



MRC
Biostatistics
Unit



UNIVERSITY OF
CAMBRIDGE

Short course on Response-Adaptive Methods for Clinical Trials

*Lecture 5: Implementing Bayesian RAR in a rare
disease setting*

Rajenki Das

MRC Biostatistics Unit

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Outline

1. Bayesian RAR
2. Rare disease trial
3. A challenge
4. Proposed solution
5. Performance
6. Interim report
7. Conclusion

Bayesian Response Adaptive Randomisation (BRAR)

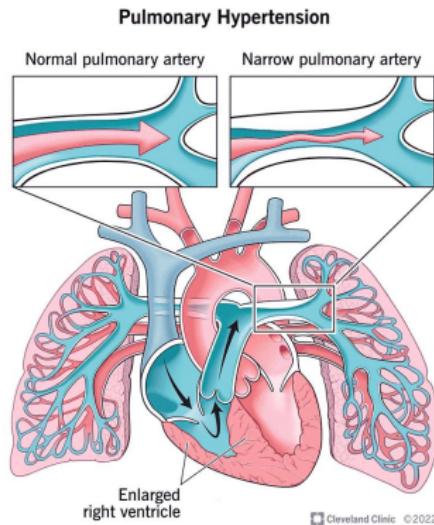
BRAR: recursively update the allocation probability for participants of a study to treatment groups based on previous outcomes using the Bayes' theorem. (Robertson et al. (2023); Atkinson and Biswas (2014))

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Pulmonary Arterial Hypertension

- Pulmonary Arterial Hypertension (PAH) is a life-threatening progressive disorder.
- Rare disease, characterised by high blood pressure in the arteries of lungs.
- Treatable, but no known cure yet, and the exact cause is still unknown.
- Mutations in the bone morphogenetic protein receptor type-2 (BMPR2) are the most common genetic cause of familial PAH.



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StratosPHere 2

- Three-armed, placebo controlled, phase II trial.
- The participants of this trial are stratified according to their mutation group- Haploinsufficiency or Missense.
- Tests efficiency of two repurposed drugs hydroxychloroquine (T_1) and phenylbutyrate (T_2) for the treatment of PAH by targeting the genetic BMPR2 pathway of the disease.
- **Primary objective:** To test the hypothesis that two treatments can rescue the BMPR2 pathway.

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- Tests efficiency of two repurposed drugs hydroxychloroquine (T_1) and phenylbutyrate (T_2) for the treatment of PAH by targeting the genetic BMPR2 pathway of the disease.
- **Primary objective:** To test the hypothesis that two treatments can rescue the BMPR2 pathway.
- **Primary endpoint:** $\mathbb{1}(\Delta\text{BMPR2}) > 0.3$.
- More details are provided in the Protocol of the trial by Deliu et al. (2024).

Trial design

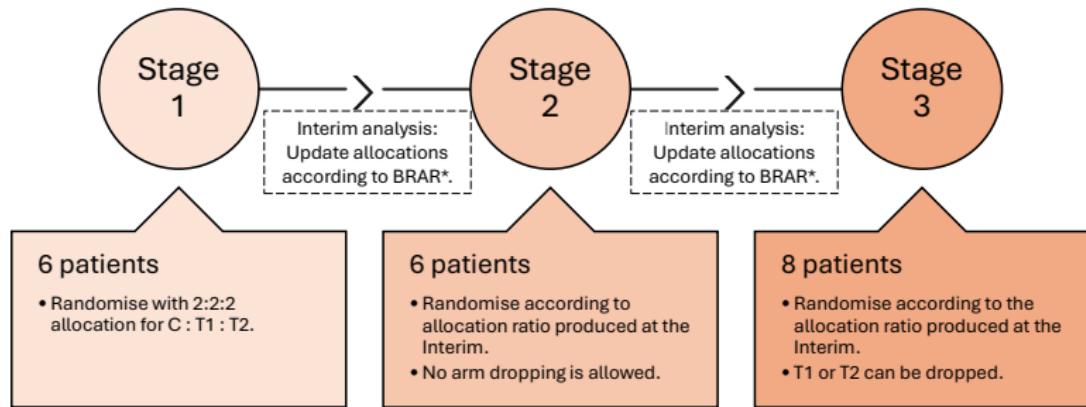


Figure: StratosPHere trial design for one mutation group. *The BRAR algorithm is based on the Bayesian design proposed by Trippa et al. (2012) and Wason and Trippa (2014).

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Challenge

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Example description:

- Take randomisation probabilities $\pi = (\pi_0, \pi_1, \dots, \pi_K)$ where π_k is the randomisation probability of arm k and,
- allocation proportions $\rho = (\rho_0, \rho_1, \dots, \rho_K)$ where ρ_k is the proportion of participants assigned to arm k i.e. $\rho_k = \frac{n_k}{n}$ where n_k is the number of participants in arm k and n is the trial sample size.
- We want $n\pi_k \approx n\rho_k \forall k$. A concern in rare disease/ small sized trials.

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Proposed solution

- **Mapping:** Intermediate step that involves a decision rule to map the continuous randomisation probabilities at the interim analyses to a target vector of discrete allocation ratios. Detailed in Das et al. (2024).

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- **Mapping:** Intermediate step that involves a decision rule to map the continuous randomisation probabilities at the interim analyses to a target vector of discrete allocation ratios. Detailed in Das et al. (2024).
- Allocation probabilities derived at Interim → Convert to target allocation ratio → Generate a random sequence based on this ratio
- Propose two types of Mapping: *Mapped-LowerGranularity* and *Mapped-HigherGranularity*

Adaptation list

Category	Description	Stage 1	Stage 2	Stage 3
Drop	T_1 can be dropped	Never	Never	2 : 0 : 6
Disfavour	T_1 can be disfavoured, but not dropped	Never	2 : 1 : 3 2 : 2 : 4	2 : 1 : 5
Balance	The active arms can be allocated equally	2 : 2 : 2	2 : 2 : 2	2 : 3 : 3
Favour	T_1 can be favoured, without dropping the other	Never	2 : 3 : 1 2 : 5 : 1	2 : 4 : 2
Keep	T_1 can be kept, while dropping the other	Never	Never	2 : 6 : 0

Table: Possible allocations for $C : T_1 : T_2$ at each stage of the trial based on the categories of the active arms.

Mapping decision line

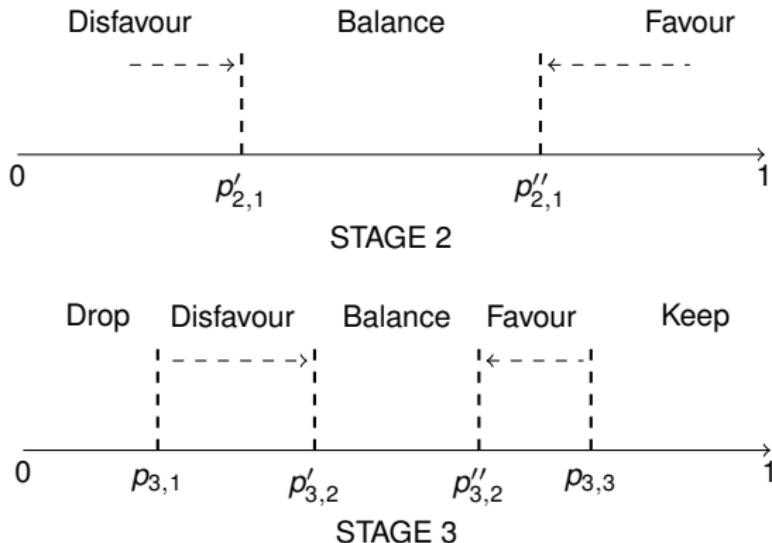


Figure: Schematic of the proposed *Mapped-HigherGranularity* design. Closing the Balance region converts it into the proposed *Mapped-LowerGranularity*.

Mapping decision function

Given a vector of allocation probabilities $\pi = [\pi_C, \pi_{T_1}, \pi_{T_2}]$, we define the adaptation-decision for an active arm as $D_m(\pi_k, t)$, where m is *Mapped-HigherGranularity*:

$$D_m(\pi_k, t) = \begin{cases} \begin{cases} Disfavour & \text{if } \pi_k \in [0, p'_{2,1}) \\ Balance & \text{if } \pi_k \in [p'_{2,1}, p''_{2,1}] \\ Favour & \text{if } \pi_k \in (p''_{2,1}, 1] \end{cases} & t = 2 \\ \begin{cases} Drop & \text{if } \pi_k \in [0, p_{3,1}) \\ Disfavour & \text{if } \pi_k \in [p_{3,1}, p'_{3,2}) \\ Balance & \text{if } \pi_k \in [p'_{3,2}, p''_{3,2}] \\ Favour & \text{if } \pi_k \in (p''_{3,2}, p_{3,3}] \\ Keep & \text{if } \pi_k \in (p_{3,3}, 1] \end{cases} & t = 3 \end{cases}$$

where $k = T_1$ or T_2 .

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BRAR designs

Design type	Design name	Allocation rule	Stage 1	Stage 2	Stage 3
Unmapped	<i>Fully Unrestricted</i>	$TS\text{-}BRAR(\gamma)$	—	—	—
	<i>Control Protected</i>	$Trippa\text{-}BRAR(\gamma_t, \eta_t)$	—	—	—
	<i>StratosPHere 2</i>	$Trippa\text{-}BRAR(\gamma_t, \eta_t)$	2 : 2 : 2	No arm dropping	—
Mapped	<i>Mapped-LowerGranularity</i>	$Trippa\text{-}BRAR(\gamma_t, \eta_t)$	2 : 2 : 2	No arm dropping; #C = 2	#C = 2
	<i>Mapped-HigherGranularity</i>	$Trippa\text{-}BRAR(\gamma_t, \eta_t)$	2 : 2 : 2	No arm dropping; #C = 2	#C = 2

Table: Taxonomy of the evaluated BRAR designs, with corresponding allocation rule and restrictions per stage. #C = 2 indicates the exact number of controls allocated.

Operating characteristics

Design	Frequentist properties		Empirical Allocation		
	Power	Type-I error	Arm C	Arm T_1	Arm T_2 (Sup. arm)
<i>Fully Unrestricted</i>	0.751	0.09	0.24 (0.12)	0.23 (0.12)	0.53 (0.17)
<i>Control Protected</i>	0.785	0.09	0.34 (0.07)	0.20 (0.12)	0.46 (0.13)
<i>StratosPHere 2</i>	0.788	0.10	0.32 (0.07)	0.21 (0.10)	0.47 (0.12)
<i>Mapped-LowerGranularity</i>	0.795	0.11	0.30 (0)	0.20 (0.11)	0.50 (0.11)
<i>Mapped-HigherGranularity</i>	0.789	0.11	0.30 (0)	0.20 (0.11)	0.50 (0.11)

Table: The significance level is set to $\alpha = 12.8\%$ to meet a 10% error control under the adaptive design. Values are averaged across 10,000 independent replicas; allocations are reported in terms of mean (standard deviation). Here, a value 0 for the standard deviation reflects the imposed restrictions on number of control arms.

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Example of first interim report

	Control	Hydroxychloroquine	Phenylbutyrate
No. of successes	0	1	2
Alloc. Probs. (Design)	0.25	0.27	0.48
Is it $> p^*$ (Mapping)	NA	0	1
Is it $< p^*$	NA	1	0
Adaptation	NA	Disfavour	Favour
Alloc. ratio	2	1	3

primary endpoint

BRAR formula

mapping

target ratio

Do we adapt the randomisation ratio for stage 2?

Example of first interim report

primary endpoint				
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	Is it $> p^*$ (Mapping)	NA	0	1
	Is it $< p^*$	NA	1	0
	Adaptation	NA	Disfavour	Favour
target ratio	Alloc. ratio	2	1	3

Do we adapt the randomisation ratio for stage 2?

YES:

From 2 : 2 : 2 to 2 : 1 : 3.

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Conclusion

The proposed general Mapping criterion:

- ensures good performance of the randomisation procedure.
- provides a viable strategy to empower small-sample trials while preserving the essence of RAR.
- simplifies the implementation of RAR through external randomisation providers (e.g., Sealed Envelope) in Clinical Trial Units.

Conclusion

The proposed general Mapping criterion:

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- provides a viable strategy to empower small-sample trials while preserving the essence of RAR.
- simplifies the implementation of RAR through external randomisation providers (e.g., Sealed Envelope) in Clinical Trial Units.

Possible extension includes:

- incorporating different trial designs (larger sample sizes, bigger blocks or more number of blocks/stages etc.)

References

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The End

Thank you for your attention!

Any questions or comments?

Off to coffee break.

rajenki.dasn@mrc-bsu.cam.ac.uk