Flexible Designs for Contemporary Dose-finding Problems

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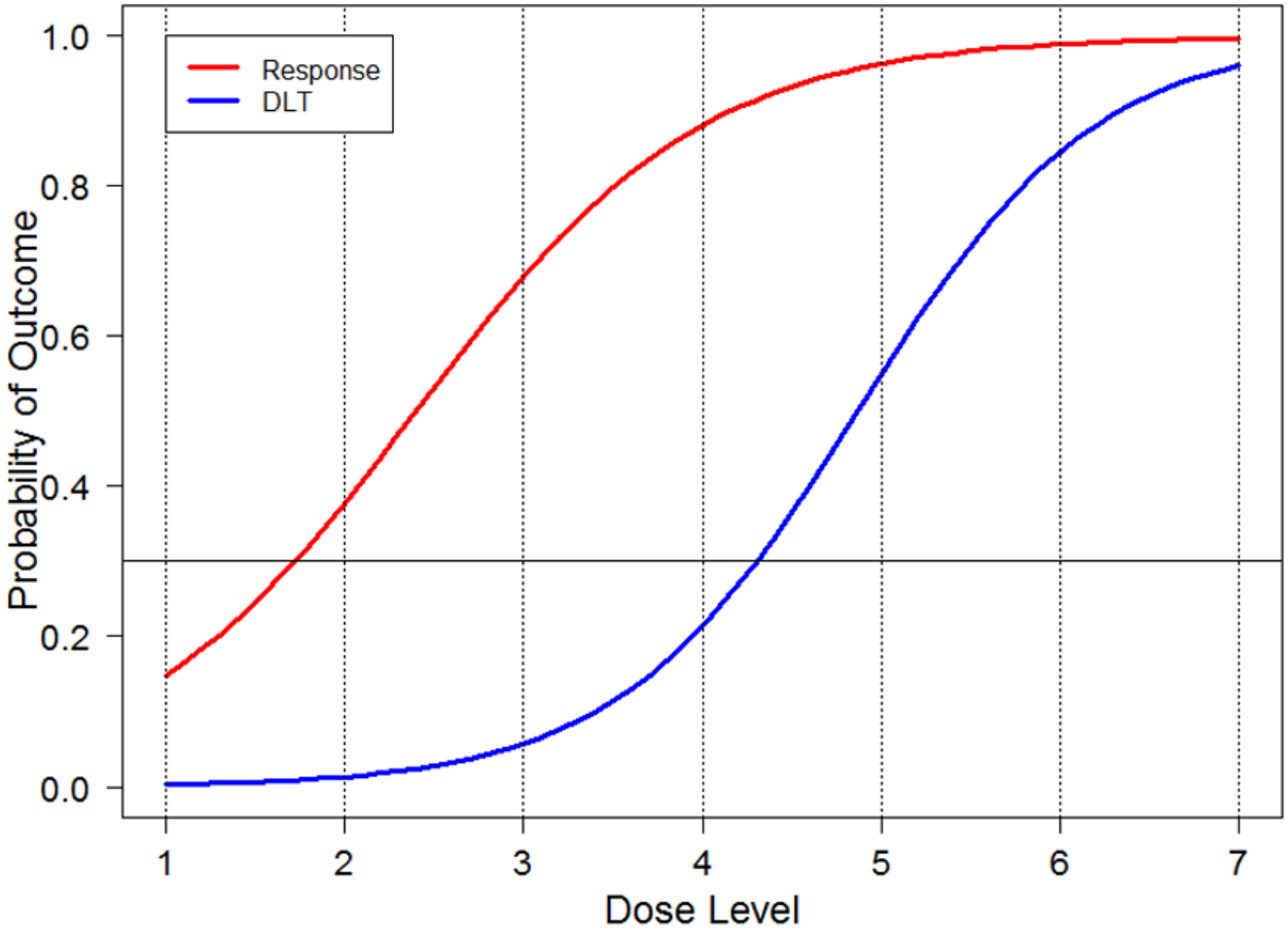
Dose-finding trials

Overview

- Initial safety studies
- Participants are sequentially assigned to doses based on accumulating safety data
- Primary objective is to recommend a dose for further testing for efficacy in Phase II from a set of doses
- The highest dose with an "acceptable" rate of dose-limiting toxicity (DLT; yes/no), defined by protocol specific adverse events
  - **Maximum tolerated dose (MTD)**

Dose-finding trials

Overview



Dose-finding trials

Traditional paradigm

- Dose levels are ordered with respect to probability of DLT (and efficacy).
- Estimate of the MTD does not account for patient heterogeneity.
- Binary DLT endpoint observed in early cycles drives dose allocation and MTD recommendation.

Dose-finding trials

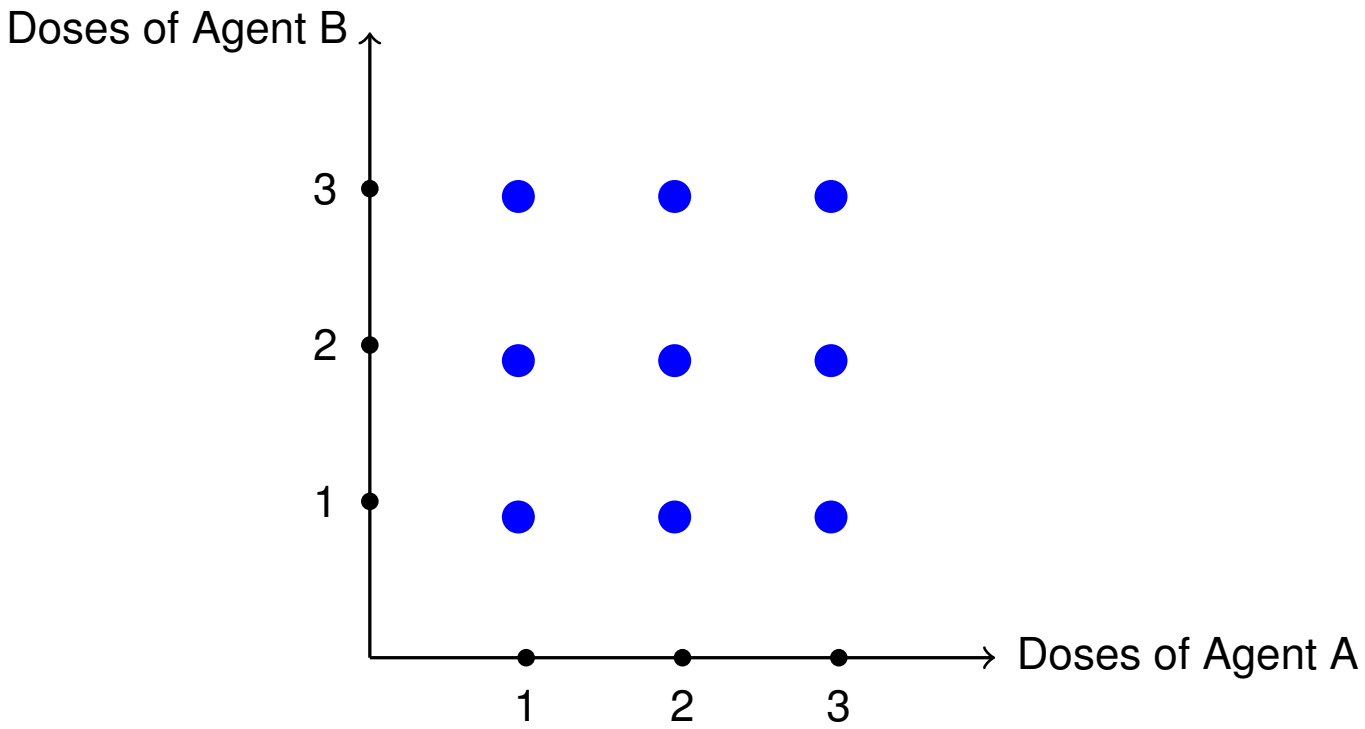
Contemporary paradigm

- **A changing landscape...**
  - Ordering of probabilities between some study dose levels may be unknown (drug combinations).
  - Objective may be to recommend group-specific MTDs (heterogeneous groups).
  - Design may be based on toxicity and efficacy (multiple endpoints).
  - Relevant toxicity events may occur in later cycles (late or chronic toxicities).

Design framework

Drug combinations

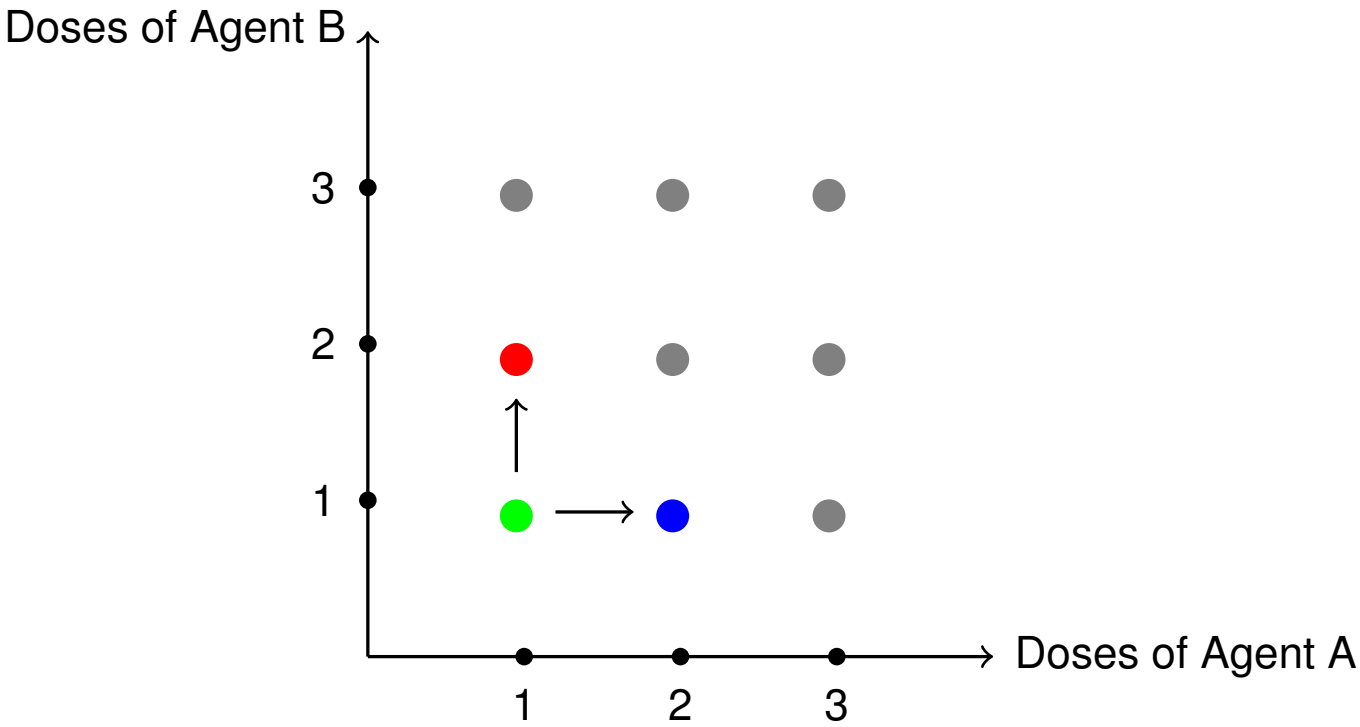
- Structure is to escalate two or more agents



Drug combination studies

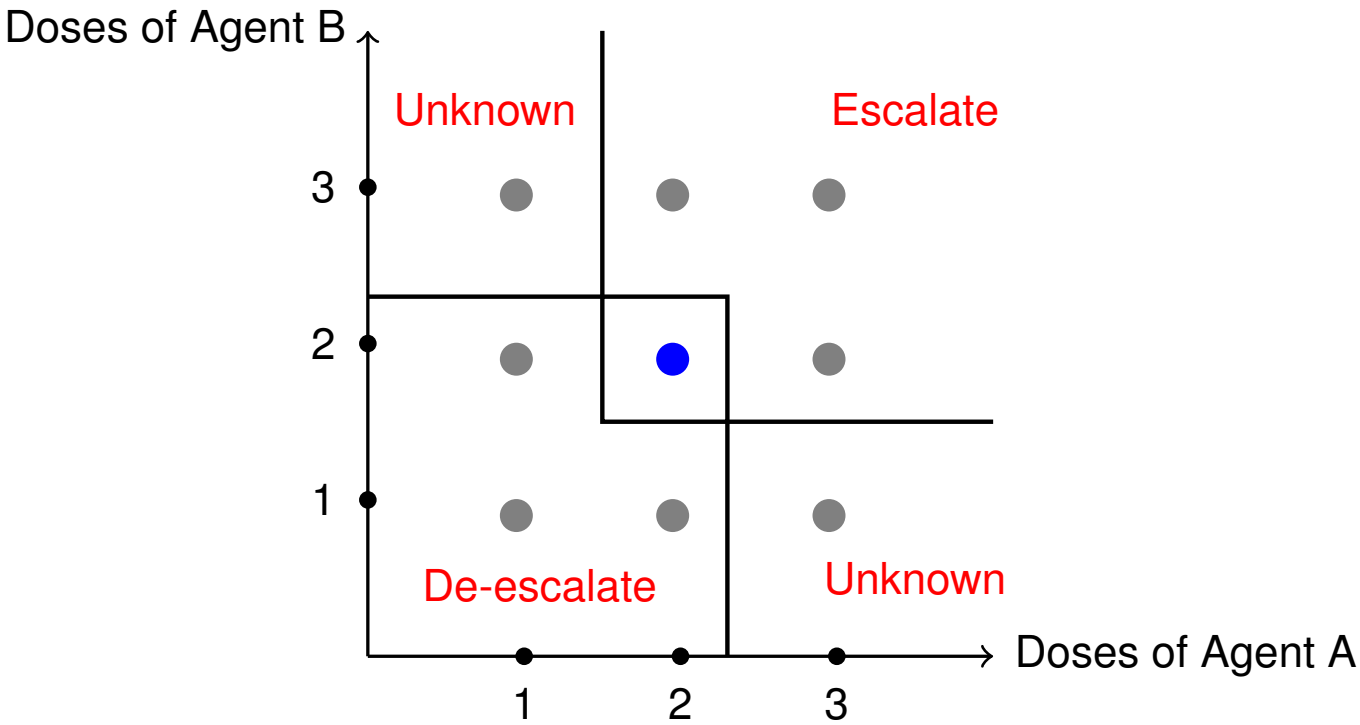
Challenges

- If ● is safe, where do we go next? ● or ●?



Drug combination studies

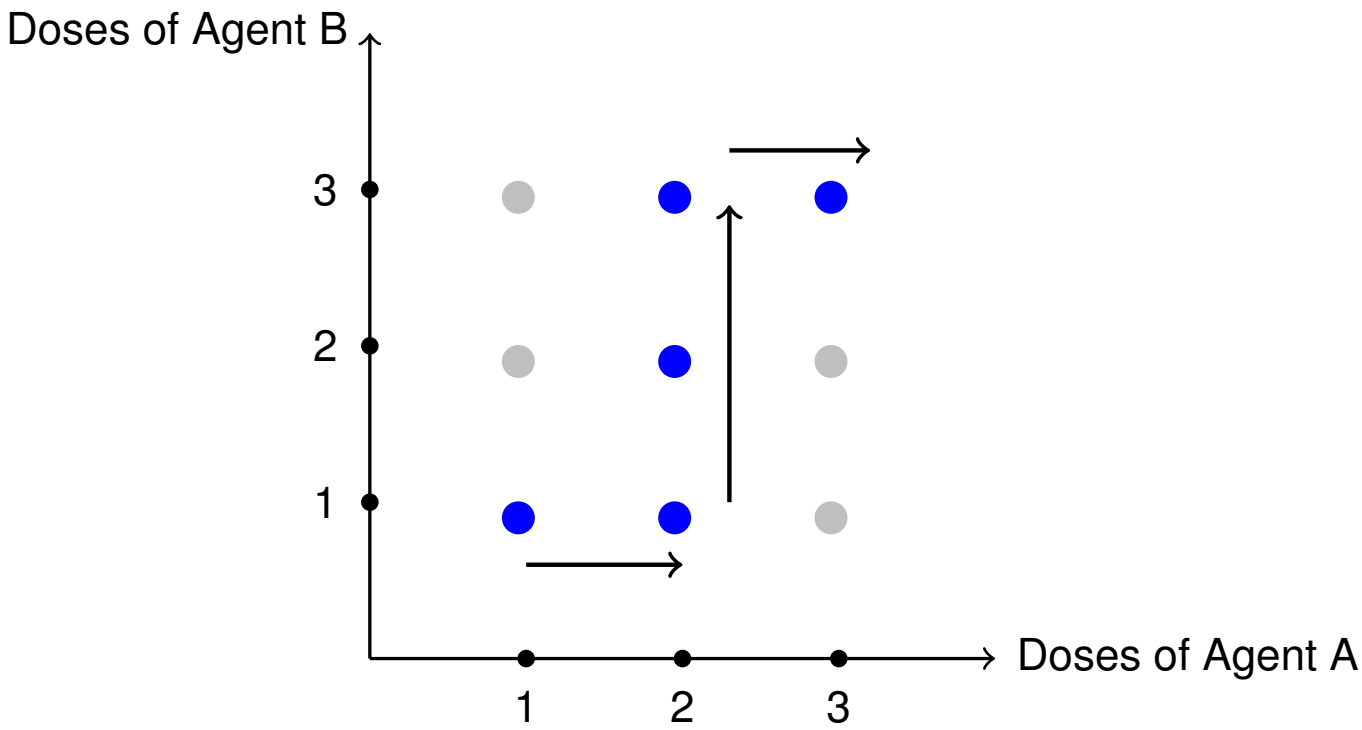
Challenges



Popular approach to drug combinations

Assume an ordering

- Choose a search path with a known ordering and apply a single agent method



Drug combination studies

What is commonly used?

- Literature review over January 2011 and December 2013[1]
  - 847 references retrieved
- 162 papers reported drug-combination in which at least two agents were escalated
  - In 88% a traditional or modified 3+3 dose-escalation design was used
  - All except one trial used a design developed for single-agent evaluation
- Novel methods for combinations are not commonly used
- Only a portion of possible combinations may be explored

[1] Riviere M-K, et al. *Ann Oncol* 2015; 26: 669–74.

Breast 49 study

Open to accrual (NCT03473639)

- A Phase I Study of the combination of Entinostat with Capecitabine in high risk breast cancer after neoadjuvant therapy.
- **Objective**: identify the maximum tolerated dose combination (MTDC) defined by DLT rate closest to target $\theta = 25\%$

Doses of Entinostat	Capecitabine	
	800 mg/m^2	1000 mg/m^2
5 mg	d_3	d_4
3 mg	d_1	d_2

PI: Patrick Dillon, MD

Breast 49 study

Open to accrual (NCT03473639)

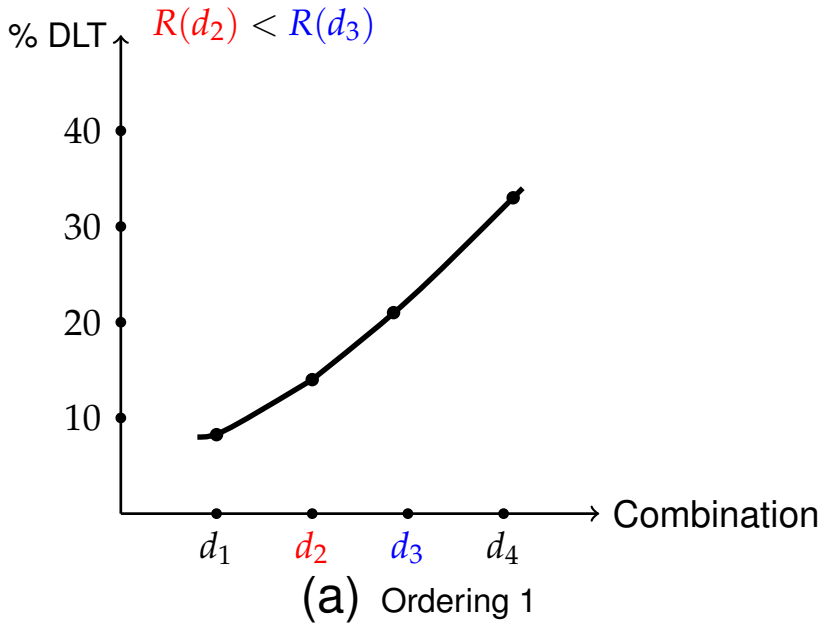
- Let $R(d_j)$ denote the probability of DLT at combination d_j.
- Is $R(d_2) > R(d_3)$ or is $R(d_3) > R(d_2)$?

Toxicity increases	Doses of Entinostat	Capecitabine	
		800 mg/m^2	1000 mg/m^2
$\uparrow$	5 mg	d_3	d_4
$\uparrow$	3 mg	d_1	d_2
		Toxicity increases $\longrightarrow$	

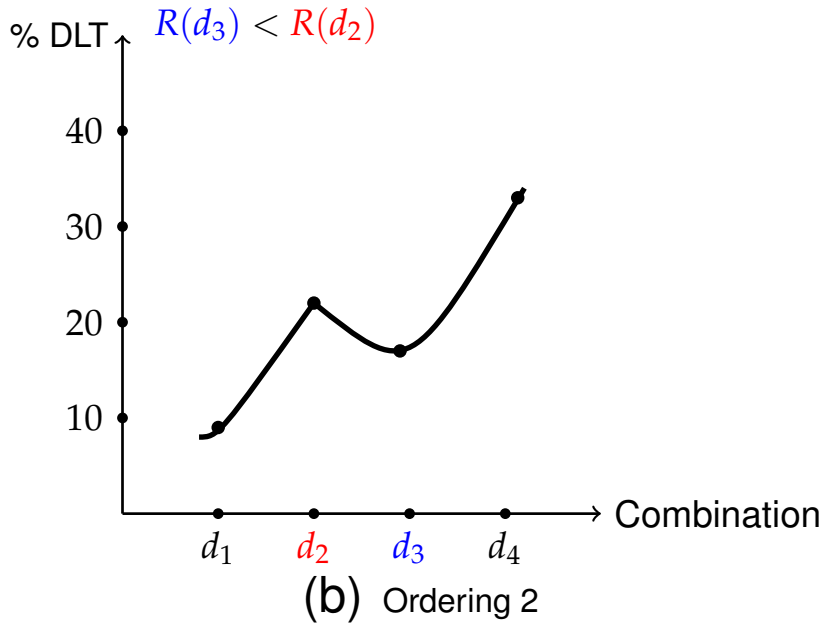
PI: Patrick Dillon, MD

Multiple possible orderings

DLT probabilities



(a) Ordering 1



(b) Ordering 2

Partial Order Continual Reassessment Method

POCRM[1]

- Extension of continual reassessment method (CRM) using multiple one-parameter models that represent possible orderings
  1. Choose the ordering that is most consistent with the data.
  2. Within the chosen ordering, use CRM to estimate DLT probabilities and allocate combinations
- The working model for the probability of DLT at combination d_j under possible ordering m is

$$R(d_j) = \Pr(\text{DLT at combination } d_j) \approx \alpha_{mj}^{\exp(a_m)}$$

[1] Wages NA, Conaway MR, O'Quigley J. *Biometrics* 2011; **67**: 1555–63.

Working model illustration

Breast 49 study

	Combinations			
Ordering	d_1	d_2	d_3	d_4
$m = 1$	$0.25^{\exp(a_1)}$	$0.35^{\exp(a_1)}$	$0.46^{\exp(a_1)}$	$0.56^{\exp(a_1)}$
$m = 2$	$0.25^{\exp(a_2)}$	$0.46^{\exp(a_2)}$	$0.35^{\exp(a_2)}$	$0.56^{\exp(a_2)}$

Class of Working Models

POCRM

- Let m index the working models
- Under working model m, probability of DLT at d_j is

$$R(d_j) \approx \psi_m(d_j, a_m) = \alpha_{mj}^{\exp(a_m)}$$

  where α_{mj} is the skeleton of the model m
- Prior on the working models

$$p = \{p(1), \ldots, p(M)\}$$

Likelihood and Prior

POCRM

- Data: $\mathcal{D} = \{y_j, n_j\}$, # DLT's and patients at each combo
- Likelihood under model m

$$\mathcal{L}_m(\mathcal{D} \mid a_m) \propto \prod_{j=1}^{K} \Big(\psi_m(d_j, a_m)\Big)^{y_j} \Big(1 - \psi_m(d_j, a_m)\Big)^{n_j - y_j}$$

- Prior $g_m(a_m)$ on a_m

$$a_m \sim \mathcal{N}(0, \sigma^2_{a_m})$$

Sequential Bayesian Model Choice

POCRM

- Posterior model probability for m is

$$\pi(m \mid \mathcal{D}) = \frac{p(m) \int \mathcal{L}_m(\mathcal{D} \mid a_m) g_m(a_m) da_m}{\sum_{m=1}^{M} p(m) \int \mathcal{L}_m(\mathcal{D} \mid a_m) g_m(a_m) da_m}$$

- After each inclusion, choose model h such that

$$h = \arg\max_m \pi(m \mid \mathcal{D})$$

DLT Probability Estimates

POCRM

- Estimated DLT probability at each combination

$$\widetilde{R}(d_j) = \int \psi_h(d_j, a_h) \frac{\mathcal{L}_h(\mathcal{D} \mid a_h) g_h(a_h)}{\int \mathcal{L}_h(\mathcal{D} \mid a_h) g_h(a_h) da_h} da_h$$

- Recommend combination closest to the target DLT rate θ

$$\widetilde{\nu} = \arg\min_j |\widetilde{R}(d_j) - \theta|$$

- Assign the next cohort to $\widetilde{\nu}$
- Observe DLT outcome(s) of new cohort and repeat model selection / estimation

Trial conclusion

Maximum sample size N participants

- Stop the trial for safety if the lowest combination is deemed too toxic as evaluated by the posterior probability of DLT at d_1
- Continual accrual until n_s participants have been treated on a combination or to maximum accrual
- MTDC is the recommended combination...
  - that has already been administered to n_s participants **or**
  - that would have been administered to participant $N + 1$

How Do We Evaluate Design Performance?

Accuracy

- How often does a method correctly identify the MTD?
- Simulate data under a **wide range** of true (assumed) dose-toxicity curves
  - What happens if true dose-toxicity curve is flat? Steep?
  - What happens if true MTD is at d_2? Or at d_3?
- Repeat trial simulation many times (i.e. 1000).
- Count the number (percentage) of times each combination is recommended as MTD at the conclusion of trial.

Simulation Study

Setting

- Compare POCRM to 3+3 and CRM using a fixed path with assumed ordering.

$$d_1 \rightarrow d_2 \rightarrow d_3 \rightarrow d_4$$

- Assess performance when this assumption is true and when it is violated.
- The 3+3 design will stop with at most 6 patients on a combo and either (1) declare an MTD or (2) declare the lowest combo is too toxic
- Model-based designs will either (1) accrue to the maximum sample size to determine MTD or (2) stop the trial if the model indicates the lowest combination is too toxic.

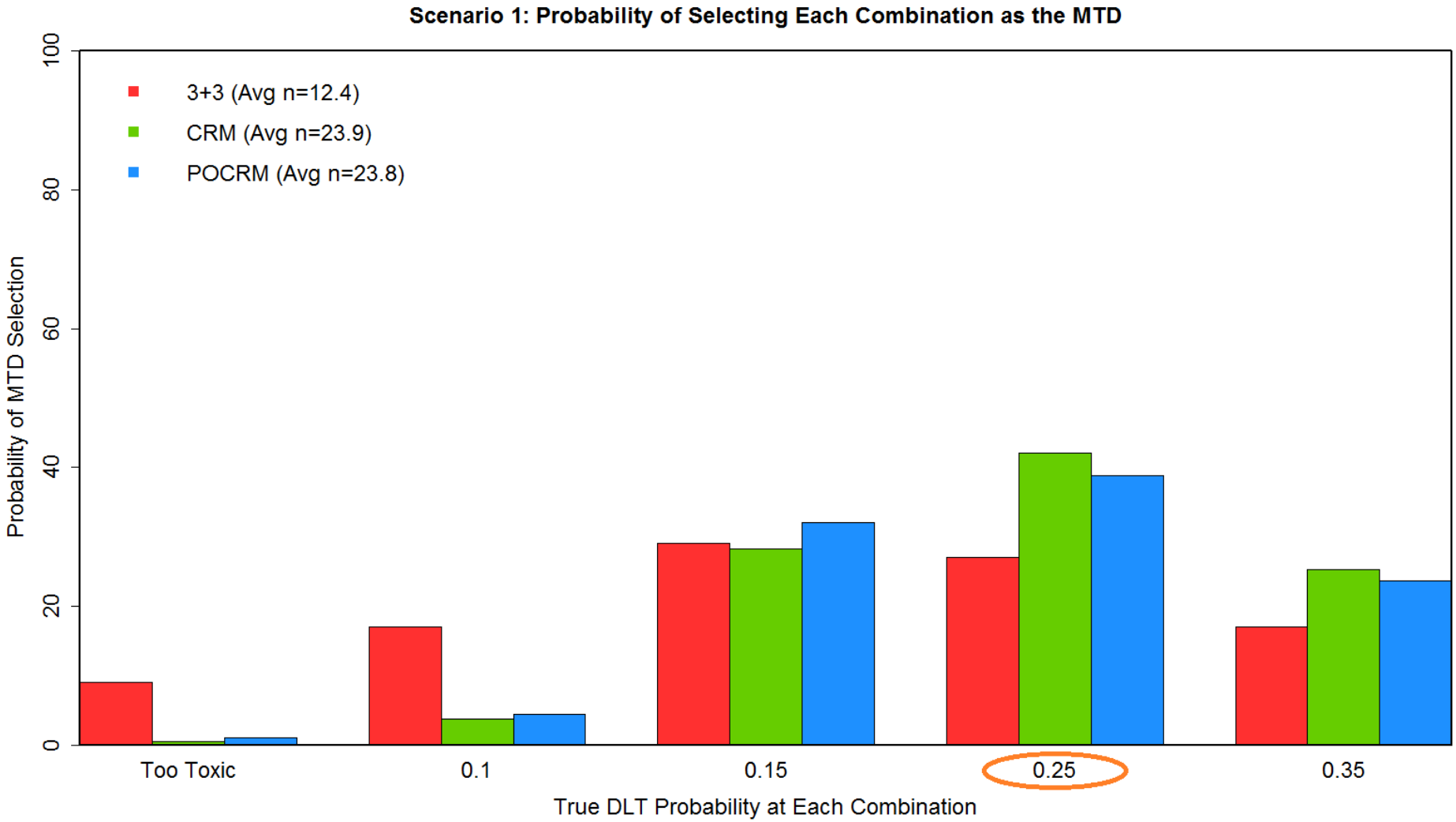
Simulation Study

Setting

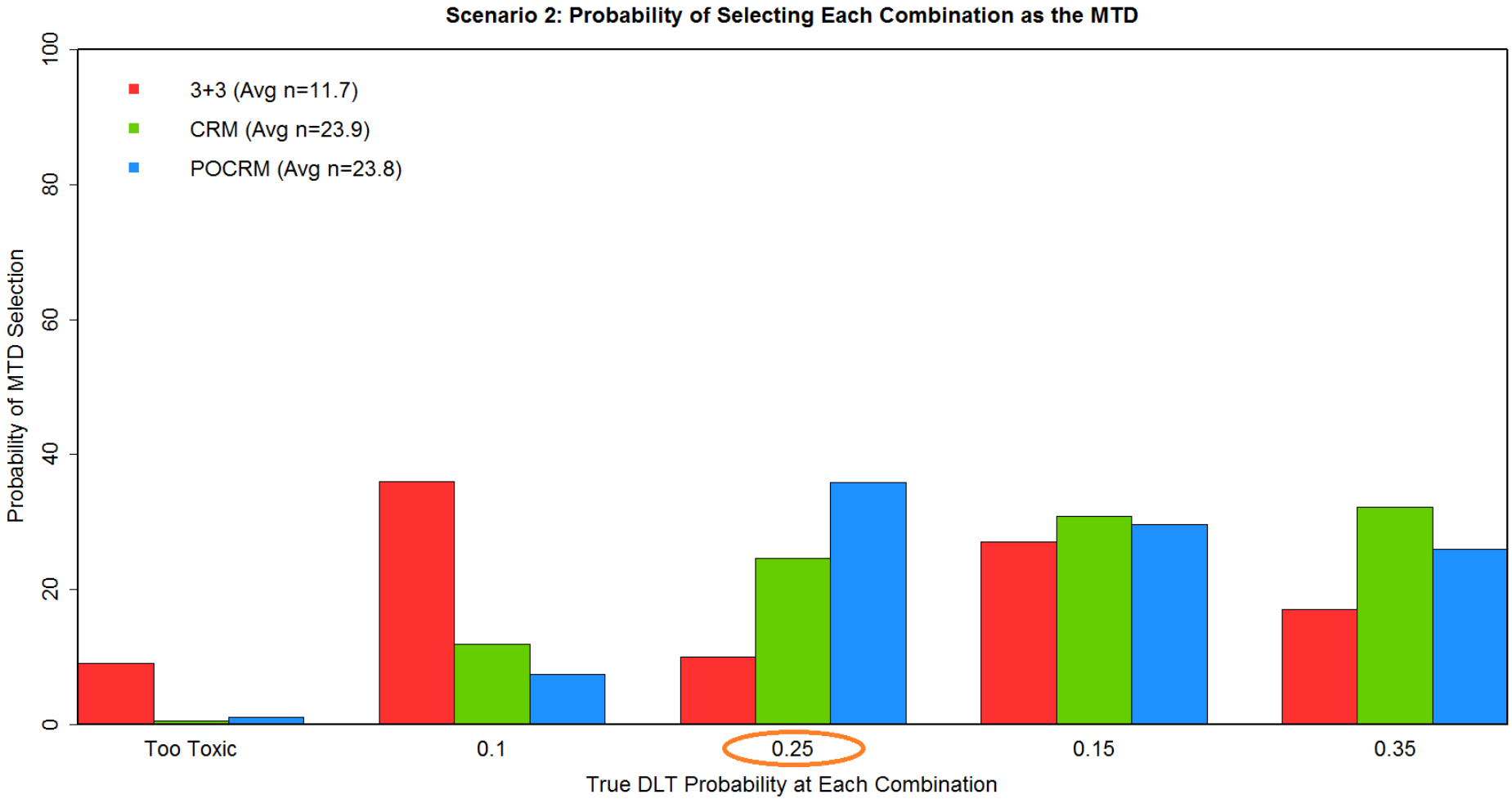
- Two assumed sets of true DLT probabilities
- Target DLT rate is $\theta = 0.25$
- Maximum sample size is 24 patients.
- 1000 simulated trials.

	Scenario 1		Scenario 2	
Doses of Entinostat	Capecitabine		Capecitabine	
	800 mg/m^2	1000 mg/m^2	800 mg/m^2	1000 mg/m^2
5 mg	0.25	0.35	0.15	0.35
3 mg	0.10	0.15	0.10	0.25

Scenario 1


Scenario 1: Probability of Selecting Each Combination as the MTD
3+3 (Avg n=12.4)
CRM (Avg n=23.9)
POCRM (Avg n=23.8)
Probability of MTD Selection
0
20
40
60
80
100
Too Toxic
0.1
0.15
0.25
0.35
True DLT Probability at Each Combination

Scenario 2


Scenario 2: Probability of Selecting Each Combination as the MTD
3+3 (Avg n=11.7)
CRM (Avg n=23.9)
POCRM (Avg n=23.8)
Probability of MTD Selection
0
20
40
60
80
100
Too Toxic
0.1
0.25
0.15
0.35
True DLT Probability at Each Combination

Mel 58

Completed (NCT01585350)

- Phase I trial of a toll-like receptor (TLR) agonists, lipopolysaccharide (LPS), with or without a form of incomplete Freund's adjuvant (IFA).
- IFA subgroups
  - V0 IFA is not administered with any of the 6 vaccines
  - V1 IFA is administered just with the first vaccine
  - V6 IFA is administered with all 6 vaccines
- 4 doses of LPS (25, 100, 400, 1600 EU)
- **Objective:** determine MTDC of LPS and IFA

PI: Craig Slingluff, MD

Melssen MM, Petroni GR, Wages NA, et al. *J Immunother Cancer* 2019; in review

Mel 58

Completed (NCT01585350)

- Phase I trial of a toll-like receptor (TLR) agonists, lipopolysaccharide (LPS), with or without a form of incomplete Freund's adjuvant (IFA).

Doses of LPS	IFA		
	V0	V1	V6
1600			
400			
100			
25			

PI: Craig Slingluff, MD

Melssen MM, Petroni GR, Wages NA, et al. *J Immunother Cancer* 2019; in review

Design specifications

Orderings and priors

- We may not be able to enumerate all possible orderings in large grids
  - A "default" set works well in many situations[1]
  - Order by rows, columns, diagonals of the matrix
- For skeleton, we can lean on the algorithms of Lee and Cheung[,3]
  1. Use **getprior** function in **R** package **dfcrm**
  2. Arrange skeleton values to correspond to possible orderings
  3. Algorithm for prior variance $\sigma^2_{a_m}$ yields least informative normal prior in terms of which dose is the MTD

[1] Wages NA, Conaway MR. *Pharm Stat* 2013; 12: 217–24

[2] Lee SM, Cheung YK. *Clin Trials* 2009; 6: 227–38

[3] Lee SM, Cheung YK. *Stat Med* 2011; 30: 2081–9

Heterogeneous Groups of Patients

Accrual completed (NCT02145286)

- Groups are defined by good/poor prognosis
- Goal is to find MTD in each group ($\text{MTD}_2 \leq \text{MTD}_1$)
- Total of 8 "group-dose combinations" labeled $d_1, \ldots, d_8$

	Doses (Gy)			
Group	8	10	12.5	15
2 (Poor prognosis)	d_5	d_6	d_7	d_8
1 (Good prognosis)	d_1	d_2	d_3	d_4

Wages NA, Read PW, Petroni GR. *Pharm Stat* 2015; 14: 302–10.

Group studies

What is commonly used?

- Parallel independent trials using single-agent design
- No formal borrowing of information across groups
- Reversal: MTD estimates that are counter to the known ordering
  - i.e., Poor prognosis has higher MTD than Good prognosis
- Inefficiency: lack of sharing of information yields less accurate MTD estimates

Group studies

Do combo methods apply?

- Mathematically, it appears combination methods would apply to groups but...
- There are some important distinctions
  - We don't get to choose both row and column for allocation
  - **Model** can choose column, but the **patient** chooses the row
  - Randomization between rows is not an option
  - What if it is expected to have a 75%/25% split between the groups?

Relative Location of MTDs

Shifts between groups

- $\{\text{Shift} = 0\}$

d_5	d_6	d_7	d_8
d_1	d_2	d_3	d_4

- $\{\text{Shift} = 1\}$

d_5	d_6	d_7	d_8
d_1	d_2	d_3	d_4

- $\{\text{Shift} = 2\}$

d_5	d_6	d_7	d_8
d_1	d_2	d_3	d_4

- $\{\text{Shift} = 3\}$

d_5	d_6	d_7	d_8
d_1	d_2	d_3	d_4

Working Models Under Various Shifts

Model	group	Doses in Gy 8	10	12.5	15
$m = 1$	2 - Poor	$0.03^{\exp(a_1)}$	$0.07^{\exp(a_1)}$	$0.13^{\exp(a_1)}$	$0.20^{\exp(a_1)}$
	1 - Good	$0.03^{\exp(a_1)}$	$0.07^{\exp(a_1)}$	$0.13^{\exp(a_1)}$	$0.20^{\exp(a_1)}$
$m = 2$	2 - Poor	$0.07^{\exp(a_2)}$	$0.13^{\exp(a_2)}$	$0.20^{\exp(a_2)}$	$0.29^{\exp(a_2)}$
	1 - Good	$0.03^{\exp(a_2)}$	$0.07^{\exp(a_2)}$	$0.13^{\exp(a_2)}$	$0.20^{\exp(a_2)}$
$m = 3$	2 - Poor	$0.13^{\exp(a_3)}$	$0.20^{\exp(a_3)}$	$0.29^{\exp(a_3)}$	$0.38^{\exp(a_3)}$
	1 - Good	$0.03^{\exp(a_3)}$	$0.07^{\exp(a_3)}$	$0.13^{\exp(a_3)}$	$0.20^{\exp(a_3)}$
$m = 4$	2 - Poor	$0.20^{\exp(a_4)}$	$0.29^{\exp(a_4)}$	$0.38^{\exp(a_4)}$	$0.47^{\exp(a_4)}$
	1 - Good	$0.03^{\exp(a_4)}$	$0.07^{\exp(a_4)}$	$0.13^{\exp(a_4)}$	$0.20^{\exp(a_4)}$

Allocation Algorithm in Groups

- Estimate which model is best represented by the data
- Under chosen model, estimate DLT probabilities for all group-dose combinations
- Allocate patients to dose with estimate rate closest to target, in respective group
- MTD's are doses that would be recommended in each group at the conclusion of the trial

Other completed studies

Multiple endpoints

- Cancer vaccine studies in melanoma based on safety and biologic activity endpoints (NCT02126579, NCT02425306)
  - Regimens are partially ordered but not a matrix of drug combinations
- Phase Ib study of ABT-199 and ibrutinib in mantle cell lymphoma based on safety and efficacy (CR+PR) at 2 months from start of treatment (NCT02419560)
  - Efficacy may increase or plateau with increasing dose level or each agent

Concluding remarks

- Number of working models increases as dimension/complexity of problem grows
- Design has good operating characteristics
  - extension of well-known CRM
- Can be adapted for application in a broad class of partial order problems
- **R** code for simulation and implementation available at `http://faculty.virginia.edu/model-based_dose-finding/`

Implementation of novel dose-finding methods

"As research statisticians, it is our responsibility not only to develop new and better designs, but to shepherd new methods into clinical practice."

- Huang B, Bycott P, Talukder E. *J Biopharm Stat* 2017; 27: 44–55.

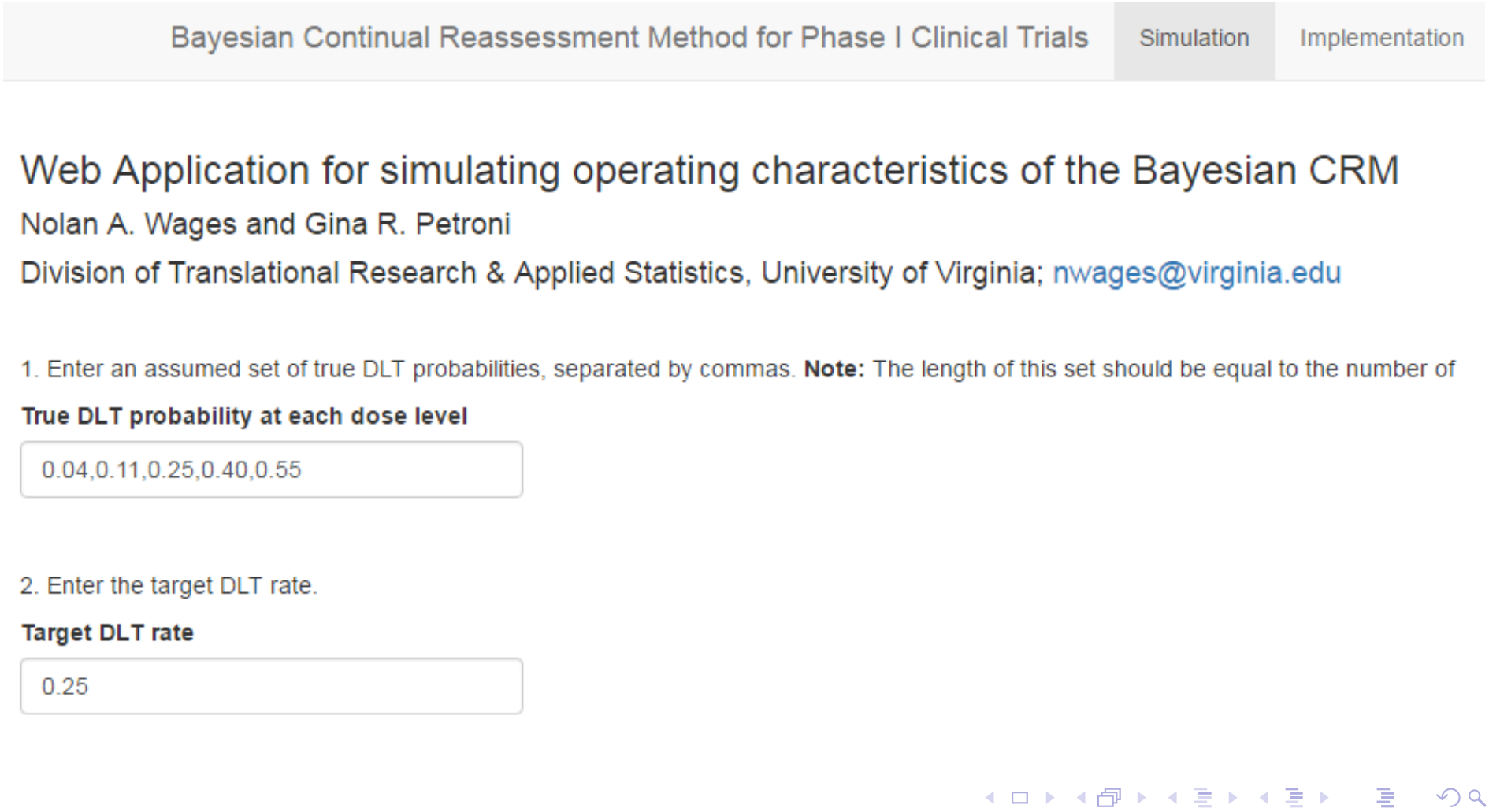
Implementation of novel dose-finding methods[1]

- Novel statistical methods are being developed but not used.
- Single-agent design structure should not limit goals of the study.
- Requirements:
  - time, effort, and personnel
  - attention to detail up-front
  - strong communication, team effort
  - statistical expertise throughout
  - available software
  - flexible clinical research management system

[1] Petroni GR, Wages NA, et al. *Stat Med* 2017; 36: 215–24.

R Shiny Web Applications

https://uvatrapps.shinyapps.io/crmb/



Future work[1]

Early and late toxicities

- Dosing decisions historically guided by binary DLT events occurring in early cycles of treatment
  - Appropriate for cytotoxic chemotherapy
- Patients on targeted/immune therapies are on therapy longer
  - Fewer acute DLTs; more in later cycles
  - Chronic lower grade toxicities over several cycles result in dose reductions
- Require designs that refine recommended doses based on richer toxicity information

[1] R01CA229414 (PI: Wages); review pending 2/14/19.

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