Implementing a Bayesian Response Adaptive Randomisation design in a rare disease setting

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Bayesian Response Adaptive Randomisation (BRAR)

- Adaptive designs:

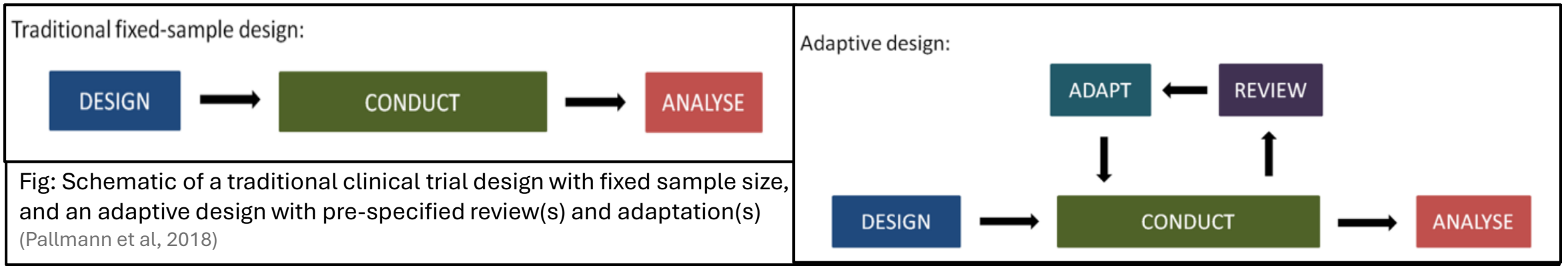
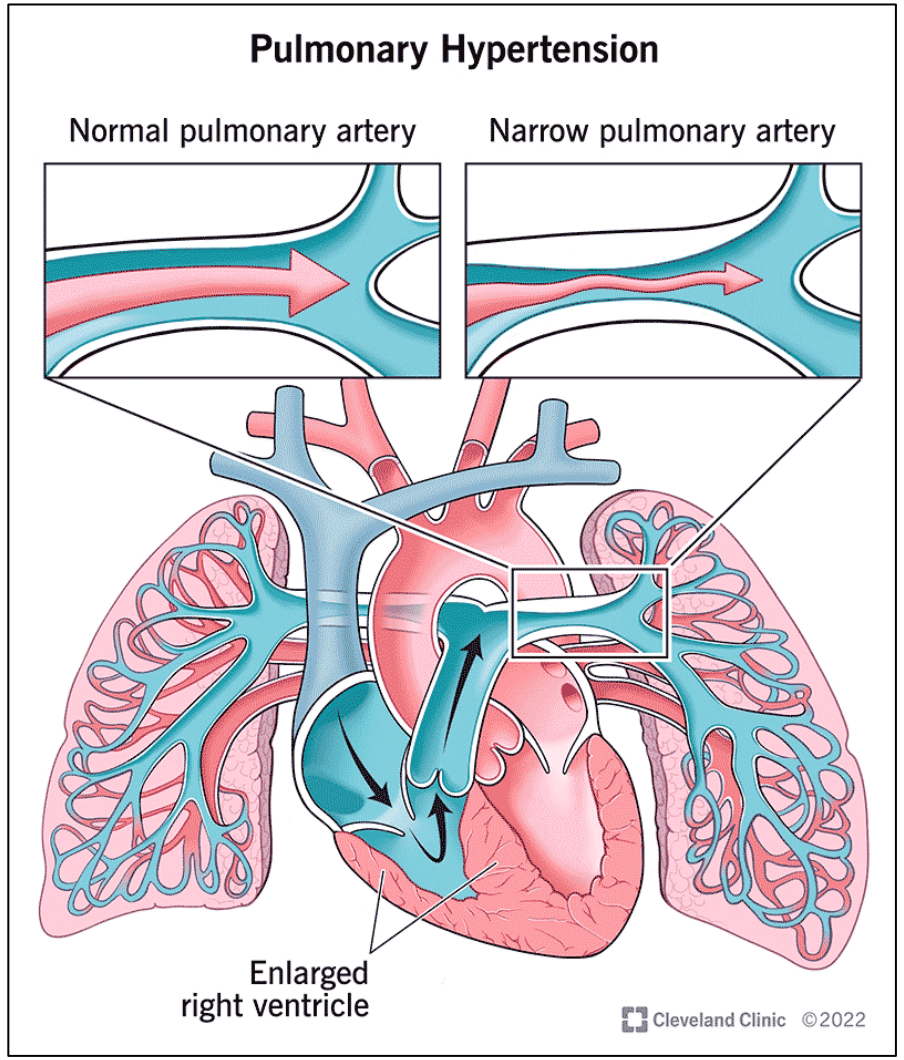


Fig: Schematic of a traditional clinical trial design with fixed sample size, and an adaptive design with pre-specified review(s) and adaptation(s) (Pallmann et al, 2018)

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

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.

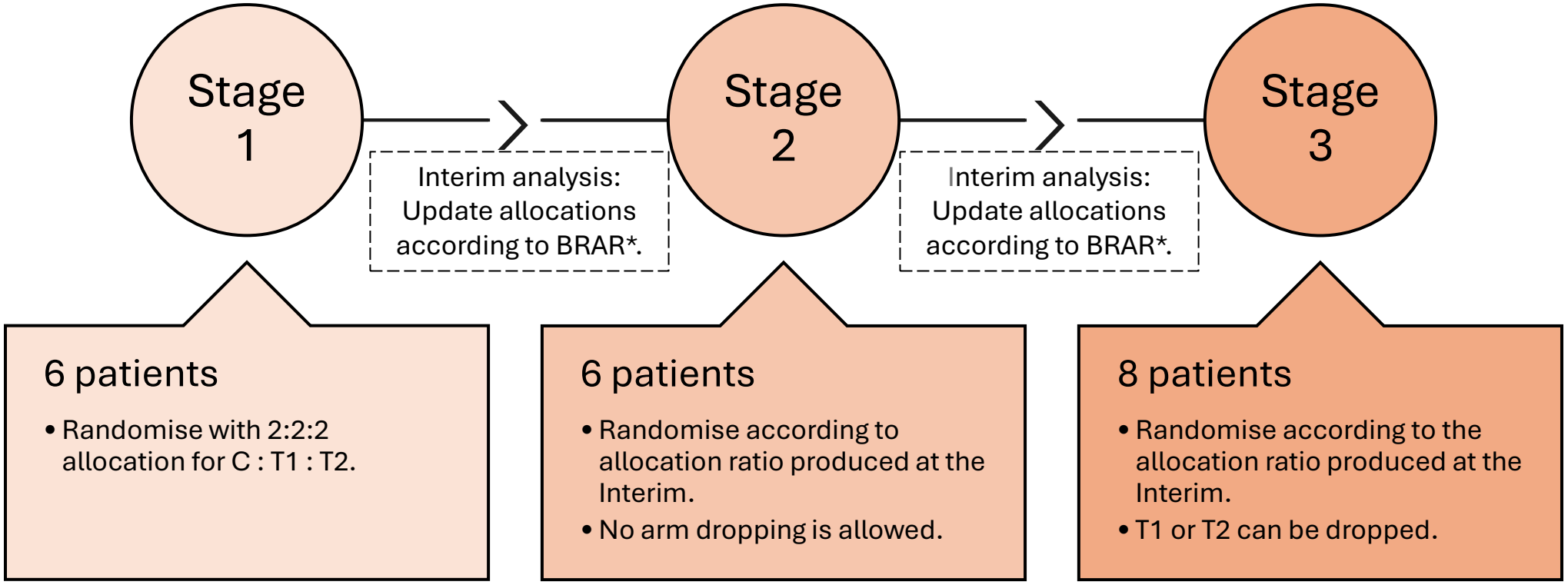


StratosPHere 2 Trial

- 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 (T1) and phenylbutyrate (T2) for the treatment of PAH by targeting the genetic $\mathrm{BMPR2}$ pathway of the disease.
- **Primary objective:** To test the hypothesis that two treatments can rescue the BMPR2 pathway.
- **Primary endpoint:** $\mathrm{I}(\Delta \mathrm{BMPR2}) > 0.3.$

Details on Deliu et al, 2024.

Trial design of one mutation group



*The algorithm is based on the Bayesian design proposed in Trippa et al, 2012, and Wason and Trippa, 2014 — protects control arm.

A challenge

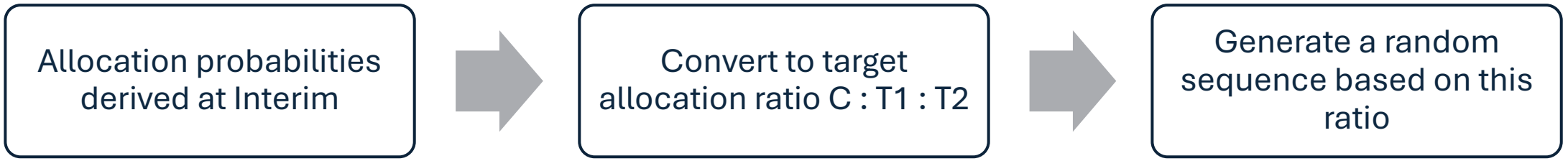
- **Challenge:** avoid generating undesirable allocation sequences through the randomisation in this small sized trial.

Example description:

- Take randomisation probabilities $\pi = (\pi_0, \pi_1, \dots, \pi_K)$ where 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 $n\pi_k \approx n\rho_k$ for all $k's$. A concern in rare disease/ small sized trials.

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.



- Propose two types of mapping: *Mapped-LowerGranularity and Mapped-HigherGranularity*.

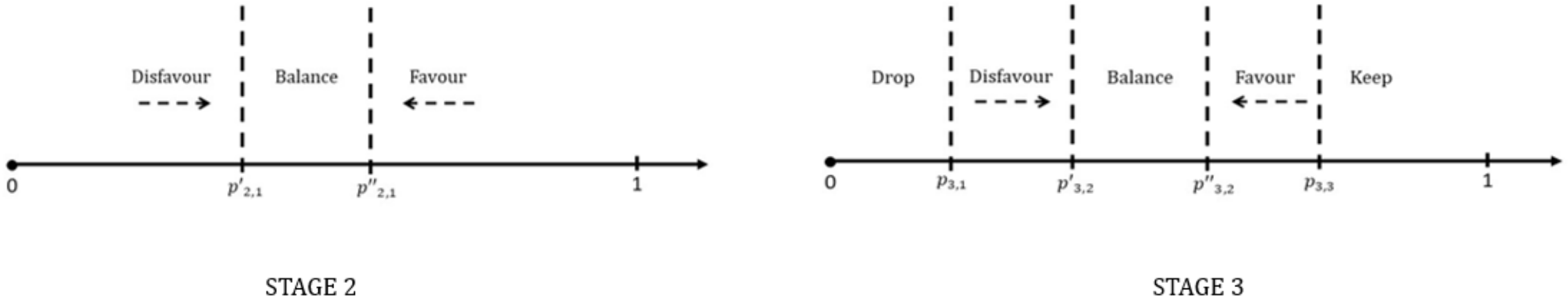
More details on Das et al, 2024.

Adaptation list

Adaptation category	Description	Stage 1	Stage 2	Stage3
Drop	T1 can be dropped	Never	Never	2:0:6
Disfavour	T1 can be disfavoured, but not dropped	Never	2:1:3	2:1:5 2:2:4
Balance	The active arms can be allocated equally	2:2:2	2:2:2	2:3:3
Favour	T1 can be favoured, without dropping the other	Never	2:3:1	2:4:2 2:5:1
Keep	T1 can be kept, while dropping the other	Never	Never	2:6:0

Possible allocations for C : T1 : T2 at each stage of the trial based on the categories of the active arms.

Mapping decision line



Schematic of the proposed *Mapped-HigherGranularity* design with Stage 2 (left) and Stage 3 (right).

Closing the Balance region converts the design into the proposed *Mapped-LowerGranularity*.

BRAR designs

Design type		Restrictions and constraints in design				
Response Adaptive Design	Design Name	Stage 1 (6 patients)	Stage 2 (6 patients)	Stage 3 (8 patients)	Allocation rule	Number of control arms
Unmapped	*Fully Unrestricted*	-	-	-	Thompson Sampling	-
	Control Protected	-	-	-	Trippa	-
	StratosPHere2	2 : 2 : 2	No active arm can be dropped	Active arm can be dropped	Trippa	-
Mapped	*Mapped-LowerGranularity*	2 : 2 : 2	No active arm can be dropped	Active arm can be dropped	Trippa	2
	Mapped-HigherGranularity	2 : 2 : 2	No active arm can be dropped	Active arm can be dropped	Trippa	2

Summary of the Unmapped and Mapped Bayesian RAR designs for StratosPHere 2.

The allocation ratios are for C : T1 : T2. Allocation rule generates the allocation probabilities for the next stage.

Operating characteristics

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

The significance level is set to α = 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.

Example of first interim report:

primary endpoint

BRAR

formula

mapping

target ratio

	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

Do we adapt the randomisation ratio for stage 2?

YES:

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

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 extensions include:

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

References

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Feedback/questions? Thank you! ☺

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