Incorporating the direct assignment option into broader design frameworks

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Outline

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The Design with Direct Assignment Option

- Two-stage Phase II design
- 2 treatment arms: experimental and control
- Binary outcome (e.g. tumor response)
- Stage I: randomize
- Possible decisions at interim analysis (IA):
  1. stop early for efficacy
  3. continue to Stage II, with randomization
  4. stop early for futility

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- 2 treatment arms: experimental and control
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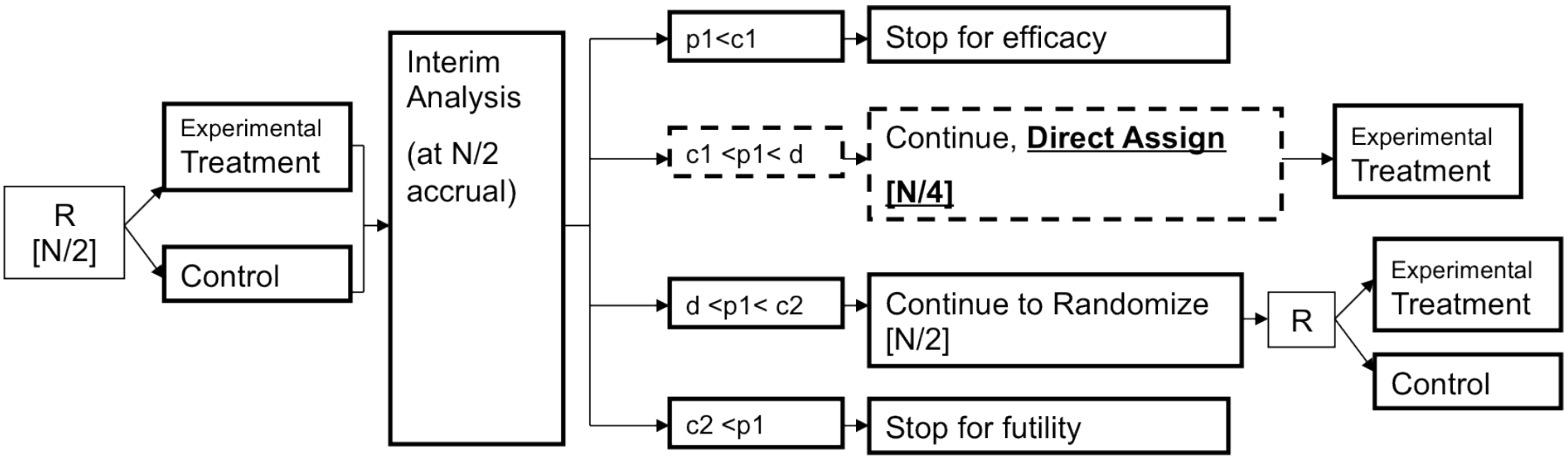
- Possible decisions at interim analysis (IA):
  1. stop early for efficacy
  2. continue to Stage II, with direct assignment of patients to experimental treatment
  3. continue to Stage II, with randomization
  4. stop early for futility

The Design with Direct Assignment Option:

Schematic

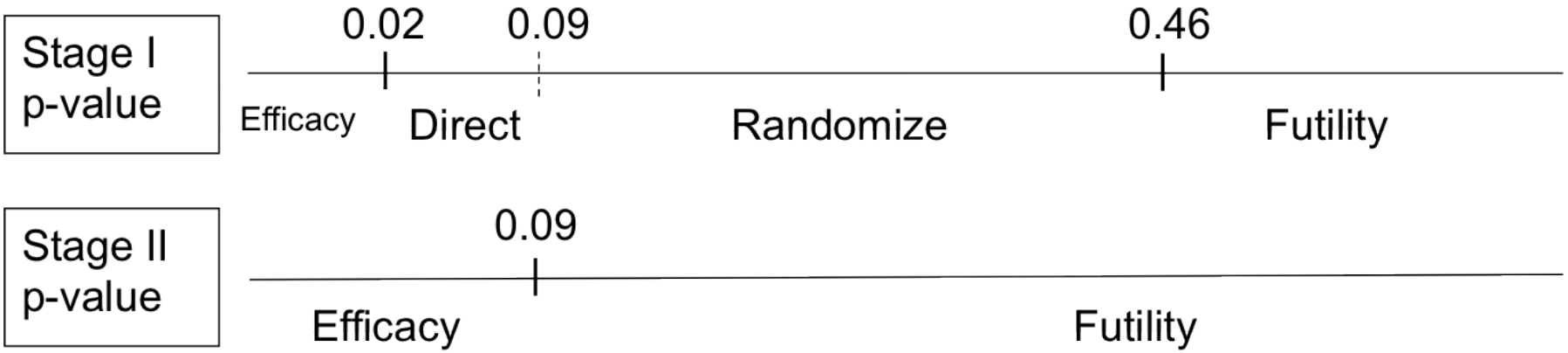


- N = total planned sample size for trial
- [ ] = number of patients enrolled
- p_1 = Stage I p-value
- c_1, c_2, d: O'Brien-Fleming cut-offs

Note: Effective trial accrual depends on decision, smaller accrual if direct design adopted

The Design with Direct Assignment Option:

Using O-F Cutoffs (example for overall $\alpha = 0.10$)



N = 101

The Design with Direct Assignment Option:

Simulation Study Results (summary)

1. Design with Direct Option vs. Balanced Randomized
   - Power: minimal loss
   - T1ER: minimal inflation

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2. Sensitivity Analyses
   - Population shift
     - Risk of false trial conclusions relatively minor
   - Unbalanced randomization
     - 4:1 Randomized Design marginally more powerful than Design with Direct Option

The Design with Direct Assignment Option:

A few remarks

The option to direct assign:

- arose from thinking about the biomarker-based therapy setting (where a treatment is thought to be "very effective" in a specific subpopulation)
- is actually a *flexible design component* that can be incorporated into many existing design frameworks, in a variety of settings (not limited to biomarker-based therapies)

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We consider 2 examples:

- Multiple interim analyses (IA)
- Multiple subgroups

Outline

Multiple IA with direct assignment option:

Motivation

- In the phase II setting,
  - many have argued that a *single* IA may be inadequate
    - $\Rightarrow$ multiple looks may improve both statistical and ethical properties of design
  - a trial with IA has the opportunity to terminate early
    - $\Rightarrow$ potentially resulting in cost savings and earlier delivery of effective treatments to patients
- The design with direct assignment option was introduced with a single IA.

$\Rightarrow$ We apply the design with direct assignment option to the setting with *two IA*.

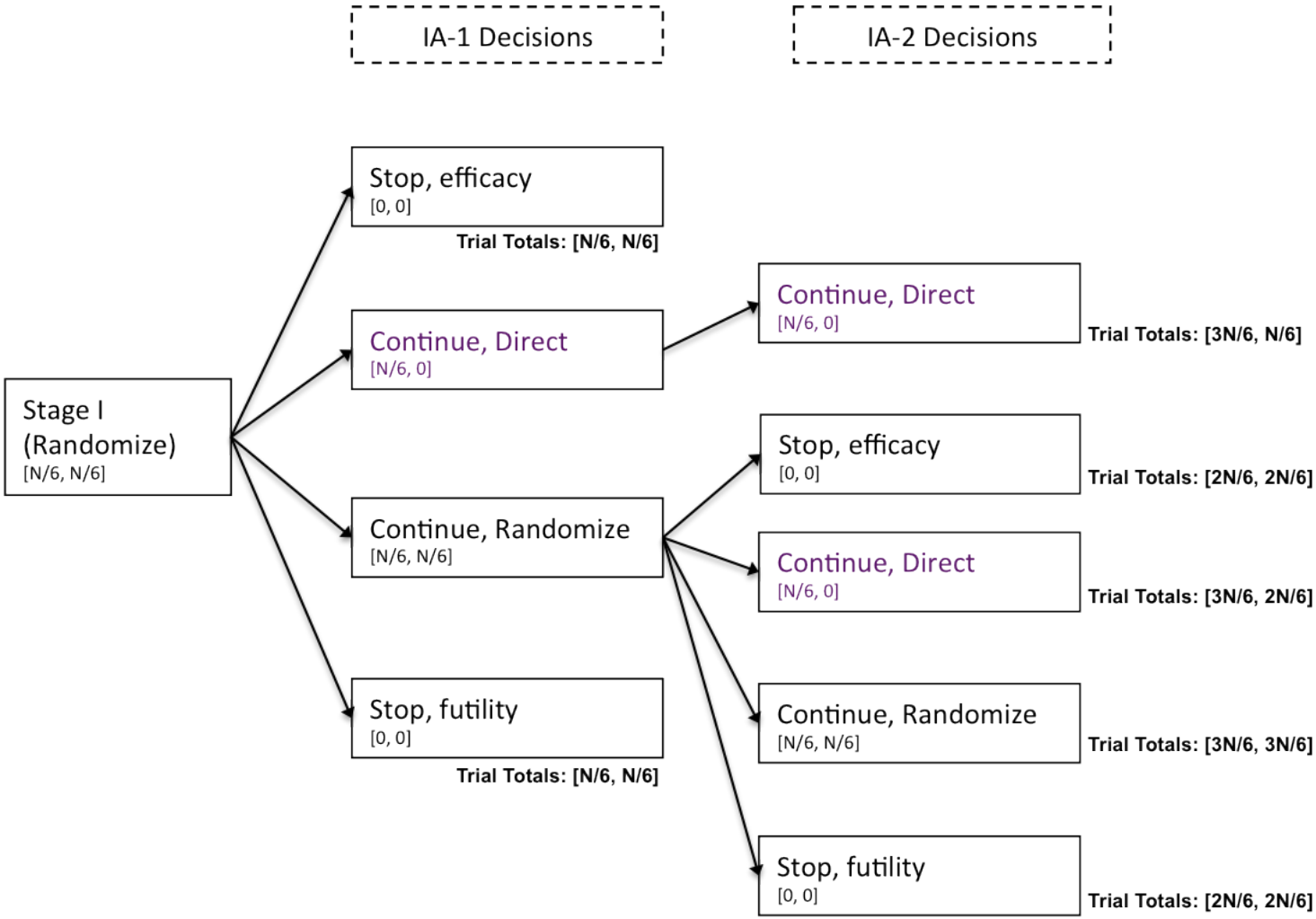
Multiple IA with direct assignment option:

Design Framework

- Timing: IA at 1/3 and 2/3 accrual
- Decision Set at first IA (IA-1):
  - Stop, futility
  - Continue, random
  - Continue, direct
  - Stop, efficacy
- Decision Set at second IA (IA-2):
  - depends on decision at IA-1 and data available at IA-2

Multiple IA with direct assignment option:

IA Decision Sets with Enrollment Numbers: [Active, Control]



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Multiple IA with direct assignment option:

Simulation Study

Simulated $6,000$ trials.

Fixed parameters:

- Response rate in control group: 0.20
- Nominal power: 80%
- Timing of IA: 1/3 and 2/3 accrual

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Variable parameters:

- Significance level (α): 0.10, 0.20
- Response Rate Ratio (RRR) = response rate in experimental treatment / response rate in control (i.e. treatment effect) = 2.00, 2.20, 2.40, 2.60, 2.80, and 3.00

For each α-level, sample sizes and O'Brien-Fleming cutoffs were determined based on RRR = 2.0, 80% power, and IA after 1/3 and 2/3 accrual.

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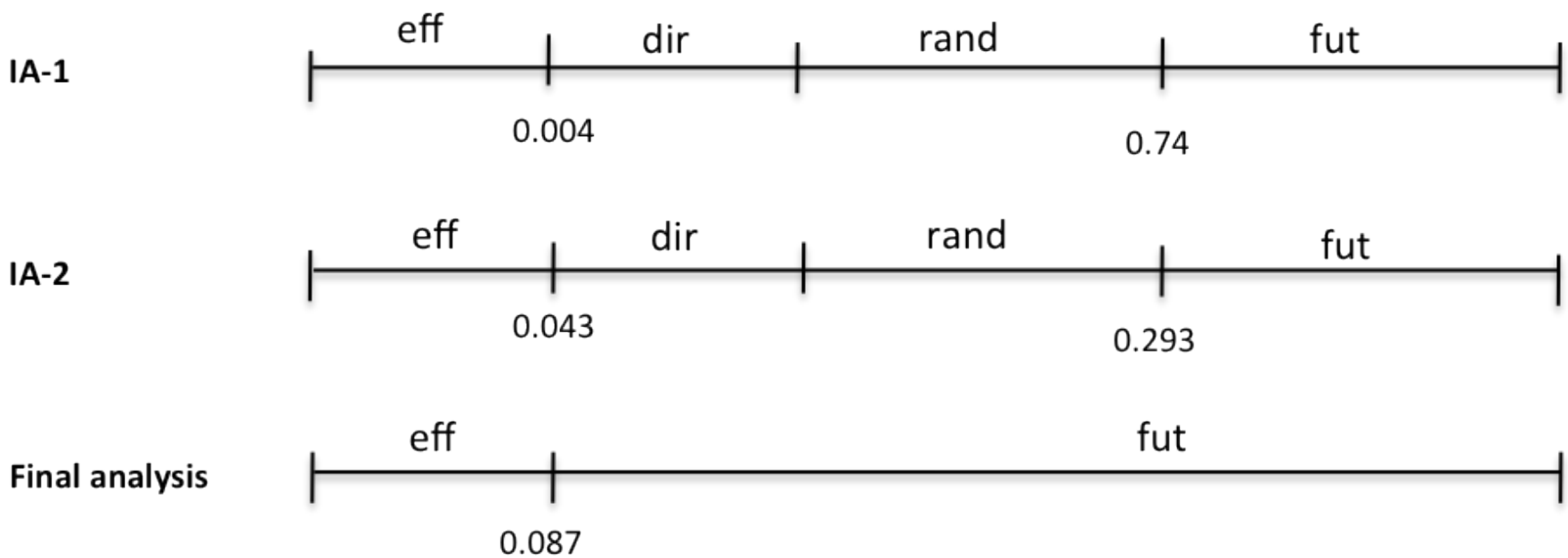
Multiple IA with direct assignment option:

O-F cutoffs and sample size



N = 98 patients

based on: $\alpha = 0.10$, $1 - \beta = 0.80$, and RRR = 2.0 (drawing not to scale)

Multiple IA with direct assignment option:

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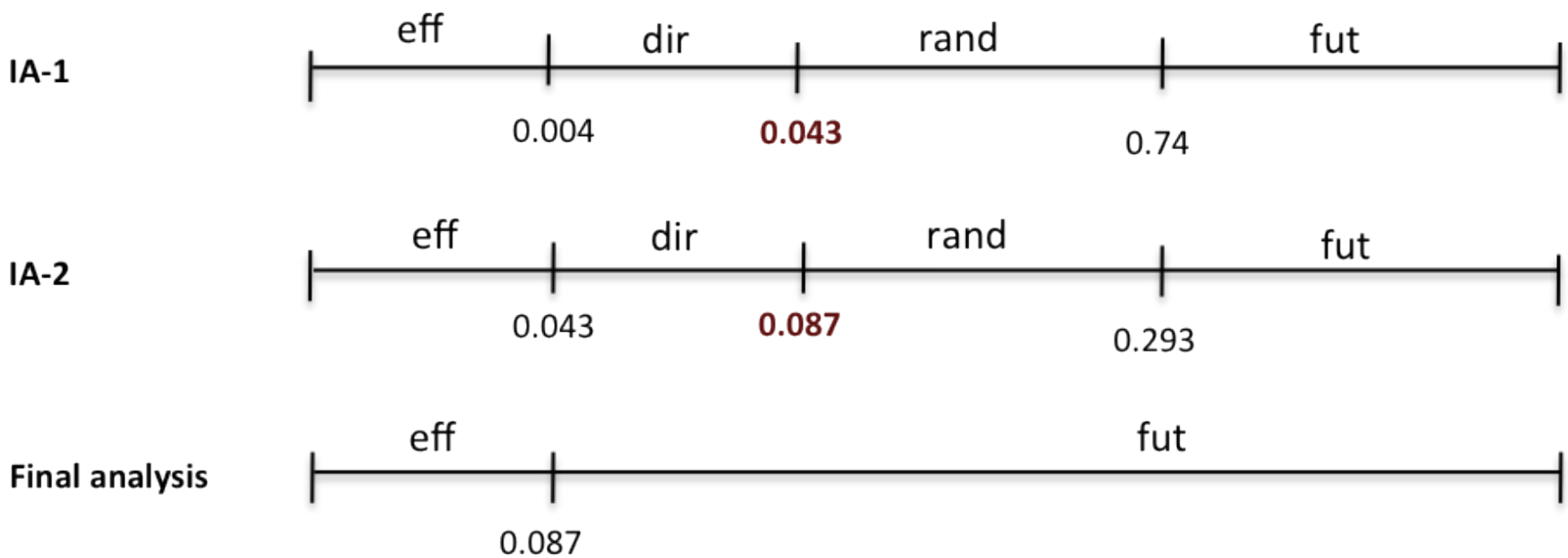

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Multiple IA with direct assignment option:

Simulation Study Results

Outcomes:

- Statistical properties
  - Power
  - Type I Error Rate
- Clinical properties
  - expected accrual, lower is better
  - expected ratio of patients treated with active vs. control, higher is better
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Compared for 3 designs:

1. Direct Assignment Design with two IA (DAD-2)
   -of primary interest
2. Direct Assignment Design with one IA (DAD-1)
   -for comparison
3. Balanced Randomized Design with two IA (BRD-2)
   -for comparison

Multiple IA with direct assignment option:

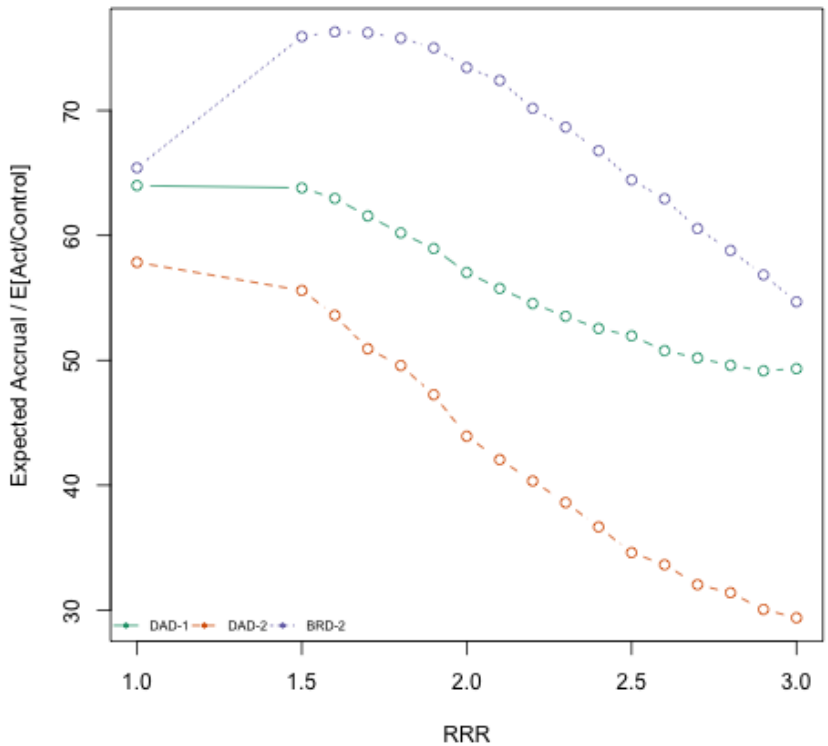
Simulation Study Results (statistical properties)

	RRR	2-IA Direct Design (DAD-2)	1-IA Direct Design (DAD-1)	2-IA Balanced Randomized Design (BRD-2)
Power	2.0	77.4	78.3	78.7
	3.0	99.4	99.6	99.7
Type I Error Rate	1.0	10.9	10.8	9.3

$\Rightarrow$ DAD-2 has desirable statistical properties (i.e. reasonably minimal power loss, type I error rate inflation)

Multiple IA with direct assignment option:

Simulation Study Results (clinical properties)



- BRD-2: Balanced Randomized Design with two IA (blue / top)
- DAD-1: Direct Assignment Design with one IA (green / middle)
- DAD-2: Direct Assignment Design with two IA (orange / bottom)

$\Rightarrow$ DAD-2 has desirable clinical properties

Multiple IA with direct assignment option:

Considerations

- Tradeoff between extra time required to collect data at IA vs. clinical gains
  - $\Rightarrow$ DAD-2 more appropriate (than DAD-1) when endpoint can be observed in reasonably short amount of time
- Other possible decision sets (e.g. no option for direct assignment at first IA) - statistical properties preserved, but clinical gains only modest

Outline

Multiple subgroups with direct assignment option:

Motivation

- In some therapeutic settings, we may expect treatment heterogeneity across subpopulations identified by some factor.
  - $\Rightarrow$ interested in treatment effect within multiple subgroups
- The design with direct assignment option was introduced for a single cohort.

$\Rightarrow$ We apply the design with direct assignment option to the setting with *two predefined subgroups*.

Multiple subgroups with direct assignment option:

Setting

Consider:

- Binary outcome (e.g. tumor response, 6-month progression-free status)
- 2 treatment arms: experimental and control
- Two subgroups, say M^- and M^+

Multiple subgroups with direct assignment option:

Testing Strategy

- (separate) Tests for subgroup main effects
  - $M^- : \Delta_- = p_{\text{exp}}/p_{\text{ctl}}$
  - $M^+ : \Delta_+ = p_{\text{exp}}/p_{\text{ctl}}$
  - Power: 80%; Significance Level (α): 0.20

  where p_{exp} is response rate on experimental arm, and p_{ctl} is response rate on control arm
    * Trial powered for this test.
    * Essentially a stratified design.

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  where p_{exp} is response rate on experimental arm, and p_{ctl} is response rate on control arm
    * Trial powered for this test.
    * Essentially a stratified design.
- Post-hoc test for subgroup-treatment interaction
  - $\Delta_- \neq \Delta_+$?
  - Significance Level (α_{int}): 0.10

Multiple subgroups with direct assignment option:

Simulation Study

Simulated 500 trials, under the following two settings:

	M+			M-		
Setting	p_{exp}	p_{ctl}	N	p_{exp}	p_{ctl}	N
I (no interaction)	0.4	0.2	65	0.4	0.2	65
II (interaction)	0.4	0.2	65	0.1	0.2	161

Sample size calculations based on balanced randomized design with 1 IA, $1 - \beta = 0.80$, and $\alpha = 0.20$.

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Compared for 2 designs:

1. Multiple subgroups, Direct Assignment Option with one IA (DAD-1)
2. Multiple subgroups, Balanced Randomized Design with one IA (BRD-1)

Multiple subgroups with direct assignment option:

Simulation Study Results

- Separate subgroup main effects
  - Power: 78-83% for DAD-1 vs. 79-84% for BRD-1
  - TIER: 19-24% for DAD-1 vs. 18-21% for BRD-1

$\Rightarrow$ Power and Type I Error Rate preserved, as expected

Multiple subgroups with direct assignment option:

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  - TIER: 19-24% for DAD-1 vs. 18-21% for BRD-1

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- Subgroup-treatment interaction
  - Post-hoc power: 64% for DAD-1 vs. 68% for BRD-1

$\Rightarrow$ Reasonable post-hoc power for planning purposes

Outline

Concluding Remarks

- The "direct assignment" idea is:
  - not entirely new (e.g. Colton, 1963)
  - flexible (i.e. could be incorporated into many existing trial frameworks)
- We considered 2 applications of the direct assignment option in broader design frameworks:
  - 2 interim analyses
  - 2 subgroups
- Designs incorporating the direct assignment option:
  - fit somewhere between adaptive designs, fixed balanced randomized designs, and single-arm designs
  - offer:
    - Relative logistical simplicity
    - Adaptation based on accumulated data
    - Desirable statistical properties
    - Potential appeal for clinicians and patients

Thank you!

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