



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

October 24, 2024

# 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)

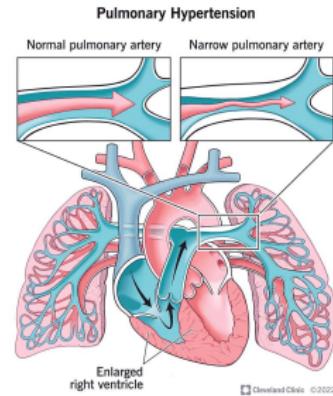
BRAR: recursively update the allocation probability for participants of a study to treatment groups based on previous outcomes using Bayesian theorem. (Robertson et al. , 2023; Atkinson and Biswas , 2014)

# Outline

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

# 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.

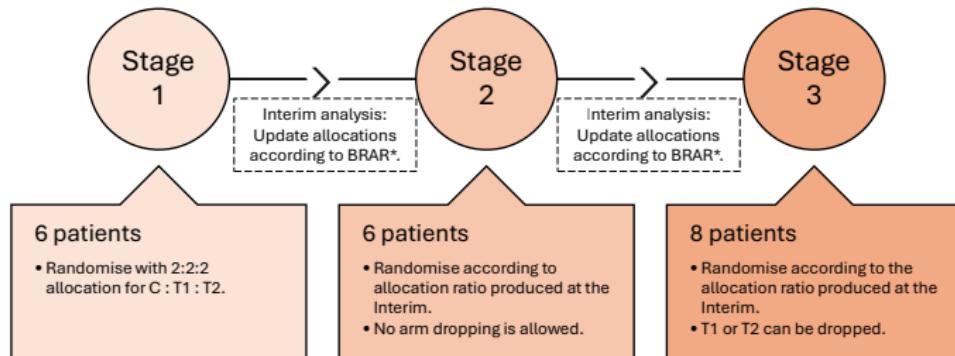


Cleveland Clinic ©2022

# 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.
- **Primary endpoint:**  $\mathbb{1}(\Delta\text{BMPR2}) > 0.3$ .
- More details are provided in the Protocol of the trial (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).

# Outline

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

# Challenge

**Challenge:** avoid generating undesirable allocation sequences through the randomisation in this small sized trial. Example description:

- Take randomisation probabilities  $\pi = (\pi_0, \pi_1, \dots, \pi_K)$  where  $\pi_k$  is the randomisation probability of arm  $k$  and,
- allocation proportions  $\rho = (\rho_0, \rho_1, \dots, \rho_K)$  where  $\rho_k$  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.

# Outline

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

# Proposed solution

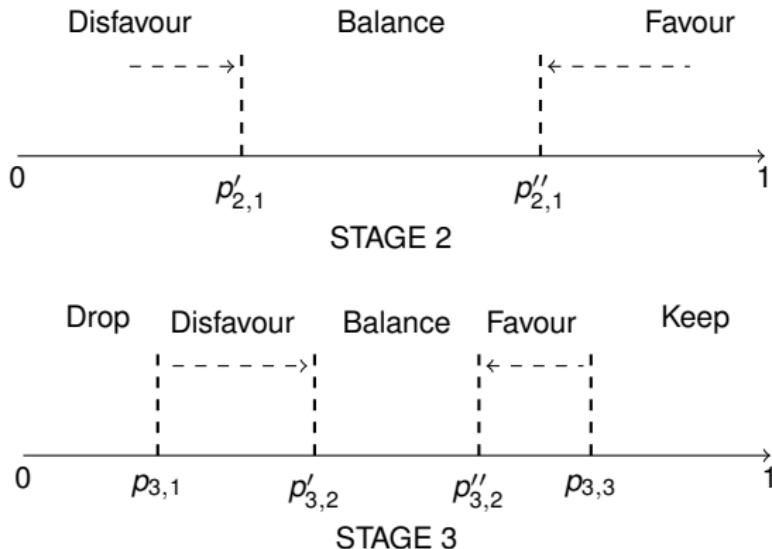
- **Mapping:** Intermediate step that involves a decision rule- to map the continuous randomisation probabilities at the interim analyses to a target vector of discrete allocation ratios. Detailed in Das et al. (2024).
- Propose two types of Mapping: *Mapped-LowerGranularity* and *Mapped-HigherGranularity*

# 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*.

# Outline

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

# 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.

# Outline

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

# Example of first interim report

	Control	Hydroxychloroquine	Phenylbutyrate
<b>No. of successes</b>	0	1	2
<b>Alloc. Probs. (Design)</b>	0.25	0.27	0.48
<b>Is it <math>&gt; p^*</math> (Mapping)</b>	NA	0	1
<b>Is it <math>&lt; p^*</math></b>	NA	1	0
<b>Adaptation</b>	NA	Disfavour	Favour
<b>Alloc. ratio</b>	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				
	Control	Hydroxychloroquine	Phenylbutyrate	
BRAR formula	No. of successes	0	1	2
mapping	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
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.

# Outline

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

# 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.

Possible extension includes:

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

## References

- Atkinson, A. C. and Biswas, A. Randomized Response-Adaptive Designs in Clinical Trials, CRC Press, Boca Raton, FL (2014).
- Robertson, David S. and others. Response-adaptive randomization in clinical trials: from myths to practical considerations, *Statistical Science: A Review Journal of the Institute of Mathematical Statistics* 38.2 185 (2023).
- Trippa, Lorenzo and others. Bayesian adaptive randomized trial design for patients with recurrent glioblastoma, *Journal of Clinical Oncology* 30.26 3258 (2012).
- Wason, James MS and Trippa, Lorenzo. A comparison of Bayesian adaptive randomization and multi-stage designs for multi-arm clinical trials, *Statistics in Medicine* 33.13 2206–2221 (2014).
- Deliu, N. and Das, R. and May, A. and Steele, J. and Duckworth, M. and Jones, R. J. and Wilkins, M. R. and Toshner, M. and Villar, S. S. Stratosphere 2: A response-adaptive randomised placebo-controlled phase II trial to evaluate hydroxychloroquine and phenylbutyrate in pulmonary arterial hypertension caused by mutations in BMPR2, *Trials* 25.1 (2024)
- Das, R. and Deliu, N. and Toshner, M. and Villar, S. S. Implementing response-adaptive randomisation in stratified rare-disease trials: Design challenges and practical solutions, arXiv (2024).

The End

Thank you for your attention!

Any questions or comments?

Off to coffee break.

[rajenki.dasn@mrc-bsu.cam.ac.uk](mailto:rajenki.dasn@mrc-bsu.cam.ac.uk)