Continual Reassessment Method for Partially Ordered Groups

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Outline of Talk

- Background on methods for groups
- Proposed method for partially ordered groups
- Simulation study

Existing methods

- The proposed method is extension of the 2 group shift model
  - O'Quigley and Paoletti (2003)
  - O'Quigley and Iasonos (2014)
- Phase I design for completely or partially ordered treatment schedules
  - Wages, O'Quigley,Conaway (2014)
- Partially ordered groups
  - Conaway (2017)

Example of a group trial

- Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer.
  - Innocenti et al. (2014)
  - Three patient groups defined by *1/*1, *1/*28, and *28/*28 genotypes
  - Greatest DLT risk associated with the *28/*28 genotype
  - Individual group trials implemented using a modified 6+6 design
  - MTD selection followed known ordering information (no reversals)

Reversals in individual trials by group

		MTD Selection				
Group	Grp Identity	All too toxic	1	2	3	4
1	less frail	✓				
2	less frail				✓	
3	most frail					✓

- Reversal of magnitude 4 between groups 1 and 3
- Reversal of magnitude 1 between groups 2 and 3

- What is the final MTD decision for each group?

Process of choosing skeletons

- Skeleton values of length 7 generated with getprior function in the dfcrm package
  - 4 doses and potential shift of 3 dose levels
  - skeleton values: 0.10, 0.19, 0.30, 0.42, 0.54, 0.64, 0.73
- Multiple skeletons generated to allow for different shift patterns

Group	Grp Identity	1	2	3	4
3	most frail	0.10	0.19	0.30	0.42
2	less frail	0.10	0.19	0.30	0.42
1	less frail	0.10	0.19	0.30	0.42

No dose level shifts

Process of choosing skeletons

Dose level shifts of 1, 2, and 3 for Group 3

Group	Grp Identity	1	2	3	4
3	most frail	0.19	0.30	0.42	0.54
2	less frail	0.10	0.19	0.30	0.42
1	less frail	0.10	0.19	0.30	0.42

Group	Grp Identity	1	2	3	4
3	most frail	0.30	0.42	0.54	0.64
2	less frail	0.10	0.19	0.30	0.42
1	less frail	0.10	0.19	0.30	0.42

Group	Grp Identity	1	2	3	4
3	most frail	0.42	0.54	0.64	0.73
2	less frail	0.10	0.19	0.30	0.42
1	less frail	0.10	0.19	0.30	0.42

Process of choosing skeletons

Dose level shifts of 1 and 2 between the groups

Group	Grp Identity	1	2	3	4
3	most frail	0.30	0.42	0.54	0.64
2	less frail	0.19	0.30	0.42	0.54
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1	less frail	0.19	0.30	0.42	0.54

Process of choosing skeletons

- 16 skeletons generated to allow for different shift patterns
- Use one parameter power model as a working model for the probability of toxicity for each group and dose level
- Select the skeleton that maximizes the likelihood
- Within groups, identify the dose with probability of toxicity closest to the target

First stage considerations for Partially Ordered Groups

- Patient group order is random
- A ”less frail“ (groups 1 and 2) patient can receive the highest dose observed +1
- A ”most frail“ (group 3) patient can receive the highest dose observed among patients in group 3 +1

Patient	Group	Grp Identity	Dose	DLT
1	3	most frail	1	no
2	2	less frail		
3	2	less frail		
4	3	most frail		
5	1	less frail		
⋮	⋮	⋮		

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Patient	Group	Grp Identity	Dose	DLT
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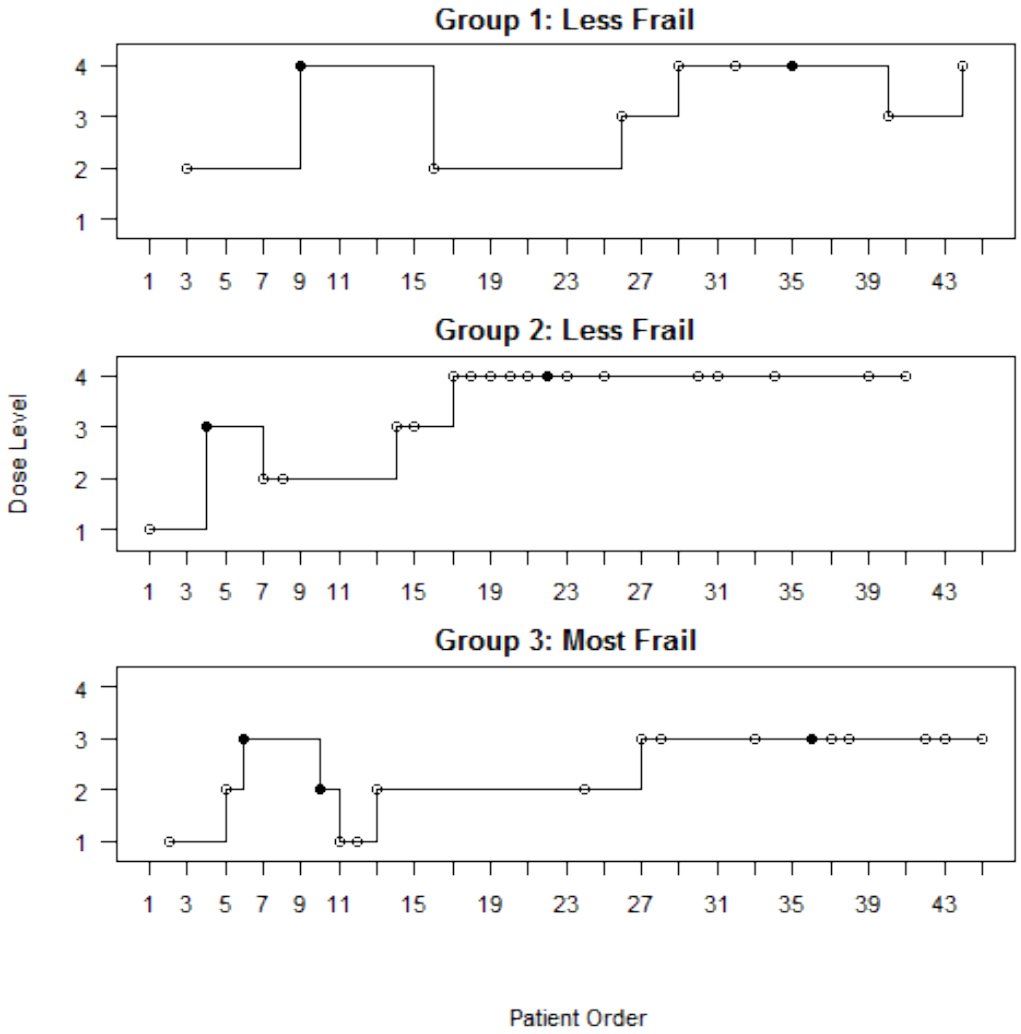
2	2	less frail	2	no
3	2	less frail	3	no
4	3	most frail	2	no
5	1	less frail	4	yes
End stage 1. Begin modeling.				

Individual trial

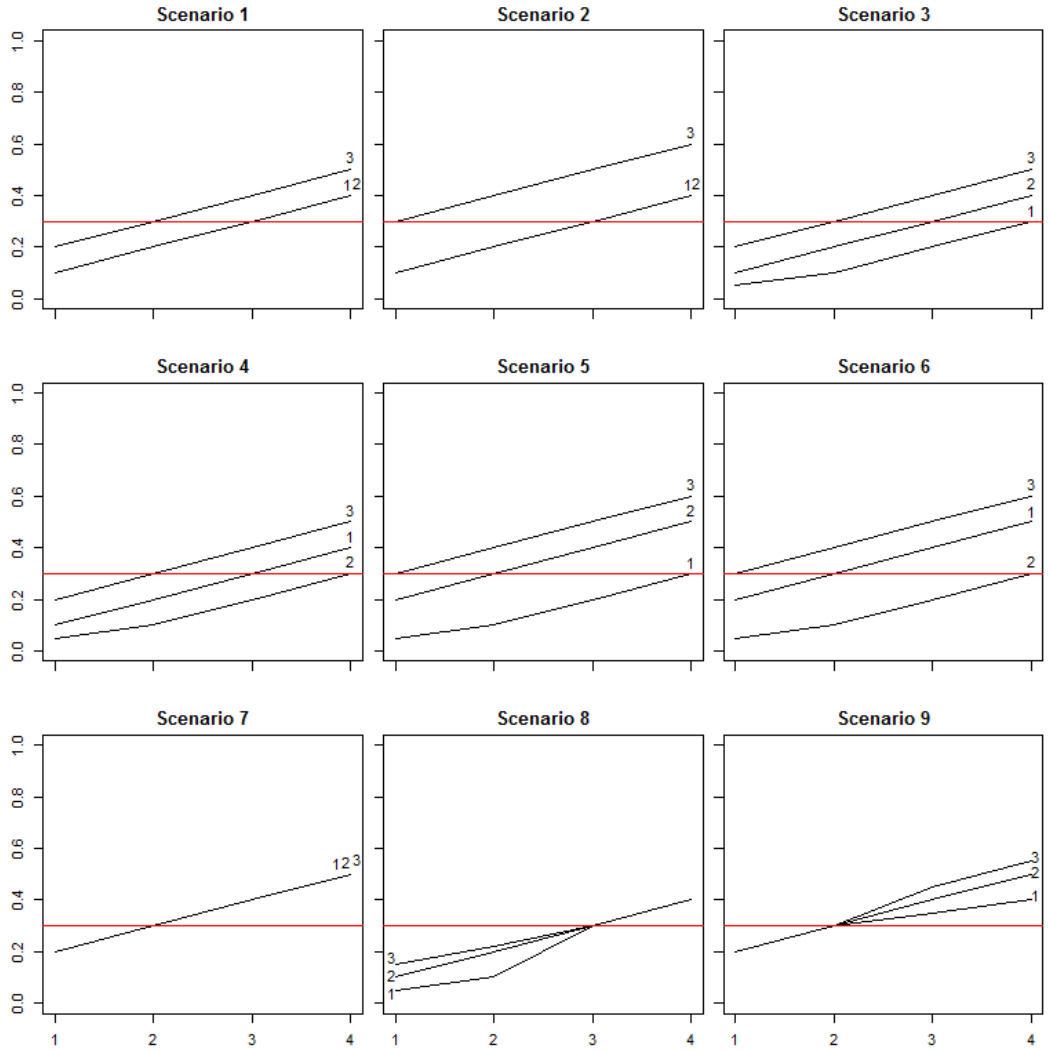


Simulation setup

- 3 groups
  - Group 3 has greatest DLT risk
  - Unknown order between groups 1 and 2
- 4 dose levels
- Target DLT rate, $\theta = 0.3$
- 1,000 simulated trials
- Sample size of 45 overall
  - Group sizes are random
- Same simulated data used for both methods

Dose-toxicity curves

- 9 scenarios considered



Comparisons to be made

- Dose finding methods
  - Proposed CRM for partially ordered groups
  - Individual CRM trials by group
- Method of comparison
  - Reversals
  - Percentage of correct selection (PCS)
  - Accuracy index (AI) (Cheung, 2011)
    - For dose selection and subject allocation

Reversals

- CRM for partially ordered groups cannot have reversals
- Individual trials by group can have reversals
  - May observe 0 to 2 reversals
  - Magnitude of reversal ranges from 1 to 4 dose levels

Reversals in individual trials by group

		MTD Selection				
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1	less frail	✓				
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- Reversal of magnitude 4 between groups 1 and 3
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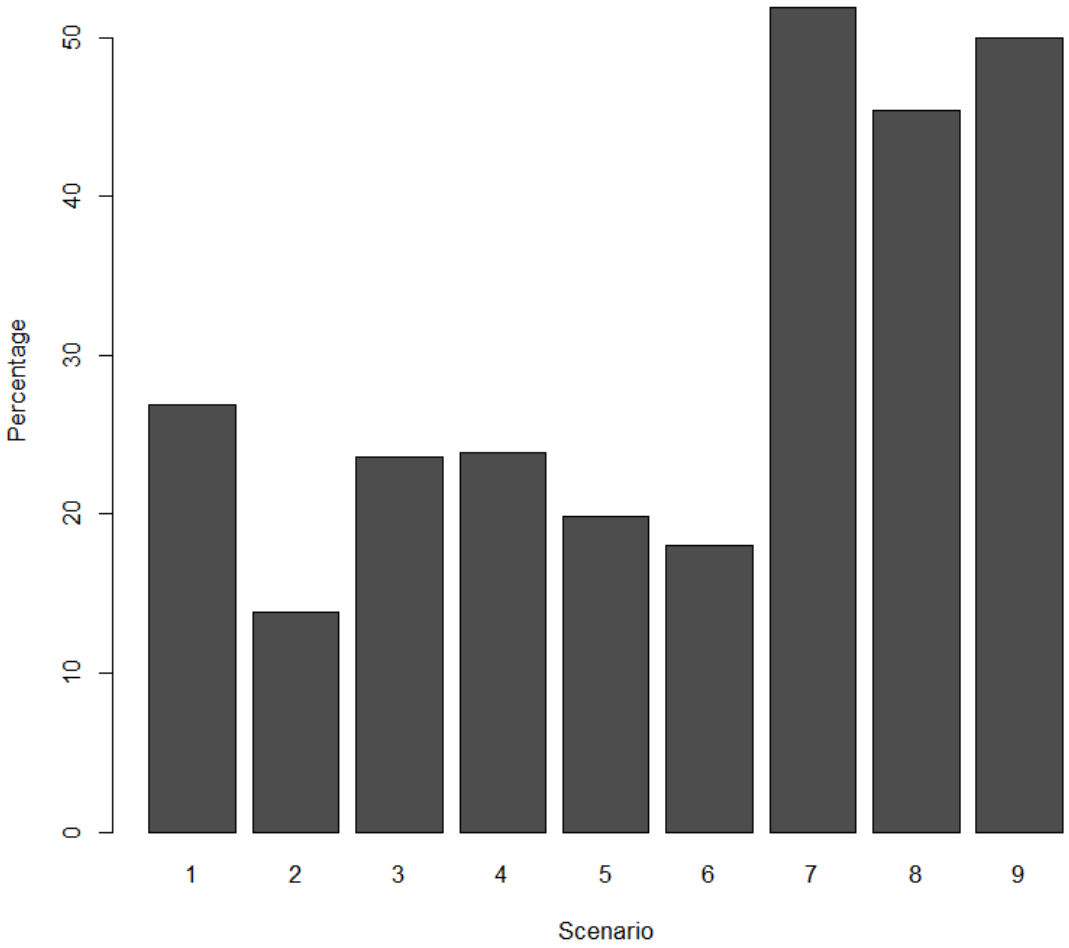
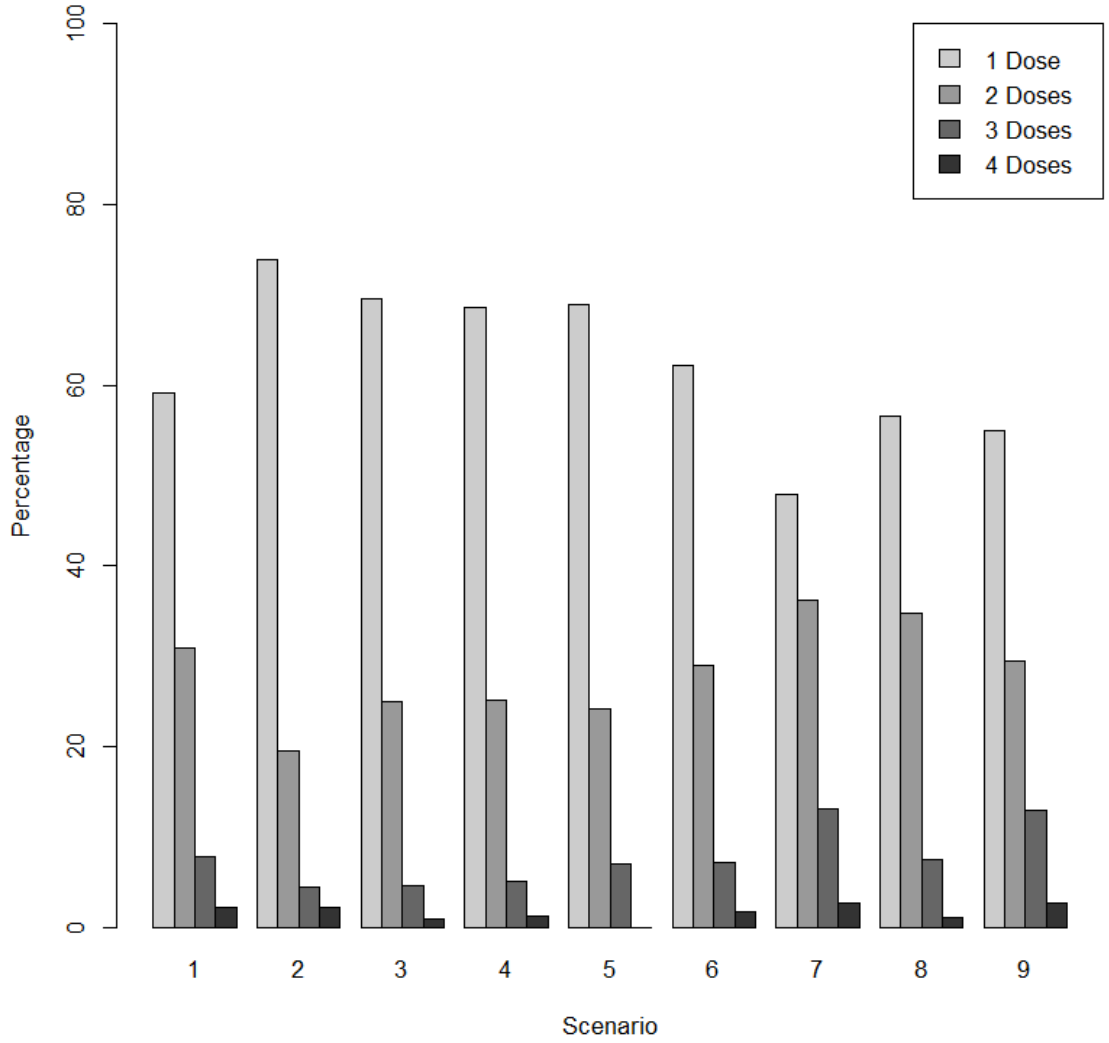
- What is the final MTD decision for each group?

Reversals in individual trials by group



- Scenarios 2 - 6
- More distance between true group MTDs
- Scenarios 7 - 9
- All groups have same true MTD

Reversals in individual trials by group



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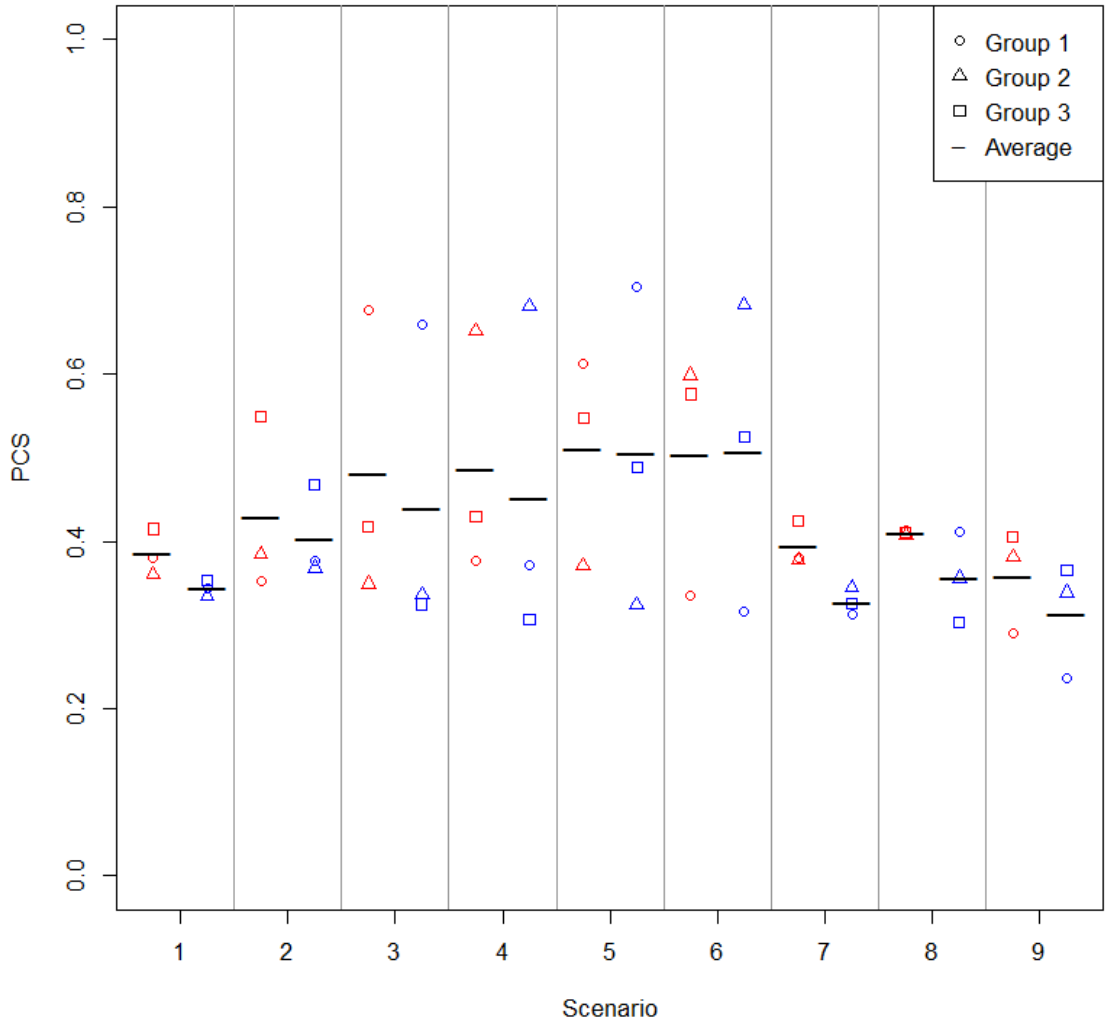
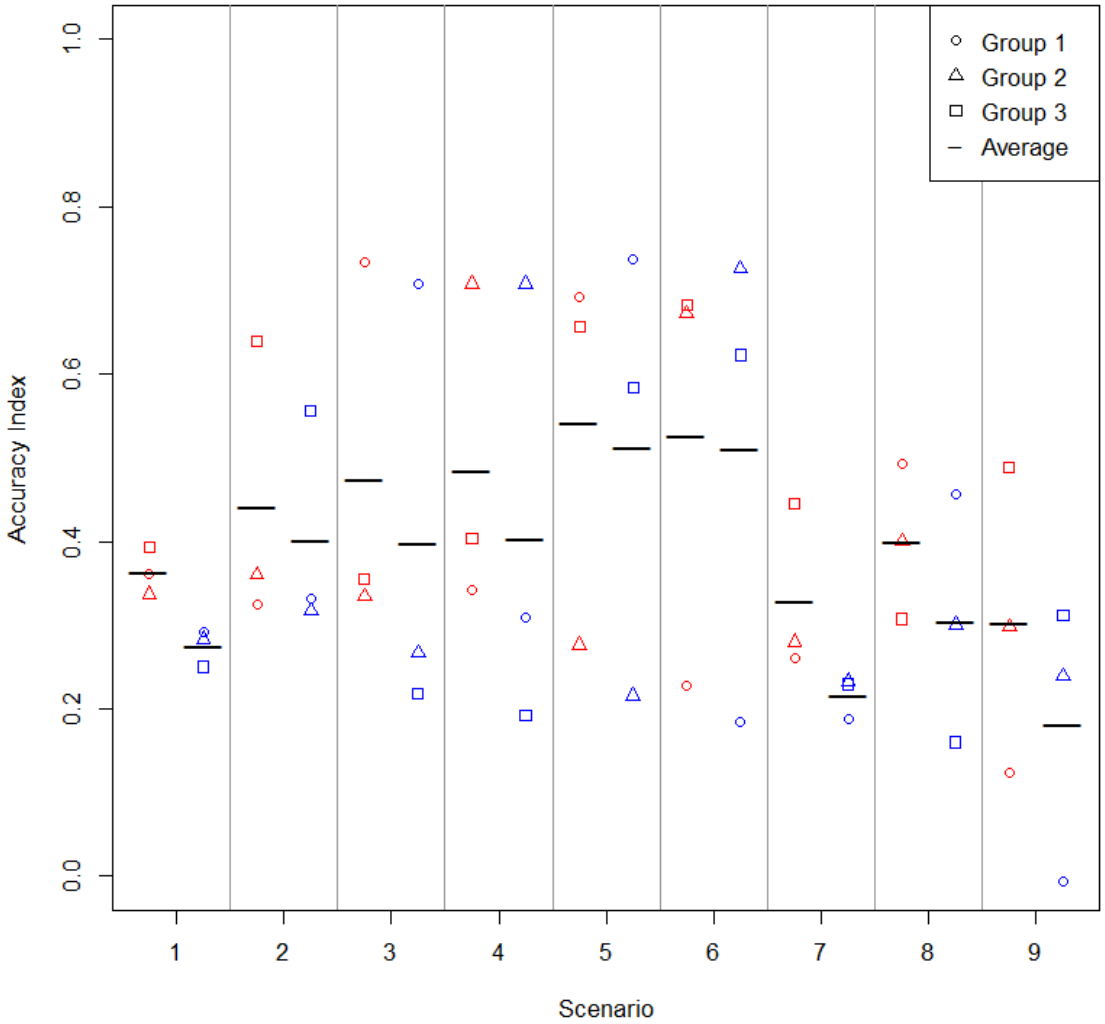
Percentage of correct selection



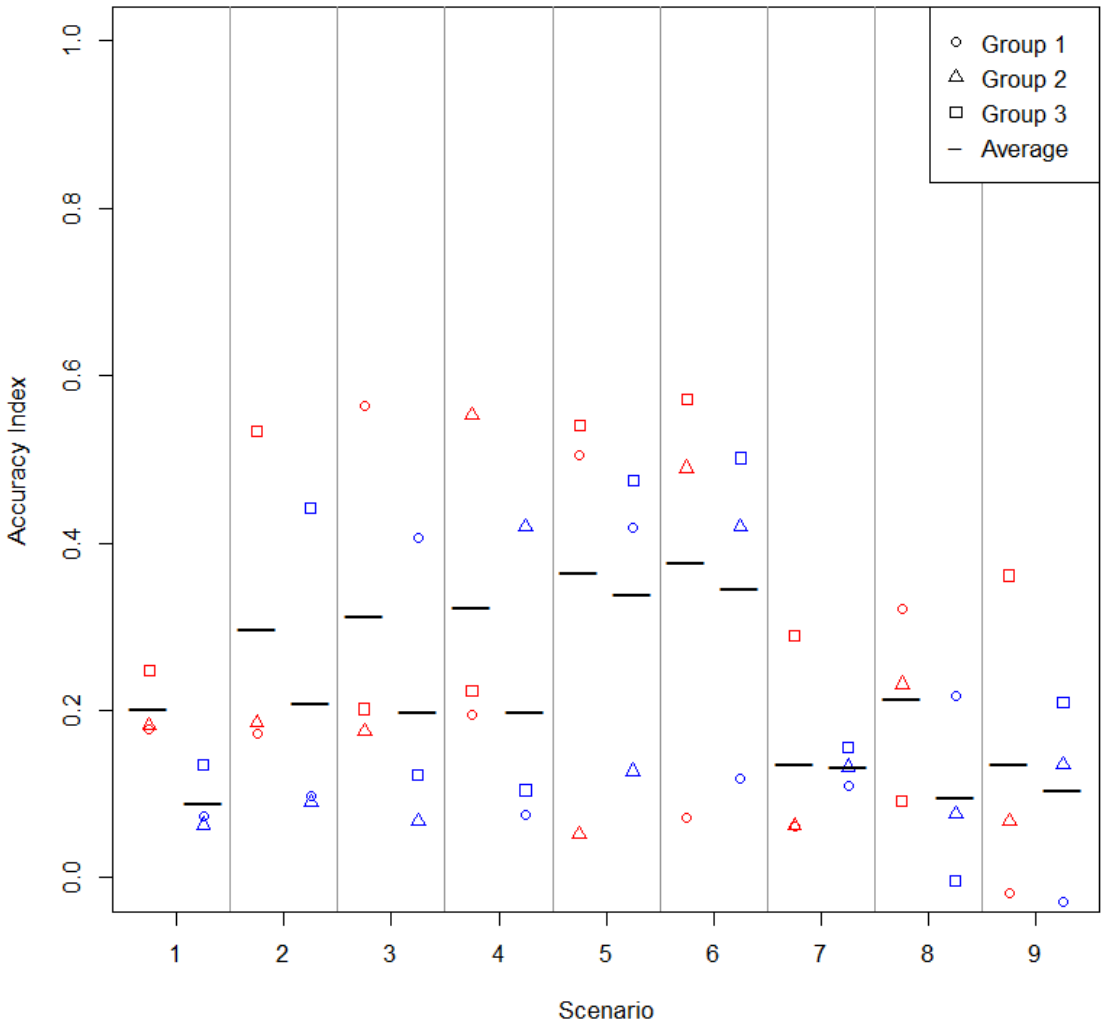
- Scenarios 2 - 4
- Max. shift of 2 dose levels
- Scenarios 5 - 6
- Max. shift of 3 dose levels
- Scenarios 7 - 9
- All groups have same true MTD

Accuracy index for dose selection



- Scenarios 2 - 4
- Max. shift of 2 dose levels
- Scenarios 5 - 6
- Max. shift of 3 dose levels
- Scenarios 7 - 9
- All groups have same true MTD

Accuracy index for subject allocation



- Scenarios 2 - 4
- Max. shift of 2 dose levels
- Scenarios 5 - 6
- Max. shift of 3 dose levels
- Scenarios 7 - 9
- All groups have same true MTD

Dose-toxicity curves

- Limited options with partially ordered groups
- Reversals are a common problem when using independent trials by group
  - Creates a need for additional decision rules
  - Ignoring reversals is not a good option
- PCS and AI have better properties for the proposed CRM for partially ordered groups