MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Short course on Response-Adaptive Methods for Clinical Trials

Lecture 4: Applications of RAR: Backfill in dose finding and RAR Repository

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Outline

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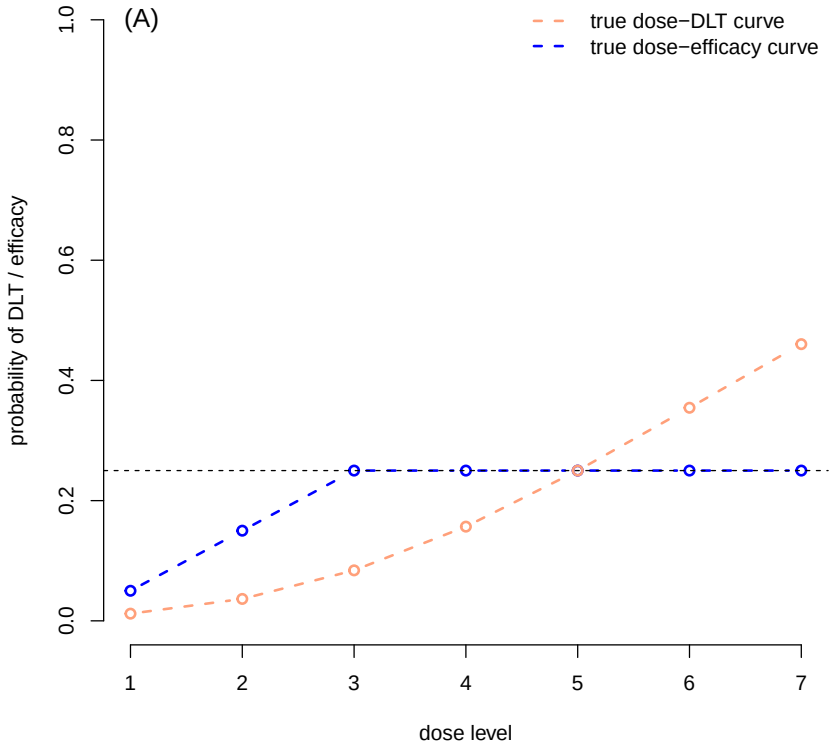
Motivation

- Phase-II Dose-Finding Study
- Efficacy Plateau
  - in oncology with targeted agents or immunotherapy
- **Identify** the lowest dose level that maximises efficacy whilst remaining tolerable and **allocating** patients close to that dose level
  - Backfill + RAR



Previous Work

- Continual Reassessment Method (CRM) to identify *Maximum Tolerated Dose (MTD)* [O'Quigley et al (1990)]
- Backfill with Equal Randomization (ER) under MTD to identify *Recommended Phase 2 Dose (RP2D)* [Dehbi et al (2021)]
- Backfill with Response Adaptive Randomization (RAR) under MTD to identify RP2D and allocated patients better [Pin et al (2024)]

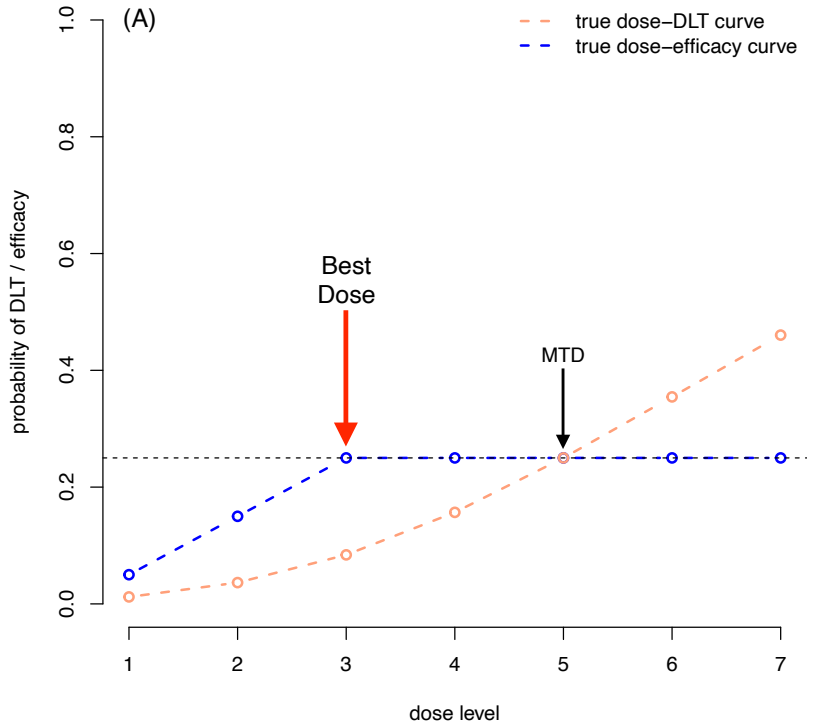


Figure: Dose 3 (RP2D) $<$ Dose 5 (MTD)

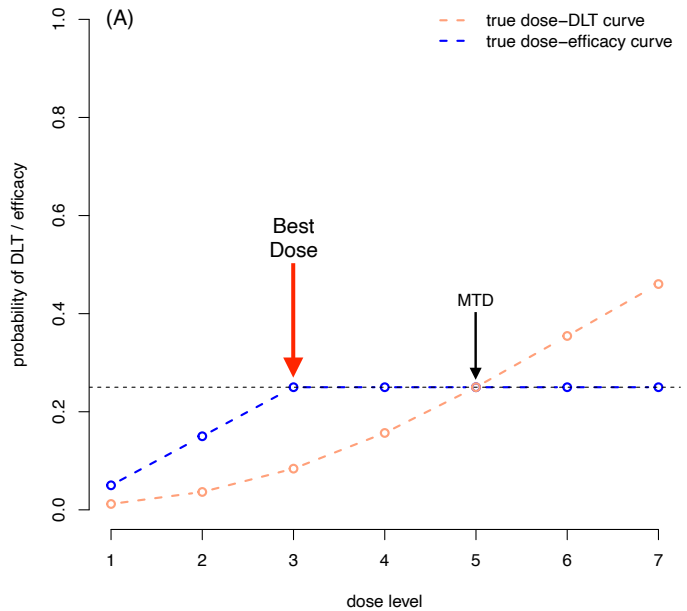
Outline

Notation

- Multi-armed trial: 1,...,K different dose levels
- Fix number of patients in the trial: $n = \sum_{k=1}^{K} n_k$
  - n_k is the number of patients on dose level k
- Potential efficacy outcomes: $Y_{ki} \overset{\text{iid}}{\sim} Bern(p_k)$
  - p_k is success probability
- Binary indicator a_{ki} s.t. $\sum_{k=1}^{K} a_{ki} = 1 \; \forall i$
- Response-adaptive-randomization: $P(a_{ki} = 1 | a^{(i-1)}, Y^{(i-1)})$

How does Backfill work?

Algorithm backfill($n = 57, c = 3$)
$MTD \leftarrow 1$
while $MTD = 1$ **do**
  allocate c patients to dose level 1
  $MTD \leftarrow$ update through CRM
end while
while Number of allocated patients $< n$ **do**
  allocate c patients to MTD
  randomise c backfill-patients with ER or RAR to dose levels 1, ..., $MTD - 1$
  $MTD \leftarrow$ update through CRM
end while
Choose Model with(out) Plateau
return RP2D



ER vs. RAR

- **Equal randomisation (ER)** allocated backfill patients with equal probability *(1/(size of backfill set))* to one of the dose level in the backfill set

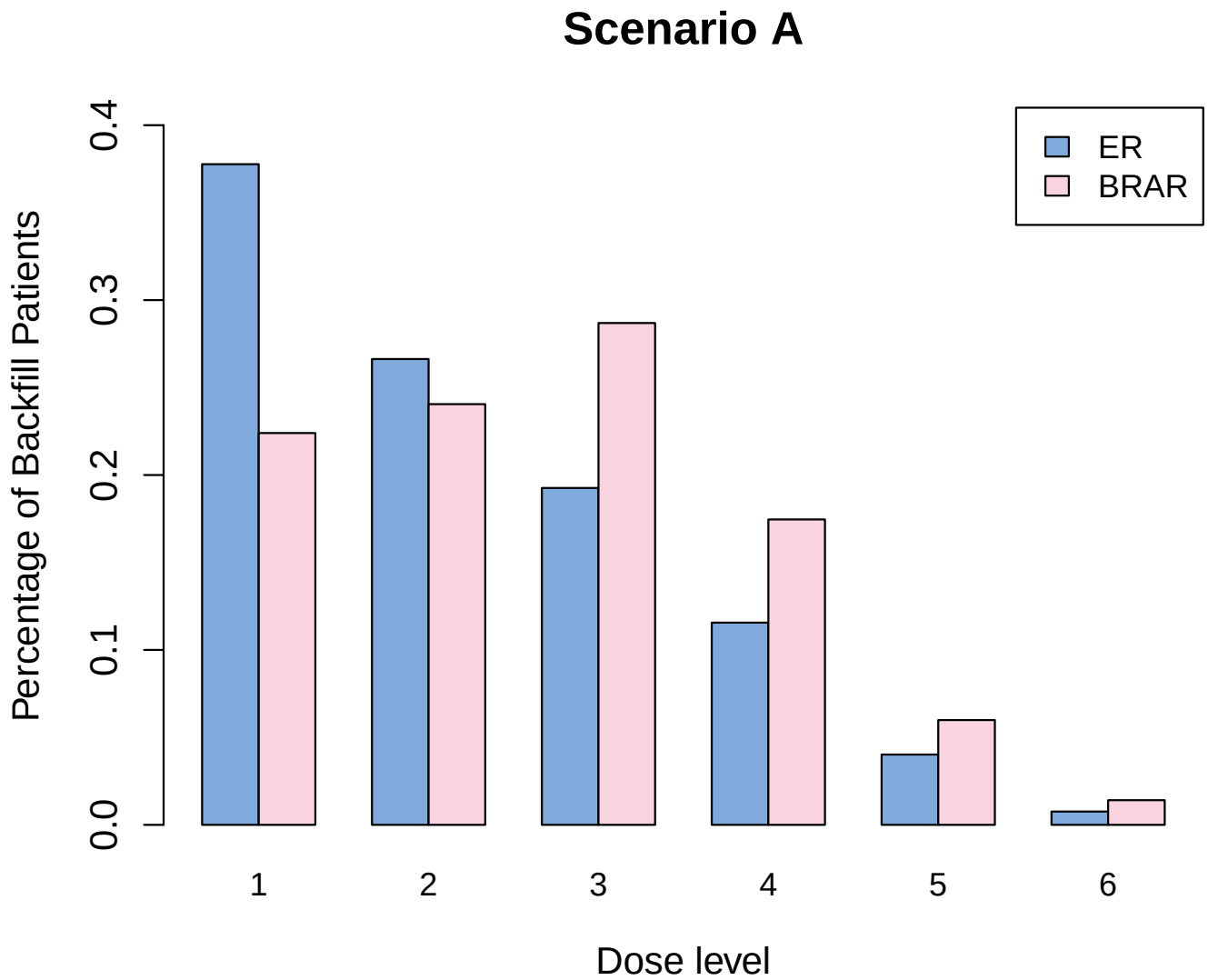
- **Bayesian RAR (BRAR)** adjusts probabilities based on efficacy data from dose-escalation and backfill patients

  - BRAR design: use a posterior probability of interest to determine assignment **probabilities** [Thompson (1933)].

  - BRAR allocation probability: $P(a_{k,i} = 1|\mathbf{A}^{(i-1)}, Y^{(i-1)}) = P(\max_{1\leq h\leq MTD-1} p_h = p_k|\mathbf{A}^{(i-1)}, Y^{(i-1)}) = q^{(i-1)}$

Outline

Allocation of Backfill Patients



Recommendation of Dose Level

Scenario A: % of recommendations per dose			
Dose Level	CRM	Backfill & ER	Backfill & BRAR
1	0%	0%	0%
2	0%	0.3%	0.1%
3	0.2%	27.3%	30.8%
4	15.7%	43.7%	44.7%
5	62.0%	19.4%	16.9%
6	20.7%	7.3%	5.9%
7	1.4%	2.0%	1.6%
RP2D	0.2%	27.3%	30.8%
[RP2D, MTD)	15.9%	70.9%	75.5%
[RP2D, MTD]	78.0%	90.4%	92.4%
(MTD , 7]	22.1%	9.3%	7.5%

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Final Thoughts

1. Whether backfill is beneficial depends on true DLT and Efficacy curves (7 other scenarios in [Pin et al (2024)]).

2. If Backfill is beneficial, using BRAR leads to *allocating more patients close to RP2D* and an *increased probability of recommending the correct dose* level at the end of the trial.

3. Future Research
   - 3.1 Impact of different cohort sizes on the design
   - 3.2 Other dose-escalation methods: 2-parameter CRM, BOIN
   - 3.3 Continuous endpoints $\rightarrow$ nonparametric RAR

References I

O'Quigley, John and Pepe, Marcello and Fisher, Lloyd (1990)

Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer.

Biometrics, 46(1): 33–43. ISSN 0006341X. doi: 10.2307/2531628.

Dehbi, Hakim M. and O'Quigley, John and Iasonos, Alexia (2021)

Controlled backfill in oncology dose-finding trials.

Contemporary Clinical Trials, 111. ISSN 15592030. doi: 10.1016/j.cct.2021.106605.

Pin, Lukas and Villar, Sofia S. and Dehbi, Hakim M. (2024)

Implementing and assessing Bayesian response-adaptive randomisation for backfilling in dose-finding trials.

Contemporary Clinical Trials. doi: 10.1016/j.cct.2024.107567.

Thompson, William R. (1933)

On the likelihood that one unknown probability exceeds another in view of the evidence of two samples.

Biometrika, 25(3-4): 285–294. ISSN 0006-3444. doi: 10.1093/biomet/25.3-4.285. URL .

Outline

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The Gap: Theory vs. Practice

The Current Perception:

- RAR is often dismissed as a ”methodological curiosity.”
- ”Great theory, but nobody uses it.”
- **Reality Check:** Is it truly absent, or just hard to find?

The Problem

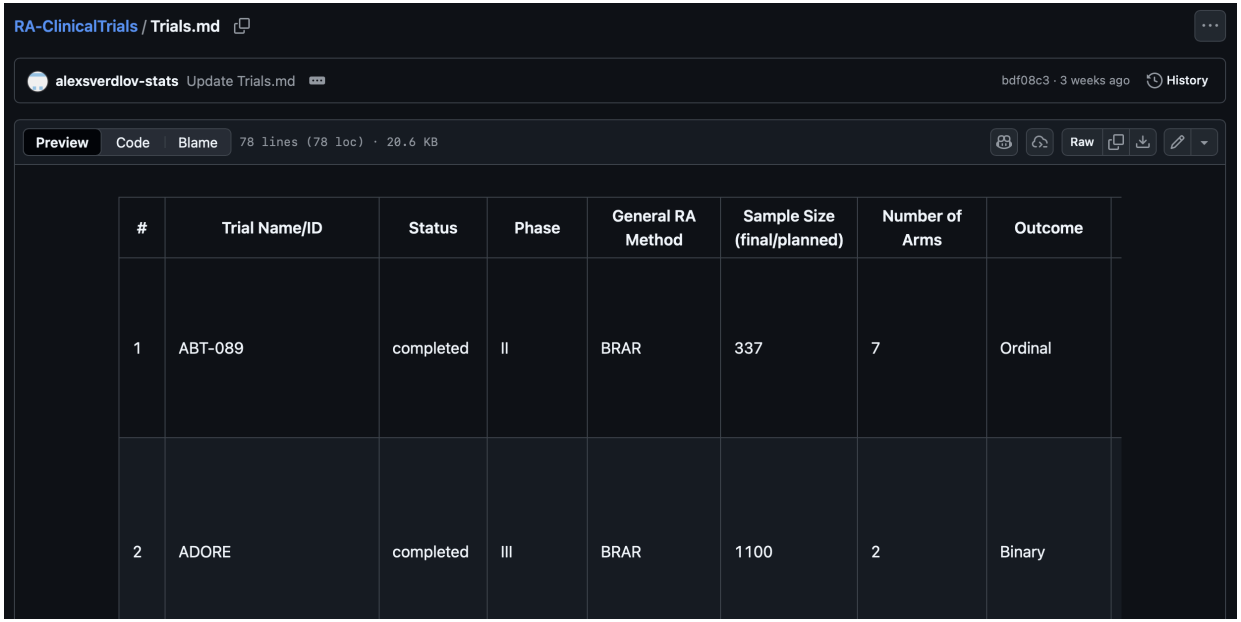
“The uptake of RAR in clinical trial practice remains disproportionately low...” —

Robertson et al. (2023)

Our Solution: A living, crowd-sourced evidence base.

Outline

RA-ClinicalTrials: A Living Database



RA-ClinicalTrials / Trials.md

alexsverdlov-stats Update Trials.md bdf08c3 · 3 weeks ago History

Preview Code Blame 78 lines (78 loc) · 20.6 KB Raw

#	Trial Name/ID	Status	Phase	General RA Method	Sample Size (final/planned)	Number of Arms	Outcome
1	ABT-089	completed	II	BRAR	337	7	Ordinal
2	ADORE	completed	III	BRAR	1100	2	Binary

- **Open Source:** Hosted on GitHub.
- **Community Driven:** Additions via Pull Requests.
- **Quality Control:** Curated by MRC BSU.
- **Permanent:** Archived on Zenodo.

Outline

Analysis: Breaking Down the 74 Trials

Trial Landscape (Nov 2025)

Category	Sub-Category	%
Method	**BRAR**	**83.8%**
	RPTW	2.7%
Phase	Phase II (Exploratory)	44.6%
	Phase III (Confirmatory)	**20.3%**
	Phase I/II or Seamless	6.8%

Key Insights:

- **Dominance:** BRAR is the standard.
- **Scale:** Used in massive platform trials (e.g., REMAP-CAP).
- **Scope:** Not limited to early phase oncology.

Outline

Support this Project

Help us grow the evidence base

Have we missed a trial?

`github.com/lukaspinpin/RA-ClinicalTrials`

How to Contribute

1. Fork the repository.
2. Add the trial to `trials.md`.
3. Open a **Pull Request**.

How to Cite

Official Citation (Zenodo)

Please use the DOI, not the GitHub link:

Pin, L., Neubauer, M., Voller, C., Wilson, I., Deliu, N., Baas, S., Dimairo, M., Robertson, D., & Villar, S. (2025).
Clinical Trials Using Response Adaptive Randomization (Version 1.1.1) [Computer software].
Zenodo. **https://doi.org/10.5281/zenodo.17493900**

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The End

Thank you for your attention!

Any questions?

Please reach out:

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