Boehringer Ingelheim

How the Chosen Randomisation Method Affects the Individual Clinical Trial Participant

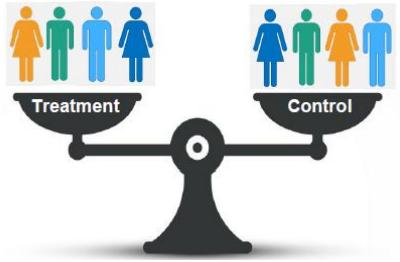
2026 PSI Conference, Belfast

Johannes Krisam, joint work with colleagues from the
“Randomization Working Group”/“Randomisation SIG”

Life forward

Randomisation and its role for statisticians… and trial participants!

- Randomisation is a cornerstone for clinical trials due to its many favorable aspects from a statistical perspective
  - ➢ Balancing treatment assignments and covariates
  - ➢ Reduces the risk for selection bias
  - ➢ Foundation for statistical inference



- What randomisation means for trial participants is something of a more complex topic
  - ➢ Trial participants do not experience randomisation in their regular clinical care → „*Procedures related solely to research must be explained (for example […] randomized assignment to treatment […])*" (FDA, 2023)
  - ➢ ICH E6(R3) (ICH, 2023) requires that "*the informed consent materials to be provided to participants should explain […] the probability for random assignment to the investigational product*" but also that "*the information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity.*"

Food and Drug Administration (2023). Informed consent guidance for IRBs, clinical investigators, and sponsors. Available from: https://www.fda.gov/media/88915/download
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2023) ICH guideline E6(R3): Good Clinical Practice. Available at: https://www.ich.org/page/efficacy-guidelines

Boehringer Ingelheim

How randomisation is explained in the ICF – computers, coins/dice, chance

Table I Descriptions of randomisation

1	Once you have agreed to enter the trial, your treatment is not chosen by yourself or a doctor but by a computer. There is usually a 50:50 chance of receiving either treatment	Royal Marsden Website, 2003
2	Once you have agreed to enter the trial, a computer will allocate you randomly (as if by the roll of a dice) to receive the 'standard treatment' or one of the new treatments being tested. Neither your doctor nor you yourself will choose which treatment you receive	MRC FOCUS Trial Patient info sheet
3	Once you have agreed to enter the trial, you will be randomised to a course of treatment. This is a process that assigns participants by chance, rather than by choice, to either the investigational group or the control group	NCI website, 2003
4	Once you have agreed to enter the trial the decision regarding which treatment you receive will be made by a process called 'randomisation'. This means that your specialists will not make the decision themselves, but it will be made by chance	BNL Trial Patient info sheet
5	Once you have agreed to enter the trial, the treatment you receive will be selected by a process called randomisation, that is, it will not be chosen by you or your doctor, but by a computer and it is like the toss of a coin. This is to prevent bias in the results of the trial	CLL4 Trial Patient info sheet
6	Once you have agreed to enter the trial, you will be randomised to a course of treatment. This means that there are at least two different groups in the trial and those taking part are put into one or other group at random. This 'randomisation' is usually done by a computer	CancerHelp website, 2003
7	Once you have agreed to enter the trial, you will be randomised to a course of treatment. This means that a computer will randomly allocate patients to treatment groups in the trial. This is done so that each group has a similar mix of patients of different ages, sex and state of health	CancerBACUP website, 2003

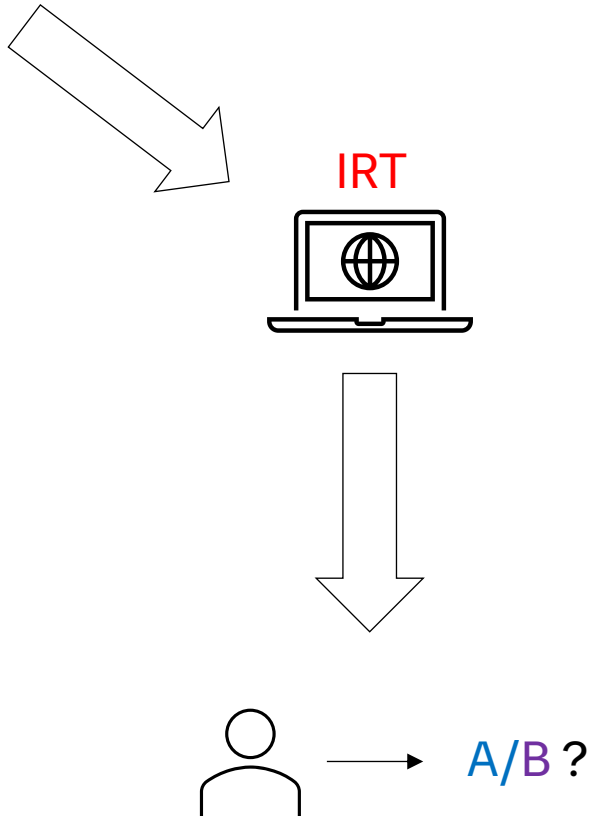
- Similar explanations also featured in videos by public health bodies/initatives explaining randomisation (HHS, Cancer Research UK, Australian Clinical Trials Alliance)

Jenkins, V., Fallowfield, L., & Cox, A. (2005). The preferences of 600 patients for different descriptions of randomisation. British Journal of Cancer, 92(5), 807–810. https://doi.org/10.1038/sj.bjc.6602445

How randomisation is actually done in clinical trials

- For trials using standard (non-adaptive) randomisation methods, **randomisation lists are pre-generated in advance,** based on a chosen randomisation methodology with defined parameters
- For most trials, (stratified) permuted block methodology is still used for list creation (Sverdlov al. 2024)
- Those lists are then usually implemented in an **IRT** (Interactive Response Technology) system, which then uses the list to **assign patients entering the trial in sequence**, starting with the smallest available sequence number

Sequence No	Block No	Trt
101	1	A
102	1	B
103	1	B
104	1	A
105	2	A
106	2	A
107	2	B
108	2	B
109	3	B
110	3	A
111	3	B
112	3	A
...	...	...



Sverdlov, O., Carter, K et al. (2024). Which Randomization Methods Are Used Most Frequently in Clinical Trials? Results of a Survey by the Randomization Working Group. Statistics in Biopharmaceutical Research, 16(4), 441–455. https://doi.org/10.1080/19466315.2023.2225451

A little thought experiment (from participant perspective)

Assumption:

- You are a patient entering a clinical trial because you have heard that there is a promising treatment A that can help your condition;
- You are **not** a statistician.
- Permuted block design (PBD) is used. ← i.e. a standard randomisation method

Question:

What are your expectations when you enter a clinical trial and are told that the trial has 2 trt arms, with 1:1 allocation?

What do you think is your chance of getting desirable trt A?

A) 50-50

B) Something else

Answer: As the patient enters the trial, their chance of receiving desirable trt A is more often not 50-50, if PBD is used.

Boehringer Ingelheim

Let's look at the blocks that make up a PBD list

- In a PBD with block size 4, the treatments A and B are permuted so that in every block of 4 the treatments A and B appear twice.

Sequence	Block Type	Treatment	Conditional allocation probability for A
1	1		
2	1		
3	1		
4	1		
5	2		
6	2		
7	2		
8	2		
	3		
	3		
	3		
	3		

Block Type	Treatment	Conditional allocation probability for A
4		
4		
4		
4		
5		
5		
5		
5		
6		
6		
6		
6		

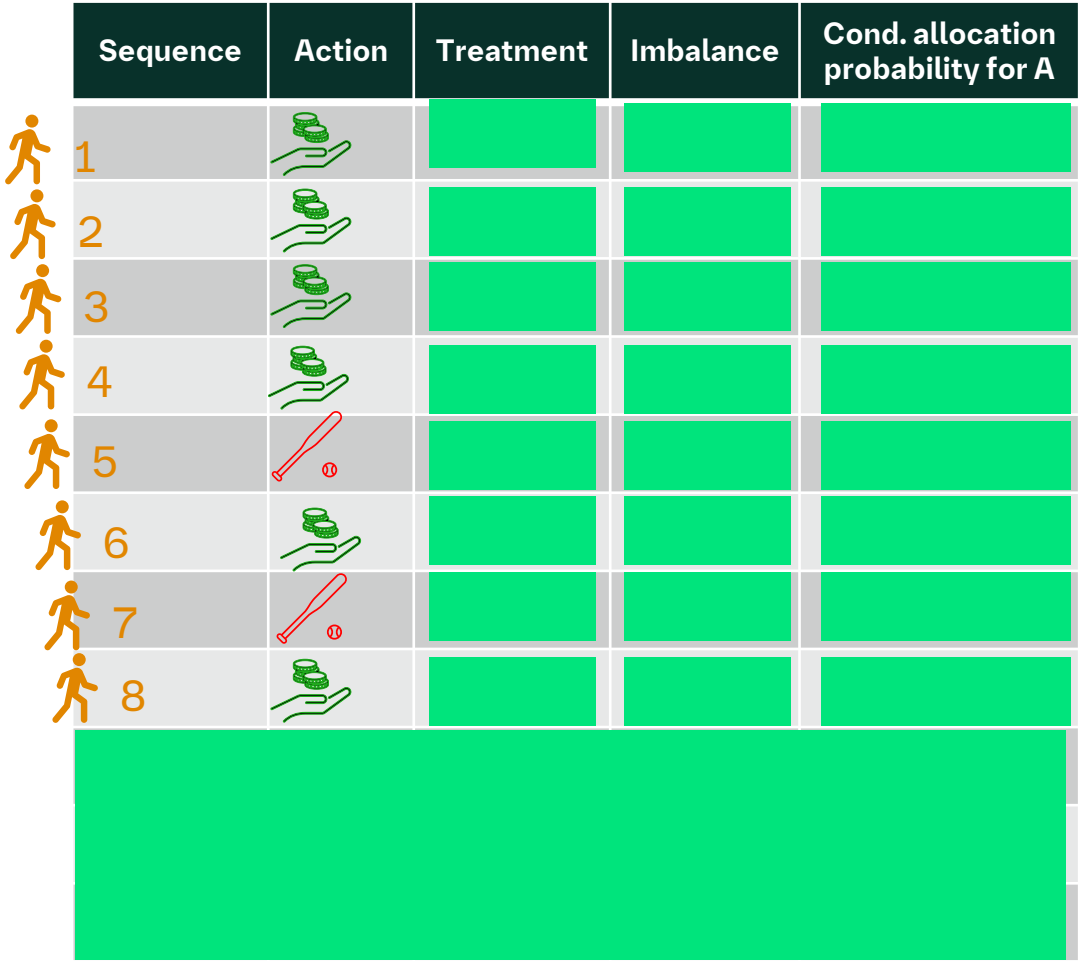
Let's try this thought experiment again… using Big Stick Design (BSD)

- As a patient you are enrolling into a clinical trial and have heard
- that a promising treatment A could help your condition.
- This clinical trial is 1:1 allocation.
- What are your chances for receiving treatment A?

➢ Same experiment with Big Stick Design (BSD) by Soares & Wu (1983), mti = 2

Results:

- In this experiment, out of 11 participants, 8 had a 50-50 chance of receiving treatment A
- Total sample distribution: 6 to 5, i.e, balanced



Soares, J.F., & Jeff Wu, C.F. Some Restricted randomization rules in sequential designs. Communications in Statistics - Theory and Methods, 1983 Jan; 12(17), 2017-2034

Boehringer Ingelheim

Comparing PBD(4) against BSD(2) in terms of completely random assignments (CR)

- P_A : Random variable of the probability of assigning a subject to arm A
- $E[P_A = k]$ can be determined for PBD(4) and BSD(2) using steady-state probabilities (Zhao et al. 2024)

k	$E[P_A = k]$	
	PBD(4)	BSD(2)
0	16.7%	12.5%
0.33	12.5%	0%
0.50	**41.7%**	**75%**
0.67	12.5%	0%
1	16.7%	12.5%

CR=$E[P_A = 0.5]$: Probability for **completely random assignments**

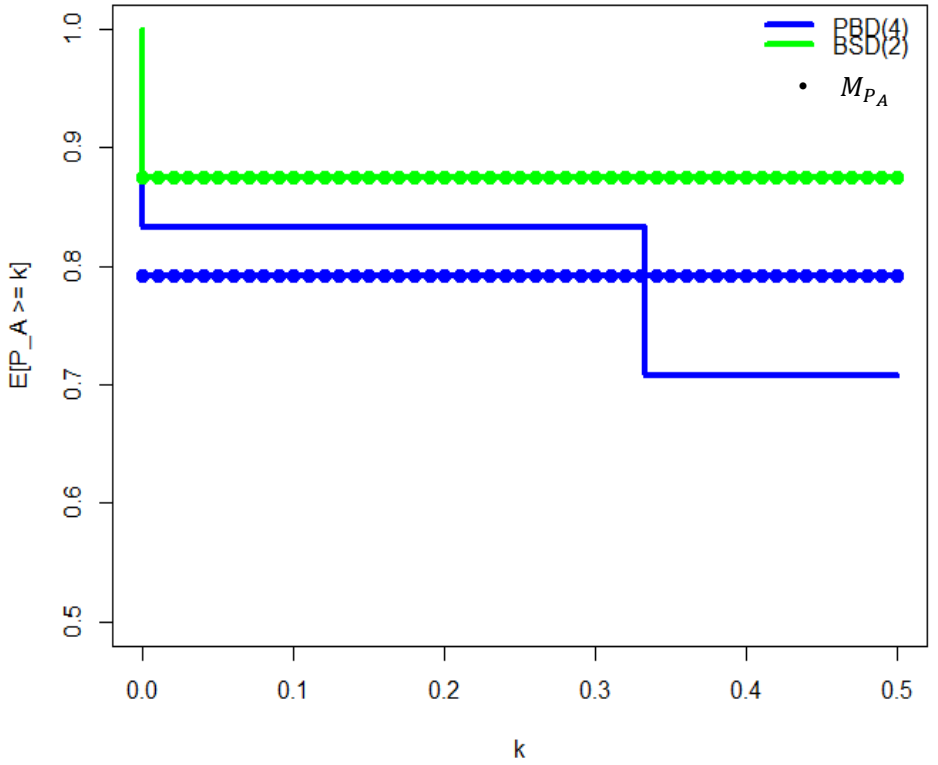
As a reference design, unrestricted/simple randomisation will always have CR=100%

Zhao, W., Carter, K., Sverdlov, O., Scheffold, A., Ryeznik, Y., Cassarly, C., & Berger, V. W. (2024). Steady-state statistical properties and implementation of randomization designs with maximum tolerated imbalance restriction for two-arm equal allocation clinical trials. Statistics in Medicine. https://doi.org/10.1002/sim.10013

Proposing another patient-relevant performance measure

- Besides using $CR = \boldsymbol{E}[\boldsymbol{P_A} = \boldsymbol{0.5}]$ as a measure of fairness of a procedure, we could also assume that patients would like to have a chance of at least $k \in (0,0.5)$ to receive a promising treatment A
- $\boldsymbol{E}[\boldsymbol{P_A} \geq \boldsymbol{k}]$ can be calculated as another performance measure
- As $\boldsymbol{E}[\boldsymbol{P_A} \geq \boldsymbol{k}]$ depends on a rather subjective threshold k, one can consider averaging over k, yielding a unified measure $\boldsymbol{M_{P_A}} \coloneqq 2\int_0^{0.5} E[P_A \geq k]dk$

k	$\boldsymbol{E}[\boldsymbol{P_A} \geq \boldsymbol{k}]$	
	PBD(4)	BSD(2)
0	100%	100%
(0, 0.33)	83.3%	87.5%
[0.33, 0.5]	70.8%	87.5%



Boehringer Ingelheim

Assessing designs with different imbalance restrictions

Design	Maximum tolerated imbalance	CR
PBD(2)	1	50%
PBD(4)	2	41.7%
BSD(2)	2	75%
PBD(6)	3	36.7%
BSD(3)	3	83.3%
Unrestricted Randomisation	∞	100%

- CR decreases with an increasing block size for PBD
  - Reason: Completely random allocations only happen
    1. at the **beginning of a block** or
    2. when **allocation is balanced during a block**
  - The **first component** is the main driver for the decrease in CR
- CR increases for an increasing MTI for BSD

- 75% is worst-case benchmark for M_{P_A} (met by PBD(2))
- M_{P_A} comparable for PBD(4) and PBD(6)
- M_{P_A} much higher for BSD(2) and BSD(3)

The relevance of our assessment for the trial participants

- We presented the previous slides to the members of our **patient advisory board** and got the following feedback
  - The majority of the advisory board members **struggled to understand the methodological difference** between PBD and BSD → reflects a generally low understanding of randomisation for trial participants (Shiely et al. 2024)
  - Their point also was that
    - ➢ participants **do not necessarily need to understand the full details** behind randomisation;
    - ➢ but rather **must understand the concept behind it and how it differs from general care** (see also Wendler, 2009)
  - However they stated explicitly that
    - ➢ such assessments of randomisation procedures are highly relevant;
    - ➢ it is our **duty as statisticians**, as being knowledgable in these aspects, **to choose a method which is in the participants‘ best interest**

Shiely, F., Murphy, E., Gilles, K., Hood, K., O'Sullivan, L., Harman, N., Isaacs, T., & Treweek, S. (2024). Trial participants' self-reported understanding of randomisation phrases in participation information leaflets can be high, but acceptability of some descriptions is low, especially those linked to gambling and luck. *Trials*, *25*(1), 391. https://doi.org/10.1186/s13063-024-08217-3
Wendler, D. (2009). Must Research Participants Understand Randomization? *The American Journal of Bioethics*, *9*(2), 3–8. https://doi.org/10.1080/15265160802654145

Boehringer Ingelheim

What does this mean for us statisticians?

- **Investigations of different randomisation methods** and an assessment of their properties are also of **value to the participants.**
- The choice of just **one ultimate measure** for fairness is difficult.
  - Such a measure should generally represent **how close we are to the ideal case of unrestricted/simple randomisation** (which undoubtedly is the fairest procedure, also per ICH E9 (1998));
  - CR and $\boldsymbol{M}_{\boldsymbol{P}_A}$ are **two potential measures** indicating a high fairness if close to 100%.
  - Alternatively, a low probability of an **investigator correctly guessing the next treatment assignment** can also be considered as indicating fairness for participants (see Berger et al. 2021)

    → Rationale: it will be in the **participants' interest that an investigator cannot influence their treatment assignment.**
- Ultimately, we think that the **topic of randomisation and what it means to participants** should be discussed more prominently in the statistical community.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (1998). ICH guideline E9: Statistical Principles for Clinical Trials. Available at: https://www.ich.org/page/efficacy-guidelines

Thank you!

- The **Randomization Working Group** is a group of statisticians from industry, academia and regulatory working to promote the use of novel randomisation methods and advance the scientific understanding of these methods in the global community. We‘re a ***Special Interest Group of PSI***, members of the ***ASA Biopharmaceutical Section***, and the ***IDSWG within DahShu***.
- Some topics are:
  - Methodological research on statistical properties of randomisation methods
  - Randomisation-based inference
  - Development of software tools

RWG on LinkedIn:

RWG Homepage:

IDSWG on LinkedIn:

Boehringer Ingelheim

References

- Berger, V. W., Bour, L. J., Carter, K., et al. (2021). A roadmap to using randomization in clinical trials. BMC Medical Research Methodology, 21(1), 168. https://doi.org/10.1186/s12874-021-01303-z
- Food and Drug Administration (2023). Informed consent guidance for IRBs, clinical investigators, and sponsors. Available from: https://www.fda.gov/media/88915/download
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2023) ICH guideline E6(R3): Good Clinical Practice. Available at: https://www.ich.org/page/efficacy-guidelines
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (1998). ICH guideline E9: Statistical Principles for Clinical Trials. Available at: https://www.ich.org/page/efficacy-guidelines
- Jenkins, V., Fallowfield, L., & Cox, A. (2005). The preferences of 600 patients for different descriptions of randomisation. British Journal of Cancer, 92(5), 807–810. https://doi.org/10.1038/sj.bjc.6602445
- Shiely, F., Murphy, E., Gilles, K., Hood, K., O'Sullivan, L., Harman, N., Isaacs, T., & Treweek, S. (2024). Trial participants' self-reported understanding of randomisation phrases in participation information leaflets can be high, but acceptability of some descriptions is low, especially those linked to gambling and luck. *Trials*, *25*(1), 391. https://doi.org/10.1186/s13063-024-08217-3
- Soares, J.F., & Jeff Wu, C.F. (1983) Some Restricted randomization rules in sequential designs. Communications in Statistics - Theory and Methods, 12(17), 2017-2034. https://doi.org/10.1080/03610928308828586
- Sverdlov, O., Carter, K et al. (2024). Which Randomization Methods Are Used Most Frequently in Clinical Trials? Results of a Survey by the Randomization Working Group. Statistics in Biopharmaceutical Research, 16(4), 441–455. https://doi.org/10.1080/19466315.2023.2225451
- Wendler, D. (2009). Must Research Participants Understand Randomization? *The American Journal of Bioethics*, *9*(2), 3–8. https://doi.org/10.1080/15265160802654145
- Zhao, W., Carter, K., Sverdlov, O., Scheffold, A., Ryeznik, Y., Cassarly, C., & Berger, V. W. (2024). Steady-state statistical properties and implementation of randomization designs with maximum tolerated imbalance restriction for two-arm equal allocation clinical trials. Statistics in Medicine. https://doi.org/10.1002/sim.10013

Videos explaining randomisation

- U.S. Department of Health and Human Services (2017) Explaining randomization in clinical trials. YouTube, 29 September. Available at: https://youtu.be/MmpF1zxfQZ8 (Accessed: 11 May 2026).
- Cancer Research UK (2014) What is a randomised trial? | Clinical trials. YouTube. Available at: https://www.youtube.com/watch?v=fkOCYov1p-o (Accessed: 11 May 2026).
- Australian Clinical Trials Alliance (2019) What is randomisation? YouTube. Available at: https://www.youtube.com/watch?v=YreT2eQWJ-E (Accessed: 11 May 2026).