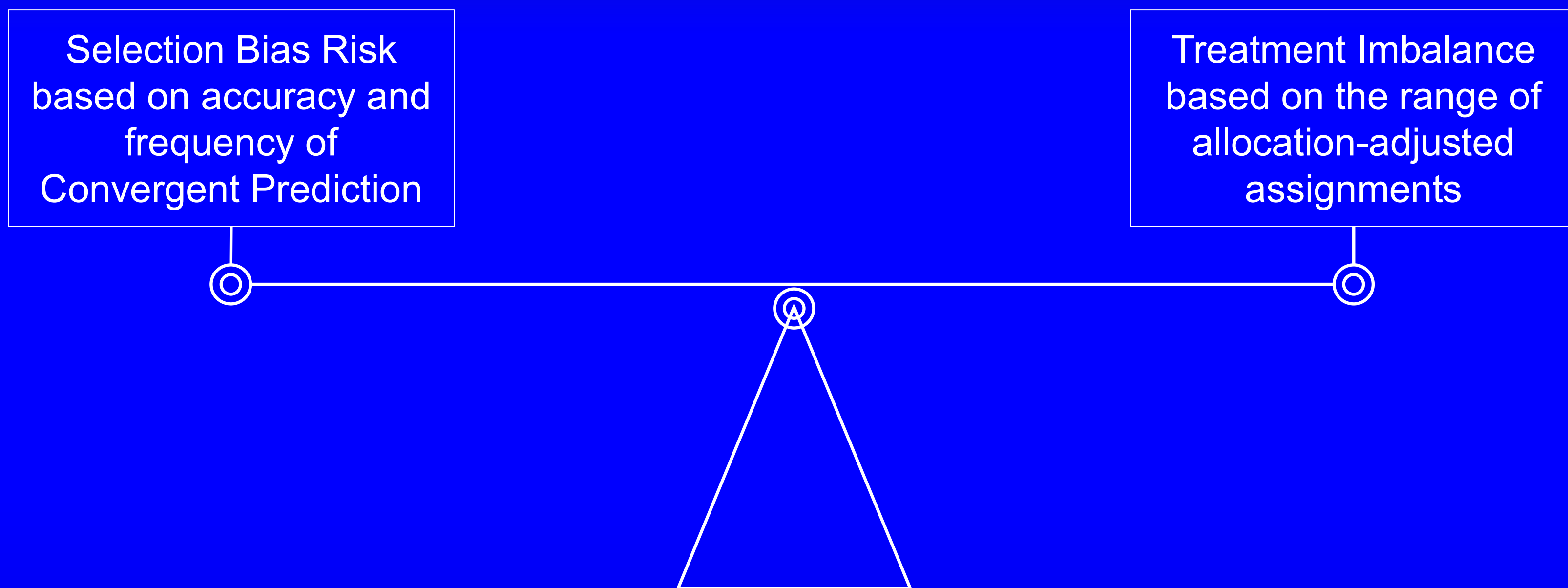
Arm	Target Allocation Probability	Assessment	Maximum Probability Prediction	Deterministic Prediction	Convergent Prediction
A	$p_A = \frac{1}{3}$	Prediction Accuracy	8/9=88.9%	6/6=100%	19/33=57.6%
		Prediction Frequency	9/90=10%	6/90=6.7%	33/90=36.7%
		Selection Bias Risk	0.083	0.067	0.133
B	$p_B = \frac{2}{3}$	Prediction Accuracy	52/67=77.6%	20/20=100%	30/33=90.9%
		Prediction Frequency	67/90=74.4%	20/90=22.2%	33/90=36.7%
		Selection Bias Risk	0.244	0.222	0.267
Overall		Selection Bias Risk	0.328	0.289	0.400
					Most vulnerable prediction to selection bias

Universal Measure for Selection Bias Risk

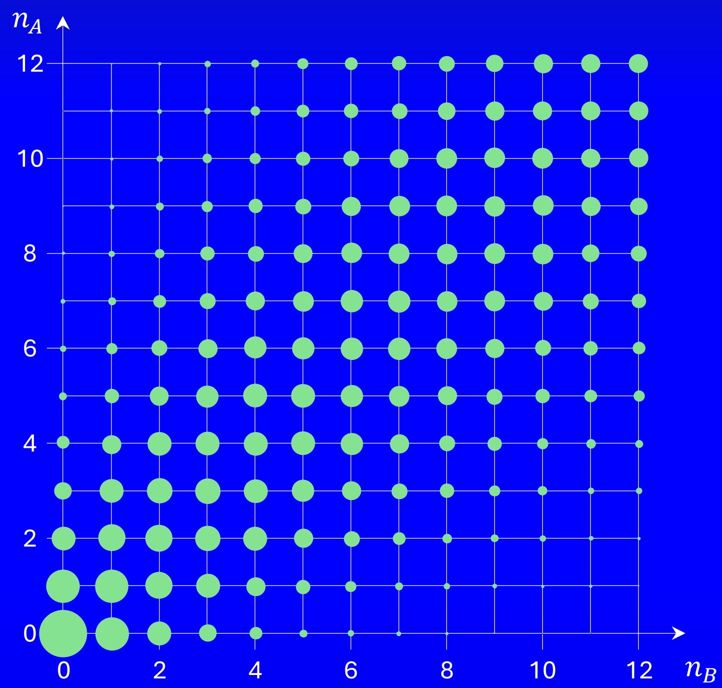
Selection Bias Risk = Expected chance of making correct prediction above target allocation probability under the convergent prediction strategy

$$SBR = E\left[\sum_{j=1\sim m} v_j \left(\frac{\hat{p}_j - p_j}{1 - p_j}\right)\right]$$

Measures for Imbalance and Randomness



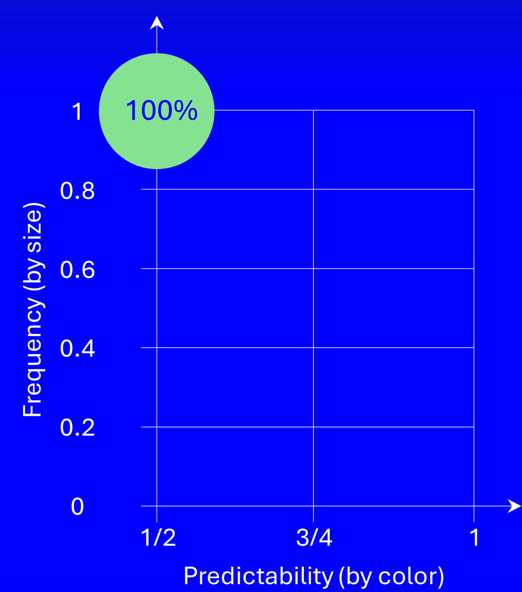
Complete Randomization



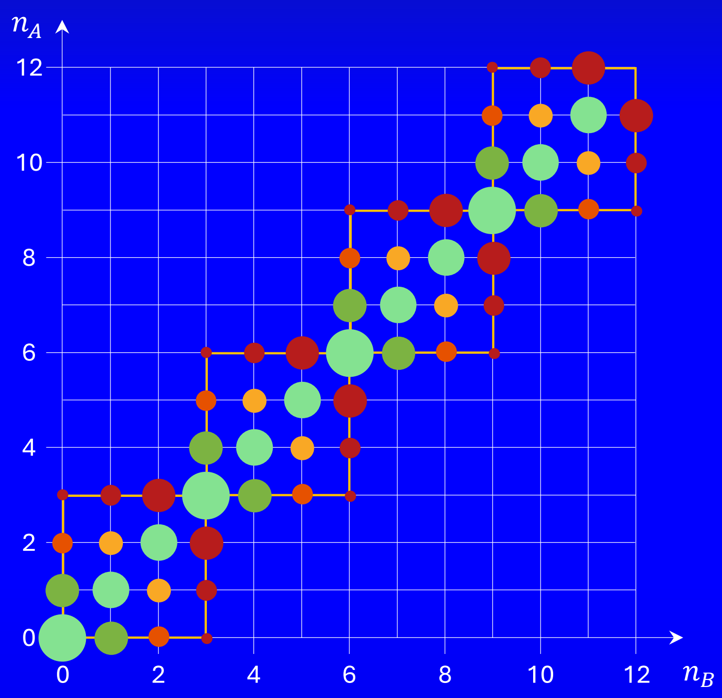
Treatment Imbalance >?

Selection Bias Risk

Frequency	Predictability	SBR
1	1/2	0
Overall SBR		0



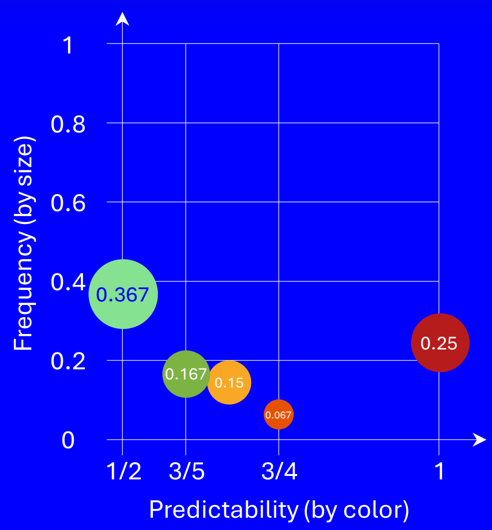
Permuted Block Design, 1:1 Allocation, Block Size 6



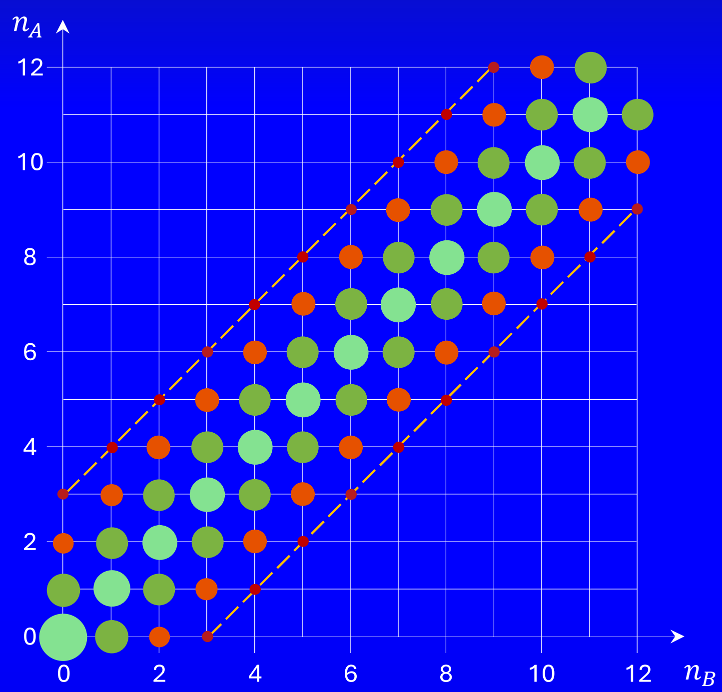
Treatment Imbalance ≤ 3

Selection Bias Risk

Frequency	Predictability	SBR
0.367	1/2	0
0.167	3/5	0.333
0.150	2/3	0.05
0.067	3/4	0.033
0.25	1	0.25
Overall SBR		0.367



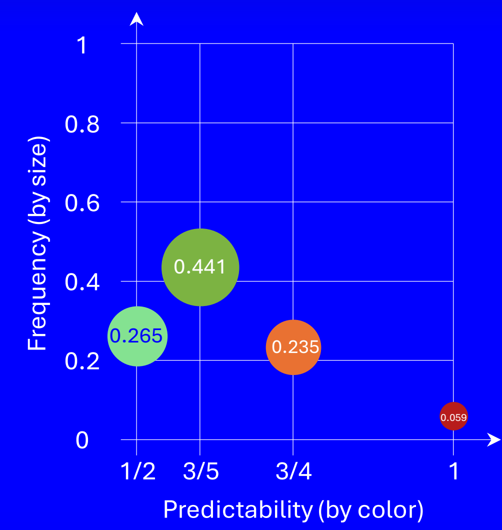
Block Urn Design, 1:1 Allocation, MTI = 3



Treatment Imbalance ≤ 3

Selection Bias Risk

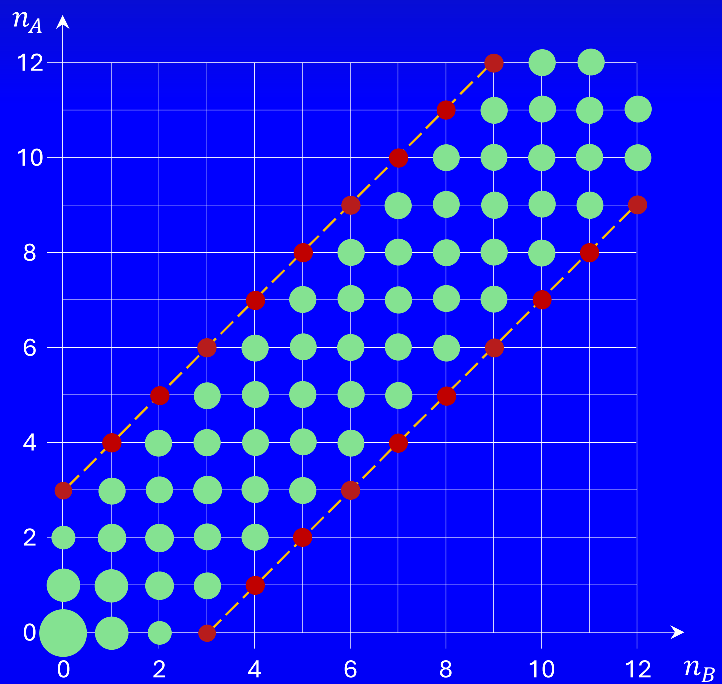
Frequency	Predictability	SBR
0.265	1/2	0
0.441	3/5	0.088
0.235	3/4	0.118
0.059	1	0.059
	Overall SBR	0.265



Replace blocks with maximum tolerated imbalance (MTI) boundaries.

[2]: Zhao W, Weng Y. Block urn design - a new randomization algorithm for sequential trials with two or more treatments and balanced or unbalanced allocation. *Contemp Clin Trials*. 2011;32(6):953-961.

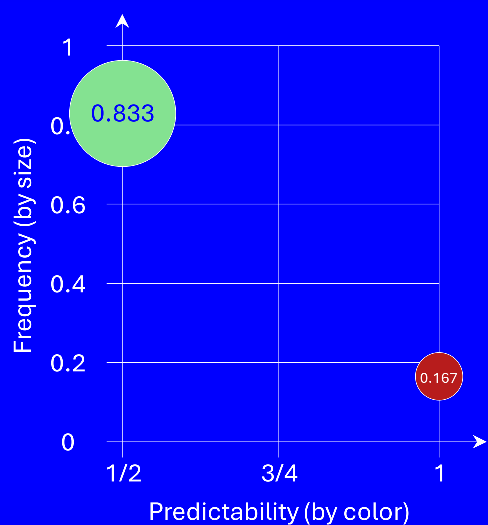
Big Stick Design, 1:1 Allocation, MTI = 3



$Treatment\ Imbalance \leq 3$

$Selection\ Bias\ Risk$

Frequency	Predictability	SBR
0.833	1/2	0
0.167	1	0.167
Overall SBR		0.167

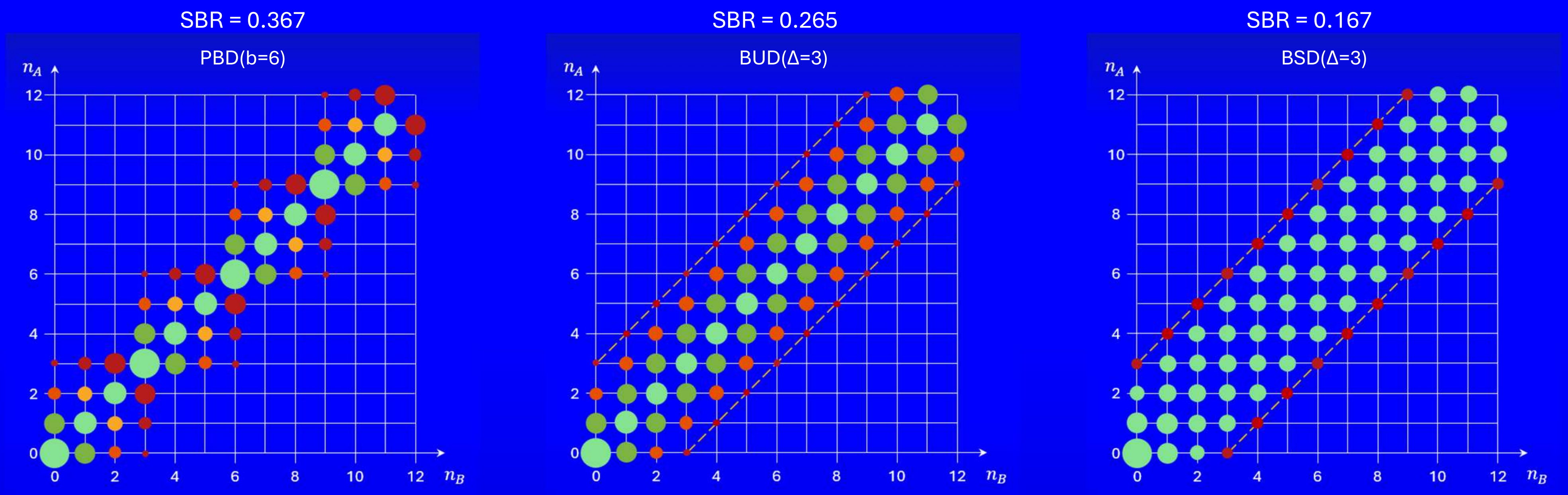


Use complete random assignments until achieved the maximum tolerated imbalance (MTI) boundary.

[3]: Soares JF, Wu CF, Some restricted randomization rules in sequential designs. *Commun Stat*. 1983; 12:2017-2034.

Evolution from Permuted Block to Big Stick

Use **max**imum tolerated imbalance (MTI) to replace blocks.
Use **mini**mal intervention, for ensuring MTI only.



From Big Stick Design to Minimax Allocation Procedure

Define Minimax Allocation Procedure

With: Target allocation $r = r_1 : r_2 : \cdots : r_m$ where $1 = r_1 \le r_2 \le \cdots \le r_m$.

Maximum tolerated imbalance Δ.

Current treatment assignments $n_1, n_2, \cdots, n_m$.

Do: Step 1: For each arm $j = 1,2, \cdots, m$

Assume $n_j = n_j + 1$.

$$\tilde{p}_j = \begin{cases} 0 & \text{if } max\left(\frac{n_k}{r_k}\right) - min\left(\frac{n_k}{r_k}\right) > \Delta \\ r_j & \text{Otherwise} \end{cases}$$

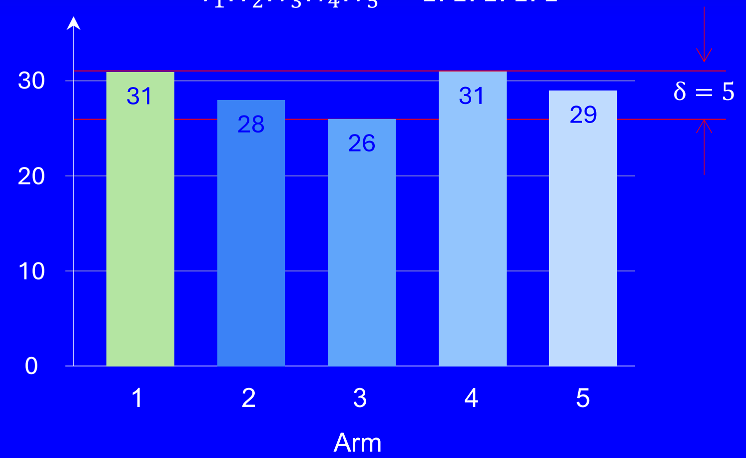
Step 2: Obtain conditional allocation probability $\hat{p}_j = \frac{\tilde{p}_j}{\sum_{k=1}^{m} \tilde{p}_k}$

Step 3: Assign current subject to arm j if $\sum_{k=1}^{j-1} \tilde{p}_k > Rand < \sum_{k=1}^{j} \tilde{p}_k$

For two-arm equal allocation, Minimax Allocation Procedure is equivalent to Big Stick Design.

Minimax Allocation Procedure for Multi-arm Equal Allocations

$r_1 : r_2 : r_3 : r_4 : r_5 = 1:1:1:1:1$



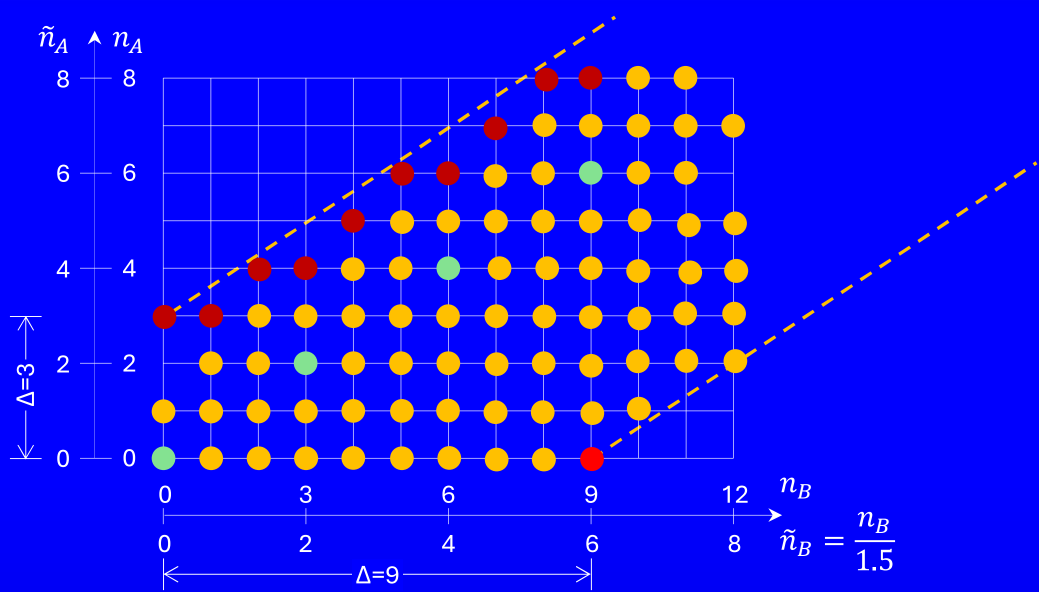
Range of assignments : $\delta = 5$

If $MTI > 5$, complete random assignment among all arms 1 ~ 5.

If $MTI = 5$, exclude arm 1 and arm 4 for the current assignment. The subject will be randomly assigned to one of the three remaining 3 arms, 2, 3, or 5.

Mass-weighted Urn Design for Two-arm Unequal Allocations

allocation $r_A : r_B = 1 : 1.5$ $\quad p_A = 0.4, \quad p_B = 0.6$
Imbalance Control Parameter α = 3



$$\hat{p}_A = \frac{\max(0, \alpha p_A - n_A p_B + n_B p_A)}{\alpha}, \quad p_B = 1 - p_A$$

$$\hat{p}_A = \alpha p_A - n_A p_B + n_B p_A = 0$$

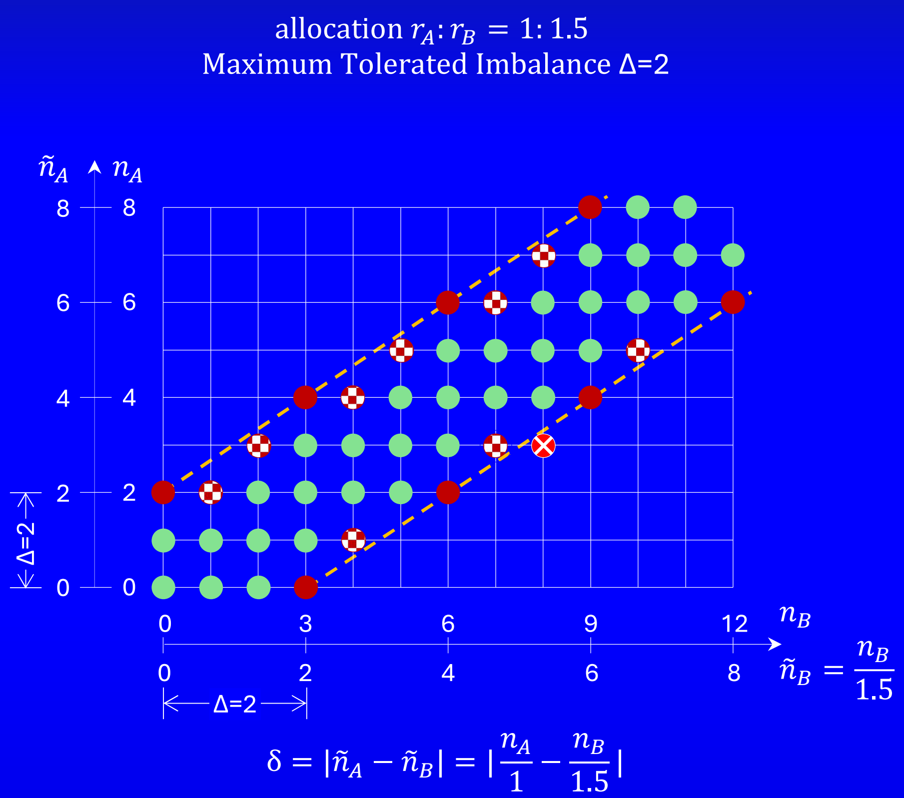
When $n_B = 0$, $n_A = \alpha \frac{p_A}{p_B}$

$$\hat{p}_A = \frac{\max(0, \alpha p_A - n_A p_B + n_B p_A)}{\alpha} = 1$$

When $n_A = 0$, $\quad n_B = \alpha \frac{p_B}{p_A}$

$$\frac{\max(\Delta_A)}{\max(\Delta_B)} = \left(\frac{p_A}{p_B}\right)^2$$

Minimax Allocation Procedure for Two-arm Unequal Allocations

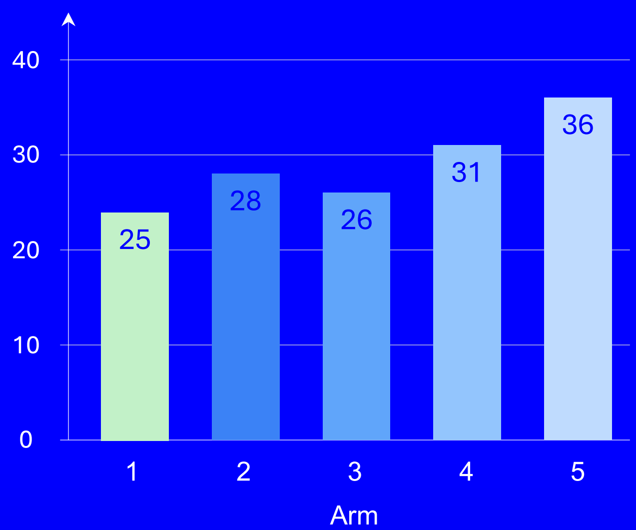


1. Define Δ based on the allocation-adjusted assignments.
2. Use complete random assignment (green dot) by default.
3. Use deterministic assignment (red dot) when δ = Δ.
4. Use deterministic assignment (checkered dot) to *prevent* δ > Δ.

	Current	After $n_B = n_B + 1$
(n_A, n_B)	$(3, 7)$	$(3, 8)$
$(\tilde{n}_A, \tilde{n}_B)$	$(3, 4.667)$	$(3, 5.333)$
δ	1.4667	$2.333 > 2$

Minimax Allocation Procedure for Multi-arm Unequal Allocations

$r_1 : r_2 : r_3 : r_4 : r_5 = 1 : 1.2 : 1.25 : 1.4 : 1.65 \qquad \Delta = 3$

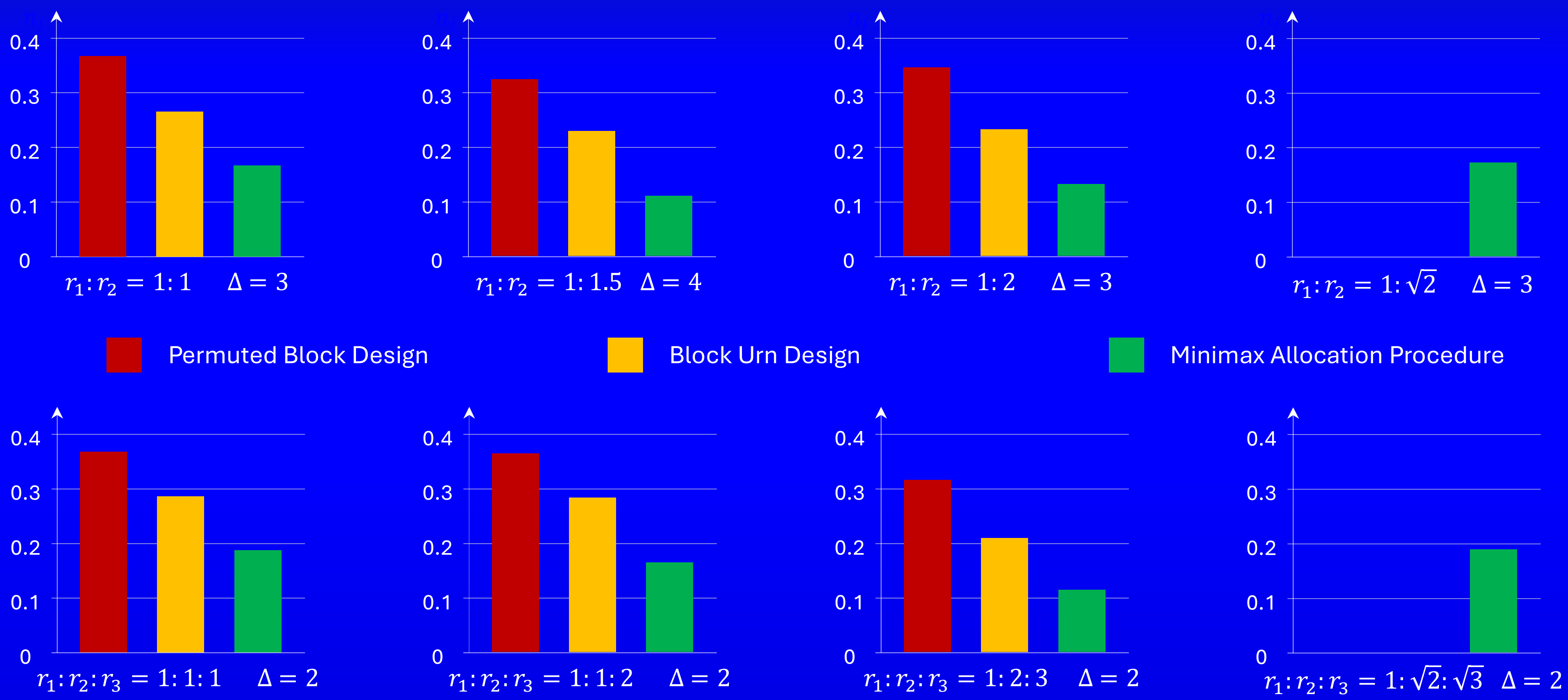


Arm		1	2	3	4	5	Treatment Imbalance δ
r_j		1	1.2	1.25	1.4	1.65	
n_j		23	28	26	31	36	
$\tilde{n}_j$		23	23.33	20.8	22.14	21.82	2.53
$n_1 = n_1 + 1$	n_j	**23+1**	28	26	31	36	
	$\tilde{n}_j$	**24**	23.33	20.8	22.14	21.82	3.2
$n_2 = n_2 + 1$	n_j	23	**28+1**	26	31	36	
	$\tilde{n}_j$	23	**24.17**	20.8	22.14	21.82	3.37
$n_3 = n_3 + 1$	n_j	23	28	**26+1**	31	36	
	$\tilde{n}_j$	23	23.33	**21.6**	22.14	21.82	1.73
$n_4 = n_4 + 1$	n_j	23	28	26	**31+1**	36	
	$\tilde{n}_j$	23	23.33	20.8	**22.86**	21.82	2.53
$n_5 = n_5 + 1$	n_j	23	28	26	31	**36+1**	
	$\tilde{n}_j$	23	23.33	20.8	22.14	**22.42**	2.53
$\hat{r}_j$		0	0	1.25	1.4	1.65	
$\hat{p}_j$		0	0	0.2907	0.3256	0.3837	

Selection Bias Risk Comparison

Number of treatment arms = 2					Number of treatment arms = 3				
Target Allocation	MTI Δ	Permuted Block Design	Block Urn Design	Minimax Allocation Procedure	Target Allocation	MTI Δ	Permuted Block Design	Block Urn Design	Minimax Allocation Procedure
1 : 1	1	0.5	0.5	0.5	1 : 1 : 1	1	0.417	0.417	0.336
	2	0.417	0.337	0.250		2	0.367	0.285	0.186
	3	0.367	0.265	0.166		3	0.220	0.234	0.128
1 : 1.5	2	0.417	0.417	0.239	1 : 1 : 2	1	0.444	0.444	0.351
	3	NA	NA	0.154		1.5	NA	NA	0.247
	4	0.323	0.229	0.110		2	0.363	0.281	0.163
1 : 2	1	0.5	0.5	0.445	1 : 2 : 2	1	0.383	0.383	0.268
	2	0.4	0.301	0.205		2	0.304	0.221	0.126
	2.5	NA	NA	0.160	1 : 2 : 3	1	0.377	0.373	0.257
	3	0.345	0.232	0.131		2	0.315	0.208	0.114
$1 : \sqrt{2}$	2	NA	NA	0.282	$1 : \sqrt{2} : \sqrt{3}$	1.4	NA	NA	0.313
	3	NA	NA	0.171		2	NA	NA	0.188

Selection Bias Risk Comparison



Minimax Allocation Procedure Summary

Complete random by default.
Intervene for MTI only.
Lowest predictability under convergent strategy.

$\mathbf{r} = (r_1, r_2, \cdots, r_m)$
where $r_j \in \mathbb{R}^+$

- ✓ *Low allocation predictability.*
- ✓ *With maximum tolerated imbalance control.*
- ✓ *Applicable to all trial settings: two-arm or multi-arm; equal or unequal allocations.*
- ✓ *Easy to implement with explicit conditional allocation probability formula.*

Fixed allocation-adjusted treatment imbalance

Requires basic arithmetic
+, -, x, /.

Define Minimax Allocation Procedure

With: Target allocation $r = r_1 : r_2 : \cdots : r_m$ where 1= $r_1 \le r_2 \le \cdots \le r_m$.

Maximum tolerated imbalance Δ.

Current treatment assignments $n_1, n_2, \cdots, n_m$.

Do: Step 1: For each arm $j = 1,2,\cdots,m$

Assume $n_j = n_j + 1$.

$$\tilde{p}_j = \begin{cases} 0 & \text{if } max\left(\frac{n_k}{r_k}\right) - min\left(\frac{n_k}{r_k}\right) > \Delta \\ r_j & \text{Otherwise} \end{cases}$$

Step 2: Obtain conditional allocation probability $\hat{p}_j = \frac{\tilde{p}_j}{\sum_{k=1}^{m} \tilde{p}_k}$

Step 3: Assign current subject to arm j if $\sum_{k=1}^{j-1} \tilde{p}_k > Rand < \sum_{k=1}^{j} \tilde{p}_k$

Thank You!