A new Bayesian adaptive decision-theoretic design for multi-arm multi-stage clinical trials illustrated by an application in exercise oncology

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Disclosure slide

Disclosures

- I am seconded for 0.4 FTE to the Dutch Medicines Evaluation Board (CBG-MEB) as a methodology assessor
- I do not have any disclosures that are relevant for the presented work
- I here present my personal views

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Outline

- Motivation

- Outline of the methodology

- Simulation studies and results

- Retrospective application to a trial in exercise oncology

- Concluding remarks

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Motivation

- Rapid increase in available treatments (in development/approved/used in practice)
- A large proportion of phase III trials is negative (in oncology approximately 65%[1])
- Long timespan until approval of new drugs (10-15 years)
- Most phase II trials are single-arm trials and most phase III trials are two-arm trials
- How to compare effectiveness of different treatments that are all standard of care?

There is a clear need for more efficient trials that compare multiple treatment options and use decision-criteria that fit a trial's objective

[1] Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019 Apr 1;20(2):273-286. doi: 10.1093/biostatistics/kxx069. Erratum in: Biostatistics. 2019 Apr 1;20(2):366.

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Outline of methodology: Trial design

Multi-arm multi-stage design: equal randomization to active treatment arms in each stage
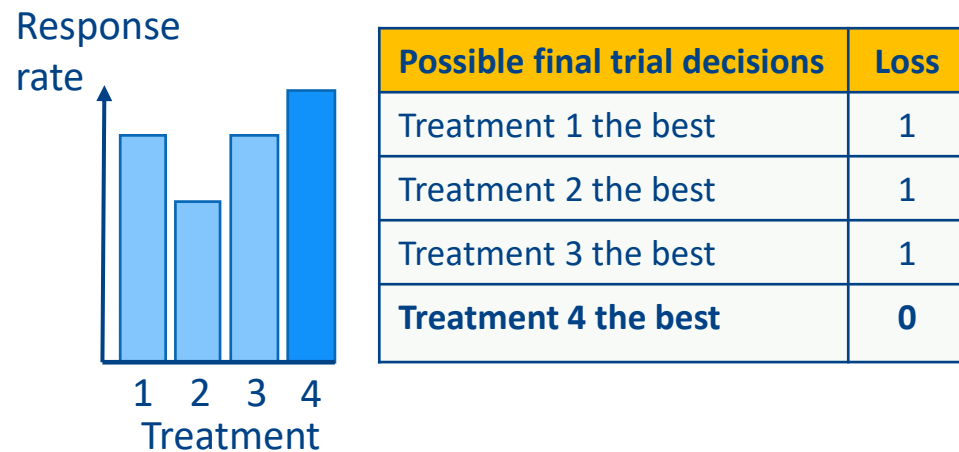
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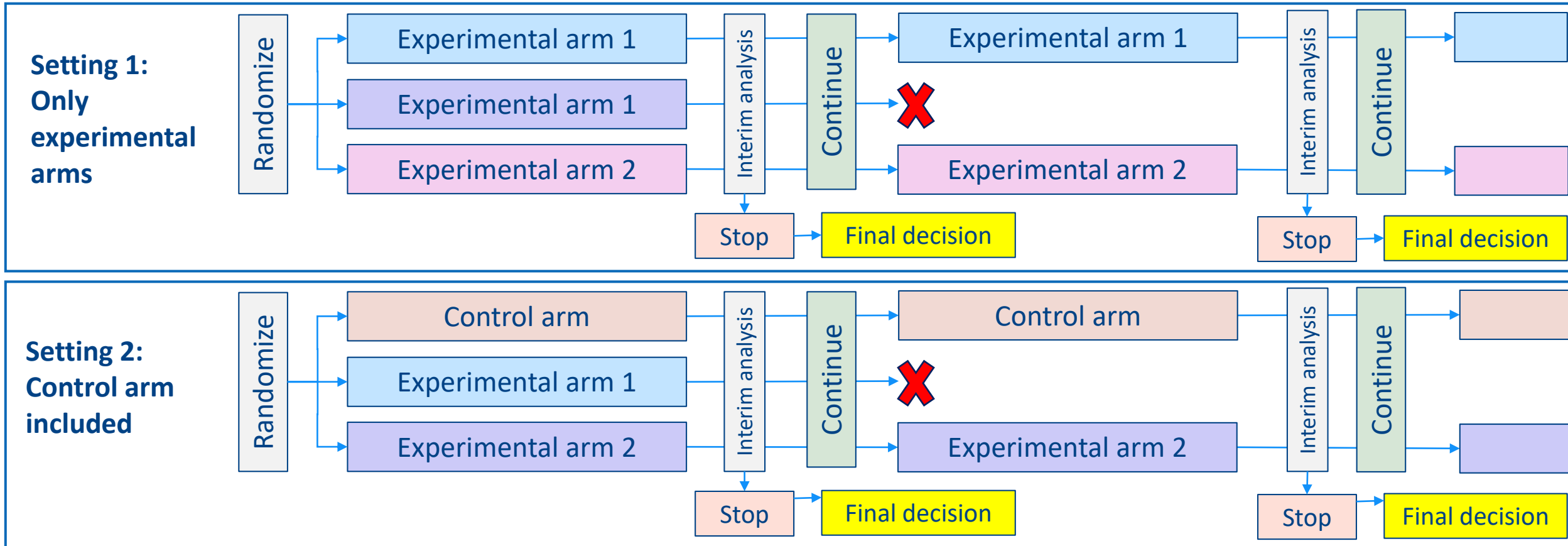
Outline of methodology: Decision-theoretic framework

Loss functions

Bassi et al. (SMMR, 2020): 0-1 loss function with loss of 1 for incorrect decisions and loss of 0 for correct decision: expected loss is probability of making an incorrect final decision

Setting 1: Pick-the-winner

Select the experimental treatment with highest response rate

Possible final trial decisions	Loss
Treatment 1 the best	1
Treatment 2 the best	1
Treatment 3 the best	1
Treatment 4 the best	**0**

Setting 2: Pick-all-treatments-superior-to-control

Select all experimental treatments that outperform the control treatment by an absolute margin of δ

Possible final trial decisions	Loss
Neither treatment 1 nor 2 superior to control	1
Only treatment 1 superior to control	1
Only treatment 2 superior to control	**0**
Treatment 1 and 2 superior to control	1

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Outline of methodology: Interim analyses

Model

- Response of subject in treatment arm j: Bernoulli distributed with probability p_j
- Independent, non-informative uniform priors for p_j ($j = 1, .., T$)

Interim analyses

- Equal number of subjects per stage (expect for first)
- **One-stage ahead approach**, comparing
  - Expected loss in case of <u>stopping now</u> and making a final decision
  - Expected loss in case of <u>continuing for a single stage</u> and making a final decision:
    - Keeping all active arms in the trial
    - After dropping a single treatment arm from the trial
- Based on economic principle of diminishing returns: **Continue trial when the reduction in expected loss exceeds a predefined threshold**
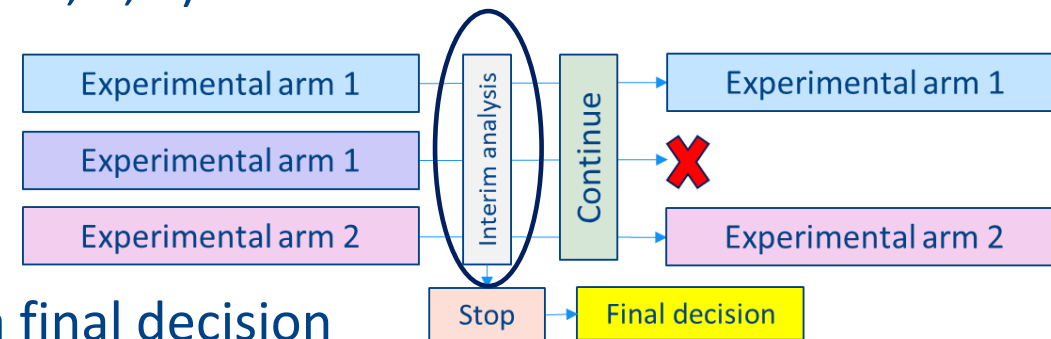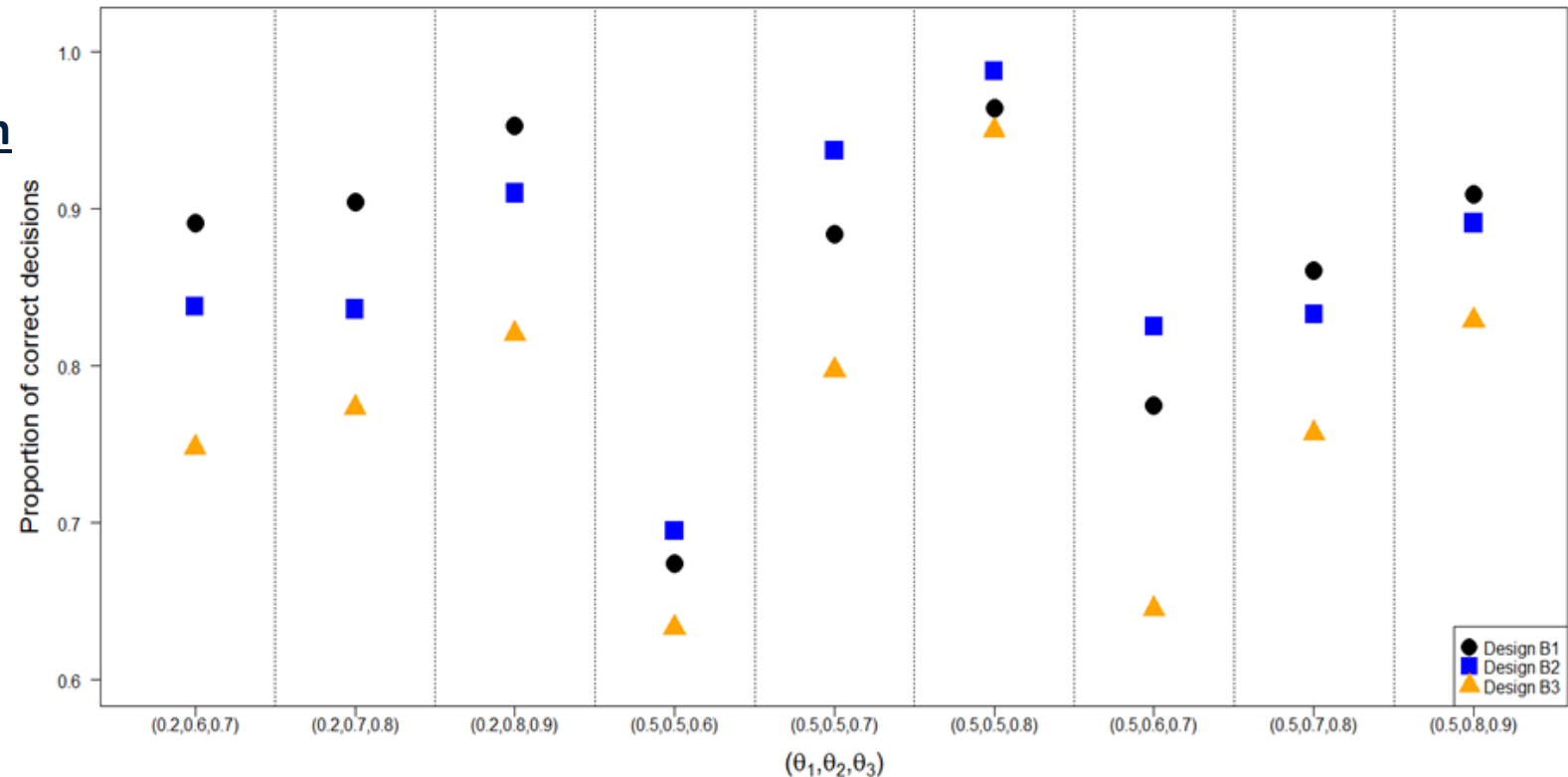
Simulation studies and results: Experimental arms only

- **Pick-the-winner**: 3 treatment arms
- Threshold for continuation fixed at 1/2500 for design B1
- Designs B2 and B3 matched in terms of (expected) sample size
- 12 subjects per stage

Design B1: Bayesian adaptive decision-theoretic design **with dropping** of arms

Design B2: Bayesian adaptive decision-theoretic design **without dropping** of arms

Design B3: Single stage (**non-adaptive**) Bayesian decision-theoretic design

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8

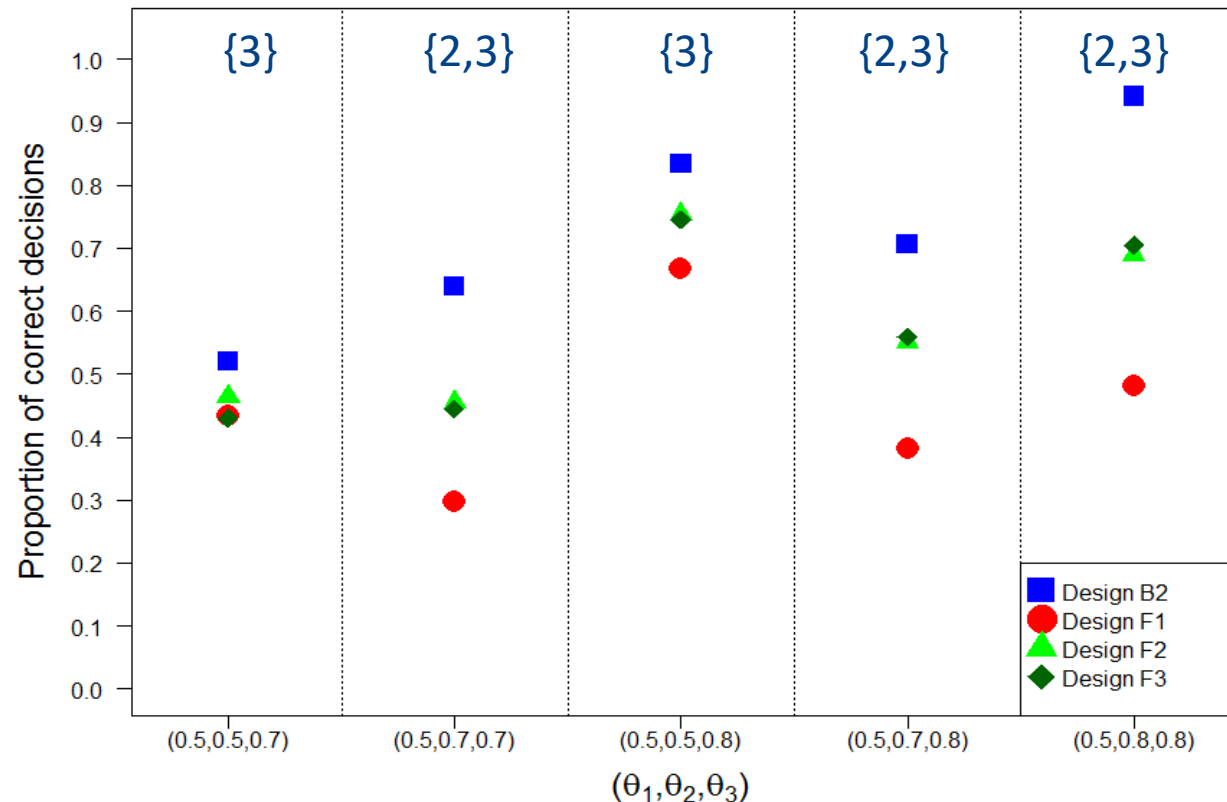# Simulation studies and results: Comparison to control

- **Pick-all-treatments-superior-to-control:** 2 experimental arms and 0.15 margin
- Threshold tuned for design B2 to have overall type I error of 5% (one-sided testing)
- Frequentist designs F1, F2 and F3 matched to B2 on (expected) sample size
- 12 subjects per stage, 24 in first stage
- Arm 1 is the control arm

Design B2: **Bayesian adaptive decision-theoretic** design **without dropping** of arms

Design F1: **Single-stage**, Dunnett's procedure

Design F2: **Two-stage procedure** of Urach and Posch, O'Brien Fleming spending function

Design F3: **Two-stage procedure** of Urach and Posch, Pocock spending function

Simulation studies and results

Simulations showed increased efficiency compared to single- and two-stage designs through:

- Adaptive stopping when probability of an incorrect decision is not expected to sufficiently reduce in the next stage
- Dropping of arms, provided that differences between the arms are large

Simulations (not presented here) further showed that:

- Frequentist two-stage procedures required average trial sizes that were 14%-67% higher (matching proportion of correct decisions)
- In pick-the-winner setting with up to five arms proportions of correct decisions of >80% could be obtained with average trial sizes of 100-150

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Retrospective application: PACES trial

- Trial included 230 patients with breast cancer receiving adjuvant therapy
- Compared 2 exercise programmes to usual care
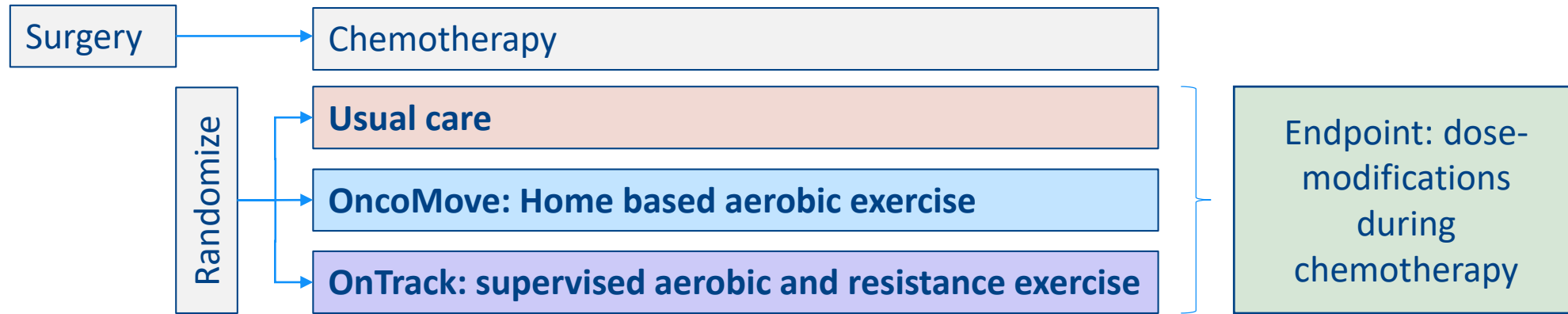
- Endpoint: dose-modifications for chemotherapy (yes/no)
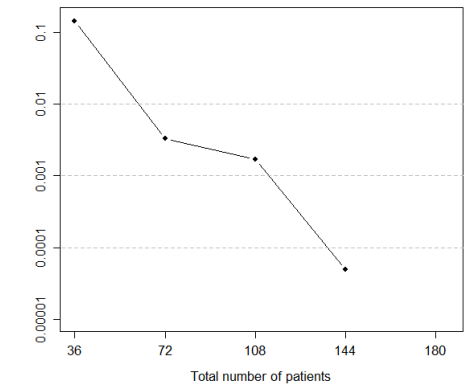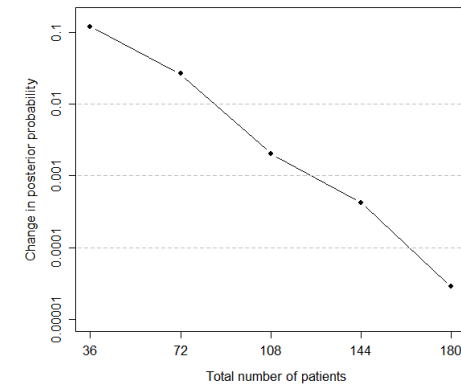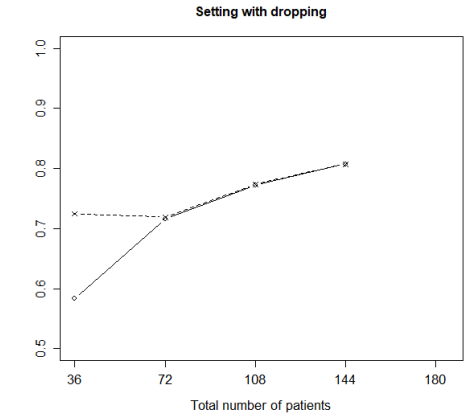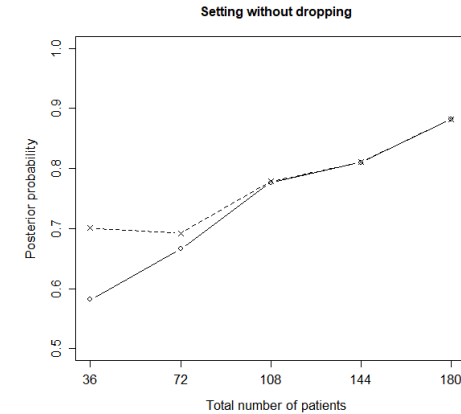
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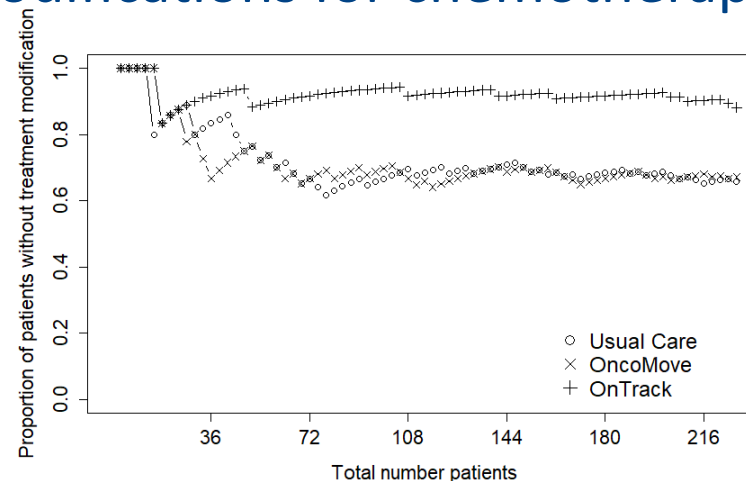
Retrospective application: PACES trial

Reanalysis using Bayesian adaptive decision-theoretic method

- 36 patients per stage

- Pick-all-treatments-superior-to-control setting with absolute margin of 0.10

- Total trial size between 108 and 180 depending on threshold for continuation and dropping of arms

Threshold for continuation	Reanalysis of PACES trial data		Type 1 error probability evaluation[a]	
	Number of patients included in the trial	Posterior probability that only OnTrack was superior to UC	Average trial size	Type 1 error probability
Without arm dropping				
0.01	108	0.777	139	9.7%
0.001	144	0.810	195	5.3%
0.0001	180	0.881	250	2.5%
With arm dropping				
0.01	72	0.713	126	18.4%
0.001	144	0.814	174	16.3%
0.0001	144	0.814	216	14.3%

Concluding remarks

- We introduced a general Bayesian-adaptive decision-theoretic framework for multi-arm multi-stage trials

- We focused on binary loss functions, focusing on the posterior probability of a correct final decision

- Control of type I error possible, but requires tuning of threshold in combination with sample size for first stage (latter in presence of dropping of arms)

- Efficiency shown in various settings and scenarios

- Currently applied in multi-arm AMICO trial: Aerobic fitness or Muscle mass training to Improve Colorectal cancer Outcome

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Bayesian adaptive decision-theoretic designs for multi-arm multi-stage clinical trials

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Check for updates

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ORIGINAL ARTICLE

A Bayesian-adaptive decision-theoretic approach can reduce the sample sizes for multiarm exercise oncology trials

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