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Predictability of allocation sequences under central randomization in a multi-center clinical trial

Why the patient enrollment pattern matters

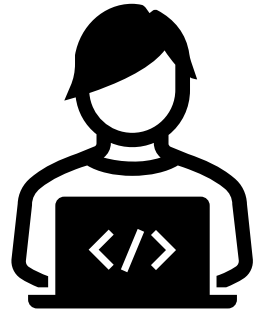
Life forward

Planning a randomized multi-center trial

- Imagine you‘re a trial statistician planning a **randomized multi-center clinical trial**
- One important aspect is the definition of the **randomization design**

- The **permuted block design (PBD)** is the first option that comes to your mind
- Also you‘ve recently come across the so-called **big stick design (BSD)** that can achieve the **same degree of imbalance control**, accompanied with a **higher degree of randomness**

- The trial you‘re planning is supposed to be **an open-label trial**, so **selection bias** could be an issue – maybe it might make sense to take a look into the **BSD**?

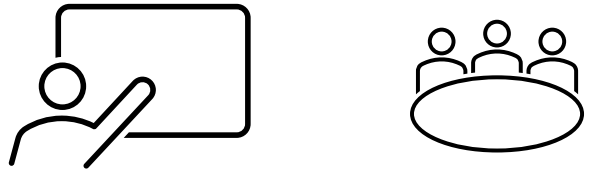


PBD vs BSD – which design to choose for your trial?

Source:
Berger *et al. BMC Med Res Methodol* (2021) 21:168

MTI	Design	Excess correct guess probability
2	PBD	20.8%
	BSD	12.5%
3	PBD	18.3%
	BSD	8.3%

- You do some literature research and find out that there is some real benefit in terms of excess correct guess probability when using **BSD** over **PBD** – this seems to be the way to go for your multi-center open-label trial!
- Enthusiastically, you propose using the **BSD** to your team of stakeholders!



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- However, to your surprise, they are not very enthusiastic about all of your arguments regarding the benefits of BSD:

What is center-stratified randomization?

Randomization list

SeqNo	RandNo	Block	Treatment
1	154	1	B
2	254	1	B
3	212	1	A
4	184	1	A
5	152	2	A
6	135	2	A
7	289	2	B
8	105	2	B
9	222	3	A
10	114	3	B
11	153	3	B
12	285	3	A

Schedule of enrolment

PatNo	Time	Center
1	7/27/2022 (9:45 AM)	Center 1 (France)

- If the randomization is stratified by center:
  - ➢ The IRT allocates complete blocks to each center.

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5	7/29/2022 (10:04 AM)	Center 1 (France)
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- If the randomization is stratified by center:
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What is central randomization (not stratified by center)?

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10	114	3	B
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12	285	3	A

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- If the randomization is not stratified by center:
  - The blocks are shared between the centers that currently enroll

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7	7/30/2022 (11:00 AM)	Center 2 (Italy)

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Advantages of central randomization over center-stratified randomization

- Central randomization ensures that, overall, the treatment assignments are practically balanced
- In theory, it could be expected that there is little potential for an investigator to guess the subsequent treatment assignment within his or her own center, as other centers also enroll patients concurrently and the investigator only knows the assignments in his or her own center.
- Thus, there should indeed be not too much benefit from using a BSD over a PBD in a multi-center RCT using central-randomization – but what if…

Randomization list			**Schedule of enrolment**		
SeqNo	Block	Treatment	PatNo	Time	Center
1	1	B	1	7/27/2022 (9:45 AM)	Center 1 (France)
2	1	B	2	7/28/2022 (9:52 AM)	Center 2 (Italy)
3	1	A	3	7/28/2022 (4:00 PM)	Center 3 (Belgium)
4	1	A	4	7/29/2022 (10:03 AM)	Center 4 (Italy)
5	2	A	5	7/29/2022 (10:04 AM)	Center 1 (France)
6	2	A	6	7/29/2022 (10:08 AM)	Center 4 (Italy)
7	2	B	7	7/30/2022 (11:00 AM)	Center 2 (Italy)
8	2	B	8	7/30/2022 (11:05 AM)	Center 2 (Italy)
9	3	A	9	7/31/2022 (11:12 AM)	Center 1 (France)
10	3	B	10	7/31/2022 (5:02 PM)	Center 5 (Canada)
11	3	B	11	8/1/2022 (9:44 AM)	Center 4 (Italy)
12	3	A	12	8/1/2022 (9:44 AM)	Center 1 (France)

…clinical practice contradicts the assumption of a „random patient flow“

- Some study centers may have **„spikes“** in recruitment when multiple participants in a sequence are enrolled and randomized on the same day.
- Reasons:
  - ➢ Specialized institution has eligible patients waiting for a study to initiate – all of these patients are enrolled once the study goes live
  - ➢ Study may require some highly time-consuming tasks to be done at the randomization visit - center schedules the visit for their patients on the same time day to save time

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4	1	A	4	7/29/2022 (9:45 AM)	Center 1 (France)
5	2	A	5	7/29/2022 (10:03 AM)	Center 3 (Belgium)
6	2	A	6	7/29/2022 (10:08 AM)	Center 3 (Belgium)
7	2	B	7	7/29/2022 (10:15 AM)	Center 3 (Belgium)
8	2	B	8	7/29/2022 (10:18 AM)	Center 3 (Belgium)
9	3	A	9	7/29/2022 (10:23 AM)	Center 3 (Belgium)
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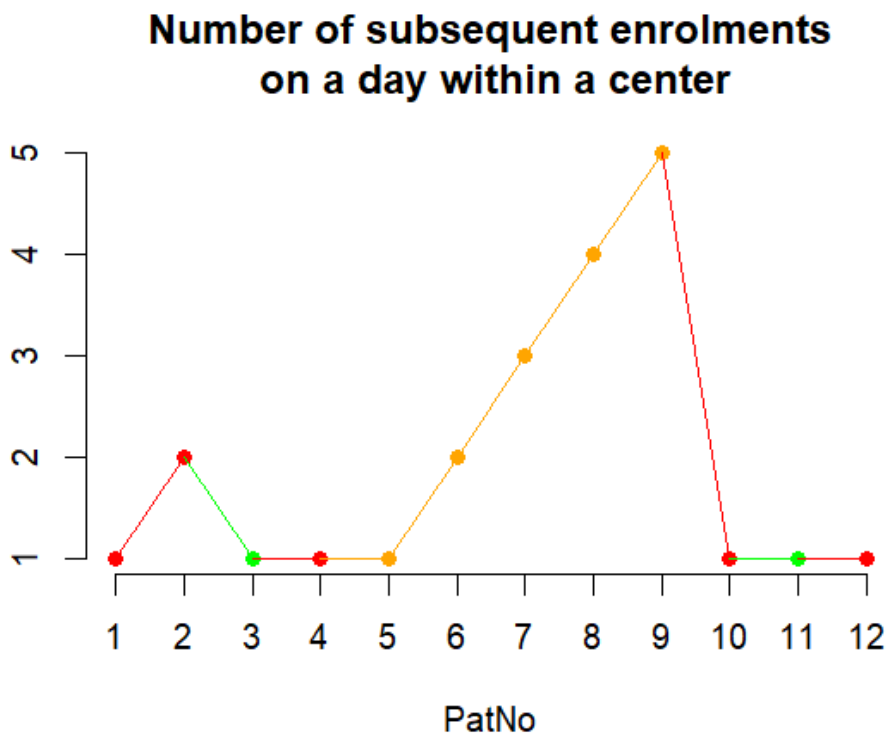

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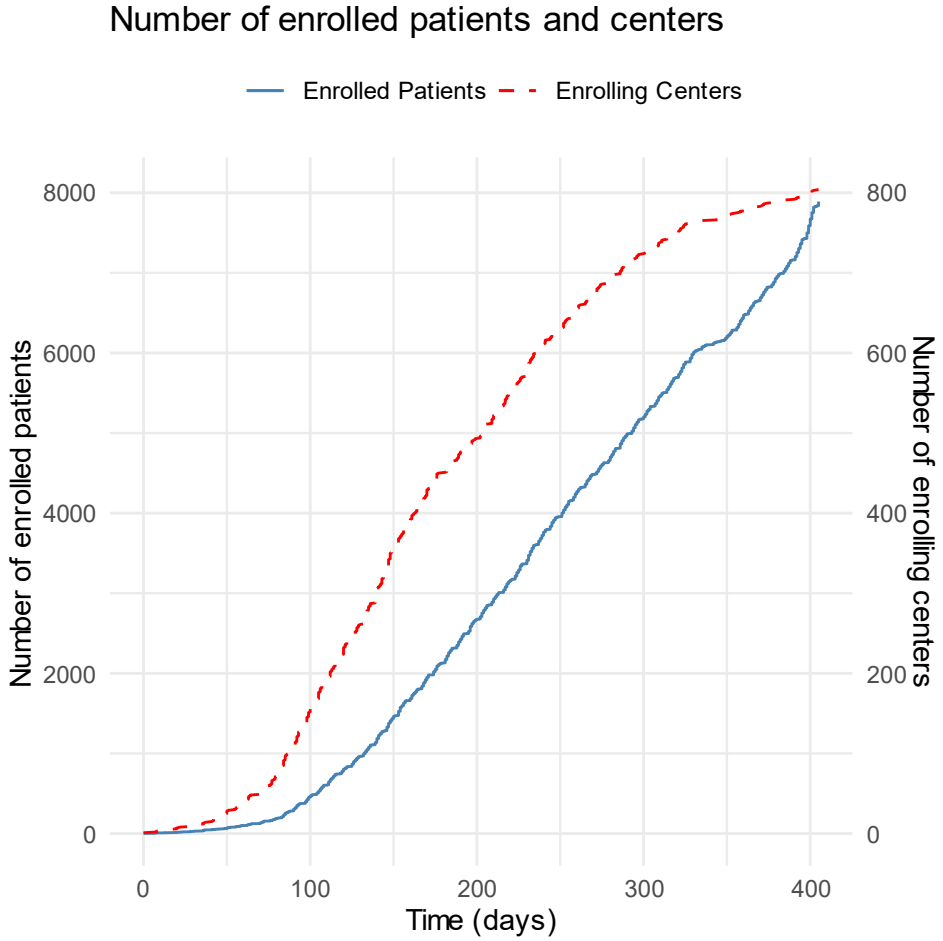
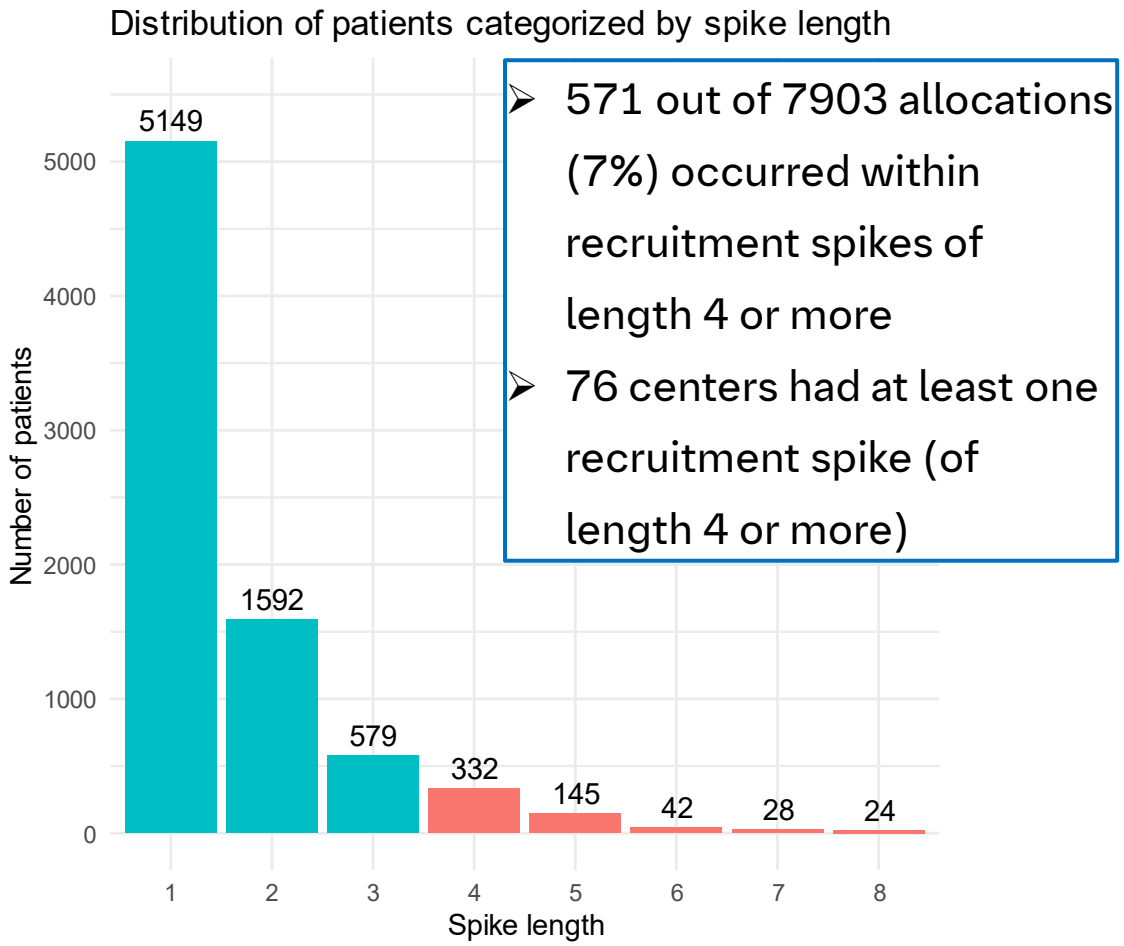
Do these recruitment spikes really happen in clinical practice? Assessments based on a clinical trial data example





- 571 out of 7903 allocations (7%) occurred within recruitment spikes of length 4 or more
- 76 centers had at least one recruitment spike (of length 4 or more)

Source: Krisam et al. (2024): Understanding an impact of patient enrollment pattern on predictability of central (unstratified) randomization in a multi-center clinical trial. Accepted at Statistics in Medicine

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PBD vs BSD: Predictability revisited unter central randomization

- Now being aware of these recruitment spikes in our clinical trial data example, let‘s assess the impact on the **excess correct guess probability**

MTI	Design	Outside of recruitment spikes* (n=7332)	Within recruitment spikes* (n=571)	Overall in the study (n=7903)	Probability for monocenter trial (Berger et al. 2021)
2	PBD	1.9%	10.5%	2.6%	20.8%
	BSD	1.8%	7.9%	2.2%	12.5%
3	PBD	1.3%	7.5%	1.7%	18.3%
	BSD	1.2%	5.1%	1.5%	8.3%

*: A recruitment spike is defined as four or more patients being enrolled within one center on the same day

Note: Results are based on 10,000 simulated datasets

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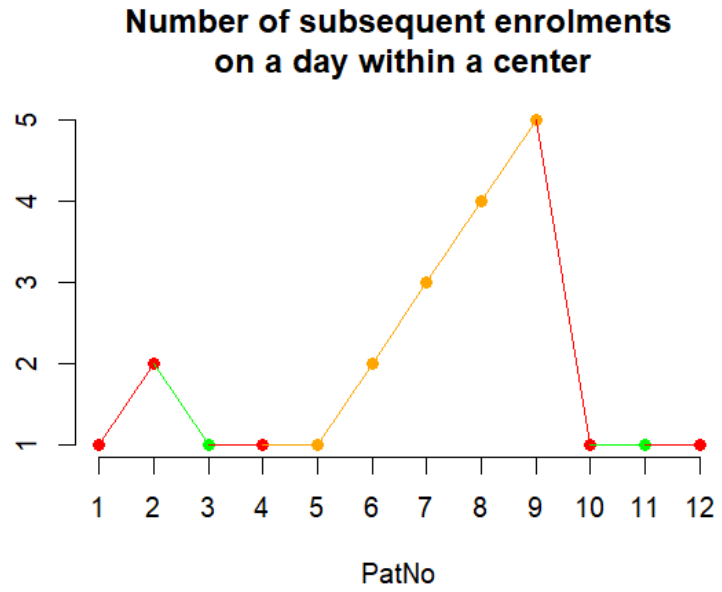
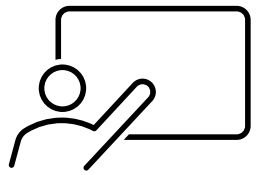
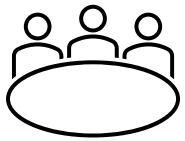
Going back to the design discussion



„We‘re using central randomization, so there‘s **no selection bias with PBD**!“

“Well that’s not true. Depending on the **patient enrollment pattern**, there still might be selection bias due to **recruitment spikes**. A BSD could still prove beneficial for our centrally randomized trial!





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	BSD	1.2%	5.1%	1.5%	8.3%

Summary

- In a multi-center RCT using central randomization, it is possible to have so-called **recruitment spikes.**
- Spikes can occur if **multiple participants are recruited by the same center on the same day** (or over a longer time interval if other centers are not recruiting participants)
- Such spikes may open the **potential for making intelligent guesses** of treatment assignments in the sequence which may lead to **selection bias**
- If such spikes are expected, the following strategies may be useful:
  - Consider **evaluating the predictability of the chosen randomization design** through simulations at the study planning stage
  - Instead of permuted block design**, consider using MTI randomization procedures** such as the big stick design
  - **Avoid disclosure of the overall recruitment progress** to individual investigators such that an investigator from a given study center is not aware of the possible lack of recruitment activity at other centers
  - Use **scrambled allocation numbers** instead of consecutive allocation numbers to make it more difficult for an investigator to e.g. figure out whether they still are on an uninterrupted recruitment spike

References

- Krisam J, Ryeznik Y, Carter K, Kuznetsova O, Sverdlov O (2024): Understanding an impact of patient enrollment pattern on predictability of central (unstratified) randomization in a multi-center clinical trial. Statistics in Medicine 43(17): 3313-3325.
- Berger V, Bour L, Carter K et al. (2021). A roadmap to using randomization in clinical trials. BMC Med Res Methodol 21, 168

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