Shift models for dose-finding in partially ordered groups

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Shift models for dose-finding in partially ordered groups

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Abstract

Background: Limited options are available for dose-finding clinical trials requiring group-specific dose selection. While conducting parallel trials for groups is an accessible approach to group-specific dose selection, this approach allows for maximum tolerated dose selection that does not align with clinically meaningful group order information.

Methods: The two-stage continual reassessment method is developed for dose-finding in studies involving three or more groups where group frailty order is known between some but not all groups, creating a partial order. This is an extension of the existing continual reassessment method shift model for two ordered groups. This method allows for dose selection by group, where maximum tolerated dose selection follows the known frailty order among groups. For example, if a group is known to be the most frail, the recommended maximum tolerated dose for this group should not exceed the maximum tolerated dose recommended for any other group.

Setting

- Dose finding in multiple risk groups
- Goal is to find a MTD in each group
  - defined by target DLT rate θ
- In some cases, the ordering of the DLT probabilities among the groups is known
  - groups are **completely ordered**
- Use of this information improves efficiency

Dose finding in two groups

Example

- Dose finding trial of radiation therapy in two prognosis groups[1]
- $R(d_{g,k})$ denotes the probability of DLT at dose d_k in group g

	Doses (Gy)			
Group	8	10	12.5	15
2 (Poor prognosis)	$R(d_{2,1})$	$R(d_{2,2})$	$R(d_{2,3})$	$R(d_{2,4})$
1 (Good prognosis)	$R(d_{1,1})$	$R(d_{1,2})$	$R(d_{1,3})$	$R(d_{1,4})$

[1] Wages NA, Read PW, Petroni GR. *Pharm Stat* 2015; **14**: 302-310.

Completely ordered groups

- Within each row (groups), probabilities are increasing across columns (i.e., with increasing dose)

$$R(d_{1,2}) < R(d_{1,3})$$

- Within columns (fixed dose), probabilities are increasing up rows (i.e., poor group has higher risk of DLT)

$$R(d_{1,2}) < R(d_{2,2})$$

- $\text{MTD}_2 \leq \text{MTD}_1$

Parallel independent trials

- Commonly used in practice
- 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**: sharing of information yields more accurate MTD estimates

Existing methods

Ordered groups

- Two-sample CRM (O'Quigley, Shen, Gamst, 1999)
- Yuan and Chappell (2004)
- Ivanova and Wang (2006)
- **Shift model** (O'Quigley, 2006; O'Quigley and Iasonos, 2014)
- Conaway and Wages (2017)

Relative Location of MTD's

Shift Model*

- MTD for Group is "shifted" $0, 1, 2$ or 3 levels away from MTD for other group
  - $\Delta \in \{0, 1, 2, 3\}$
- The truth could be any one of the four possible values for Δ
  - Use the data to estimate the relative location of the MTD between groups
- Eliminates the possibility of a reversal
- Efficiently uses data for each group to update DLT probabilities

* O'Quigley J. *J Stat Plan Infer* 2006; **136**: 1765–80

Relative Location of MTD's

Shifts between groups

- $\{\Delta = 0\}$

$d_{2,1}$	$d_{2,2}$	**$d_{2,3}$**	$d_{2,4}$
$d_{1,1}$	$d_{1,2}$	**$d_{1,3}$**	$d_{1,4}$

- $\{\Delta = 1\}$

$d_{2,1}$	**$d_{2,2}$**	$d_{2,3}$	$d_{2,4}$
$d_{1,1}$	$d_{1,2}$	**$d_{1,3}$**	$d_{1,4}$

- $\{\Delta = 2\}$

$d_{2,1}$	$d_{2,2}$	$d_{2,3}$	$d_{2,4}$
$d_{1,1}$	$d_{1,2}$	**$d_{1,3}$**	$d_{1,4}$

- $\{\Delta = 3\}$

$d_{2,1}$	$d_{2,2}$	$d_{2,3}$	$d_{2,4}$
$d_{1,1}$	$d_{1,2}$	$d_{1,3}$	**$d_{1,4}$**

Shift models

Targeting $\theta = 0.30$

- Model $m = 1 : \{\Delta = 0\}$

0.10^{a_1}	0.19^{a_1}	0.30^{a_1}	0.42^{a_1}
0.10^{a_1}	0.19^{a_1}	0.30^{a_1}	0.42^{a_1}

- Model $m = 2 : \{\Delta = 1\}$

0.19^{a_2}	0.30^{a_2}	0.42^{a_2}	0.54^{a_2}
0.10^{a_2}	0.19^{a_2}	0.30^{a_2}	0.42^{a_2}

Shift models

Targeting $\theta = 0.30$

- Model $m = 3 : \{\Delta = 2\}$

0.30^{a_3}	0.42^{a_3}	0.54^{a_3}	0.64^{a_3}
0.10^{a_3}	0.19^{a_3}	0.30^{a_3}	0.42^{a_3}

- Model $m = 4 : \{\Delta = 3\}$

0.30^{a_4}	0.42^{a_4}	0.54^{a_4}	0.64^{a_4}
0.04^{a_4}	0.10^{a_4}	0.19^{a_4}	0.30^{a_4}

Shift model

Models and inference

- Probability of DLT for a given shift model m, group g and dose level k is modeled by

$$\begin{aligned} R_{mgk}(d_{gk}) &= \Pr\left(Y_{gk} = 1 \,|\, d_{gk}, g, m\right) \\ &= \psi_{mgk}(d_{mgk}, a_m) = p_{mgk}^{\exp(a_m)} \end{aligned}$$

- Log-likelihood is given by

$$\ell_m(a_m) = \sum_{g=1}^{G} \sum_{k=1}^{K} \{y_{gk} \log \psi_{mgk}(d_{mgk}) + (n_{gk} - y_{gk}) \log(1 - \psi_{mgk}(d_{mgk}))\}$$

Shift model

Estimation and allocation

- Choose the shift model that maximizes the log-likelihood evaluated at $\hat{a}_m$

$$m^* = \arg\max_m \ell_m(\hat{a}_m)$$

- DLT probability estimate at each group-dose combination is

$$\hat{R}_{m^*gk}(d_{gk}) = \psi_{m^*gk}(d_{m^*gk}, \hat{a}_{m^*})$$

- Next patient in group g receives dose k with $\hat{R}_{m^*gk}(d_{gk})$ closest to θ
- At study end, MTD is estimated in each group using $\hat{R}_{m^*gk}(d_{gk})$

Motivating example[1]

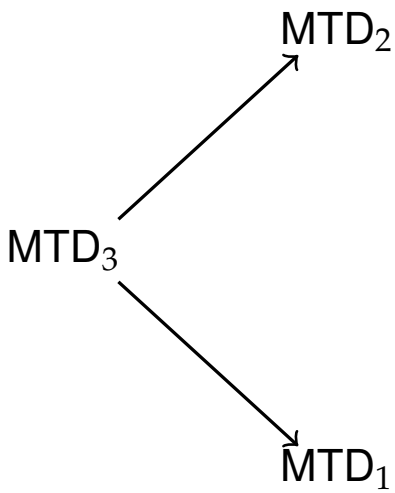
Partially ordered groups

- Dose-finding study of irinotecan for three groups of patients.[1]
- Patients are grouped by their genotype
  1. *1/*1 genotype
  2. *1/*28 genotype
  3. *28/*28 genotype
- Patients in Group 3 genotype have the greatest risk of DLT
- Unknown whether patients in Group 1 or Group 2 have a greater risk of DLT

[1] Innocenti F, et al. *J Clin Oncol* 2014; **32**: 2328-34.

Partially ordered groups

- Still assumed that DLT probabilities increase within group
- Increasing DLT probabilities between groups for fixed dose levels can no longer be assumed
- MTD for Group 3 should be lowest among the three MTDs



Existing methods

Partially ordered groups

- Conaway (*Stat Med* 2017; **36**: 2323–32.)
- Conaway (*Clin Trials* 2017; **14**: 491-s-8.)
- Both of these methods are hybrids of CRM and order restricted inference
- Horton et al. (2018) generalizes the shift model to G partially ordered groups

Shift models for partially ordered groups

- Estimation and allocation is the same as completely ordered groups.
- Requires the specification of shift models to reflect more complicated group structure.
- In Innocenti et al. (2014), there are $m = 16$ possible shift models in which
  - Group 3 is the most frail and
  - the ordering between Groups 1 and 2 is unknown

Shift models for partially ordered groups

Targeting $\theta = 0.30$

- Model $m = 8 : \{\Delta_{32} = 1, \Delta_{31} = 2\}$

Group 3	0.30^{a_8}	0.42^{a_8}	0.54^{a_8}	0.64^{a_8}
Group 2	0.19^{a_8}	0.30^{a_8}	0.42^{a_8}	0.54^{a_8}
Group 1	0.10^{a_8}	0.19^{a_8}	0.30^{a_8}	0.42^{a_8}

- Model $m = 14 : \{\Delta_{32} = 2, \Delta_{31} = 1\}$

Group 3	$0.30^{a_{14}}$	$0.42^{a_{14}}$	$0.54^{a_{14}}$	$0.64^{a_{14}}$
Group 2	$0.10^{a_{14}}$	$0.19^{a_{14}}$	$0.30^{a_{14}}$	$0.42^{a_{14}}$
Group 1	$0.19^{a_{14}}$	$0.30^{a_{14}}$	$0.42^{a_{14}}$	$0.54^{a_{14}}$

Two-stage design

- Stage 1 is rule based until at least one DLT and one non-DLT is observed
  - First patient is assigned lowest dose level
  - Subsequent assignments depend upon maximum assigned dose level
- Let $d_g^{\max}$ indicate the maximum dose level assigned to previously accrued patients in group g

Group	Dose allocation
1 (less frail)	$\min\left\{\max\left(d_1^{\max}, d_2^{\max}, d_3^{\max}\right)+1, K\right\}$
2 (less frail)	$\min\left\{\max\left(d_1^{\max}, d_2^{\max}, d_3^{\max}\right)+1, K\right\}$
3 (most frail)	$\min\left\{d_3^{\max}+1, K\right\}$

Illustration of Stage 1

Table 1: Within trial dose allocation

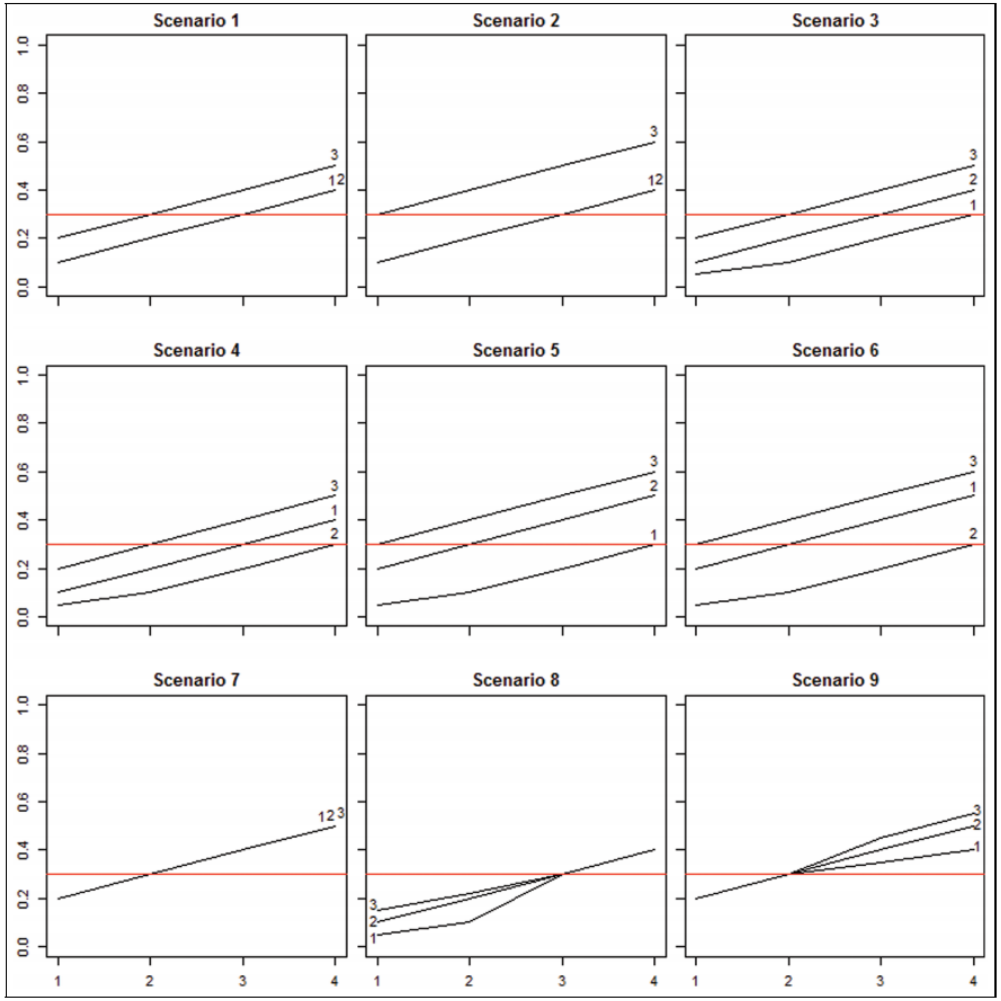
Patient	Group	$d_1^{\max}$	$d_2^{\max}$	$d_3^{\max}$	Dose allocated	DLT
1	3 (most frail)	-	-	-	1	no
2	2 (less frail)	-	-	1	2	no
3	2 (less frail)	-	2	1	3	no
4	3 (most frail)	-	3	1	2	no
5	1 (less frail)	-	3	2	4	yes

End stage 1. Begin stage 2 modeling.

Simulation setup

- Compared shift models with two alternative approaches
  - Independent CRM trials
  - Conaway (*Clin Trials* 2017)
- $\theta = 0.30$; 1000 simulated trials under 9 scenarios
- Overall sample size $N = 45$
- Studied percent of correct MTD selection (PCS) and accuracy index (Cheung, 2011) in each group.
- Also looked at reversals and discrepancies
  - method indicates that there is a group effect when there is none

True dose-toxicity curves studied

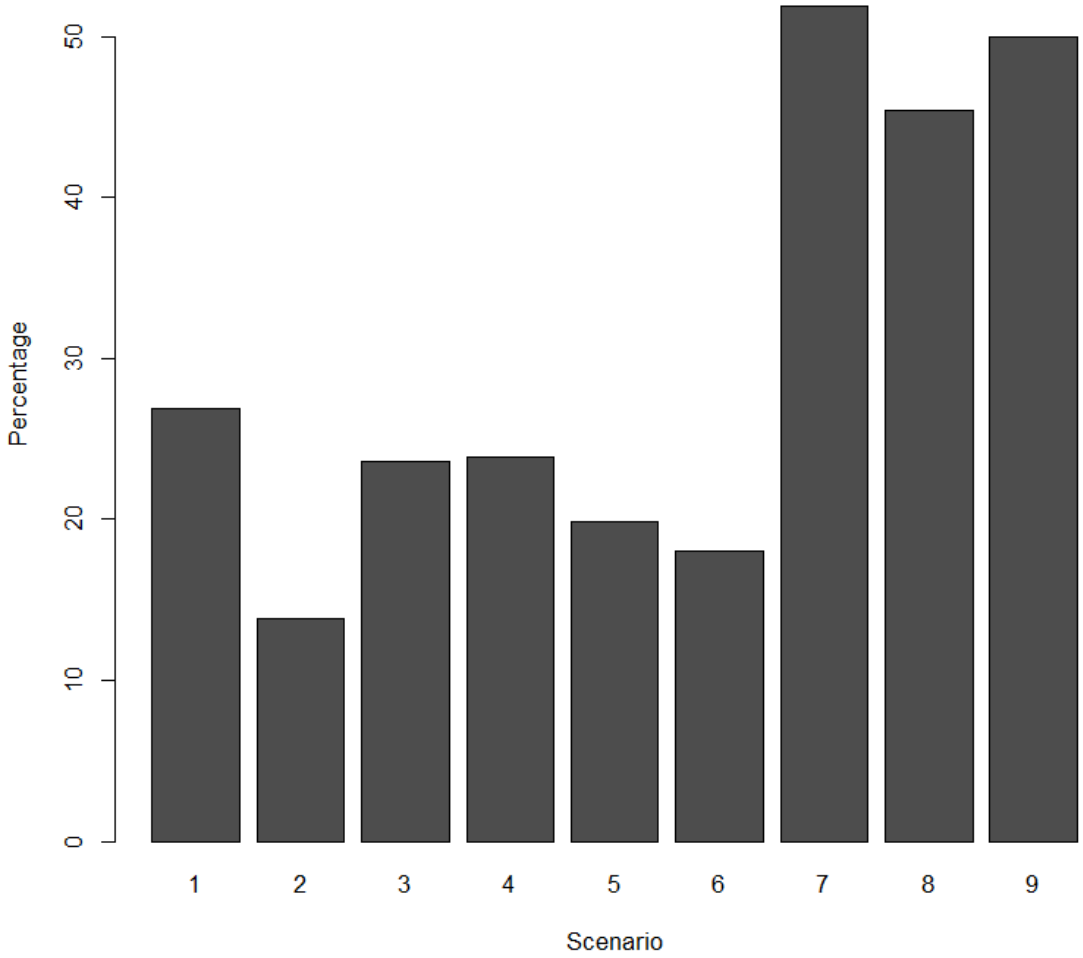


Summary of results

- In every scenario considered, the average PCS across groups was higher in methods for partially ordered groups when compared to running independent CRM trials.
- Average performance between shift models and Conaway (2017) was similar, with a slight edge to the Conaway method.
- These patterns were also observed in metrics for patient allocation
- The shift models are more computationally accessible with R code available
  - use repeated calls to package **dfcrm**

Reversals: independent CRM trials

% of simulated trials with at least one reversal (N=45)



Magnitude of reversals: independent CRM trials

Distribution of most severe reversal.

	Magnitude of reversals				
Scenario	0	1	2	3	4
1	73.1%	15.9%	8.3%	2.1%	0.6%
2	86.2%	10.2%	2.7%	0.6%	0.3%
3	76.4%	16.4%	5.9%	1.1%	0.2%
4	76.1%	16.4%	6.0%	1.2%	0.3%
5	80.1%	13.7%	4.8%	1.4%	0.0%
6	82.0%	11.2%	5.2%	1.3%	0.3%
7	48.1%	24.9%	18.8%	6.8%	1.4%
8	54.6%	25.7%	15.8%	3.4%	0.5%
9	50.0%	27.5%	14.7%	6.5%	1.3%

Discrepancies: independent CRM trials

Estimated group effect when none existed

		Magnitude of discrepancy				
Scenario	Method	0	1	2	3	4
1	Proposed method	36.2%	30.1%	26.0%	7.7%	0%
	Independent CRM trials	22.6%	36.7%	27.2%	11.0%	2.5%
2	Proposed method	22.7%	27.1%	37.3%	13.2%	0%
	Independent CRM trials	12.7%	28.9%	30.4%	23.6%	4.4%
7	Proposed method	37.3%	32.1%	24.2%	6.4%	0%
	Independent CRM trials	6.5%	31.6%	38.1%	20.1%	3.7%
8	Proposed method	36.7%	36.4%	22.4%	4.5%	0%
	Independent CRM trials	10.0%	40.4%	35.5%	11.3%	2.8%
9	Proposed method	31.6%	31.6%	28.4%	8.4%	0%
	Independent CRM trials	6.0%	29.9%	37.1%	22.5%	4.5%

Concluding remarks

- There are few existing methods available for partially ordered groups. The proposed generalization of CRM shift models...
  - performs similarly to Conaway (2017)
  - is more efficient than conducting independent trials in each group
  - avoids the problem of MTD reversal
- The design has the flexibility to handle a variety of group-dose settings
  1. More than 3 groups
  2. Various partial order structures
  3. Varying doses by group

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