**October 24 2017**

**Speaker:**
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Dr. Clement Ma is Lead Biostatistician at Dana-Farber/Boston Children's Cancer and Blood Disorders Center and Instructor of Pediatrics at Harvard Medical School. He provides statistical leadership in collaborative clinical research with pediatric hematologists and oncologists. His current methodological research focuses on the design of early-phase clinical trials for children with cancer. During his graduate and post-graduate training at the University of Michigan, he developed statistical methods for analyzing low-frequency genetic variants in single and multi-center genetic association studies of complex diseases. He completed his bachelor's (biomedical engineering) and master's (biostatistics) degrees at the University of Toronto, and was a former biostatistician at Princess Margaret Cancer Centre.

**Title:**
Dual-agent dose escalation methods for pediatric oncology clinical trials

**Abstract:**
Phase 1 clinical trials aim to identify the optimal dose for the therapeutic agent that balances patient safety and potential efficacy. Cancer therapies that include two or more agents may increase efficacy as well as toxicity. Many adaptive dose-escalation designs have been proposed for trials of combination therapies. These designs can better assign dose combinations near the maximum tolerated dose combination (MTDC) to enrolled patients but require significant resources to design and monitor. Hence, relatively few adult oncology trials have used these designs, and to our knowledge, none have been used in pediatric trials. To motivate the use of adaptive designs in pediatric oncology, we performed a simulation study to compare the performance of dual-agent dose-escalation methods in a pediatric oncology framework.

We selected four Bayesian methods, and the commonly used 3+3 rule-based design (assuming a prespecified set of dose combinations) for our study. We designed 7 simulation scenarios with a restricted number of dose combinations and low total sample size (N=24) to reflect the realities of pediatric trials. We performed 2,000 simulated trials per scenario for each method and compared the methods across six metrics. Overall, all adaptive methods had a similar performance across all metrics. The average recommendation rates for the true dose combination ranged from 37% to 43%. The average proportion of patients receiving a dose greater than the MTDC ranged from 29% to 33%, which is near our target toxicity level of 30%. As expected, the conservative 3+3 design had lower recommendation rates than the adaptive designs. Adaptive designs represent a safe and effective way for dual-agent dose escalation trials in children.

**Learning objectives:**
Learn about different dose-escalation designs for clinical trials of combination therapies; and
Understand the use of statistical simulation to evaluate the operating characteristics of clinical trial designs.

# Dual-agent dose escalation methods in pediatric oncology clinical trials

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# Outline

- Background and motivation
- Dual-agent dose escalation simulation methods
- Simulation results
- Recommendations and conclusions

# BACKGROUND AND MOTIVATION

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# Phase 1 clinical trials: National Cancer Institute description

"Phase 1 trials determine a safe and/or biologically effective dose for phase 2 trials and help define adverse effects on normal organ function."

https://ctep.cancer.gov/investigatorresources/docs/investigatorhandbook.pdf

# Primary objective and definitions

To determine the maximum tolerated dose for the therapeutic agent.

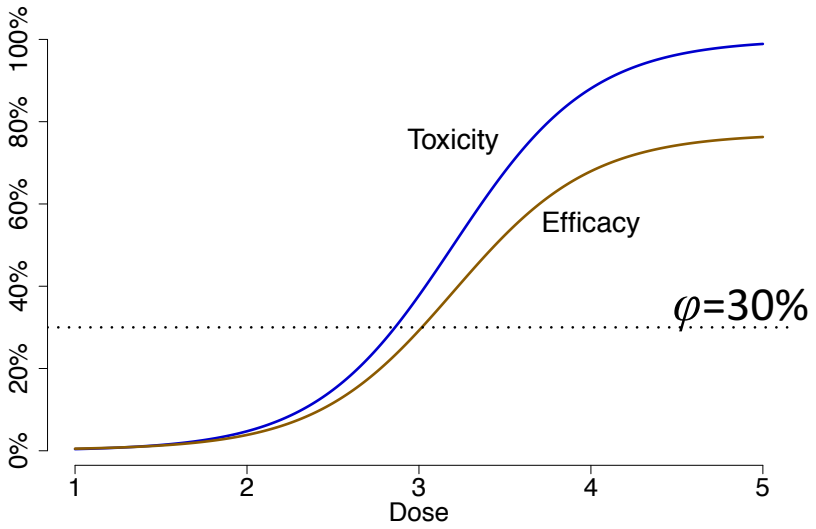
| Term | Definition |
| --- | --- |
| Target toxicity ($\varphi$) | The maximum acceptable toxicity rate |
| Maximum Tolerated Dose (MTD) | The greatest dose with an acceptable toxicity rate |
| Dose limiting toxicity (DLT) | An unacceptable adverse event |
| Recommended Phase 2 Dose (RP2D) | The dose of the drug to be recommended for further testing in phase 2 trials |

# Dose-toxicity framework for one agent

**Monotonicity assumptions:**

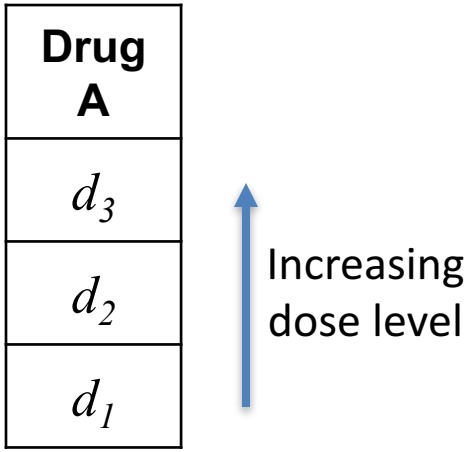
- Toxicity level increases with dose
- Efficacy increases with dose

- Note: assumptions may not hold for targeted agents




Le Tourneau, Lee, & Siu. JNCI. 2009; 101(10):708-720

# Dose escalation for one agent




Pr(Toxicity in $d_1$) ≤ Pr(Toxicity in $d_2$) ≤ Pr(Toxicity in $d_3$)

**Order doses by increasing toxicity**

$$d_1 \rightarrow d_2 \rightarrow d_3$$

# Combination therapies in oncology

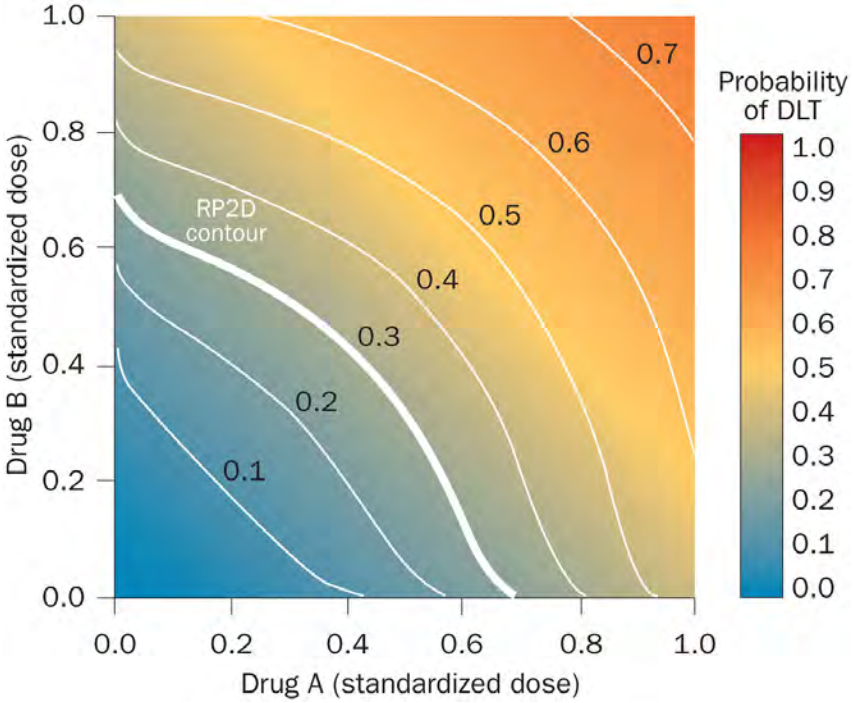
- Single anti-cancer agent may encounter drug resistance
- Combination of 2+ agents can target cancer cells with different drug susceptibilities and may improve efficacy
- However, drugs may interact and have overlapping toxicity profiles
  - The RP2D for each individual drug may be too toxic when given in combination

Harrington JA, *et al.* (2013) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.35

# Dose-toxicity framework for two agents

- **Objective:** To determine the maximum tolerated dose combination (MTDC)
- Multiple MTDC's are possible for combination therapies
- The MTDC "search space" can be much larger for 2+ agents vs. 1 agent

Example 2D dose surface formed by drug A and drug B




Harrington JA, *et al.* (2013) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.35

# Dose escalation for two agents

| | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 3 | $d_{31}$ | $d_{32}$ | $d_{33}$ | $d_{34}$ |
| | 2 | $d_{21}$ | $d_{22}$ | $d_{23}$ | $d_{24}$ |
| | 1 | $d_{11}$ | $d_{12}$ | $d_{13}$ | $d_{14}$ |

Increasing dose level

Drug A: 3 dose levels
Drug B: 4 dose levels
12 possible combinations

# Dose escalation for two agents: challenges

| | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 3 | $d_{31}$ | $d_{32}$ | $d_{33}$ | $d_{34}$ |
| | 2 | $\boldsymbol{d_{21}}$ | $d_{22}$ | $d_{23}$ | $d_{24}$ |
| | 1 | $d_{11}$ | $\boldsymbol{d_{12}}$ | $d_{13}$ | $d_{14}$ |

Order of dose combinations by toxicity probability is ambiguous:

$$d_{12} \rightarrow d_{21} \text{ OR } d_{21} \rightarrow d_{12} \text{ ?}$$

# Dose escalation for two agents: challenges

| | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 3 | $d_{31}$ | $d_{32}$ | $d_{33}$ | $d_{34}$ |
| | 2 | $d_{21}$ | $d_{22}$ | $d_{23}$ | $d_{24}$ |
| | 1 | $d_{11}$ | $d_{12}$ | $d_{13}$ | $d_{14}$ |

Escalation (or de-escalation) to which dose combination?

# Dual-agent dose escalation methods: naïve (but common) approach #1

| | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 3 | | | | |
| | 2 | $d_{21}$ → | $d_{22}$ → | $d_{23}$ → | $d_{24}$ |
| | 1 | | | | |

Select fixed dose for Drug A and escalate/de-escalate Drug B
Apply dose-escalation methods for single agents

Disadvantage: only explore a subset of possible dose combinations

# Dual-agent dose escalation methods: naïve (but common) approach #2

| | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 3 | | | | $d_{34}$ |
| | 2 | | $d_{22}$ → | $d_{23}$ → | $d_{24}$ |
| | 1 | $d_{11}$ → | $d_{12}$ | | |

Select fixed dose-escalation path for drugs A and B
Apply dose-escalation methods for single agents

Disadvantage: only explore a subset of possible dose combinations

# Summary of dose escalation designs for combination therapies

**Rule-based designs:** use pre-defined rules to determine dose for next enrolled subject

**Model-based (adaptive) designs:** use statistical model based on prior knowledge to determine dose for next enrolled subject

**Table 1** | Summary of features for various dual-agent dose escalation study designs

| Study | Number of model parameters | Stages | Outcomes | Response values | Number of RP2D combinations |
|---|---|---|---|---|---|
| ***Rule-based designs*** | | | | | |
| Hamberg and Verweij (2009)[57] | – | 1 | Toxicity | Binary | 1 or 2 |
| Lee and Fan (2012)[58] | – | 1 | Toxicity | Binary | 1 or 2 |
| Huang *et al.* (2007)[71] | – | 2 | Toxicity and efficacy | Binary | 0 or 1 |
| Lee *et al.* (2008)[59] | – | 2 | Toxicity | Binary | 1 |
| ***Model-based designs*** | | | | | |
| Wang and Ivanova (2005)[60] | 3 | 2 | Toxicity | Binary | Minimum number of doses of drug A or drug B |
| Yin and Yuan (2009)[62] | 3 | 2 | Toxicity | Binary | 1 |
| Yin and Yuan (2009)[63] | 3 | 2 | Toxicity | Binary | 1 |
| Kramar *et al.* (1999)[61] | 2 | 2 | Toxicity | Binary | 1 |
| Su (2010)[64] | 1 | 3 | Toxicity | Binary | 1 |
| Thall *et al.* (2003)[31] | 6 | 2 | Toxicity | Binary | 3 |
| Mandrekar *et al.* (2007)[73] | 6 | 1 | Toxicity and efficacy | Binary (toxicity and efficacy) | 1 |
| Houede *et al.* (2010)[77] | 21 | 1 | Toxicity and efficacy | Ordinal (toxicity and efficacy) | 1 |
| Dragalin *et al.* (2008)[79] | 8 | 2 | Toxicity and efficacy | Binary, ordinal or continuous (toxicity and efficacy) | 1 |
| Whitehead *et al.* (2011)[75] | Between $K$ and $3K$* | 1 | Toxicity and efficacy | Binary (toxicity and efficacy) | Trial dependent (0–9) |
| Conaway *et al.* (2004)[68] | $K$ | 2 | Toxicity | Binary | 1 |
| Wages *et al.* (2011)[70] | $M$‡ | 2 | Toxicity | Binary | 1 |
| Wages *et al.* (2011)[69] | $M$‡ | 1 | Toxicity | Binary | 1 |
| Braun and Wang (2010)[80] | 6 | 1 | Toxicity | Binary | 1 |
| Bailey *et al.* (2009)[67] | ≥3§ | 1 | Toxicity | Binary | 1 |

*Number of parameters depends on the choice of discrete values that 'risks' can take. ‡($M$ – 1) parameters for weights on simple orders, plus one parameter for the dose-escalation model. §Two parameters required for drug A, plus one or more parameters for number of indicator variables for drug B. Abbreviations: $K$, number of combinations; $M$, number of simple orders; RP2D, recommended phase II dose.

Harrington JA, *et al.* (2013) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.35

# Limited use of adaptive designs in phase I trials of combination therapies

Challenges:

- Lack of familiarity with adaptive designs
- May need larger N to evaluate many dose combinations (compared to naïve approach)
- Adaptive designs require:
  - Specification of multiple model parameters
  - Rapid DLT entry and reporting

Trials of combination therapies using adaptive designs

**Table 2** | Completed dual-agent phase I trials using novel adaptive designs

| Method | Agents combined | Number of dose combinations | *n* | Number of RP2D combinations |
|---|---|---|---|---|
| Lee *et al.* (2008)[59] | Cisplatin and 9-nitrocamptothecin | 12 | 54 | 1 |
| Huang *et al.* (2007)[71] | 5-Azacytidine and Ara-C | 4 | 34 | 4 |
| Whitehead *et al.* (2012)[76] | Gemcitabine and MK-0752 | 10* | 60‡ | Still recruiting |
| Yuan and Yin (2011)[65] | Decitabine and recombinant interferon derivative | 6 | 20 | 3 |
| Bailey *et al.* (2009)[67] | Nilotinib and imatinib | 5 | 53§ | 1 |

*As per Whitehead *et al.*[76] ‡Estimated. §Three patients subsequently removed from dose-determining set due to protocol deviations. Abbreviation: RP2D, recommended phase II dose.

Harrington JA, *et al.* (2013) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.35

# Phase I trials in pediatric oncology: challenges

- Cancer in children is rare: low N and accrual rate for trials
  - In 2017, only ~15,270 children and adolescents (age 0-19 years) will be diagnosed with cancer in US
  - For neuroblastoma (a solid tumor in nerve cells): only ~700 new cases per year in US
- Pediatric trials must satisfy additional FDA regulations
- Children are heterogeneous in stage of development which increases variability


1. Siegel, Miller, & Jemal. (2017) *CA Cancer J Clin.* 67(1):7-30.
2. Additional Protections for Children Involved as Subjects in Research. 45 CFR § 46, Subpart D (2009).
3. Doussau A, et al. (2016). *Contemp Clin Trials*. 47: 217–227.

# Phase I trials in pediatric oncology: other considerations

- Most pediatric trials start after completion of adult trials
  - Adult PK/PD and toxicity profile is typically available
- Pediatric starting dose: typically 80% of RP2D in adults adjusted for weight or body surface area (BSA)
- Pediatric trials typically explore fewer dose levels
  - Suggest ~4 doses (0.7, 1.0, 1.3, 1.6x RP2D in adults)
  - RP2D in children generally highly correlated with RP2D in adults

Doussau A, et al. (2016). *Contemp Clin Trials*. 47: 217–227.

# Systematic review of pediatric oncology trials

- Reviewed study design of published pediatric oncology phase 1 trials with combination therapies in 2014-2016 on PubMed

**Search term:**

```
Clinical trial, Phase I[ptyp] AND cancer[MeSH] AND
"2014/01/01"[PDAT] : "2016/12/31"[PDAT] AND
(combination OR combine OR combined OR combining) AND
(pediatric OR children OR child OR adolescent OR young
```

- None of the N=152 trials used adaptive designs for combination therapies

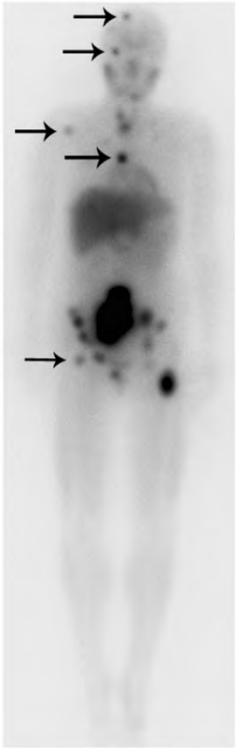
# New Approaches to Neuroblastoma Therapy (NANT) phase I study of Vorinostat & $^{131}$I-MIBG

- >50% neuroblastoma (NB) patients present with metastatic disease and have poor prognosis

- $^{131}$I-metaiodobenzylguanidine (MIBG) is a targeted radiotherapy for NB
- Vorinostat increases sensitivity of cancer cells to radiation

- **Objective:** To determine the MTDC of Vorinostat and MIBG in combination

Additional NB metastases detected on MIBG scan




1. DuBois SG, et al. (2015) *Clin Cancer Res*; 21(12) 2715-21
2. DuBois SG & Matthay KK. (2008) *Nucl Med Biol;* 35:S35-48

# Vorinostat & $^{131}$I-MIBG: study design

- Relapsed or refractory NB patients (age 2-30 years)
- N=27 enrolled; 23 evaluable
- 3+3 design
- 7 dose levels (6 planned; 1 “fall-back”)
- DLTs (within 1st course of therapy)
  - Hematologic DLTs: engraftment failure, grade 4 hemolysis, anemia, bleeding, thrombocytopenia, neutropenia
  - Non-hematological DLTs: grade≥3 toxicity (with exceptions)

DuBois SG, et al. (2015) *Clin Cancer Res*; 21(12) 2715-21

# Vorinostat & $^{131}$I-MIBG: doses

| | | $^{131}$I-MIBG (mCi/Kg) | | | |
|---|---|---|---|---|---|
| Vorinostat (mg/m$^2$/dose) | Dose | 8 | 12 | 15 | 18* |
| | 270 | | | | $d_6$ |
| | 230 | | $d_3$ | $d_4$ | $d_5$ |
| | 180 | $d_1$ | $d_2$ | | $d_{5a}$ |

"fall-back" dose

*MTD for $^{131}$I-MIBG as single agent

Select fixed dose-escalation path for drugs A and B
Used 3+3 design

DuBois SG, et al. (2015) *Clin Cancer Res*; 21(12) 2715-21

# Vorinostat & $^{131}$I-MIBG: dose-escalation results

| # DLTs / # evaluable | | $^{131}$I-MIBG (mCi/Kg) | | | |
|---|---|---|---|---|---|
| Vorinostat (mg/m$^2$/dose) | Dose | 8 | 12 | 15 | 18* |
| | 270 | | | | $d_6$ ~~Not evaluated~~ |
| | 230 | | $d_3$ 0/3 | $d_4$ 1/6 | $d_5$ 2/2 |
| | 180 | $d_1$ 0/3 | $d_2$ 0/3 | | $d_{5a}$ 0/6 |

MTDC

- Dose $d_5$ exceeded target toxicity so $d_6$ was never evaluated
- De-escalate to $d_{5a}$ to maintain highest dose of $^{131}$I-MIBG (active agent)

- Can an adaptive design identify the MTDC more efficiently?

DuBois SG, et al. (2015) *Clin Cancer Res*; 21(12) 2715-21

# Opportunities to use dual-agent designs in pediatric oncology

- Prior adult toxicity data can be used to specify model priors

- RP2D in children typically similar to adults:
  - Explore small number of dose combinations
  - May need fewer number of patients

- Pediatric oncologists have previously adopted alternate designs (Rolling 6) for single agent trials

Doussau A, et al. (2016). Contemp Clin Trials. 47: 217–227.

# Study Objective

To evaluate the relative performance of dual-agent dose escalation designs for phase I trials in pediatric oncology

# DUAL-AGENT DOSE ESCALATION SIMULATION METHODS

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# Evaluating performance of dual-agent designs using simulations

- Several studies have compared the performance of dual-agent designs using simulated data
- Simulation framework:
  - Create a set of scenarios where the true toxicity probability of each dose combination is known
  - For each scenario, run a mock trial using for each dual-agent design
  - Repeat for N trials
  - Compare average performance between designs

# Published reviews of dual-agent designs

| Published reviews | # dual-agent designs | # simulation scenarios | Dose combination matrices | Cohort size per escalation | Max N |
|---|---|---|---|---|---|
| Riviere, Dubois & Zohar (2015)* | 6 | 10 | 5x3 | 3 | 60 |
| Hirakawa et al. (2015) | 5 | 16 | 3x3, 4x4, 4x2, 5x3 | 1 | 30 |
| Lin & Yin (2015)* | 5 | 10 | 5x3 | 3 | 60 |
| Mander & Sweeting (2015) | 4 | 7 | 4x4 | 2 | 40 |
| Wages, Ivanova & Marchenko (2017) | 3 | 12 | 3x3, 4x3, 3x4, | 1 | 27, 36 |

Published reviews used large N and evaluated large dose combination matrices which may be infeasible for pediatric oncology trials

*Both papers used the same simulation scenarios and settings

# Dose escalation methods evaluated in review papers

| | | | Published reviews | | | | |
|---|---|---|---|---|---|---|---|
| **Dose escalation method** | **Authors** | **Year** | **Riviere et al. (2015)** | **Hirakawa et al. (2015)** | **Lin & Yin (2015)** | **Mander et al. (2015)** | **Wages et al. (2017)** |
| Estimation with order restrictions (CDP) | Conaway et al. | 2004 | | ✓ | | | ✓ |
| Up and down with isotonic regression | Ivanova & Wang | 2004 | ✓ | | ✓ | | |
| Two-dimension CRM | Wang & Ivanova | 2005 | ✓ | | | | |
| Copula regression (COPULA) | Yin & Yuan | 2009 | ✓ | ✓ | ✓ | ✓ | |
| Latent contingency tables w/ Gumbel | Yin & Yuan | 2009 | ✓ | | | ✓ | |
| Up and down using T-statistic | Ivanova & Kim | 2009 | ✓ | | ✓ | | |
| Hierarchical Bayesian | Braun & Wang | 2010 | | ✓ | | | |
| Partial order CRM (POCRM) | Wages et al | 2011 | ✓ | ✓ | ✓ | | ✓ |
| Generalized CRM | Braun & Jia | 2013 | | | | ✓ | |
| Shrinkage logistic model | Hirakawa et al. | 2013 | | ✓ | | | |
| Bayesian Optimal Interval (BOIN) | Lin & Yin | 2015 | | | ✓ | | ✓ |
| Product of independent beta probabilities | Mander & Sweeting | 2015 | | | | ✓ | |

# Methods with highest average probability to recommend the true MTDC (for each review)

| | | | Published reviews | | | | |
|---|---|---|---|---|---|---|---|
| **Dose escalation method** | **Authors** | **Year** | **Riviere et al. (2015)** | **Hirakawa et al. (2015)** | **Lin & Yin (2015)** | **Mander et al. (2015)** | **Wages et al. (2017)** |
| Estimation with order restrictions (CDP) | Conaway et al. | 2004 | | ✓ | | | ✓ |
| Up and down with isotonic regression | Ivanova & Wang | 2004 | ✓ | | ✓ | | |
| Two-dimension CRM | Wang & Ivanova | 2005 | ✓ | | | | |
| Copula regression (COPULA) | Yin & Yuan | 2009 | ✓ | ✓ | ✓ | ✓ | |
| Latent contingency tables w/ Gumbel | Yin & Yuan | 2009 | ✓ | | | ✓ | |
| Up and down using T-statistic | Ivanova & Kim | 2009 | ✓ | | ✓ | | |
| Hierarchical Bayesian | Braun & Wang | 2010 | | ✓ | | | |
| Partial order CRM (POCRM) | Wages et al | 2011 | ✓ | ✓ | ✓ | | ✓ |
| Generalized CRM | Braun & Jia | 2013 | | | | ✓ | |
| Shrinkage logistic model | Hirakawa et al. | 2013 | | ✓ | | | |
| Bayesian Optimal Interval (BOIN) | Lin & Yin | 2015 | | | ✓ | | ✓ |
| Product of independent beta probabilities | Mander & Sweeting | 2015 | | | | ✓ | |

# Selected methods for our simulation study

| | | | Published reviews | | | | |
|---|---|---|---|---|---|---|---|
| **Dose escalation method** | **Authors** | **Year** | **Riviere et al. (2015)** | **Hirakawa et al. (2015)** | **Lin & Yin (2015)** | **Mander et al. (2015)** | **Wages et al. (2017)** |
| **Estimation with order restrictions (CDP)** | Conaway et al. | 2004 | | ✓ | | | ✓ |
| Up and down with isotonic regression | Ivanova & Wang | 2004 | ✓ | | ✓ | | |
| Two-dimension CRM | Wang & Ivanova | 2005 | ✓ | | | | |
| **Copula regression (COPULA)** | Yin & Yuan | 2009 | ✓ | ✓ | ✓ | ✓ | |
| Latent contingency tables w/ Gumbel | Yin & Yuan | 2009 | ✓ | | | ✓ | |
| Up and down using T-statistic | Ivanova & Kim | 2009 | ✓ | | ✓ | | |
| Hierarchical Bayesian | Braun & Wang | 2010 | | ✓ | | | |
| **Partial order CRM (POCRM)** | Wages et al | 2011 | ✓ | ✓ | ✓ | | ✓ |
| Generalized CRM | Braun & Jia | 2013 | | | | ✓ | |
| Shrinkage logistic model | Hirakawa et al. | 2013 | | ✓ | | | |
| **Bayesian Optimal Interval (BOIN)** | Lin & Yin | 2015 | | | ✓ | | ✓ |
| Product of independent beta probabilities | Mander & Sweeting | 2015 | | | | ✓ | |

- CDP, Copula, POCRM have high recommendation rates across 2 reviews
- BOIN has comparable recommendation rates and is intuitive and practical

# Design considerations: cohort size and sample size

- **Cohort size:** # patients enrolled per dose combination before the next dose is determined
  - Typical cohort size = 1, 2, or 3
- **Sample size (N):** for adaptive designs, trial will end after enrolling N patients
- Sample size depends on:
  - Desired accuracy of identifying the true MTDC
  - Number of dose combinations evaluated
  - Cohort size
  - Expected accrual rates
  - Study budget

# Design considerations: allowable doses for escalation and de-escalation

| | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | | j-1 | j | j+1 |
| | | | | | |
| | i+1 | | | $d_{i+1,j}$ | |
| | i | | $d_{i,j-1}$ | $d_{ij}$ | $d_{i,j+1}$ |
| | i-1 | | | $d_{i-1,j}$ | |

- BOIN, Copula, and CDP allows only escalation or de-escalation to adjacent doses along rows or columns (no diagonal or off-diagonal doses allowed)
- POCRM allows escalation/de-escalation to any dose recommended by algorithm

Wages, Ivanova,& Marchenko. (2016) *J Biopharm Stat*; 26(1): 150-166.

# Notation and definitions

| Term | Definition |
|---|---|
| $d_{ij}$ | Combination of dose $i$ for drug A ($i=1,...,I$) and dose $j$ for drug B ($j=1,...,J$) |
| $\pi_{ij}$ | Probability of DLT at $d_{ij}$ |
| $n_{ij}$ | Number of patients treated on $d_{ij}$ |
| $y_{ij}$ | Number of observed DLTs from patients treated at $d_{ij}$ |
| $\varphi$ | Target toxicity level (e.g. 30%) |

Wages, Ivanova,& Marchenko. (2016) *J Biopharm Stat*; 26(1): 150-166.

# Bayesian Optimal Interval (BOIN) design: overview

- BOIN is a practical, intuitive, non-parametric design
- Select DLT probabilities:
  - $\varphi_1$ where escalation is needed (e.g. $\varphi_1=0.6\varphi$)
  - $\varphi_2$ where de-escalation is needed (e.g. $\varphi_1=1.4\varphi$)
  - $\varphi_1 < \varphi_2$
- Define optimal tolerance interval as:

$$[\varphi - \Delta_L, \varphi + \Delta_U]$$

where optimal cutoffs $\Delta_L = \varphi - \dfrac{\log\left(\frac{1-\varphi_1}{1-\varphi}\right)}{\log\left(\frac{\varphi(1-\varphi_1)}{\varphi_1(1-\varphi)}\right)}, \Delta_U = \dfrac{\log\left(\frac{1-\varphi}{1-\varphi_2}\right)}{\log\left(\frac{\varphi_2(1-\varphi)}{\varphi(1-\varphi_2)}\right)} - \varphi$

Lin & Yin. (2015) *Stat Methods Med Res*. 26(5):2155-2167

# BOIN: dose-finding algorithm

1. Start at lowest dose $d_{11}$
2. At current dose $d_{ij}$, calculate $\hat{\pi}_{ij} = y_{ij} / n_{ij}$
3. Select next dose

| Condition | Action |
|---|---|
| $\hat{\pi}_{ij} \leq \varphi - \Delta_L$ | Escalate to $d_{i^*j^*}$ that maximizes $\Pr\{\hat{\pi}_{i^*j^*} \in (\varphi - \Delta_L, \varphi + \Delta_U) \mid y_{i^*j^*}\}$ |
| $\varphi - \Delta_L < \hat{\pi}_{ij} < \varphi + \Delta_U$ | Stay at $d_{ij}$ |
| $\hat{\pi}_{ij} \geq \varphi + \Delta_L$ | De-escalate to $d_{i^*j^*}$ that maximizes $\Pr\{\hat{\pi}_{i^*j^*} \in (\varphi - \Delta_L, \varphi + \Delta_U) \mid y_{i^*j^*}\}$ |

(If more than one optimal dose, randomly select a dose)

4. Continue until max N
5. Calculate final $\hat{\pi}_{ij}$ using bivariate isotonic regression using all data
6. MTDC is dose with toxicity rates closest to $\varphi$

Wages, Ivanova,& Marchenko. (2016) *J Biopharm Stat*; 26(1): 150-166.

# Copula regression: overview

- Specify marginal toxicity of drugs A and B
- Model true toxicities as:

$p_i^{\alpha}$ = Probabilty of DLT at dose $i$ for drug A

$q_j^{\beta}$ = Probabilty of DLT at dose $j$ for drug B

$\alpha > 0,\ \beta > 0$ are unknown parameters

- Calculate joint toxicity probability using copula-type model

$$\pi_{ij} = 1 - \left\{(1-p_i^{\alpha})^{-\gamma} + (1-q_j^{\beta}) - 1\right\}^{-1/\gamma}$$

$\gamma > 0$ characterizes the interaction between drugs

Yin & Yuan. (2009) *JRSSC*. 58(2): 211-224

# Copula: Bayesian model

- Suggested prior distributions

$$\alpha, \beta \sim \text{Gamma}(2,2)$$

$$\gamma \sim \text{Gamma}(0.1,0.1)$$

- Likelihood function

$$L(\alpha, \beta, \gamma \mid data) \propto \prod_{i=1}^{I} \prod_{j=1}^{J} \pi_{ij}^{y_{ij}} (1-\pi_{ij})^{n_{ij}-y_{ij}}$$

- Posterior distribution

$$f(\alpha, \beta, \gamma \mid data) \propto L(\alpha, \beta, \gamma \mid data) f(\alpha) f(\beta) f(\gamma)$$

Yin & Yuan. (2009) *JRSSC*. 58(2): 211-224

# Copula: dose-finding algorithm

1. Select fixed cutoffs $c_e$ and $c_d$ for escalation or de-escalation
2. Start at lowest dose $d_{11}$
3. At current dose $d_{ij}$

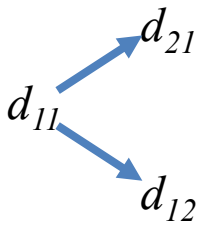
| Condition | Action |
|---|---|
| $\Pr(\hat{\pi}_{ij} < \varphi) > c_e$ | Escalate to dose with toxicity probability higher than current value and closest to $\varphi$ |
| $\Pr(\hat{\pi}_{ij} > \varphi) > c_d$ | De-escalate to dose with toxicity probability lower than current value and closest to $\varphi$. Terminate trial if current dose is $d_{11}$ |
| Otherwise | Stay at current dose |

4. Continue until max N
5. MTDC is dose with DLT rate closest to $\varphi$

Yin & Yuan. (2009) *JRSSC*. 58(2): 211-224

# Simple and partial orders

- Unclear if $d_{21}$ or $d_{12}$ is more toxic
- Represent doses as **partial order:**




- Two possible **simple orders** that satisfy this partial order

$d_{11} \rightarrow d_{21} \rightarrow d_{12}$

$d_{11} \rightarrow d_{12} \rightarrow d_{21}$

| | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | $d_{21}$ | $d_{22}$ | $d_{23}$ |
| | 1 | $d_{11}$ | $d_{12}$ | $d_{13}$ |

Wages, Ivanova,& Marchenko. (2016) *J Biopharm Stat*; 26(1): 150-166.

# Six possible orders for 2x3 matrix

| Description | Simple order |
|---|---|
| Across rows | $d_{11} \rightarrow d_{12} \rightarrow d_{13} \rightarrow d_{21} \rightarrow d_{22} \rightarrow d_{23}$ |
| Up columns | $d_{11} \rightarrow d_{21} \rightarrow d_{12} \rightarrow d_{22} \rightarrow d_{13} \rightarrow d_{23}$ |
| Up diagonals | $d_{11} \rightarrow d_{12} \rightarrow d_{21} \rightarrow d_{13} \rightarrow d_{22} \rightarrow d_{23}$ |
| Down diagonals | $d_{11} \rightarrow d_{21} \rightarrow d_{12} \rightarrow d_{22} \rightarrow d_{13} \rightarrow d_{23}$ |
| Down-up diagonals | $d_{11} \rightarrow d_{12} \rightarrow d_{21} \rightarrow d_{22} \rightarrow d_{13} \rightarrow d_{23}$ |
| Up-down diagonals | $d_{11} \rightarrow d_{21} \rightarrow d_{12} \rightarrow d_{13} \rightarrow d_{22} \rightarrow d_{23}$ |

| | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | $d_{21}$ | $d_{22}$ | $d_{23}$ |
| | 1 | $d_{11}$ | $d_{12}$ | $d_{13}$ |

Wages, Conaway, & O'Quigley. (2011) *Clin Trials*. 8(4): 380-389

# Nodal and non-nodal parameters

- **Nodal parameter:** ordering is known relative to all other parameters
- **Non-nodal parameter:** ordering is not known relative to all other parameters

| | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | $\pi_{21}$ | $\pi_{22}$ | $\pi_{23}$ |
| | 1 | $\pi_{11}$ | $\pi_{12}$ | $\pi_{13}$ |

Nodal parameter

Non-nodal parameter

Wages, Ivanova,& Marchenko. (2016) *J Biopharm Stat*; 26(1): 150-166.

# CDP design: overview

- CDP design uses different estimation procedures for nodal and non-nodal parameters
- CDP uses a two-stage design:
  - **Stage 1:** quickly escalate in single patients until first DLT
  - **Stage 2:** Bayesian dose-escalation
    - Prior distribution of $\pi_{ij} \sim Beta(\alpha_{ij},\beta_{ij})$
    - Update toxicity probabilities:

$$\hat{\pi}_{ij} = \frac{y_{ij} + \alpha_{ij}}{n_{ij} + \alpha_{ij} + \beta_{ij}}$$

    - Update posterior means using Hwang and Peddada (1994) method


1. Conaway, Dunbar, & Peddada. (2004) *Biometrics*. 60:661-669
2. Hwang & Peddada. (1994) *Ann Stat*. 22:67-93

# CDP: design specifications

- Investigators to specify:
  - Expected toxicity probability $E[\pi_{ij}]$
  - Upper limit $u_{ij}$ such that 95% certain toxicity probability ≤ $u_{ij}$

- Solve two equations to specify $\alpha_{ij}$ and $\beta_{ij}$

$$E[\pi_{ij}] = \frac{\alpha_{ij}}{\alpha_{ij} + \beta_{ij}} \qquad \Pr(\pi_{ij} < u_{ij}) = 0.95$$

- Select subset of possible orders for combination matrix

Conaway, Dunbar, & Peddada. (2004) *Biometrics*. 60:661-669

# CDP: stage 2 dose-finding algorithm

1. Define $A$ = {set of treatments administered so far}
2. Compute loss vs. target toxicity for each $d_{ij} \epsilon A$

$$Loss(\hat{\pi}_{ij}, \varphi) = \left|\hat{\pi}_{ij} - \varphi\right|$$

3. Determine dose $d_{i^*j^*}$ with minimum observed loss
   [additional rules for >1 doses with same minimum loss]

| Condition | Action |
|---|---|
| $\pi_{i^*j^*} < \varphi$ | Escalate to new dose not previously evaluated |
| $\pi_{i^*j^*} \geq \varphi$ | Next dose is $d_{i^*j^*}$ |

4. Continue until max N
5. MTDC is dose with DLT rate closest to $\varphi$

Conaway, Dunbar, & Peddada. (2004) *Biometrics*. 60:661-669

# Partial order continual reassessment method (POCRM): overview

- POCRM considers a set of simple orders consistent with combination matrix
- Applies continual reassessment method (CRM) within orders to evaluate MTDC
- Two-stage design:
  - **Stage 1:** quickly escalate in single patients until first DLT
  - **Stage 2:** Bayesian dose-escalation

Wages, Conaway, & O'Quigley. (2011) *Clin Trials*. 8(4): 380-389

# POCRM: Bayesian model

- Consider $m = 1, \ldots, \mathrm{M}$ orders
- Prior weights for orders $\tau(1), \ldots, \tau(M)$
- Model toxicity probability under power model

$$\hat{\pi}_{ij} = [\alpha_{ij}(m)]^{a_m}$$

- Select order $m^*$ that maximizes the updated order weight
- Estimate toxicity probabilities using power model assuming order $m^*$

Wages, Conaway, & O'Quigley. (2011) *Clin Trials*. 8(4): 380-389

# POCRM: stage 2 dose-finding algorithm

1. Estimate $\pi_{ij}$ based on observed data so far
2. Assign next dose $d_{i^*j^*}$ with minimum observed loss

$$Loss(\hat{\pi}_{ij}, \varphi) = \left| \hat{\pi}_{ij} - \varphi \right|$$

3. Continue until max N
4. MTDC is dose with DLT rate closest to $\varphi$

Conaway, Dunbar, & Peddada. (2004) *Biometrics*. 60:661-669

# Simulation settings and software

**Simulation settings**

- Maximum N = 24
- Cohort size = 1
- Target toxicity ($\varphi$) = 0.30
- MTDC defined as $\varphi \pm 0.05$
- Number of scenarios: 7
- Combination matrices: 2x3, 2x4
- Number of simulations = 2000

**Simulation software**

- BOIN and POCRM were simulated using available R packages
- Copula was simulated using a C++ program (courtesy of Dr. Ying Yuan)
- CDP was simulated using GAUSS (courtesy of Dr. Mark Conaway)

# Simulation scenarios (2x3)

MTDC at upper middle dose

| Scenario 1 | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | 0.10 | 0.30● | 0.60 |
| | 1 | 0.05 | 0.15 | 0.45 |

MTDC at lower middle dose

| Scenario 2 | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | 0.20 | 0.40 | 0.60 |
| | 1 | 0.15 | 0.30● | 0.45 |

MTDC at lowest dose

| Scenario 3 | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | 0.40 | 0.60 | 0.80 |
| | 1 | 0.30● | 0.45 | 0.70 |

MTDC at highest dose

| Scenario 4 | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | 0.05 | 0.15 | 0.30● |
| | 1 | 0.01 | 0.1 | 0.20 |

Safe dose ● MTDC Toxic dose

# Simulation scenarios (2x4)

MTDC at bottom-right dose

| Scenario 5 | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 2 | 0.40 | 0.45 | 0.50 | 0.60 |
| | 1 | 0.05 | 0.15 | 0.20 | 0.30● |

Two possible MTDC's

| Scenario 6 | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 2 | 0.15 | 0.27● | 0.40 | 0.60 |
| | 1 | 0.10 | 0.20 | 0.30● | 0.50 |

Two possible MTDC's with separation

| Scenario 7 | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 2 | 0.27● | 0.40 | 0.50 | 0.60 |
| | 1 | 0.10 | 0.20 | 0.30● | 0.45 |

Safe dose ● MTDC Toxic dose

# Include naïve 3+3 approach for comparison

| Scenario 1 | | Drug B | | |
|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 |
| | 2 | 0.10 | 0.30• → | 0.60 |
| | 1 | 0.05 → | 0.15 ↑ | 0.45 |

| Scenario 5 | | Drug B | | | |
|---|---|---|---|---|---|
| Drug A | Dose | 1 | 2 | 3 | 4 |
| | 2 | 0.40 | 0.45 → | 0.50 → | 0.60 |
| | 1 | 0.05 → | 0.15 ↑ | 0.20 | 0.30• |

Safe dose • MTDC Toxic dose

Select fixed paths for 2x3 and 2x4 matrices

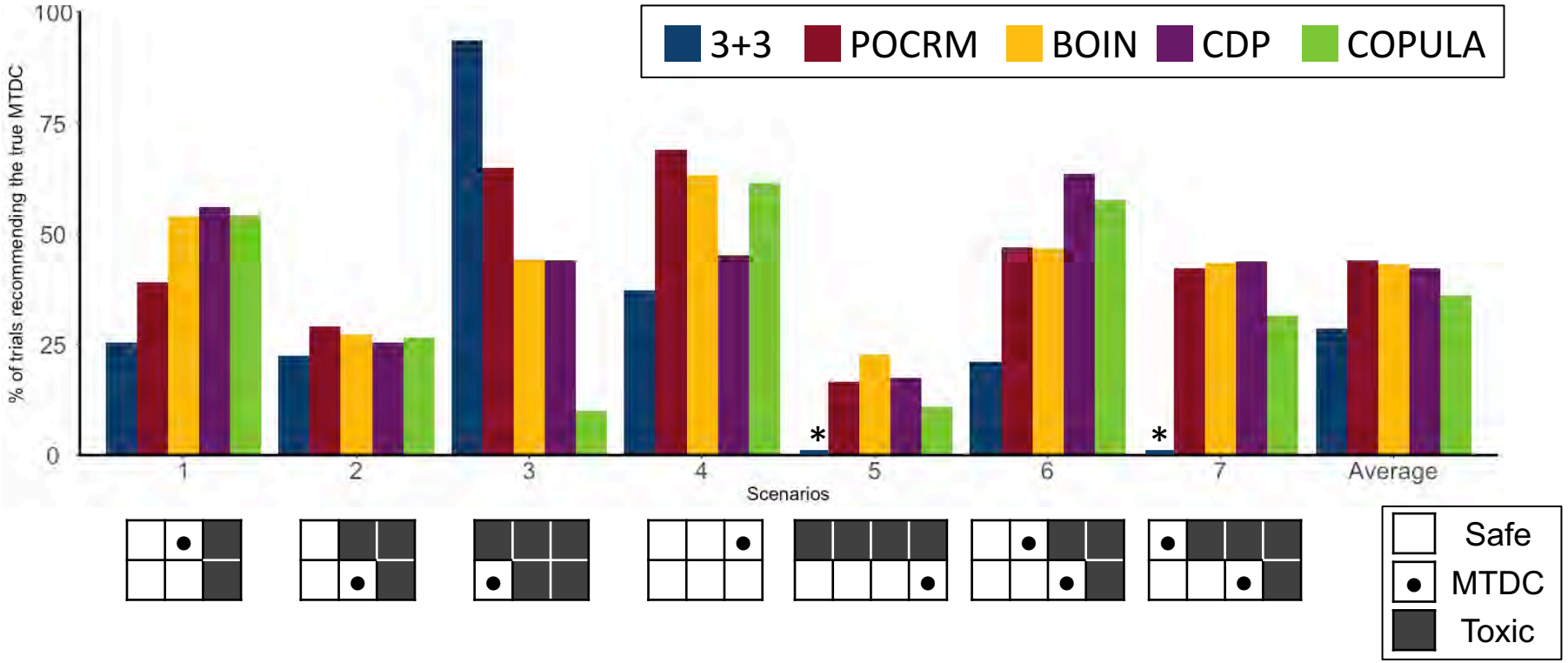
MTDC combination is not evaluated by 3+3 design in Scenarios 5 and 7

# SIMULATION RESULTS

DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

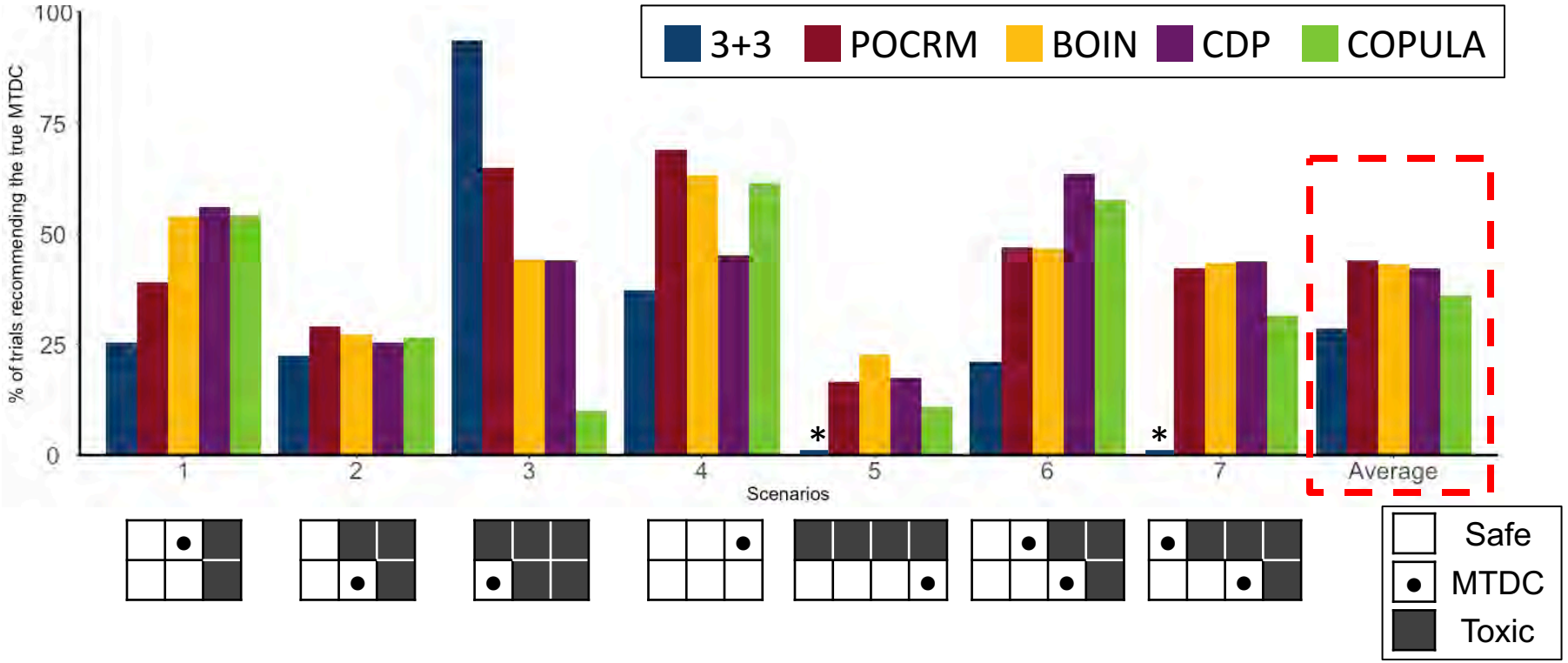
# Proportion of trials recommending true MTDC




- No single method had best performance across all 7 scenarios

* The fixed path for the 3+3 design does not evaluate the true MTDC

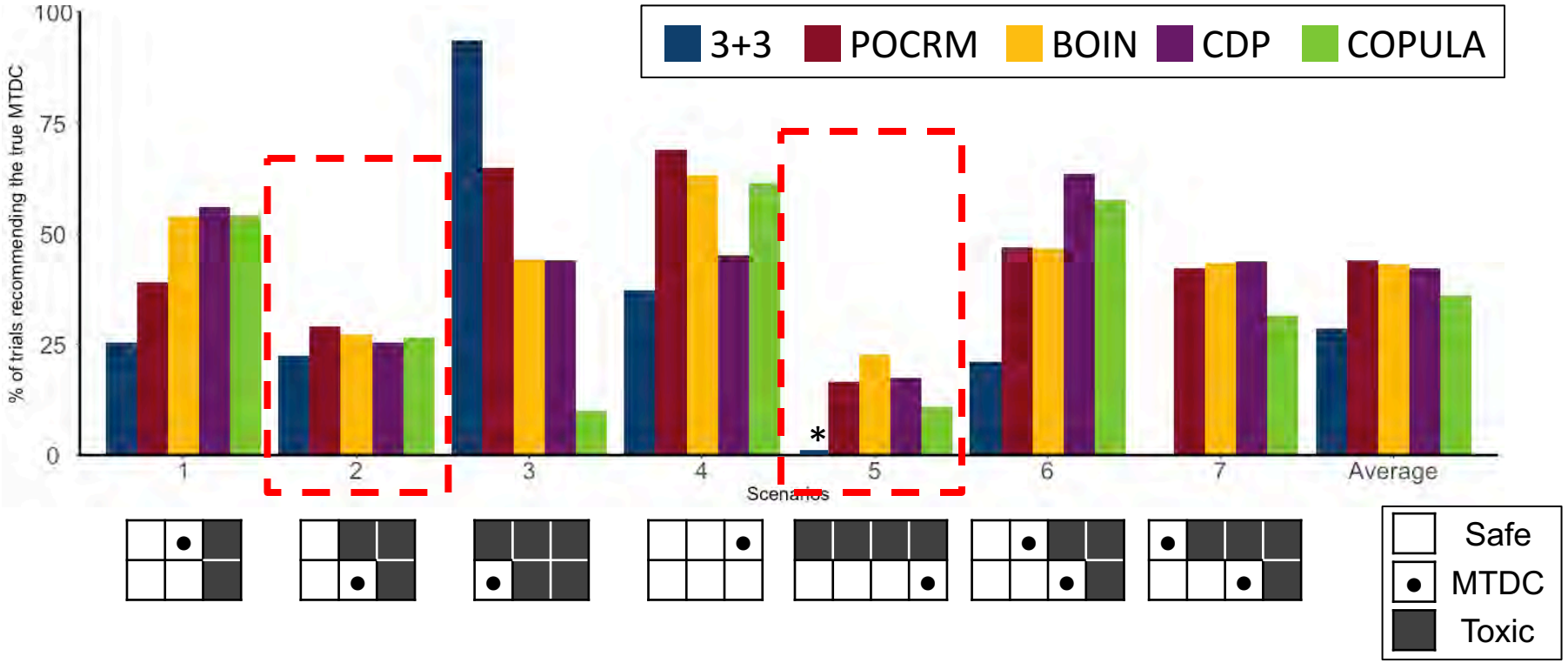
# Proportion of trials recommending true MTDC




- Mediocre average rates across all methods (29-44%) reflect small N
- POCRM, BOIN, CDP (44%) has higher rates than 3+3 (29%)

* The fixed path for the 3+3 design does not evaluate the true MTDC

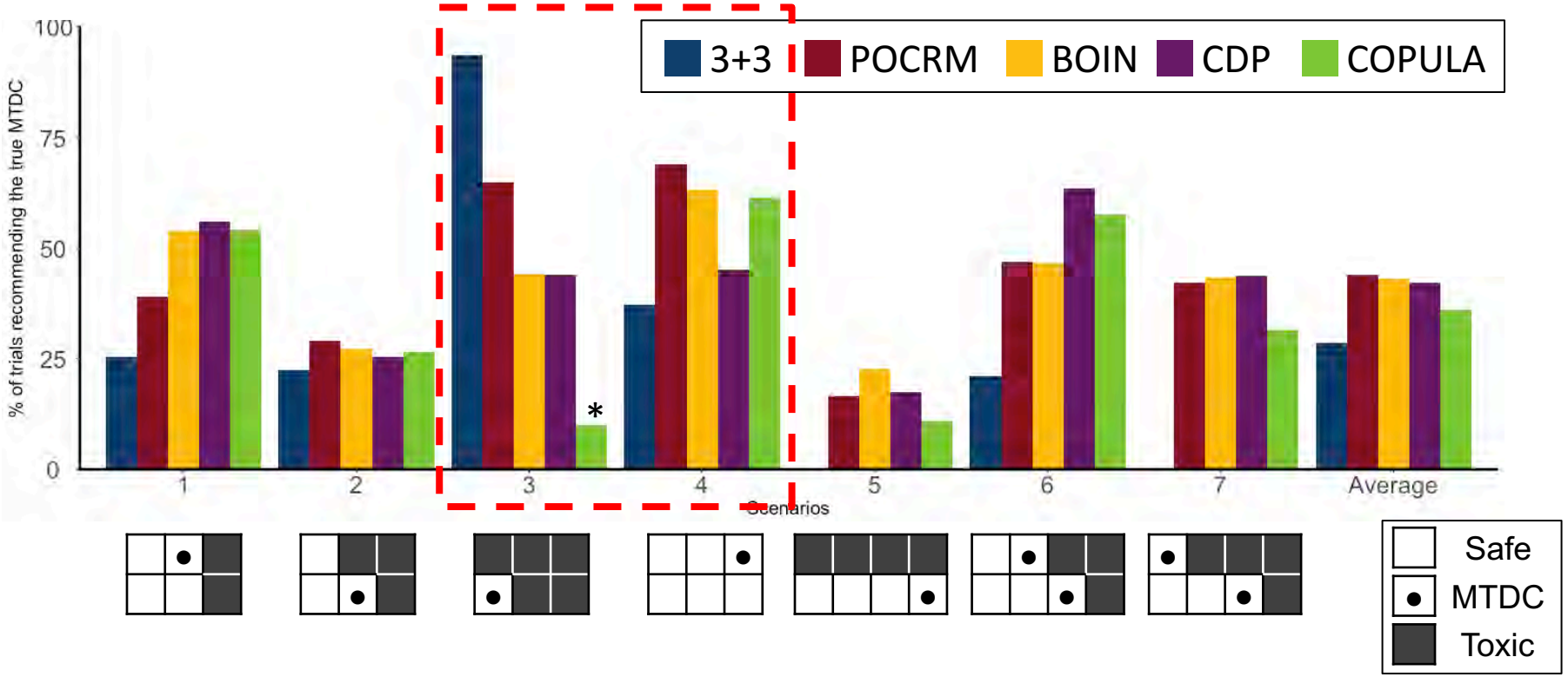
# Proportion of trials recommending true MTDC




- Relatively low recommendation rates for scenarios 2 and 5

* The fixed path for the 3+3 design does not evaluate the true MTDC

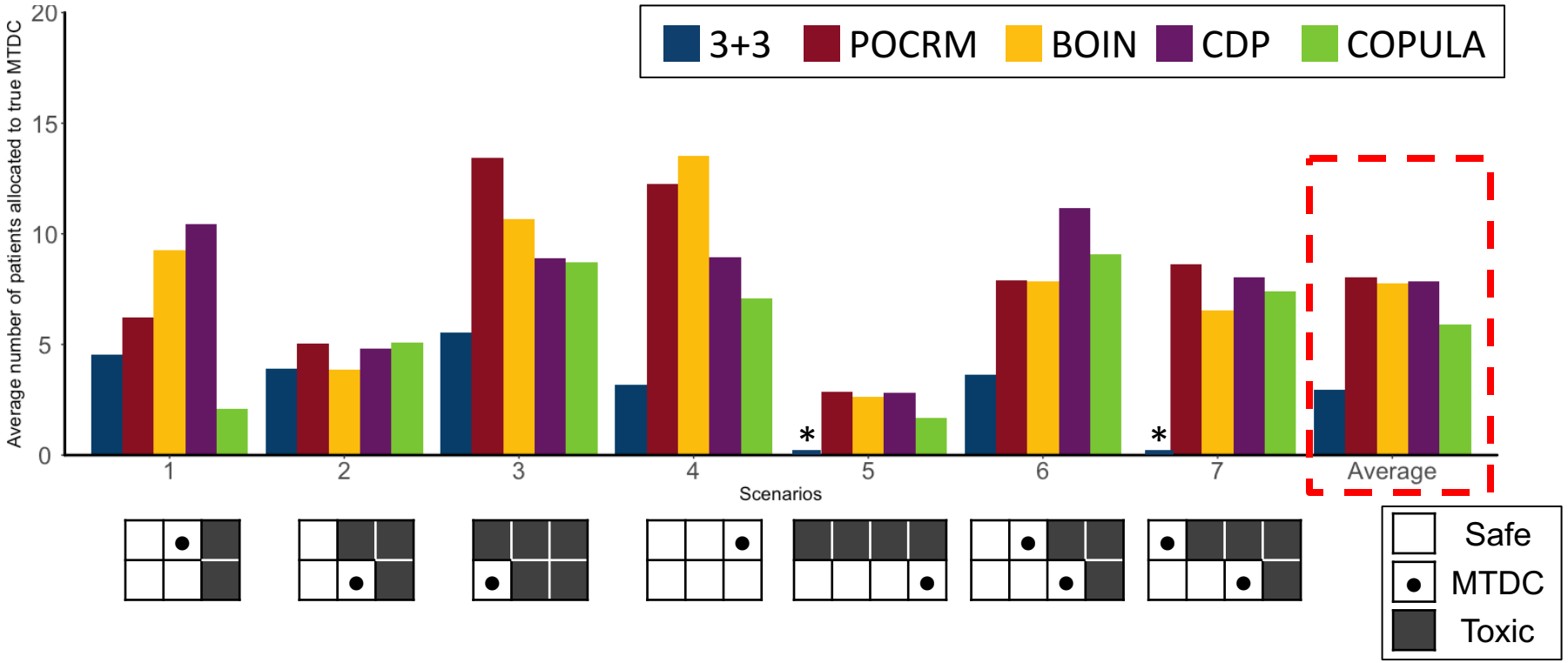
# Proportion of trials recommending true MTDC




- For scenario 3, 3+3 had highest rates since MTDC is starting dose
- For scenario 4, 3+3 had lowest rates since MTDC is highest dose

* Copula method terminates trial if need to de-escalate from starting dose d11; MTDC not declared if trial ended early

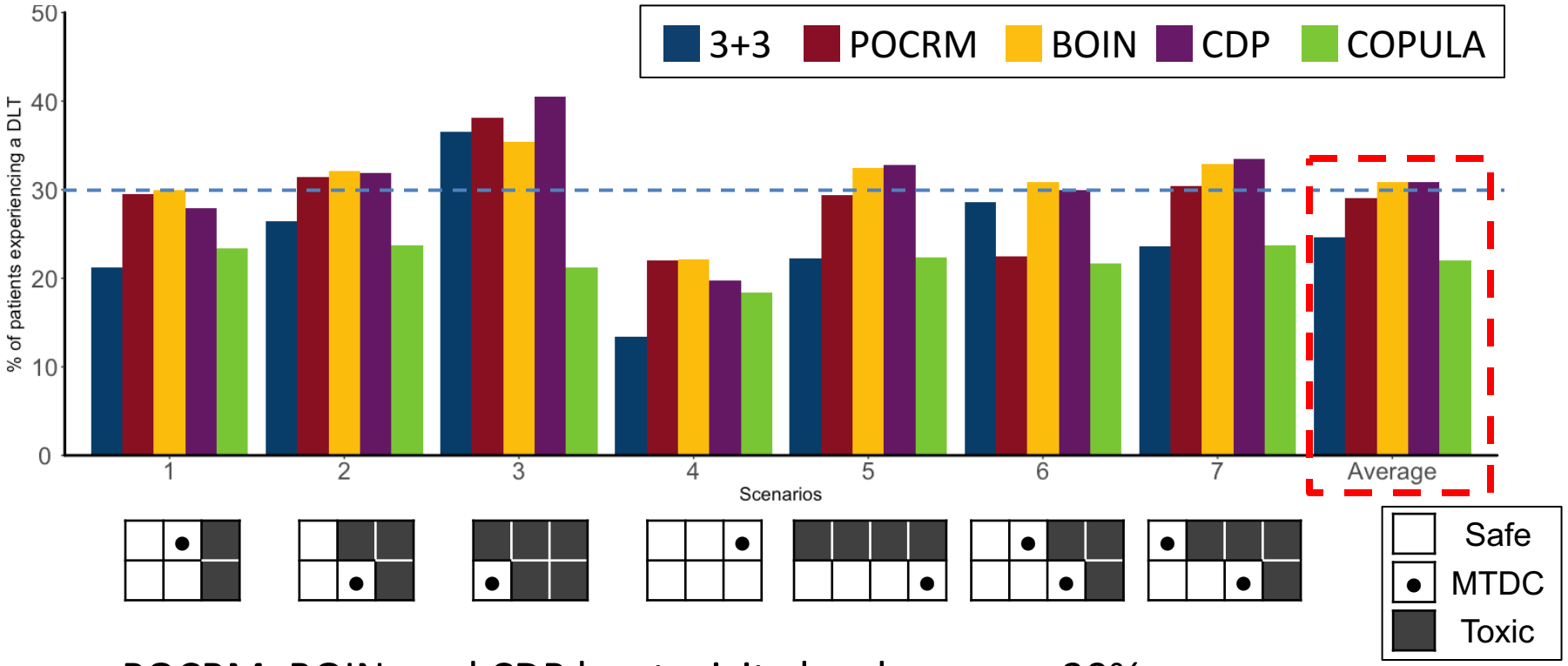
# Average number of patients allocated to MTDC




- Number of patients allocated to MTDC reflects recommendation rates (from previous plots)
- 3+3 and Copula have lower numbers of patients allocated to MTDC on average

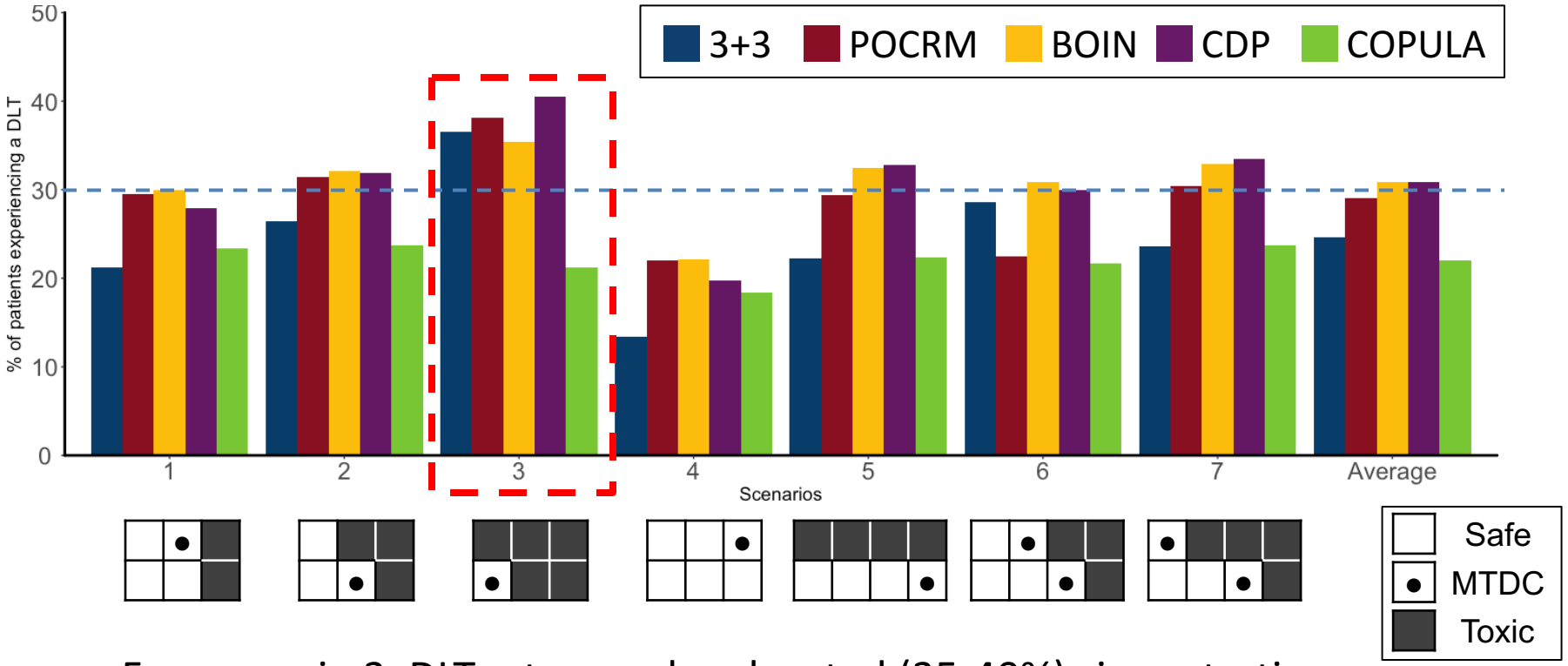
* The fixed path for the 3+3 design does not evaluate the true MTDC

# Proportion of patients experiencing a DLT



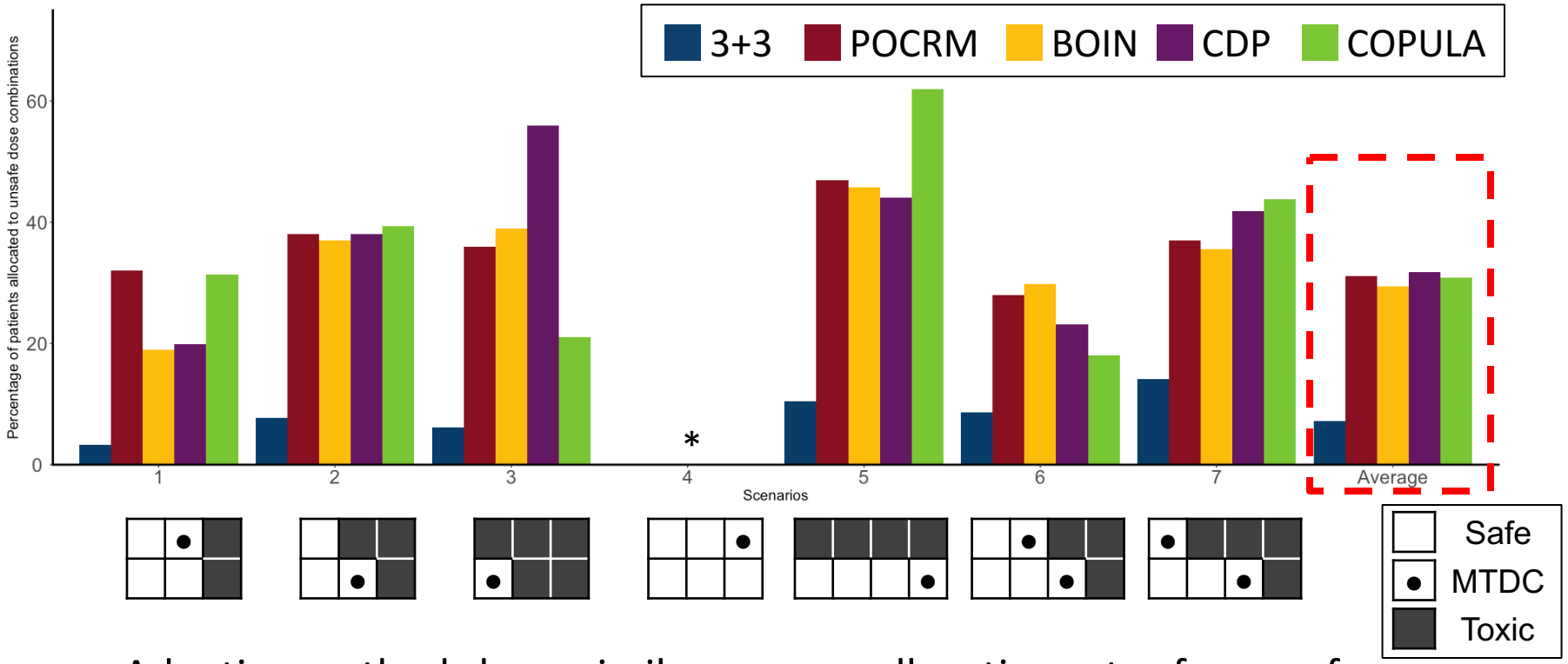

- POCRM, BOIN, and CDP has toxicity levels near $\varphi$=30% on average

# Proportion of patients experiencing a DLT




- For scenario 3, DLT rates can be elevated (35-40%) since starting dose is MTDC and other doses are increasingly toxic
- For N=24, additional 5-10% DLT rate is equivalent to an average of 1-2 additional DLTs per trial

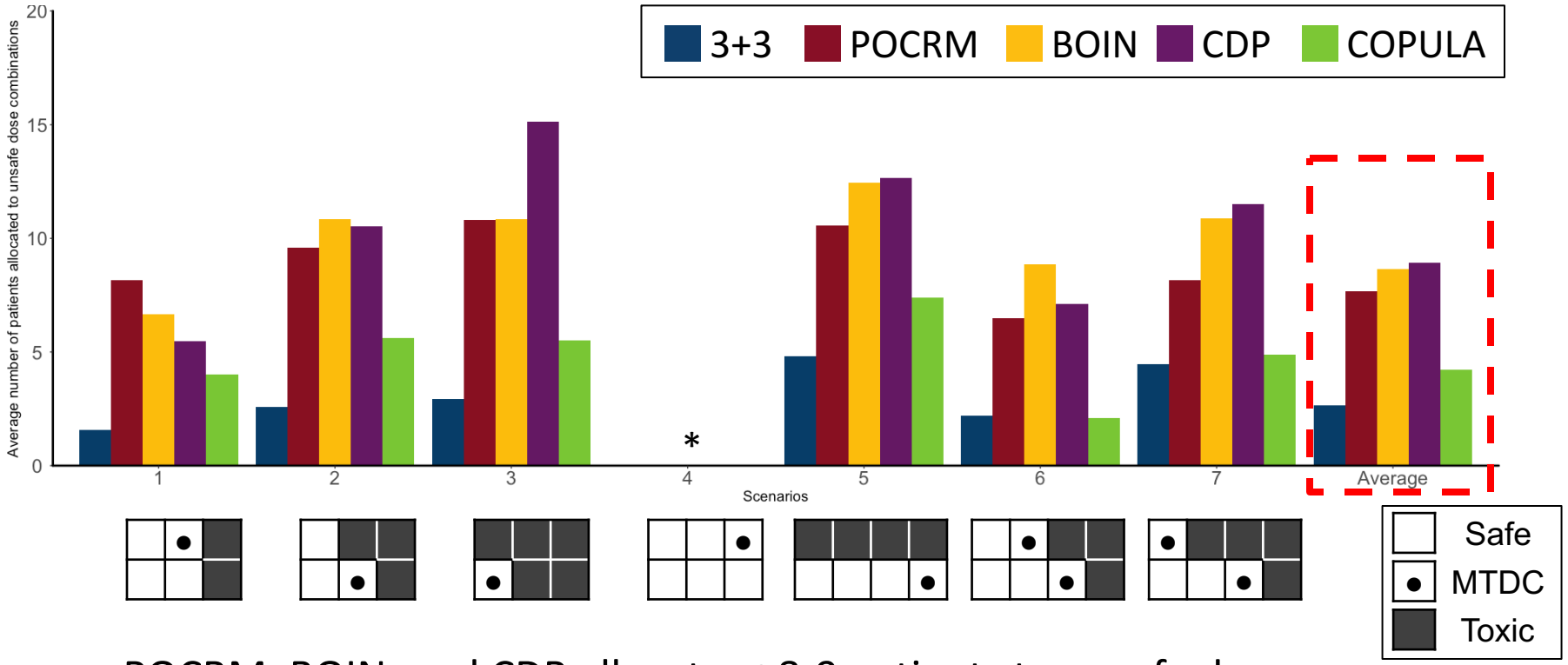
# Proportion of patients allocated to unsafe dose




- Adaptive methods have similar average allocation rates for unsafe doses (with toxicity rates above $\varphi$=30%)
- 3+3 has low allocation rates for unsafe doses but is overly conservative in dose escalation

* All doses for scenario 4 are safe by definition

# Average number of patients allocated to unsafe dose




- POCRM, BOIN, and CDP allocates ~8-9 patients to unsafe doses on average (out of N=24)
- Copula has lower # patients allocated since trials can have lower total N due to early termination rule

* All doses for scenario 4 are safe

# Dual-agent designs: recommendations for pediatric oncology

| Method | Avg % of trials recommending true MTDC | Avg % patients allocated to unsafe dose | Ease of under-standing | Software available | Other considerations |
|---|---|---|---|---|---|
| POCRM | 44% | 31% | | | |
| BOIN | 43% | 29% | | | |
| CDP | 42% | 32% | | | |
| Copula | 36% | 31% | | | |
| 3+3 | 29% | 7% | | | |

# Dual-agent designs: recommendations for pediatric oncology

| Method | Avg % of trials recommending true MTDC | Avg % patients allocated to unsafe dose | Ease of under-standing | Software available | Other considerations |
|---|---|---|---|---|---|
| POCRM | 44% | 31% | Moderate -Difficult | Yes | |
| BOIN | 43% | 29% | Easy | Yes | |
| CDP | 42% | 32% | Difficult | No, (requires GAUSS) | |
| Copula | 36% | 31% | Moderate | Yes | |
| 3+3 | 29% | 7% | Easy | N/A | |

# Dual-agent designs: recommendations for pediatric oncology

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|---|---|---|---|---|---|
| POCRM | 44% | 31% | Moderate -Difficult | Yes | Implemented in adult trials; Leverages well-known CRM method |
| BOIN | 43% | 29% | Easy | Yes | No prior specifications |
| CDP | 42% | 32% | Difficult | No, (requires GAUSS) | Need to specify priors based on expected and upper limits of toxicity rates per dose |
| Copula | 36% | 31% | Moderate | Yes | Sensitive to specification of priors |
| 3+3 | 29% | 7% | Easy | N/A | Cannot explore full combination matrix |

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# Future directions

- Evaluate methods with smaller sample size (N=18) to be comparable with average size of 3+3

- Include rule-based Rolling 6 design which is commonly used in pediatric oncology trials

# Conclusions

- BOIN and POCRM represent safe and efficient methods to determine the RP2D for pediatric oncology trials

- The naïve single-agent (3+3) approach may:
  - Be overly conservative with dose escalation
  - Potentially miss the true MTDC

# Acknowledgements


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