Minimizing Selection Bias in a Two-arm Open-Label Trial

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Contents

- Selection bias is a big part of randomization considerations in an open-label study
- Blackwell and Hodges (1957) model for selection bias
- Which guessing strategy leads to the highest selection bias?
- Which allocation procedure minimizes selection bias?
- Can we reduce the selection bias by going against the investigator's expectations?
- Open questions

How Selection Bias Arises in a 2-arm Study
[following Rosenberger & Lachin 2015]

- Classical setting: the investigator knows the sequence of treatment assignments for all already allocated patients
  - **As in an open-label single-center trial**
- The investigator tries to guess the next treatment assignment and
  - Allocates a healthier patient if the guess is Treatment A
  - Allocates a sicker patient if the guess is Treatment B
- This makes groups A better in prognosis than group B
- Introduces selection bias in the study results
- **Selection bias** is the expected difference in observed group means in absence of treatment effect due to such biasing

$$SB = E(\overline{Y_A} - \overline{Y_B})$$

  - Assume normal responses for simplicity

What Impacts the Selection Bias?

1. How heterogeneous the population is
    - Per Blackwell and Hodges (1957) model, assume two types of patients:
        - healthier patients with expected response $\mu+\Delta$
        - sicker patients with expected response $\mu-\Delta$
    - Greater Δ leads to a higher selection bias
2. What guessing strategy the investigator uses. Strategy depends on:
    - What the investigator knows (assumes) about the allocation procedure
    - Whether the investigator is willing to bias every allocation or only bias when they think the probability of a correct guess is high
        - Example: bias only the deterministic allocations assuming Permuted Block Randomization (PBR) [Zelen 1974] with the block size of 4 is used
3. The allocation procedure used in the trial
    - Complete Randomization by a flip of a fair coin (CR) leads to 0 bias

Selection Bias per Blackwell and Hodges (1957) model

- Consider a 2-arm study with $w_1 : w_2$ allocation
- For simplicity assume that at the end of allocation we will have exactly $w_1 : w_2$ split: $N_A = w_1 N$, $N_B = w_2 N$
- Then [Rosenberger and Lachin, 2015]

$$\mathbf{SB} = \boldsymbol{E}(\overline{\boldsymbol{Y_A}} - \overline{\boldsymbol{Y_B}}) = \mathbf{2}\Delta(\boldsymbol{E}(\boldsymbol{PG_A}) + \boldsymbol{E}(\boldsymbol{PG_B}) - \mathbf{1}))$$

where

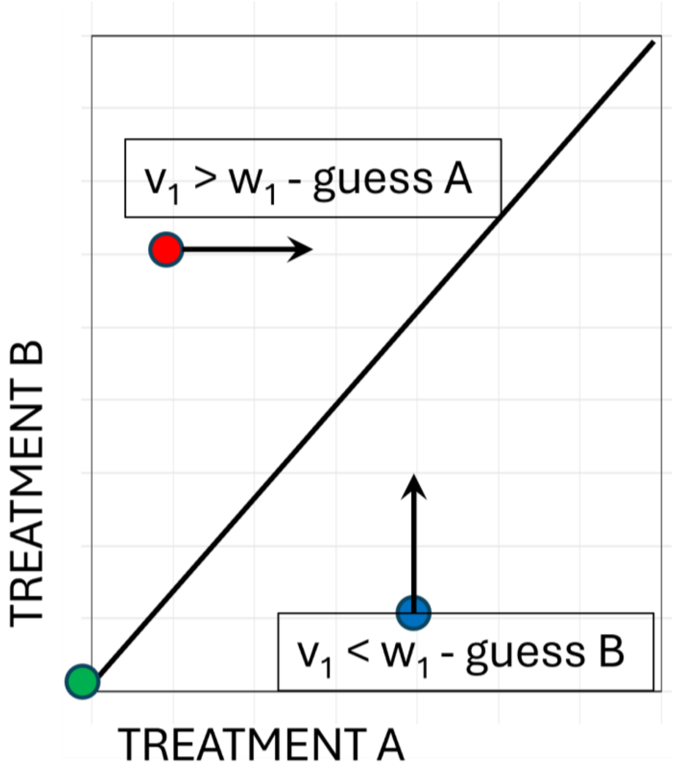
- $E(PG_A)$ is the expected Proportion of Correct Guesses (PCG) in Group A
- $E(PG_B)$ is the expected PCG in Group B

- Selection Bias is proportional to the sum of expected PCGs in Groups A and B minus 1

Selection Bias for Equal Allocation

- For equal allocation, $E(PG_A) + E(PG_B)$ reduces to Expected Proportion of Correct Guesses
- $E(\overline{Y_A} - \overline{Y_B}) = 2\Delta \frac{E(G - \frac{N}{2})}{N/2}$, where *G* is the number of correct guesses
- Multiplier $\frac{E(G - \frac{N}{2})}{N/2}$ is called average excess selection bias (Chen 1999)

What is the Best Guessing Strategy When the Investigator Knows the Allocation Procedure?



Axes: Number of subjects allocated to Treatments A and B; diagonal: Allocation Ray Y = (w_2 : w_1) X

- After X allocations to A and Y allocations to B, v_1 (X, Y) and v_2 (X, Y) are conditional probabilities of allocation to A and B, respectively
- **Directional guessing strategy:**
  - For equal allocation, guess the treatment for which conditional probability >1/2 [Berger 2005]
  - In general, guess the treatment for which conditional probability > unconditional probability
  - When v_1 (X, Y) =w_1, does not matter which arm to guess
- **Directional strategy maximizes selection bias** [Kuznetsova 2018]
  - $E(PG_A) + E(PG_B)$ is maximized
  - For permuted block randomization, translates to: above the diagonal allocate A, below the diagonal allocate B
  - Same for most other allocation procedures

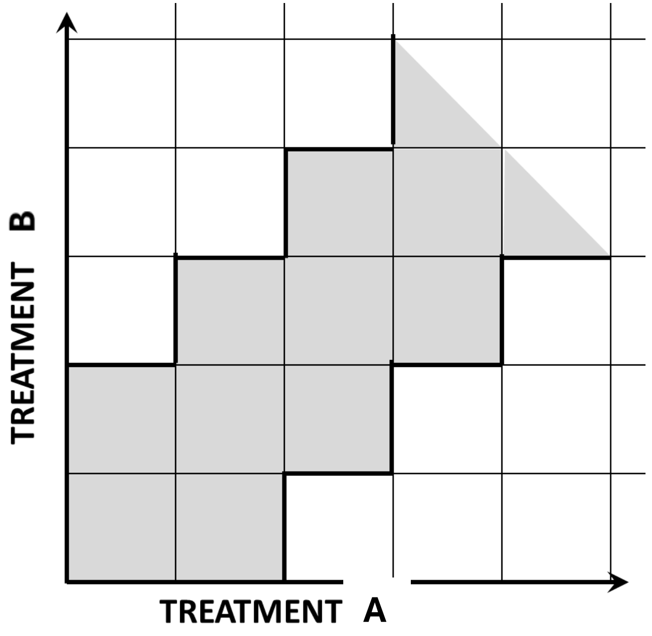
Directional Strategy for Equal Allocation Often Reduces to the Convergence Strategy

- For most equal allocation procedures, conditional probability of allocation is higher for the underrepresented treatment
  - or equal for both treatments for some (X, Y), as for Big Stick randomization
- For such procedures Directional Strategy coincides with **Convergence Strategy**:
  - If $N_A > N_B$, guess A
  - If $N_A < N_B$, guess B
  - If $N_A = N_B$, guess 50:50 (or in any other way – it does not matter)
- Investigators always expect the underrepresented treatment to be more likely to be assigned and thus use convergence strategy
- **This belief can be exploited to reduce selection bias** (to be discussed later)

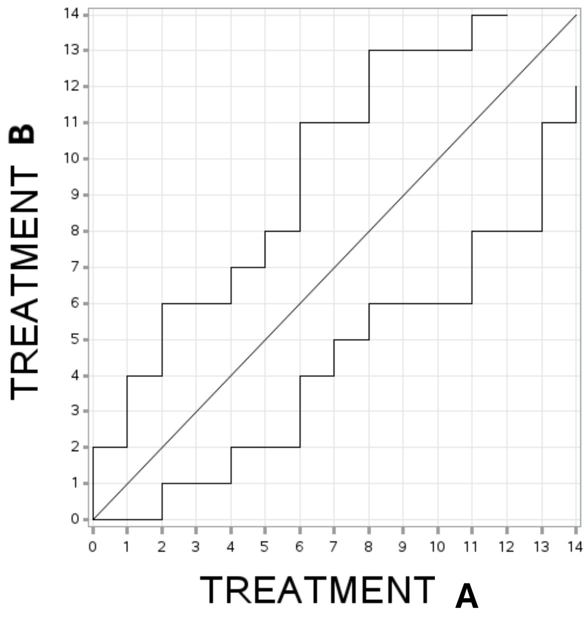
Which Allocation Procedure Minimizes the Selection Bias for Equal Allocation When the allocation procedure is known to the investigator?

- Blackwell and Hodges (1957) showed that among all 1:1 allocation procedures that assign $N/2$ subjects to each treatment, the Truncated Binomial Design (TBD) of the size N minimizes the selection bias
  - subjects are allocated at random with probability ½ until one of the treatment arms reaches $N/2$ subjects
- TBD can be considered a Big Stick Design (BSD) on the allocation space defined as the $N/2 \times N/2$ square
- **BSD: Allocate completely at random until meeting the boundary**
- This property of BSD also holds for any allocation space symmetric with respect to Treatments A and B [Kuznetsova 2024, 2019]
  - In particular, the allocation space for popular procedures with Maximum Tolerated Imbalance (MTI), that require $|N_A - N_B| \leq MTI$

BSD minimizes selection bias among all 1:1 allocation procedures symmetric with respect to Treatments A and B on an arbitrary symmetric connected allocation space [Kuznetsova 2024]



Allocation space for MTI=2



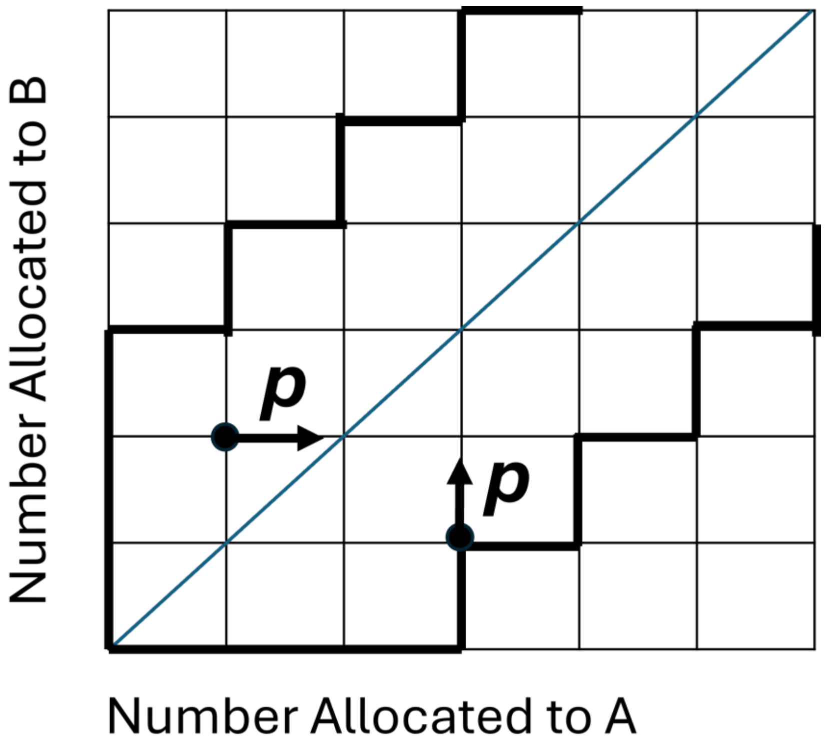
Allocation space with varying MTI

- Reminder: applies when the investigator knows the allocation procedure
  - It is sufficient to know which treatment is more likely to be assigned, not necessary to know the form for v_1 (X, Y)
- BSD can serve as a benchmark when comparing allocation procedures in selection bias

Can we Reduce Selection Bias with an Allocation Procedure that Goes Against the Investigator's Expectation?

- To reduce the selection bias under convergence guessing strategy, assign the underrepresented treatment with conditional probability of $<1/2$ for some allocations
- This reduces the proportion of correct guesses
- Example 1: Conditional Biased Coin design by Johnson (2021) with bias $p<1/2$

Example 2: Biased Coin Randomization with Imbalance Intolerance (Chen 1999) that has **bias *p*<1/2 instead of *p*>1/2**



- Allocate underrepresented treatment with probability *p*>1/2 (as in the biased coin randomization, Efron (1971) but only as long as imbalance ≤MTI
  - MTI=3 in the example on the left
- Let us use p<1/2 instead
- Investigator who follows the convergence strategy will make correct guess
  - with probability 1 when the MTI is reached
  - with probability ½ when the imbalance is 0
  - with probability *p*<1/2 otherwise
- By lowering *p*, selection bias can be lowered to 0 or even made negative
  - the investigator biases against the group they want to favor

Allocation Procedures not Favoring the Underrepresented Treatment

- In selection bias theory, it is often taken for granted that an equal allocation procedure favors the underrepresented treatment for the next allocation
- Indeed, the purpose of restricted randomization is to promote balance in treatment assignments, which assumes every allocation will work towards better balance
- However, a good balance could still be preserved with a procedure that favors overrepresented treatment for some allocations to reduce selection bias
- Some statements silently assume the procedure favors underrepresented treatment:
    - Calling the convergence strategy optimal, while in fact the directional strategy is optimal in general
    - The measure of predictability of the sequence [see Rosenberger and Lachin 2015, p.83] assumes that the investigator knows when the conditional probability is >1/2

Example: BCD with Imbalance Intolerance and p<1/2

Average Excess Selection Bias and Average Imbalance When the Investigator Follows the Convergence Guessing Strategy

MTI	Allocation Procedure	Average Excess Selection Bias	Average Imbalance
2	BCD (p=0.4) with MTI 2	0.08929	1.10000
	BCD (p=1/3) with MTI 2	0.07143	1.16667
	BCD (p=0.06667) with MTI 2	0.00000	1.43333
	BSD with MTI 2	0.11607	1.00000
3	BCD (p=0.4) with MTI 3	0.04299	1.70083
	BCD (p=1/3) with MTI 3	0.02478	1.85860
	BCD (p=0.213) with MTI 3	0.00014	2.11214
	BSD with MTI 3	0.07540	1.45238
4	BCD (p=0.4) with MTI 4	0.00979	2.29443
	BCD (p=1/3) with MTI 4	-0.01048	2.56095
	BCD (p=0.37) with MTI 4	0.00003	2.41809
	BSD with MTI 4	0.04911	1.85715

- MTI of 2 to 4 presented
- Allocation of 28 subjects
- BSD is used as a benchmark
- Provided metrics for p=0.4, 1/3, and p that results in selection bias of ~0
- Average Imbalance is (Chen 1999)

$$\delta_N = \frac{1}{N}\sum_{i=1}^{N} E(|N_{1i} - N_{2i}|)$$

- When p is too low, the allocation sequence is likely to hug the boundary – might want to avoid

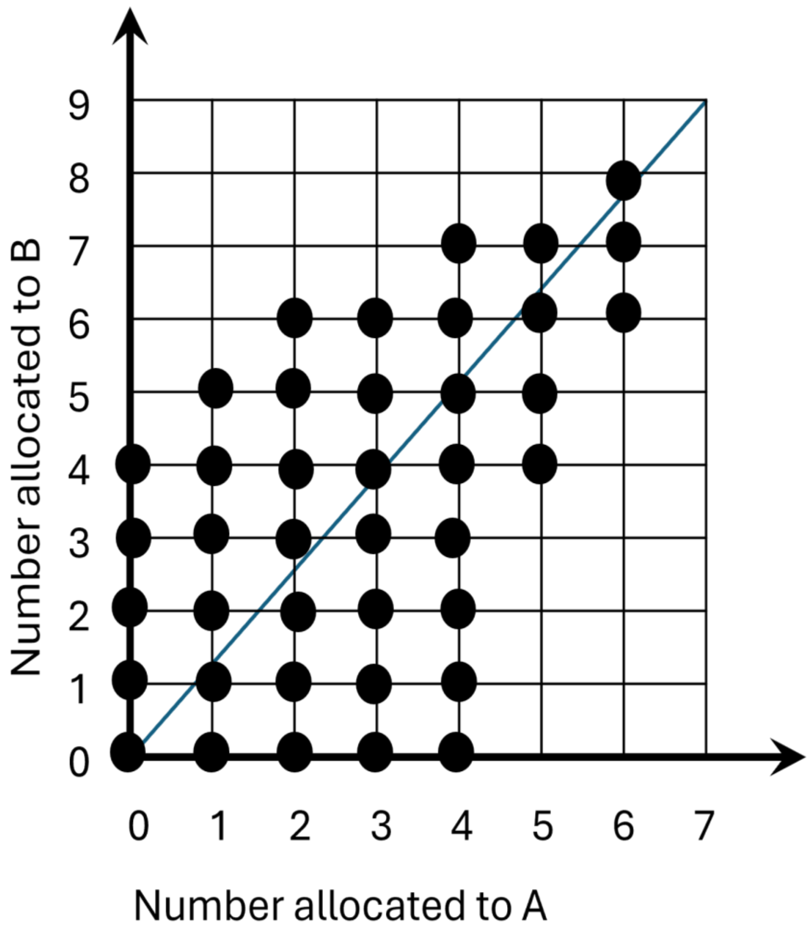
When the Investigator Does not Want to Bias Every Allocation

- Biasing is a hard work
- Under Directional Strategy with Biasing Threshold, biasing is undertaken only when the pay-off to the biasing effort is large
- Stigler (1969), Wei (1978) describe strategies related to the pay-off
- One possible criterion is to bias when the increment in the expected bias factor is above certain level T [Kuznetsova 2018]:

$$\text{Inc}=\frac{1}{4}\left|\frac{v_1\,(X,Y)}{w_1}-\frac{v_2\,(X,Y)}{w_2}\right|\geq T$$

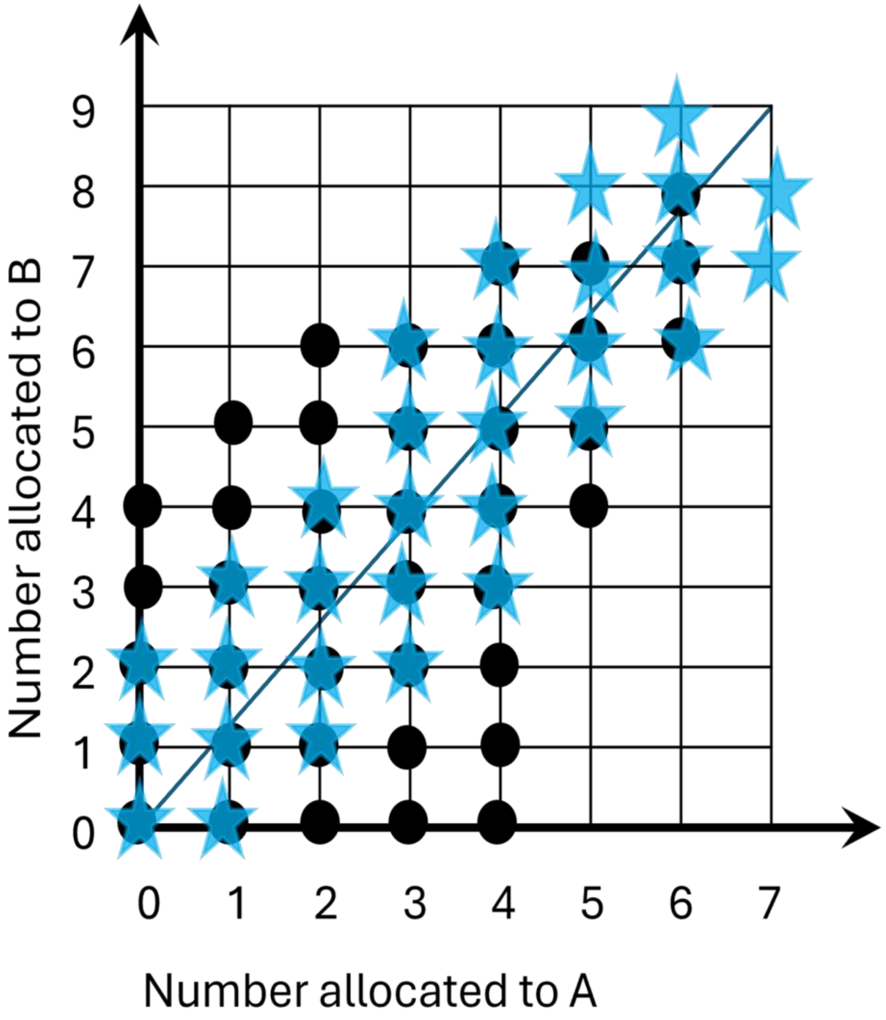
- Described for equal allocation in Berger (2005)

Example. Strategy with Biasing Threshold T=0.2 for 7: 9 Permuted Block Randomization



- Investigator, knowing the allocation ratio is 7:9, will assume permuted block randomization with block size 16 is used
- Biasing threshold is exceeded only outside of the nodes marked by the black dots
  - Includes all deterministic allocations on the top and right boundaries of the allocation space but also nodes far from the diagonal
- If actual allocation procedure has sequences mostly contained within nodes marked by black dots, selection bias will be low

Brick Tunnel Randomization Results in Low Selection Bias When the Investigator Uses Directional Strategy with Biasing Threshold



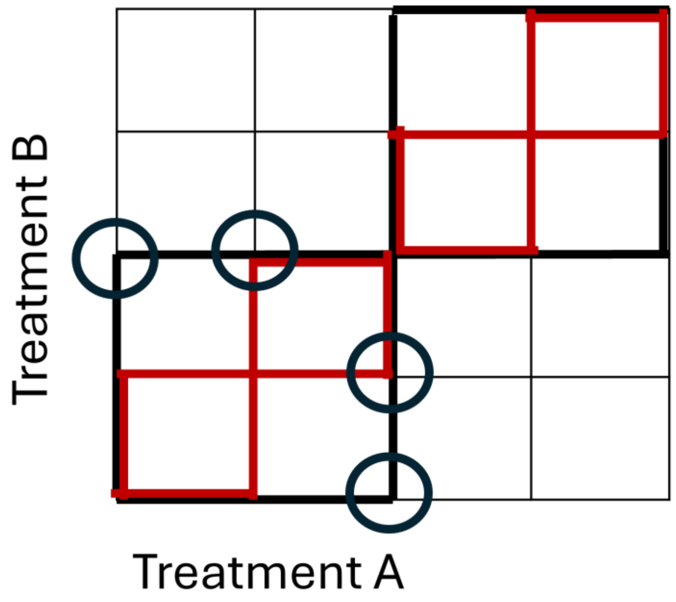
- BTR [Kuznetsova & Tymofyeyev 2011] reduces the allocation space to the unitary squares pierced by the diagonal of 7×9 rectangle
- Blue stars – nodes of the allocation space for 7:9 BTR
- Only four BTR nodes lay in the area not covered by black dots
    - The only nodes where investigator will bias
- As a result, the selection bias is low
- However, if the investigator knows that BTR is used, they will bias at every allocation
- Always recommended to conceal the allocation procedure

So Which Allocation Procedure Minimizes the Selection Bias When the Investigator Biases Only When the Pay-off is High?

- Depends on what the investigator assumes about the allocation procedure
- Most commonly, the payoff is low when the pair (N_A, N_B) is close to the diagonal
  - The conditional probabilities of allocation are close to unconditional
- Then an allocation procedure with narrow allocation space that is close to the diagonal, will result in rare biasing and thus low selection bias
  - As in the previous example
- A special, often considered case, is biasing only when the investigator expects the allocations to be deterministic
  - "Deterministic" strategy

Example. Study with Equal Allocation and "Deterministic" Biasing Strategy

- Investigator assumes PBR with the block size 4
  - Black 2×2 squares
- Biases only when thinks the allocations are deterministic
  - Four black circles
- In fact, PBR with the block size 2 was used in the trial
  - Red squares
- Allocation sequences of the PBR with block size 2 pass only through the two of the biasing nodes
  - Selection bias is reduced with PBR with block size 2 compared to block size 4



Selection Bias with “Deterministic” Strategy

- What matters, is not the probability of deterministic allocations with the actual allocation procedure, but **the probability of what the investigator thinks is a deterministic allocation**
- Even though PBR with block size 2 has higher probability of deterministic allocations than PBR with the block size 4, it leads to a higher selection bias with the “deterministic” biasing strategy only when the investigator expects block size of 2
  - Selection bias is lower if a higher block size is expected
- Higher probability of deterministic assignments does not necessarily translate into a higher selection bias

Unresolved Questions: 2-arm Unequal Allocation

- Which unequal allocation procedure minimizes selection bias when the investigator knows the procedure and applies directional strategy?
- Blackwell and Hodges (1957) showed that it is TBD on $N_1 \times N_2$ rectangular allocation space
  - However, this is not an Allocation Ratio Preserving (ARP) procedure [Kuznetsova & Tymofyeyev 2012] and this leads to a lot of problems [Proschan et al. 2011; K&T 2012]
- Solving the problem of minimizing the selection bias for ARP unequal randomization, the way it is solved for equal allocation on an arbitrary allocation space, is challenging
- It is unclear for which allocation spaces an ARP unequal allocation procedure exists
  - For equal allocation, it is sufficient for the allocation space to be symmetric w.r.t. A &B
- ARP unequal allocation procedures are known to exist on the following spaces:
  - $N_1 \times N_2$ rectangle or a sequence of rectangles (Permuted Block Design [Zelen 1974])
  - Sequence of overlapping $kM_1 \times kM_2$ rectangles (Block Urn Design by Zhao and Weng (2011))
  - MTI space $|N_B - N_A \times C_2/C_1| \leq b$ (Brick Tunnel Randomization, Wide Brick Tunnel Randomization by Kuznetsova & Tymofyeyev (2011, 2014))
  - Unrestricted allocation space (Complete Randomization; 2-arm ARP expansions of biased coin by Kuznetsova and Plamadeala Johnson (2017)

Conclusions

- When evaluating selection bias, we always need to specify under what conditions it is evaluated: what the investigator knows (assumes)
- Selection bias can be made low if the allocation procedure goes against the expectations of the investigator
- In particular, for equal allocation selection bias is reduced if the probability of the underrepresented treatment is <1/2 for some allocations
  - Unknown to the investigator
- Allocation procedure should be concealed from investigators
- In practice, the classical settings where the investigator knows the complete sequence of treatment assignments hold only in open-label trials with a single-center or randomization stratified by center
- In multi-center trials with randomization not stratified by center generally there is no opportunity for selection bias
  - Exception: a situation noted by Johannes [Krisam et al. 2024] where some centers have long uninterrupted stretches of randomizations

THANK YOU!

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