

# DESIGN-IT Session B

## Therapy to Improve Cognitive Dysfunction in Huntington Disease



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# Yesterday's Discussion

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- Treatment has been unsuccessful in other indications
- Reasons to believe it will be effective on the cognitive domains relevant to HD
- Primary objective is to determine the maximum tolerated dose (MTD)
- Additional objective is to determine if there is a “signal” of efficacy

# Yesterday's Discussion

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- 7 Dose Levels – expect MTD will be dose 3
- Toxicity events: observed within one week
  - Worsening of movement and psychiatric symptoms
  - Impaired sleep
  - Appetite disorders
  - Other grade 2 or higher AEs
- MTD is highest dose with toxicity rate  $< 30\%$

# Yesterday's Discussion

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- Efficacy – Observed at 4 weeks
  - Change from baseline on a cognitive scale
  - Clinically meaningful difference is an improvement of  $\frac{1}{2}$  SD compared to placebo
  - Would consider higher toxicity for higher efficacy

# Yesterday's Discussion

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- Planned max sample size is 20-30 pts
- Could go higher if addressing both safety and efficacy in the same study
- Accrual of 4 patients per month
- Drop-out of 10%

# Design Ideas

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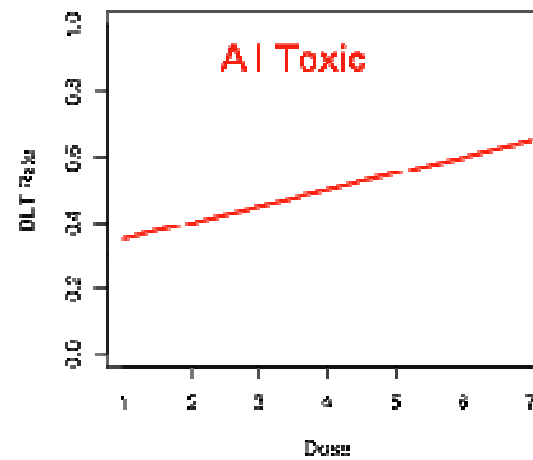
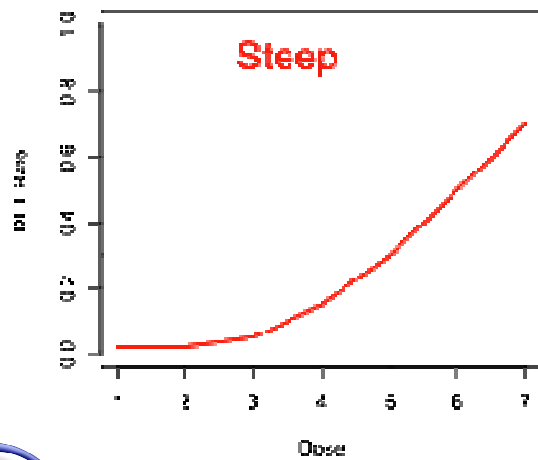
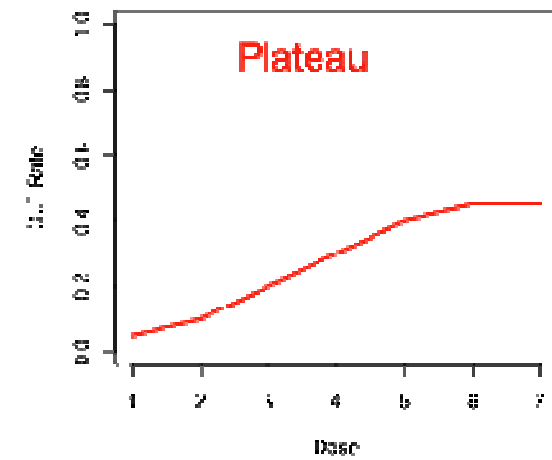
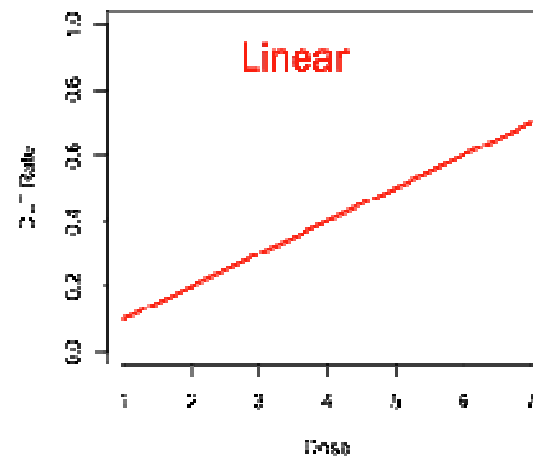
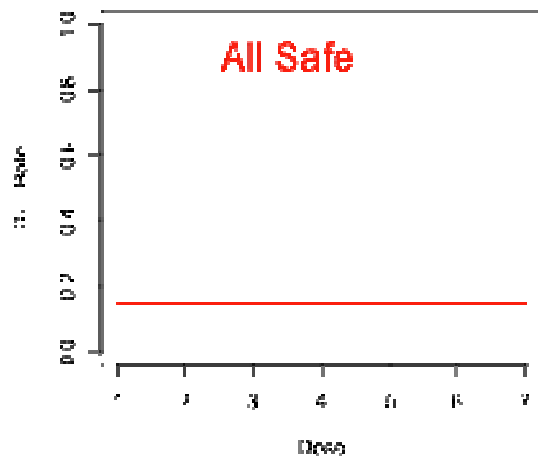
- Design 1: Continual Reassessment Method (CRM)
- Design 2: Seamless Phase I/II
- Design 3: Phase II Dose-Finding

# Design 1: Classic CRM

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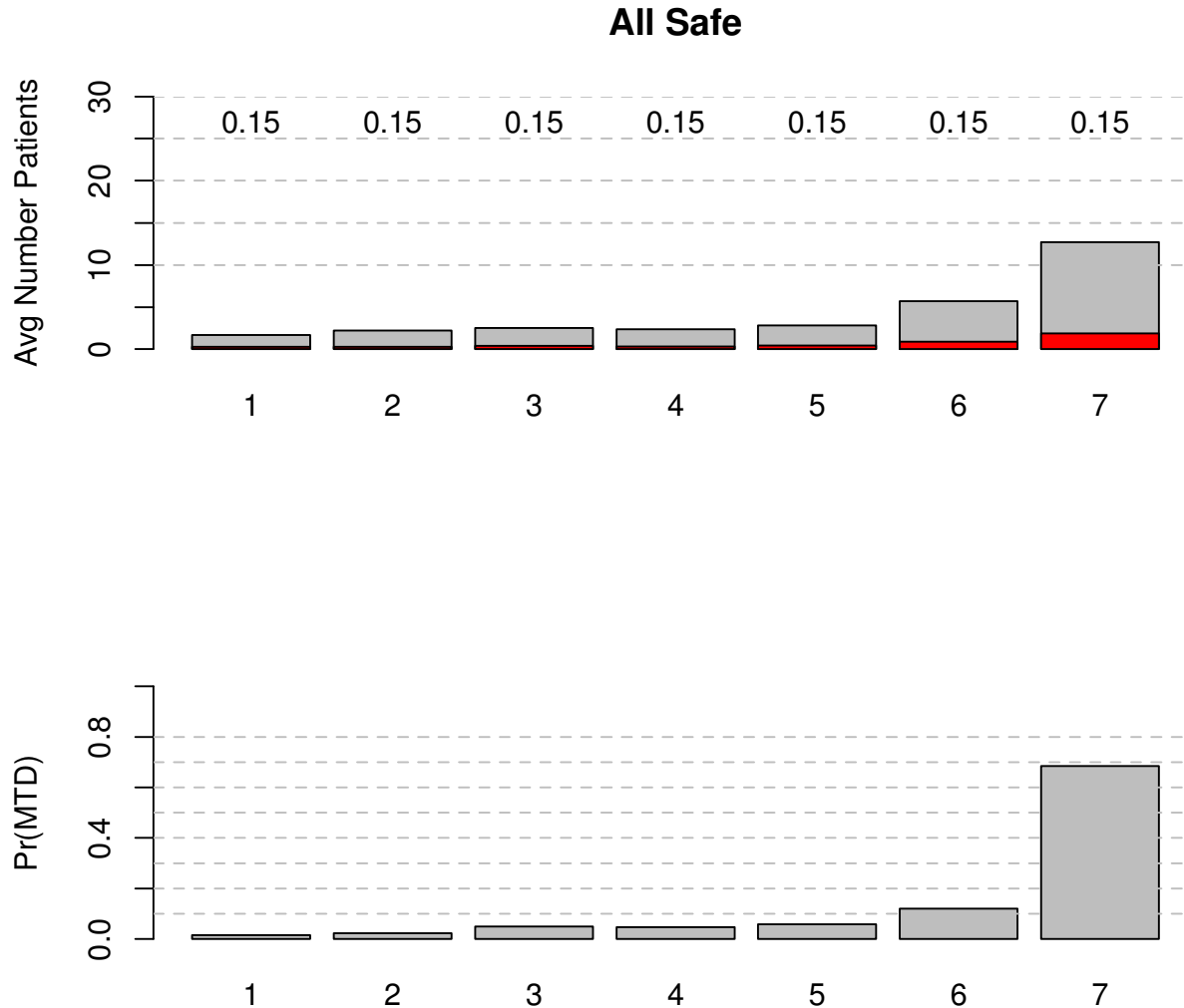
- 30 Patients
- 7 Dose levels – Start enrolling at dose 2
- MTD is dose level *closest* to 30%
- Cohort size 1

# Design 1: Toxicity Scenarios

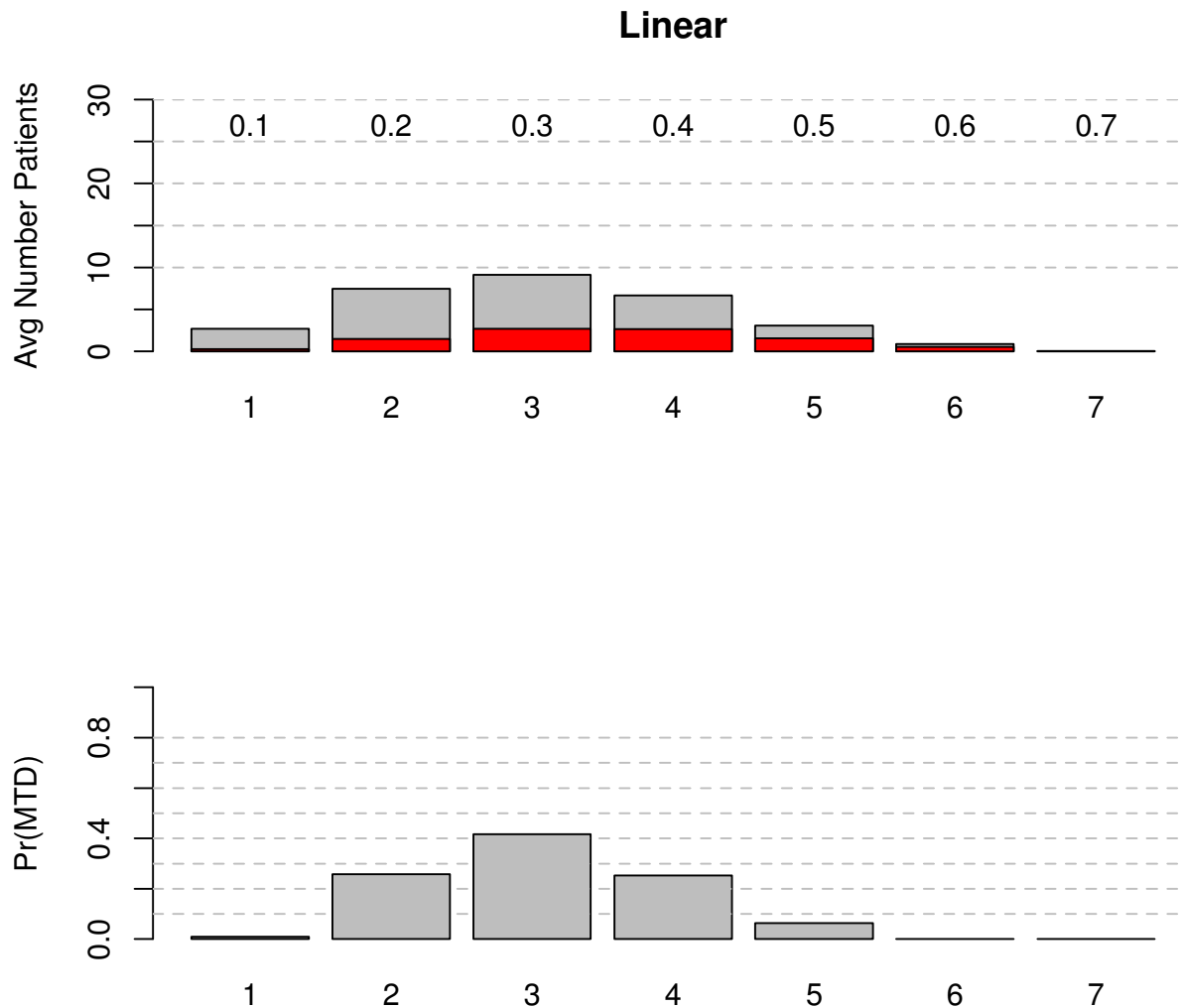




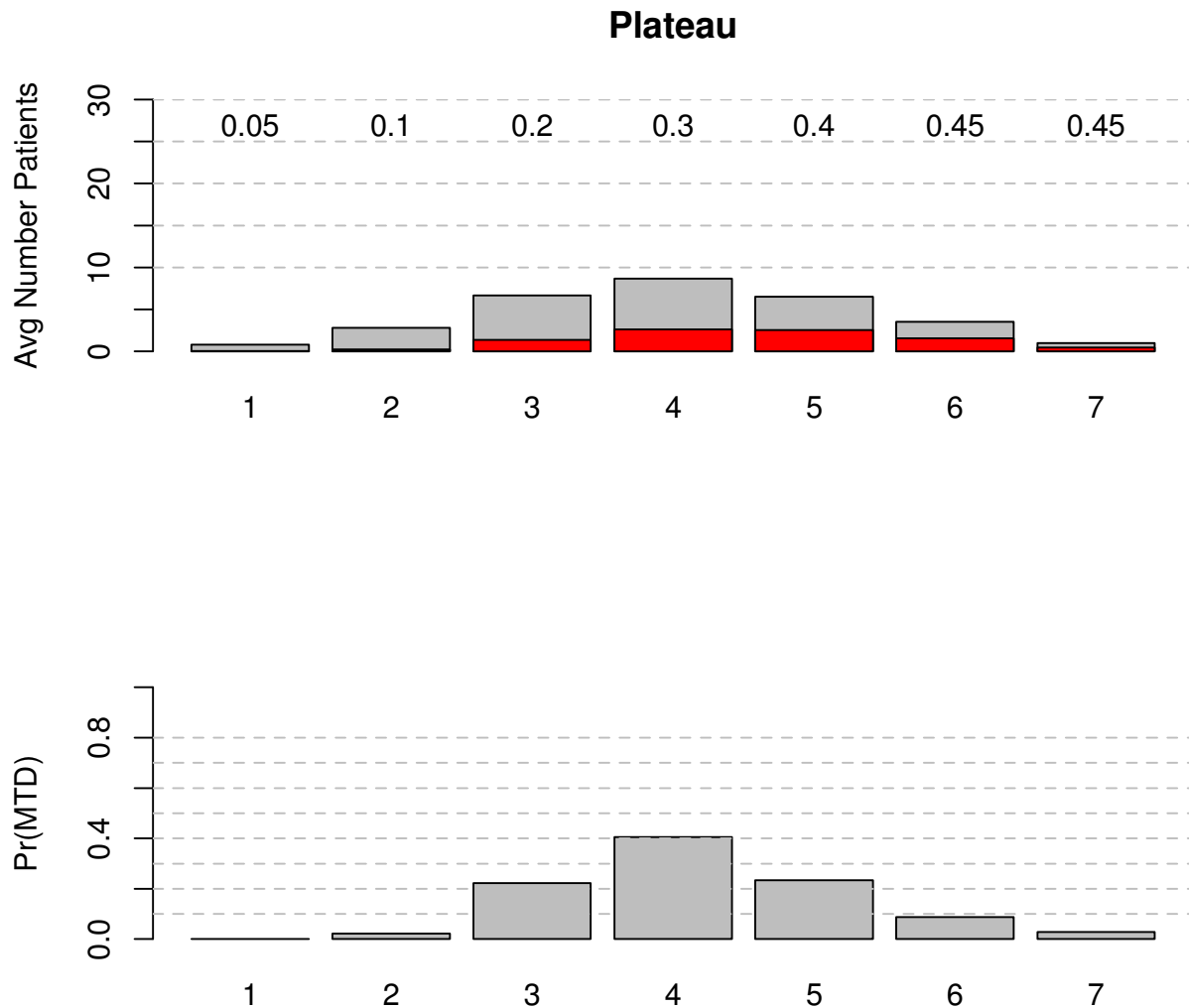
# Design 1: Operating Characteristics



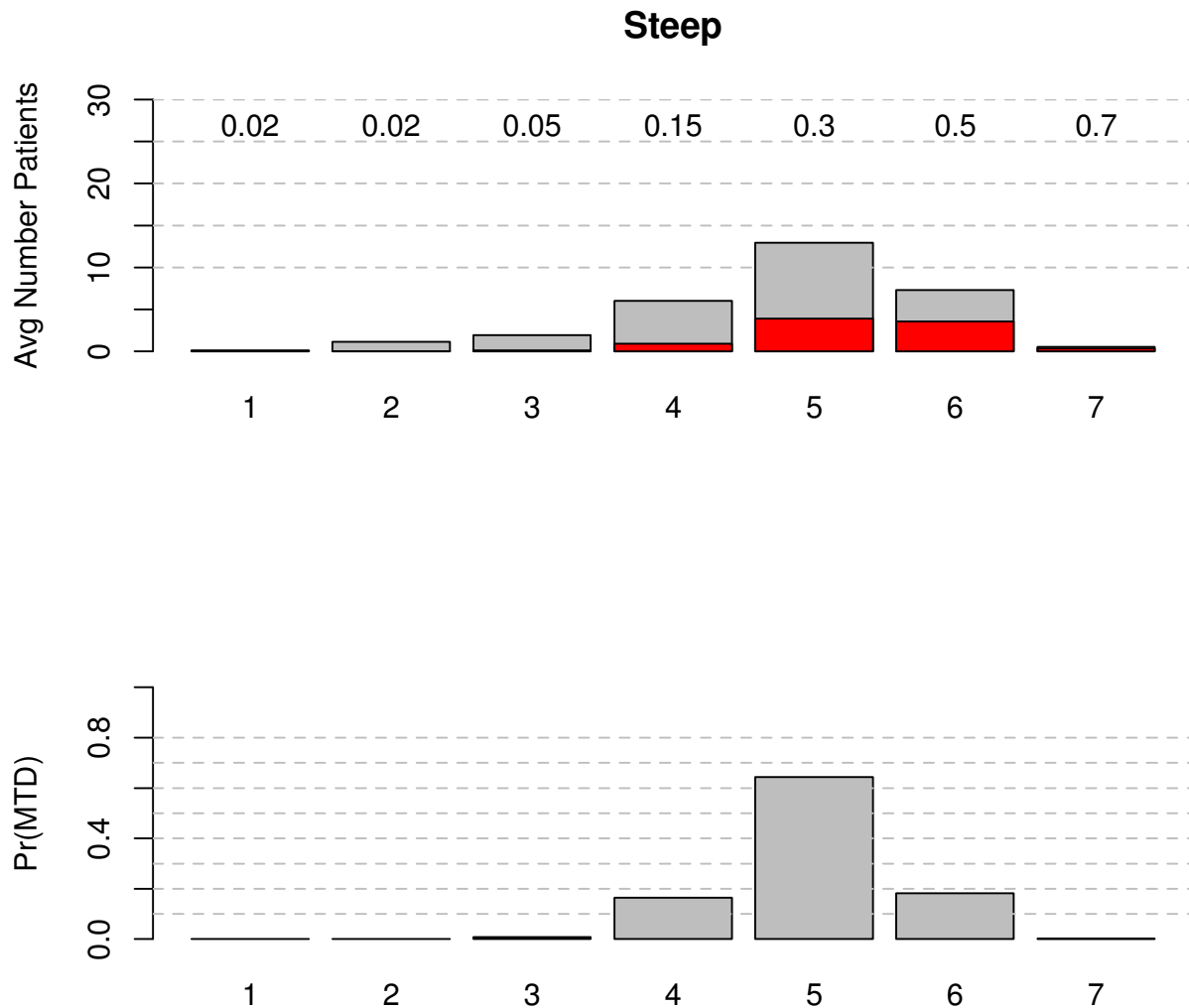
# Design 1: Operating Characteristics



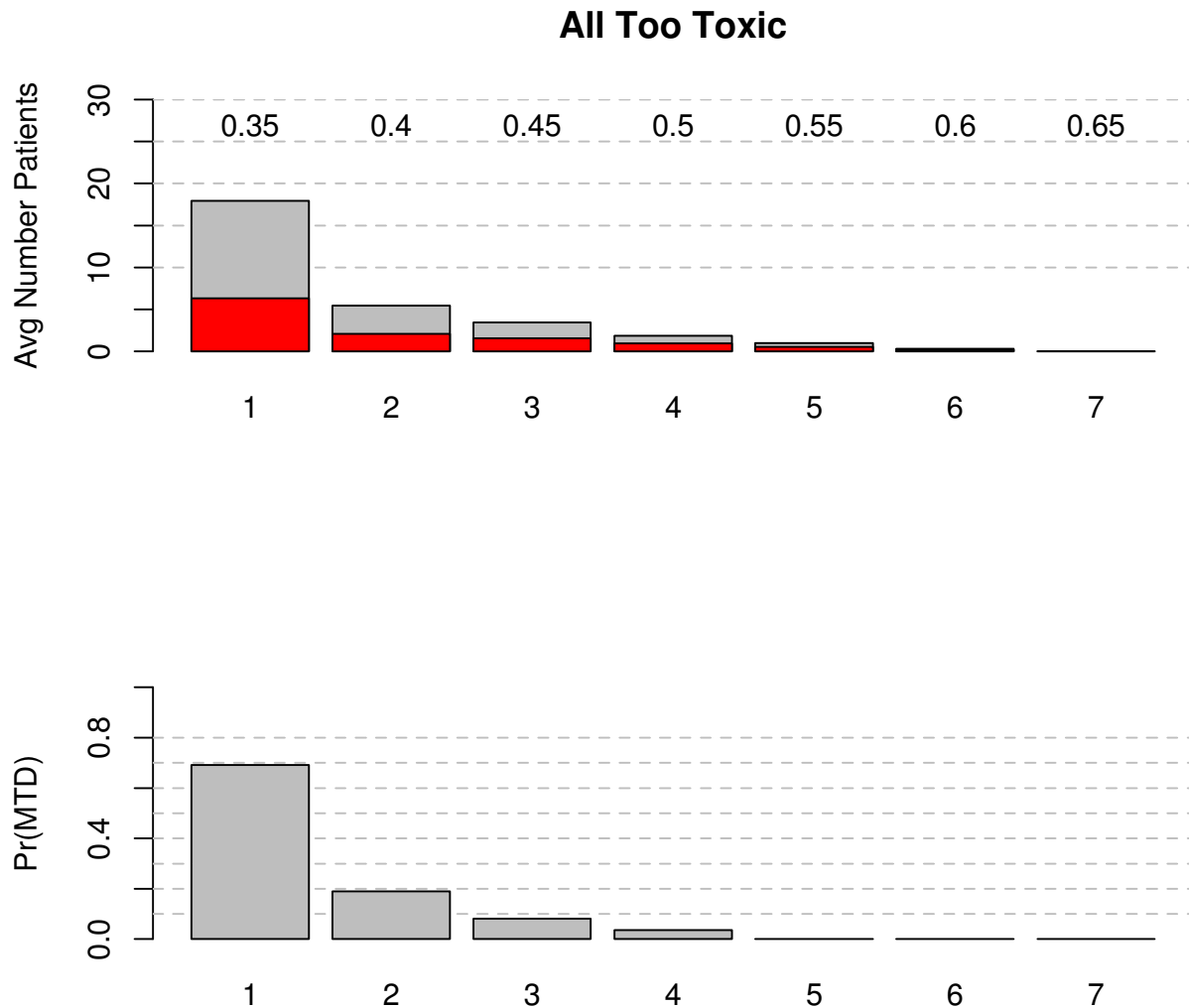
# Design 1: Operating Characteristics



# Design 1: Operating Characteristics



# Design 1: Operating Characteristics



# Design 2: Seamless Phase I/II

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- Operationally seamless
  - Phase I inferentially separate from phase II
- Phase I
  - Same classic CRM as design 1
  - Maximum 30 pts
  - Early Stopping:
    - $\Pr(\text{MTD}) > 0.80$
  - MTD selected as dose to carry forward

# Design 2: Seamless Phase I/II

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- Phase II
  - Maximum 60 pts
  - Equally randomize to MTD and placebo
  - Success in a future 170-pt Phase III
    - Randomize experimental versus placebo
    - 170 pts provides 90% for  $\frac{1}{2}$  SD
    - Alpha one-side 0.025

# Design 2: Seamless Phase I/II

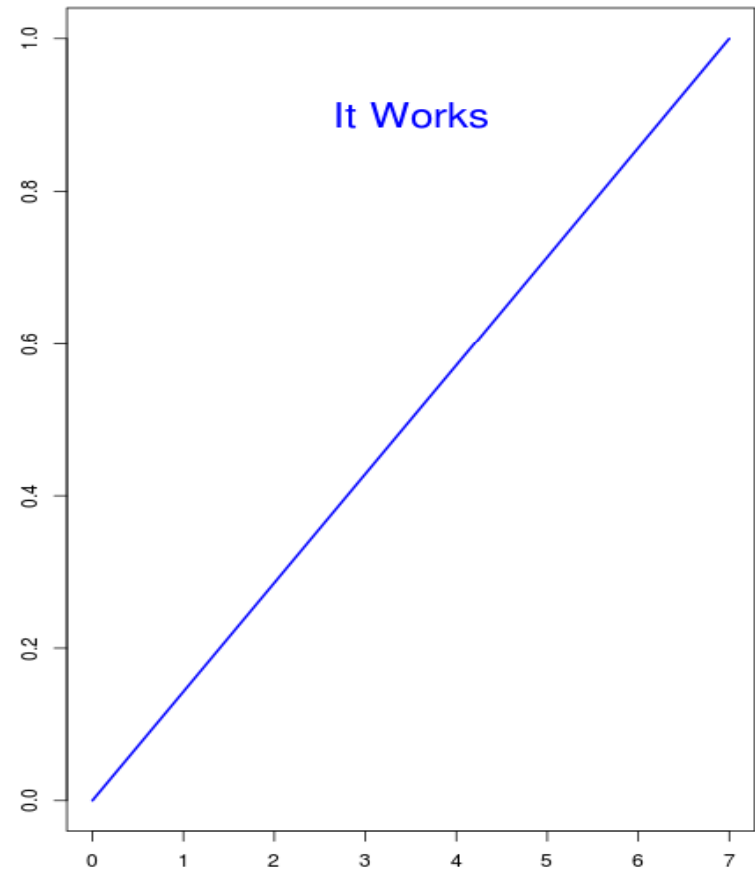
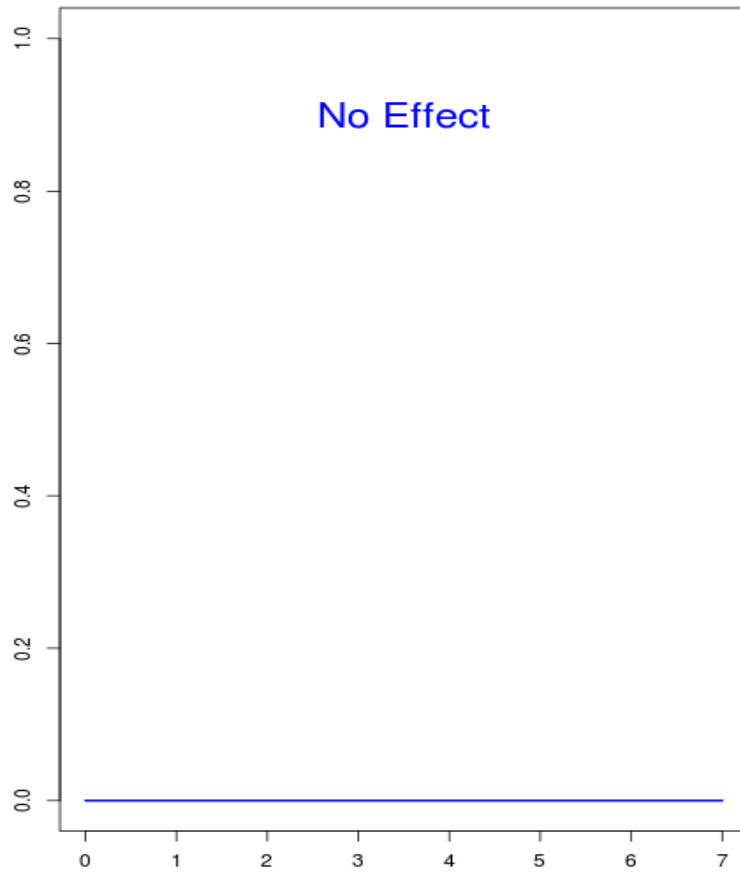
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- Interim analyses for early futility or success
- Early Futility
  - Starts when 20 pts enrolled
  - Every 4 weeks thereafter
  - $\text{Pr}(\text{Phase III Success}) < 10\%$
- Early Success
  - Starts when 30 pts enrolled
  - $\text{Pr}(\text{Phase III Success}) > 95\%$
- Final Success =  $\text{Pr}(\text{Phase III Success}) > 70\%$

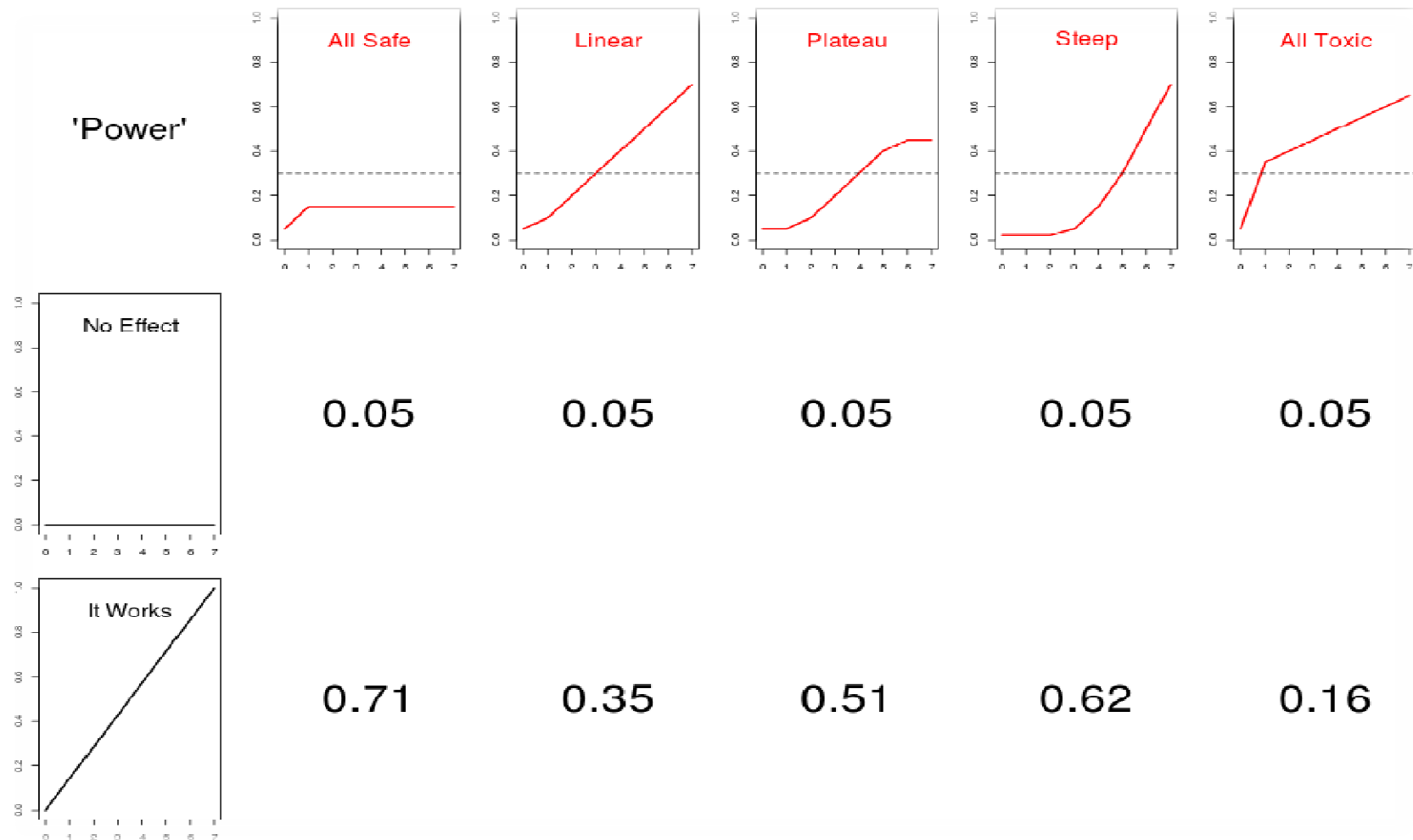


# Design 2: Scenarios

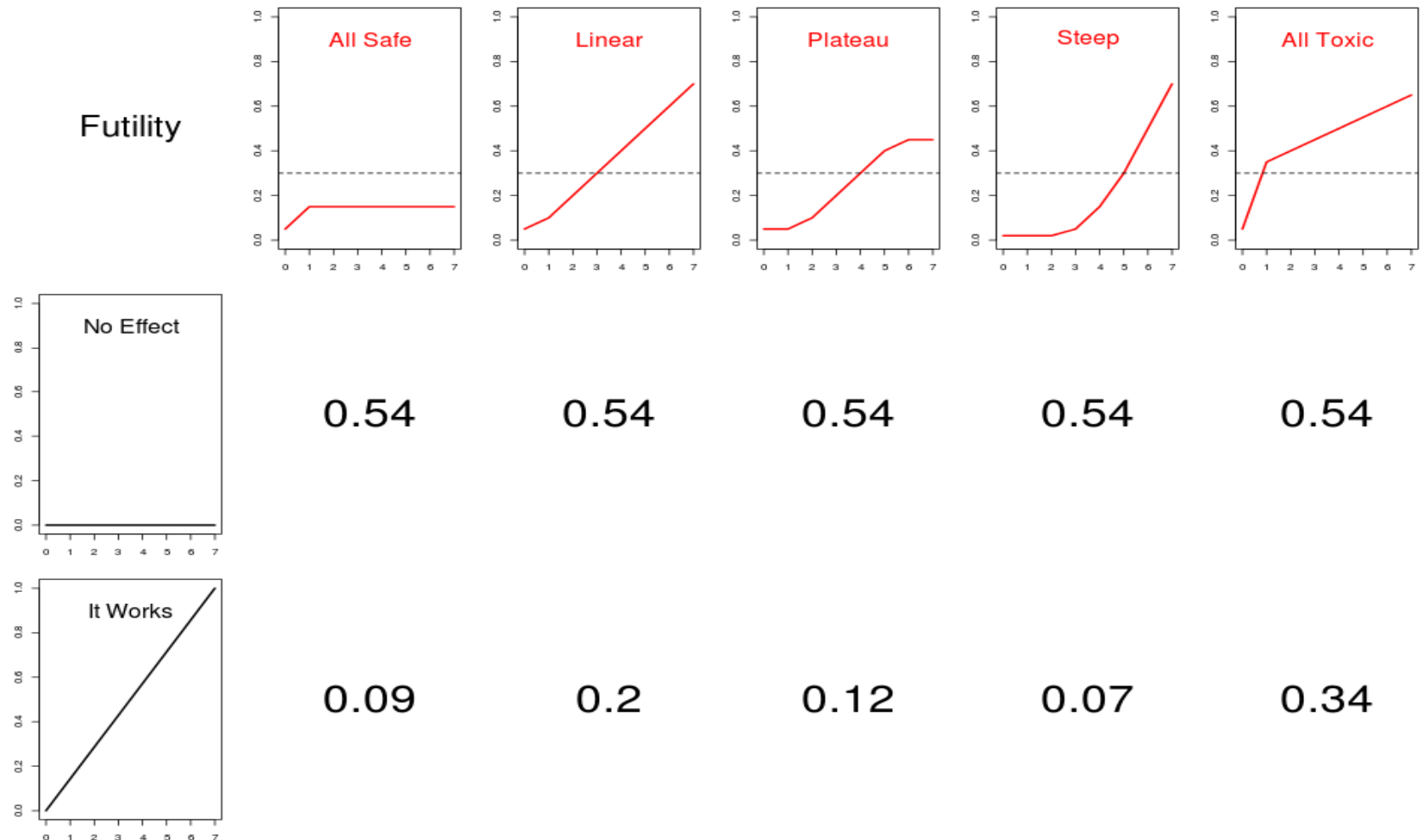
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# Design 2: Operating Characteristics

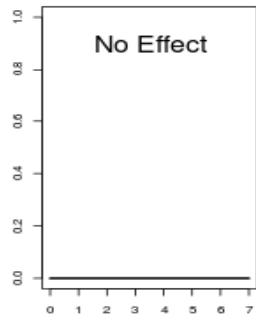
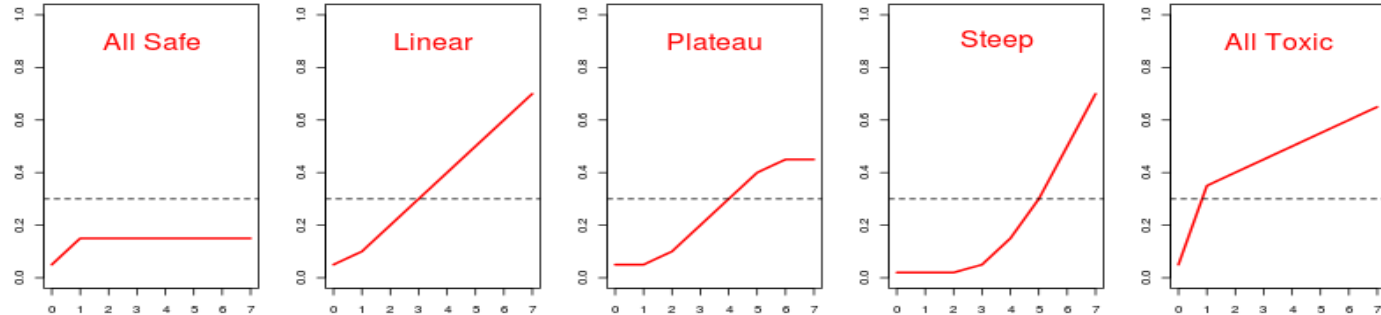


# Design 2: Operating Characteristics



# Design 2: Operating Characteristics

Early Success



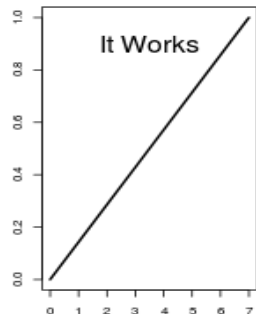
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0.01

0.01

0.01

0.01



0.42

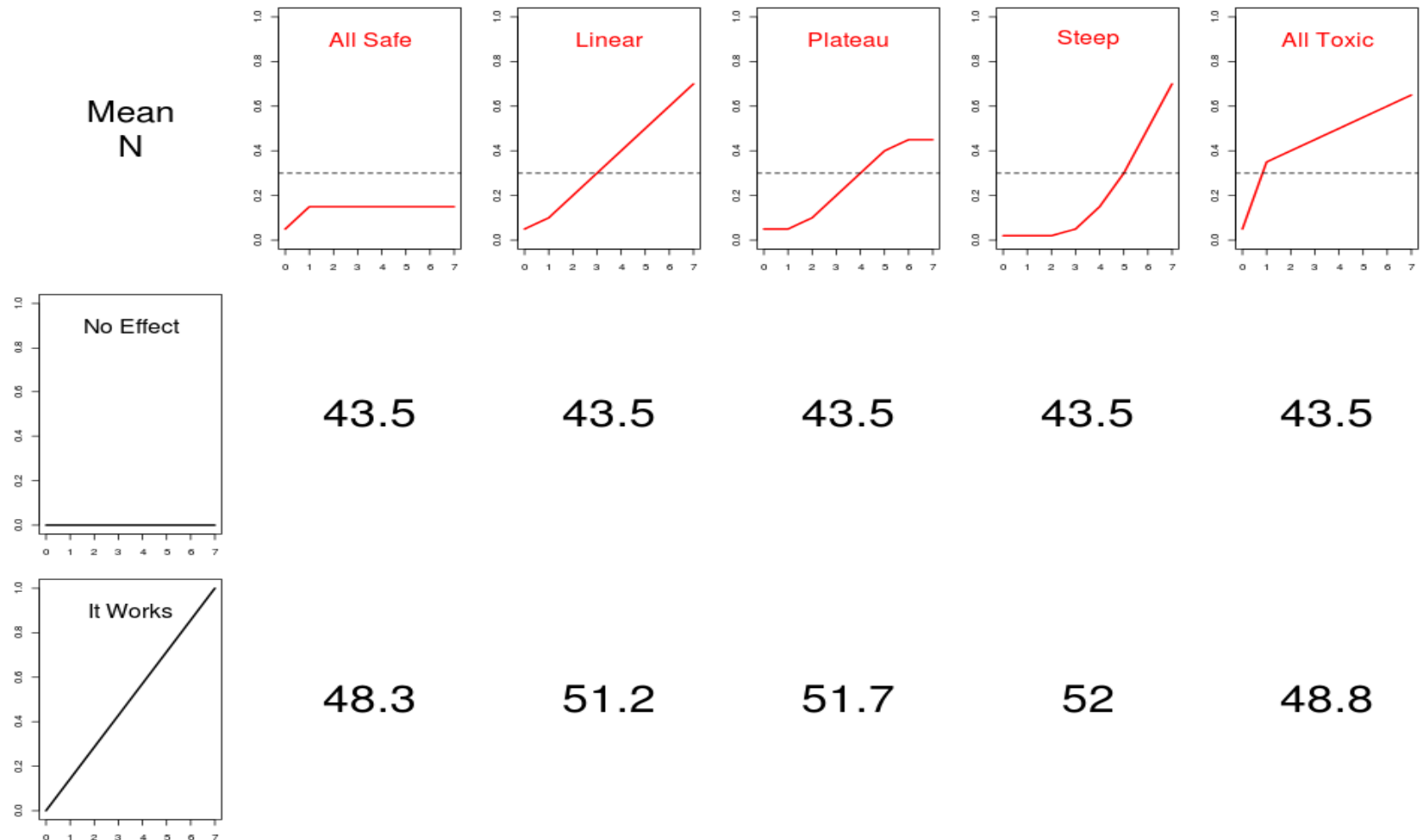
0.12

0.2

0.26

0.05

# Design 2: Operating Characteristics



# Design 3: Phase II Dose Finding

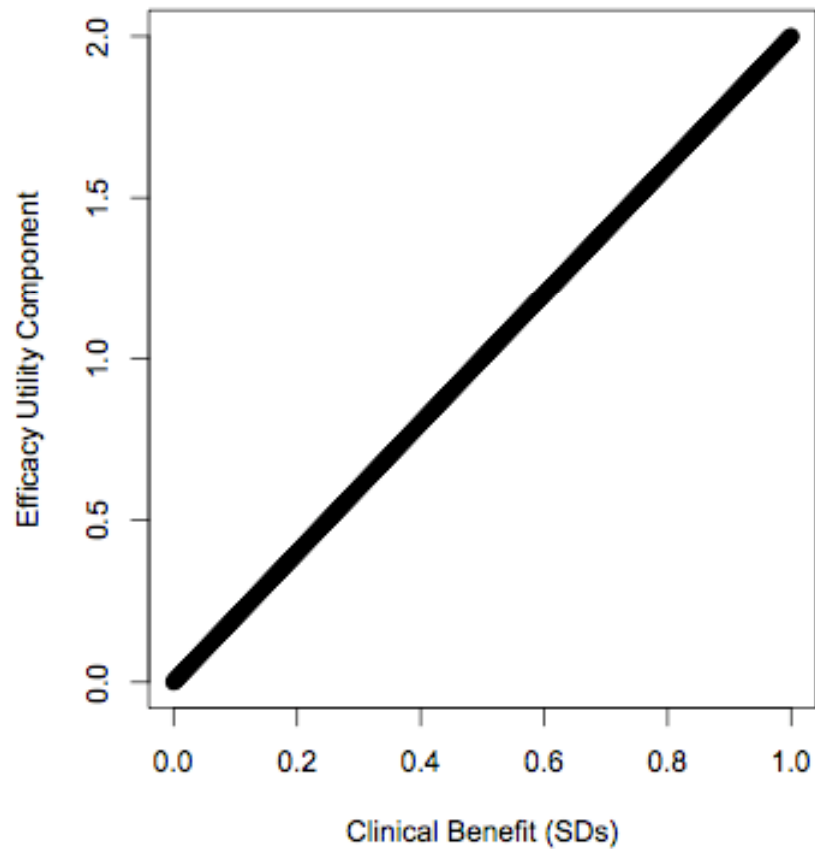
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- 7 Doses and Placebo
- Max 80 patients
- Dose-finding based on safety and efficacy
- Safety and efficacy weighted by a utility
  - Higher efficacy is greater utility
  - Lower toxicity is greater utility
- Determine the maximum *utility* dose

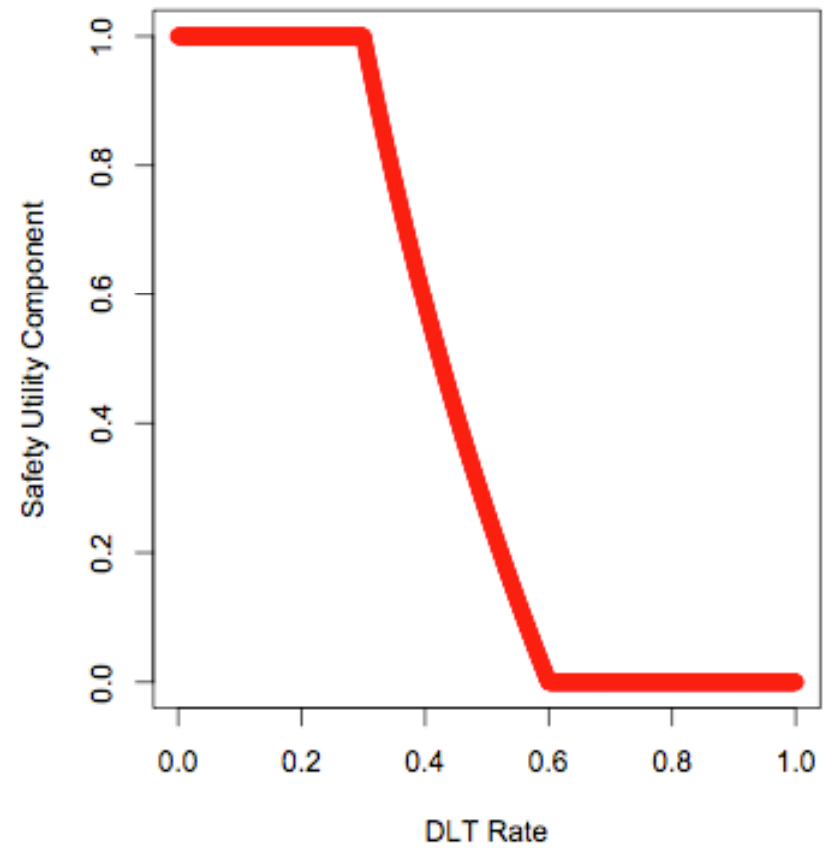
# Design 3: Utility Functions

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Utility Component  
Efficacy

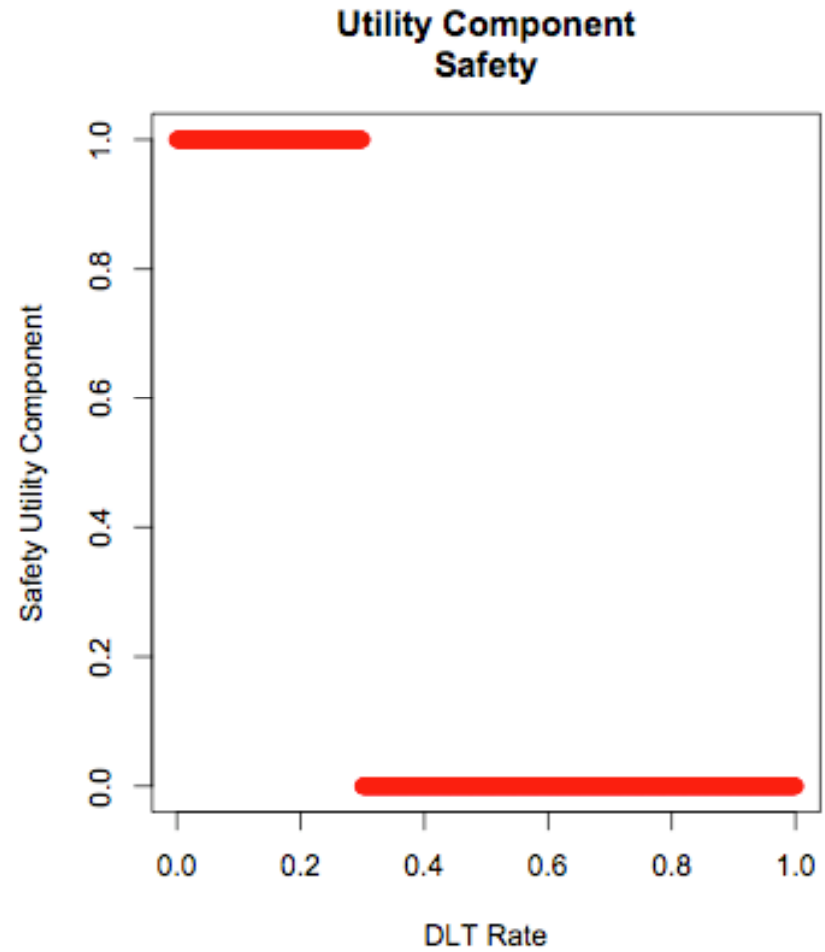
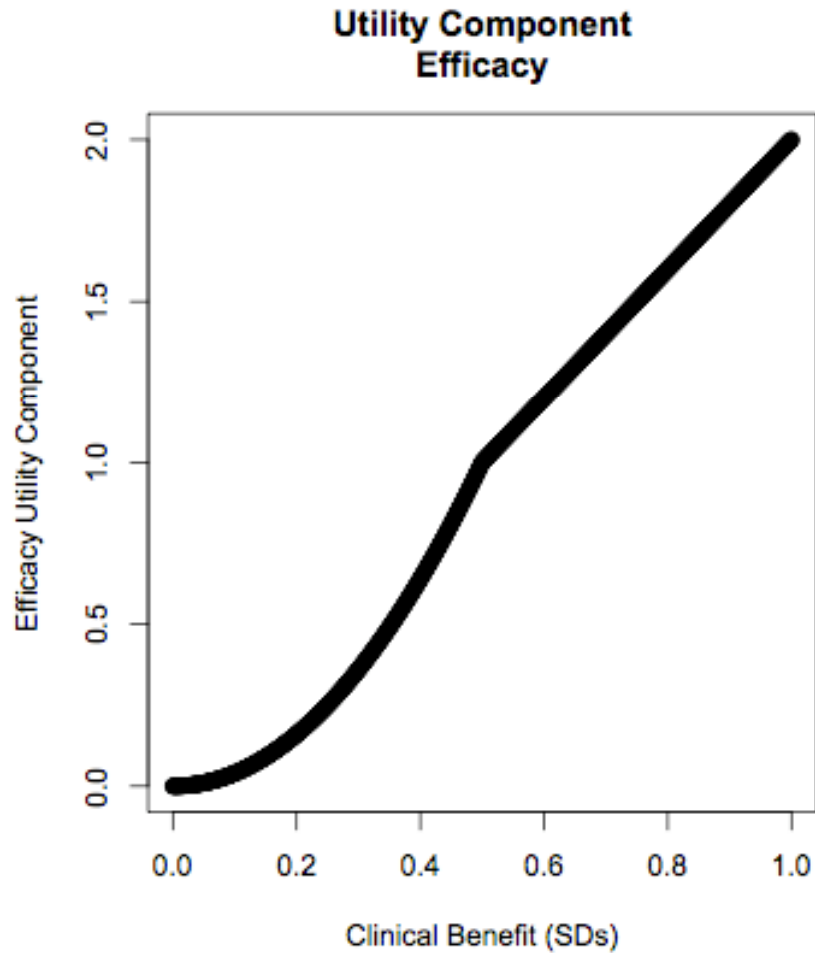


Utility Component  
Safety



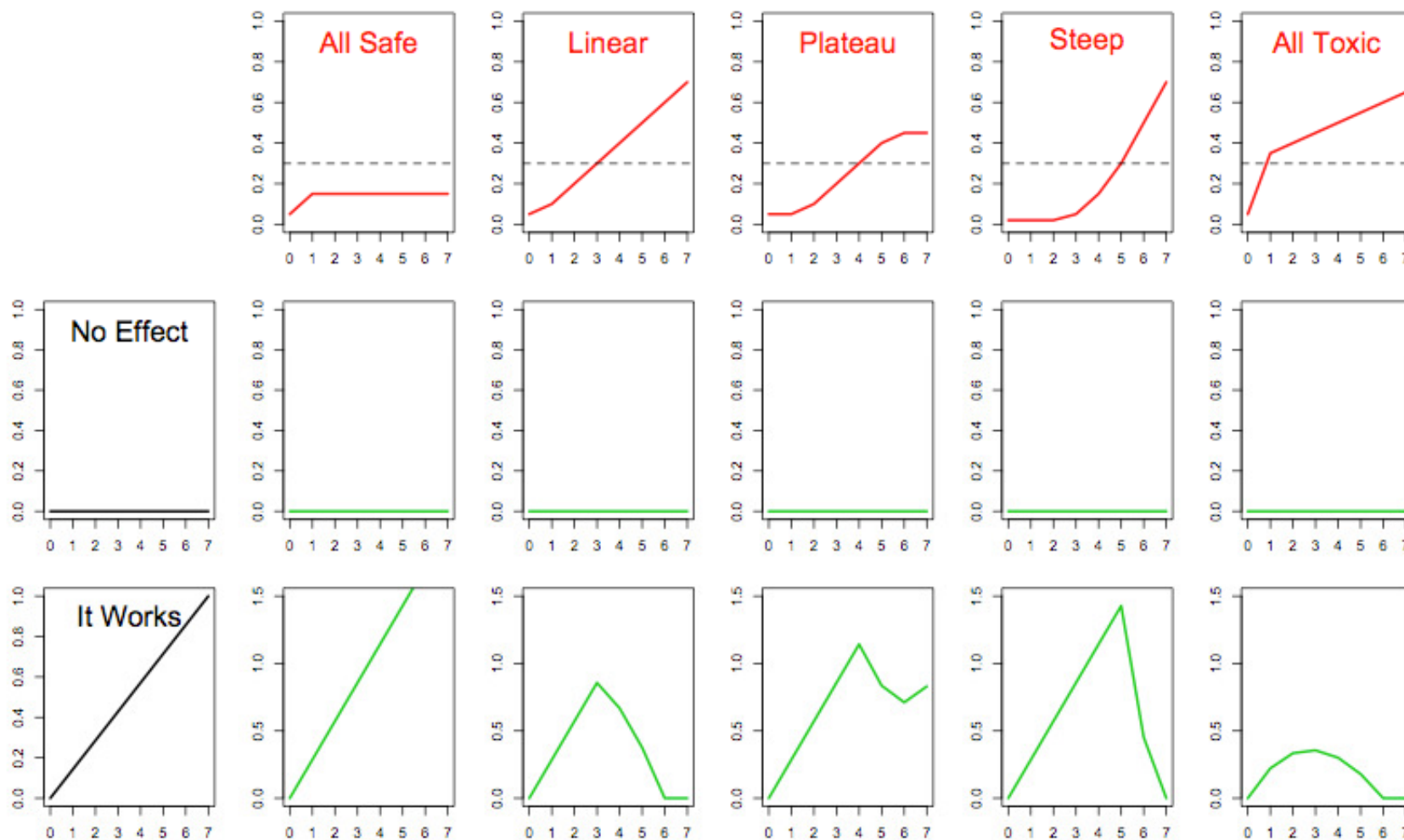
# Design 3: Utility Functions

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# Design 3: Scenarios



# Design 3: Phase II Dose Finding

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- Fixed allocation for first 40 patients
  - 5 patients per arm
- Adaptive Randomization
  - Fix randomization to placebo to 20%
  - Adaptively randomize to doses based on information
  - Update every 8 weeks

$$\sqrt{\frac{\Pr(d = d_{UMax}) \text{Var}(U_d)}{n_d + 1}}$$

# Design 3: Phase II Dose Finding

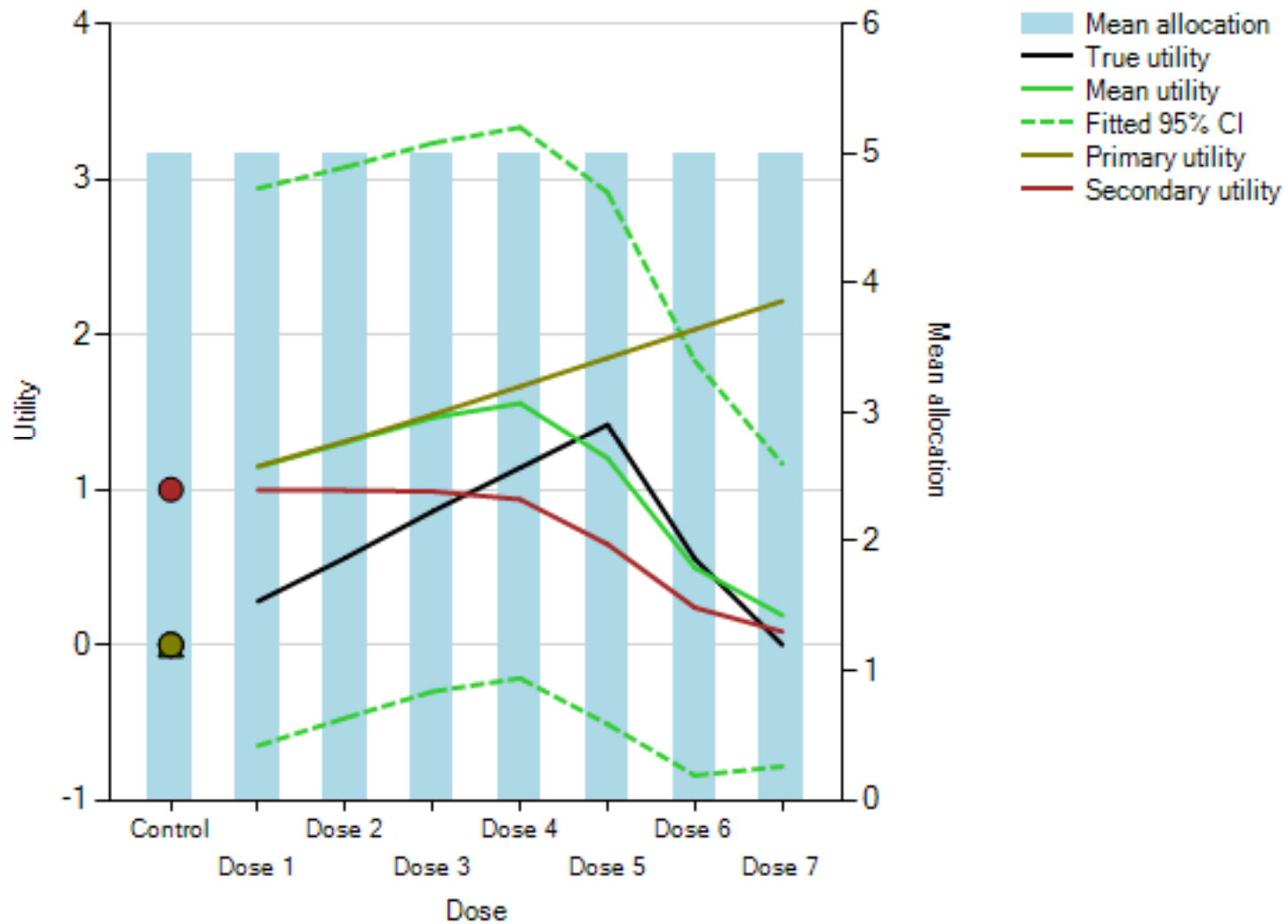
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- Interim analyses every 8 weeks
- Early Futility
  - Starts when 40 pts enrolled
  - $\Pr(\text{Util}_{\max} > 0.75) < 0.10$
- Early Success
  - Starts when 50 pts enrolled
  - $\Pr(\text{Util}_{\max} > 0.75) > 0.90$  &  $\Pr(\text{Phase III Success}) > 0.70$
- Final Success
  - $\Pr(\text{Util}_{\max} > 0.75) > 0.70$  &  $\Pr(\text{Phase III Success}) > 0.70$

N=40

### Utility per Update (Week: 36)

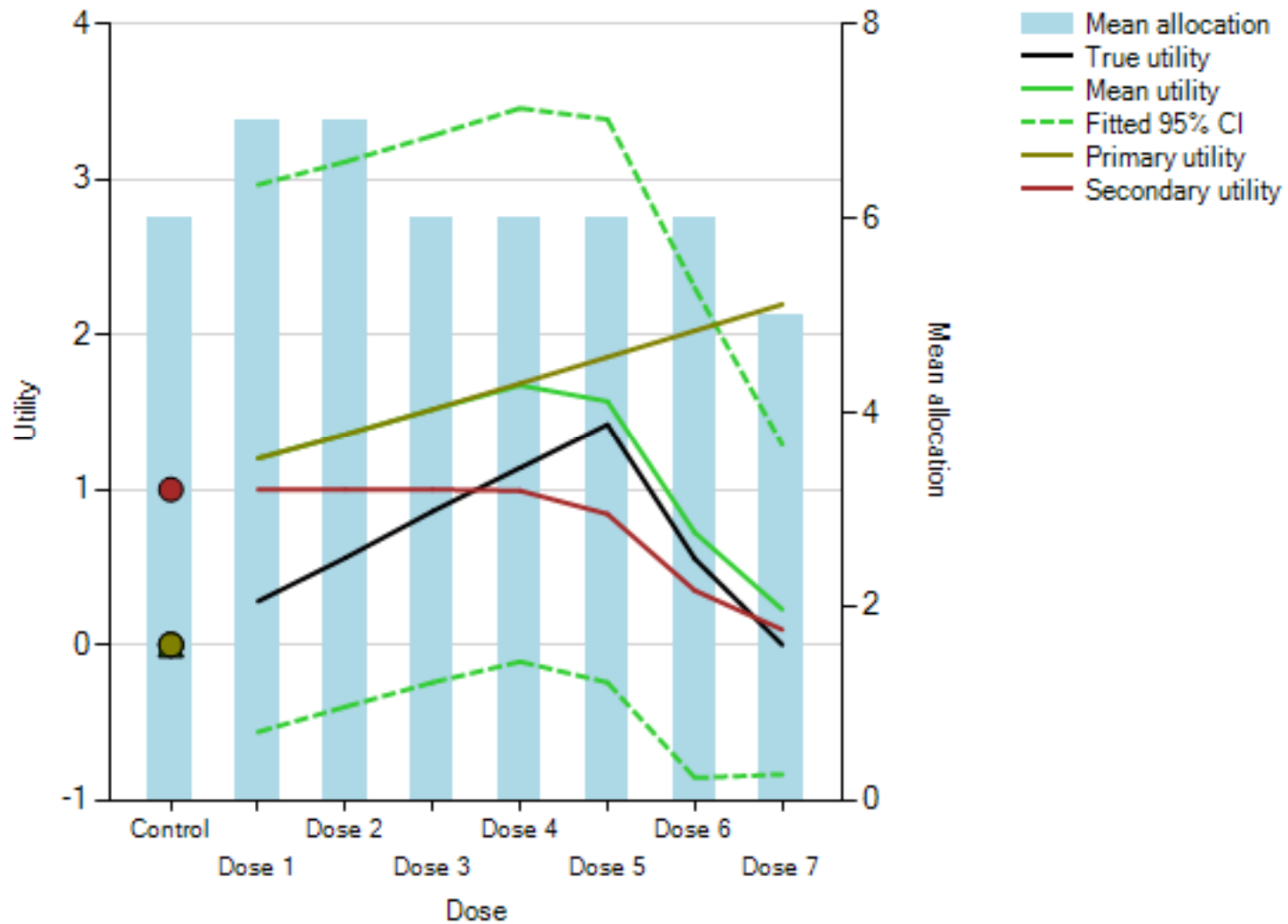
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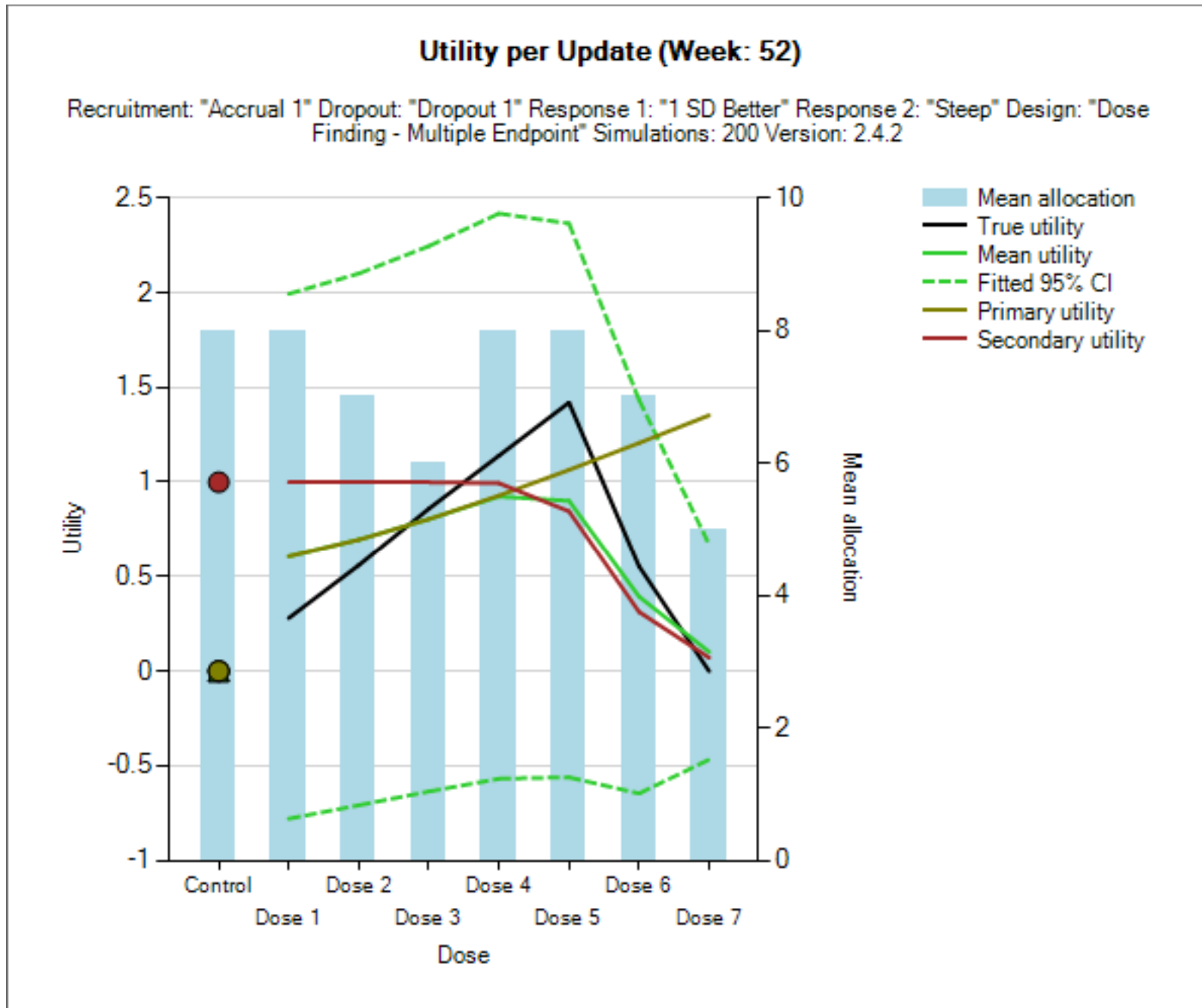
N=49

### Utility per Update (Week: 44)

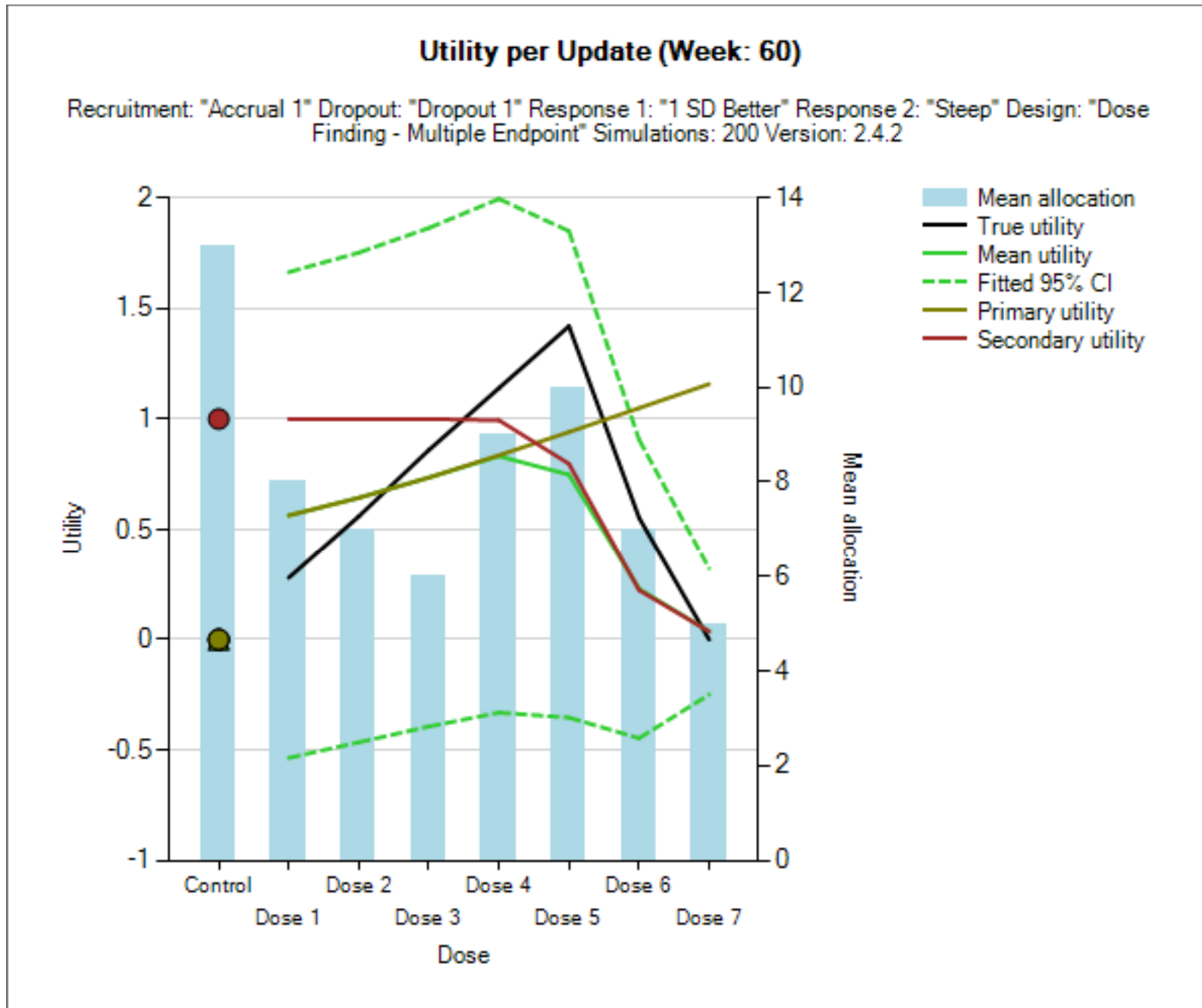
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N=57



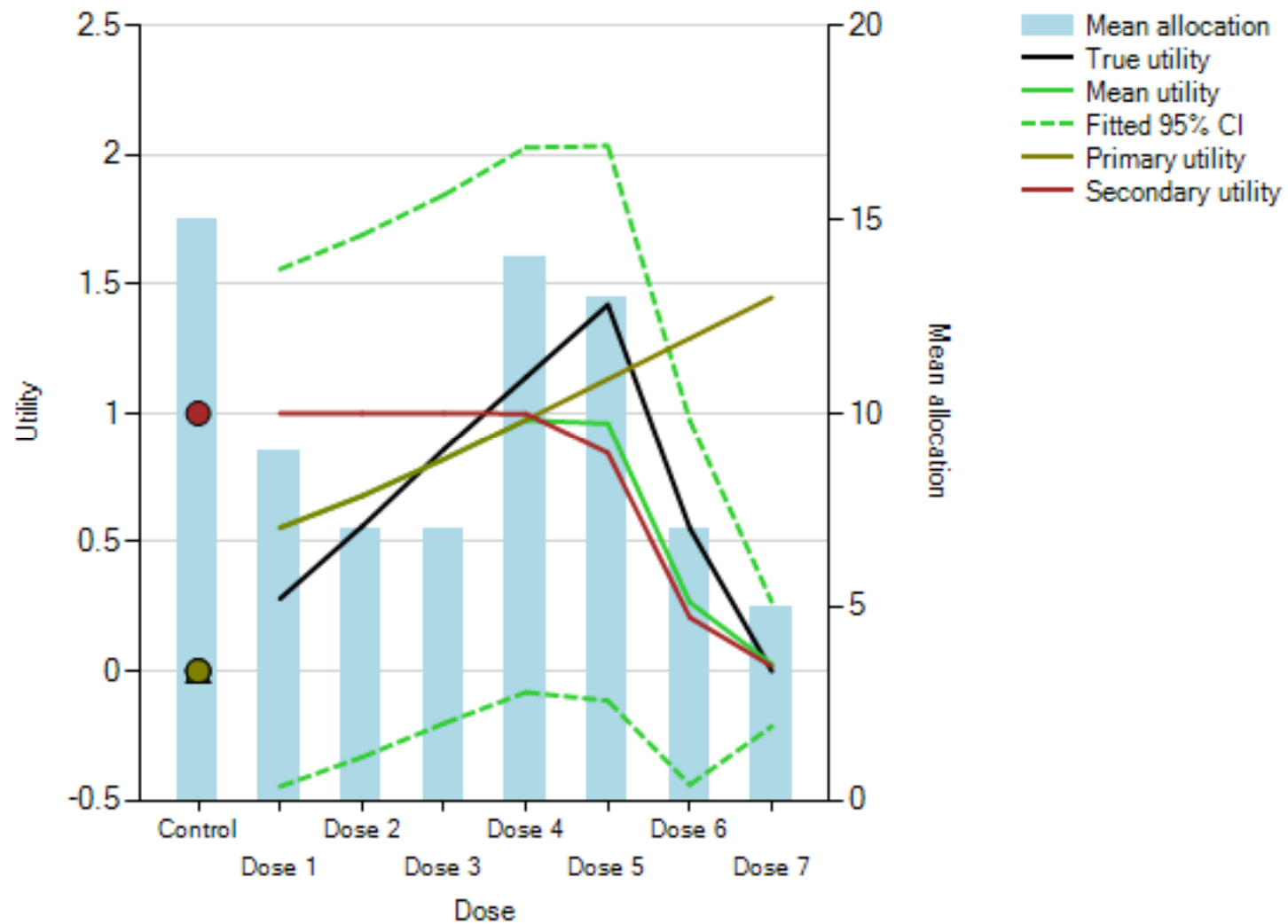
N=65



N=77

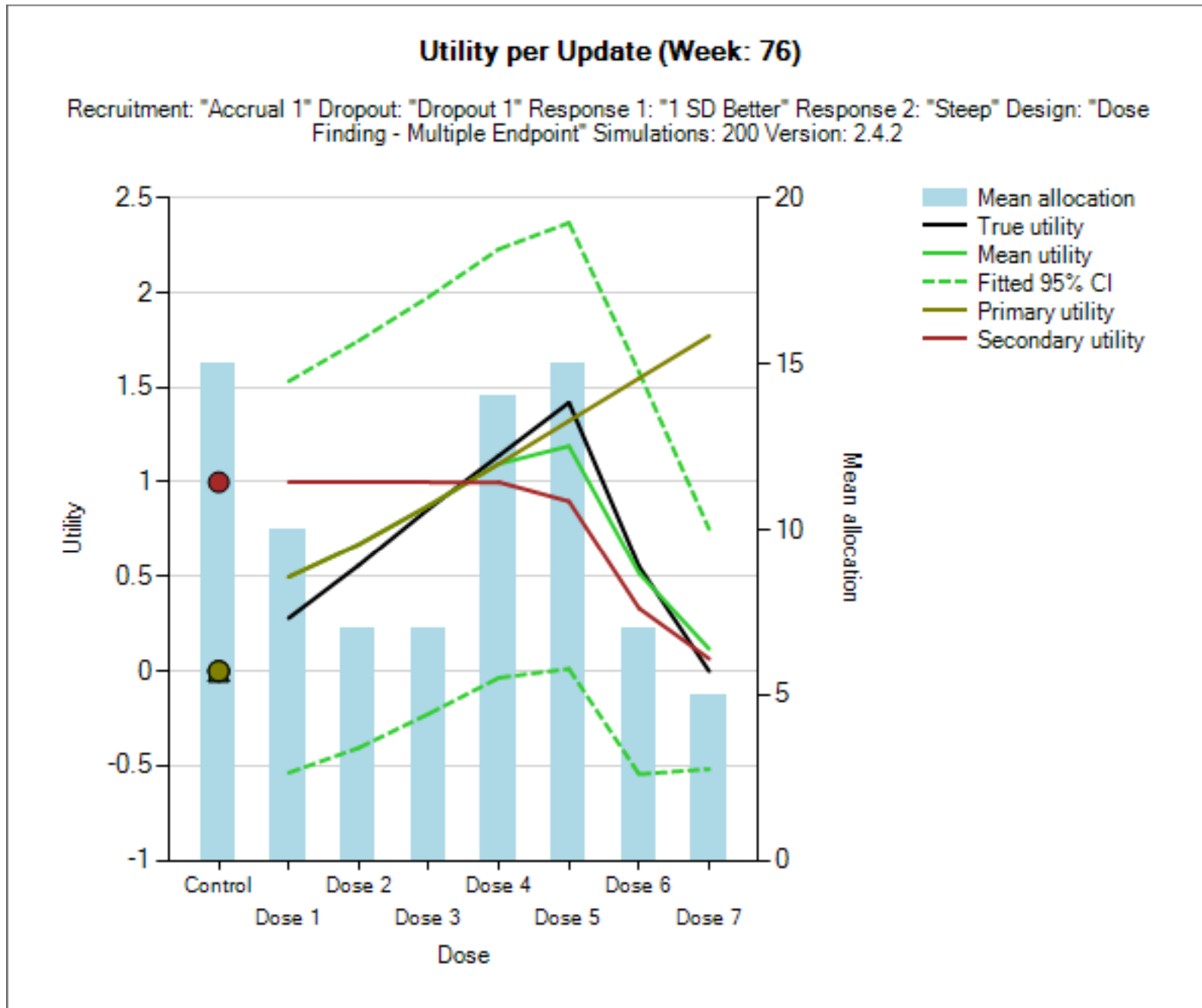
### Utility per Update (Week: 68)

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response 1: "1 SD Better" Response 2: "Steep" Design: "Dose Finding - Multiple Endpoint" Simulations: 200 Version: 2.4.2





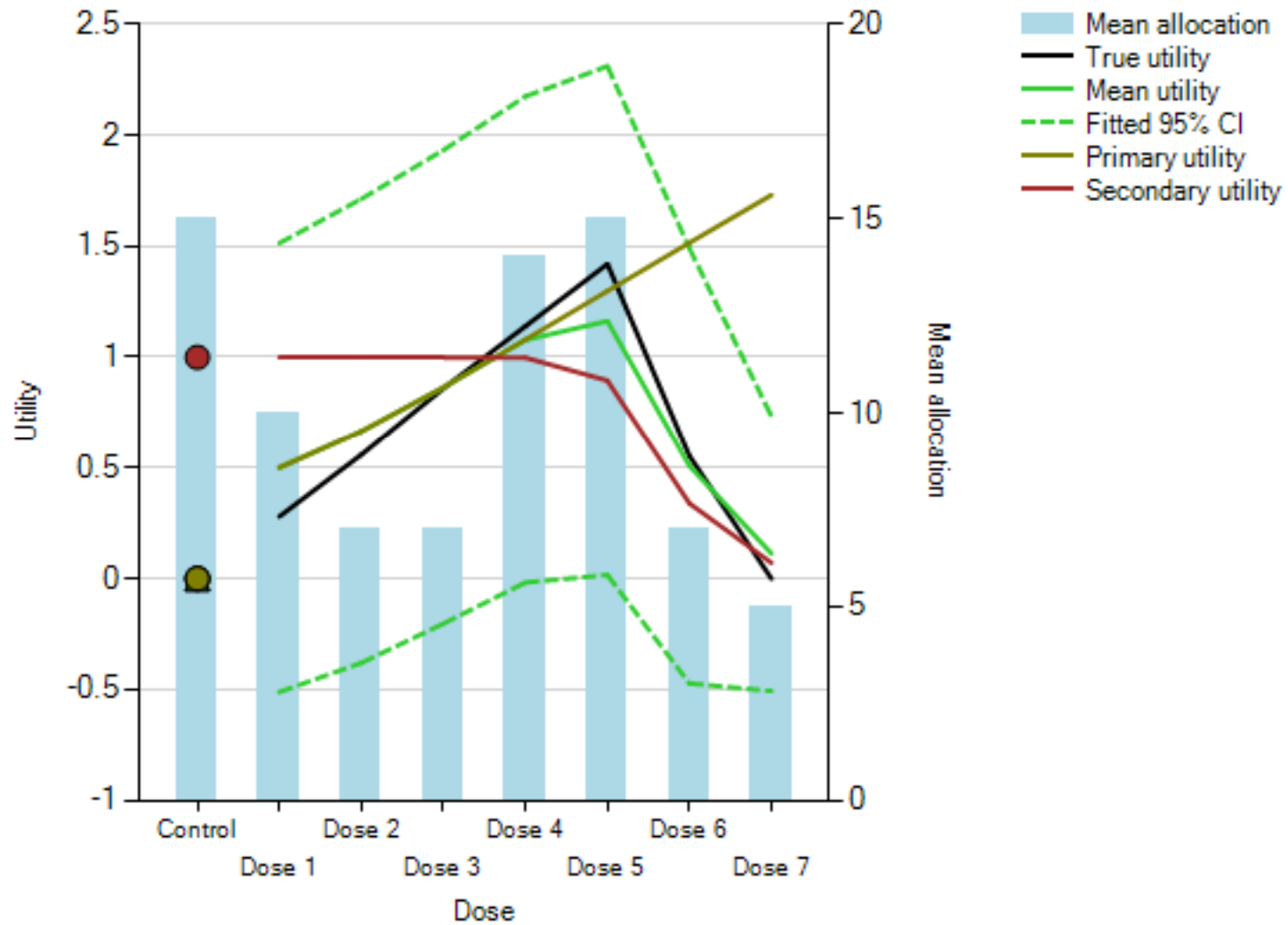
N=80



N=80 + 4 weeks

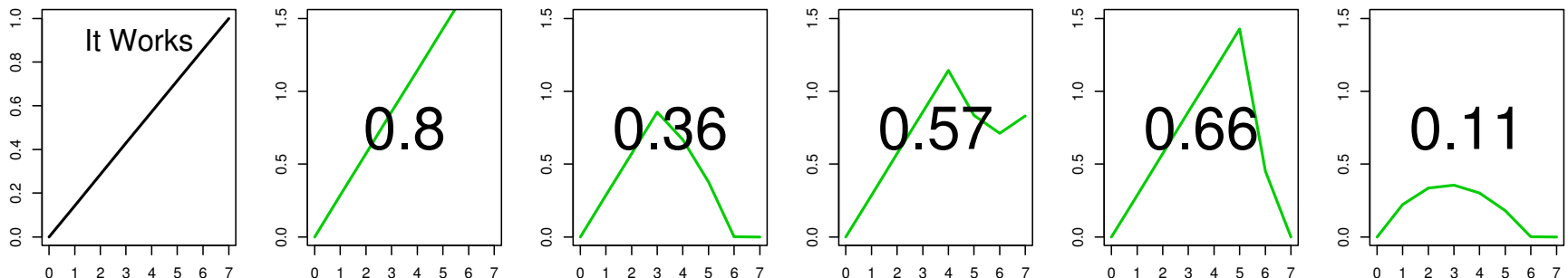
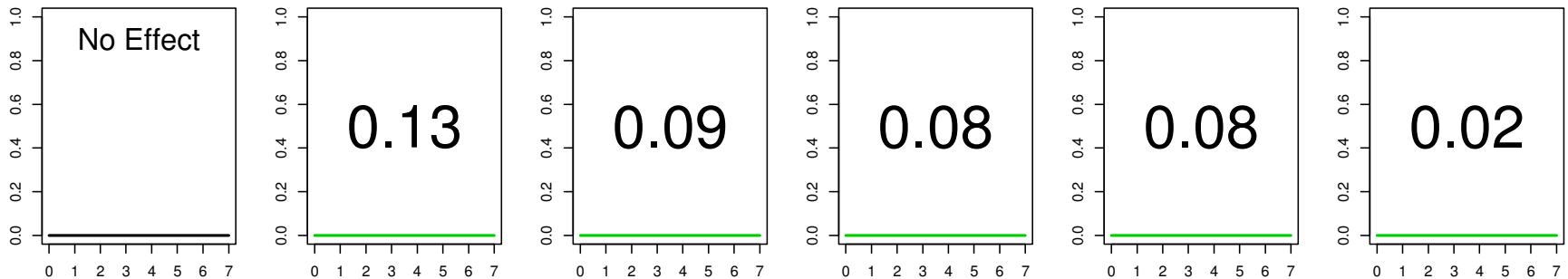
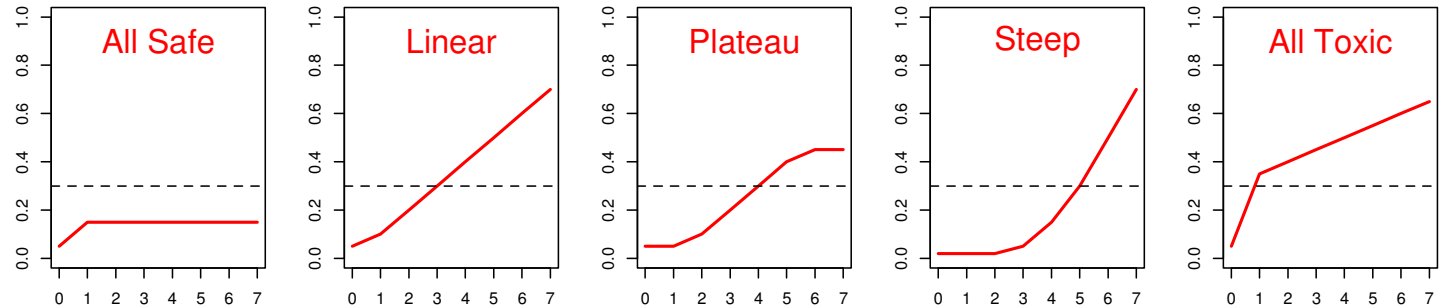
### Utility per Update

Recruitment: "Accrual 1" Dropout: "Dropout 1" Response 1: "1 SD Better" Response 2: "Steep" Design: "Dose Finding - Multiple Endpoint" Simulations: 200 Version: 2.4.2

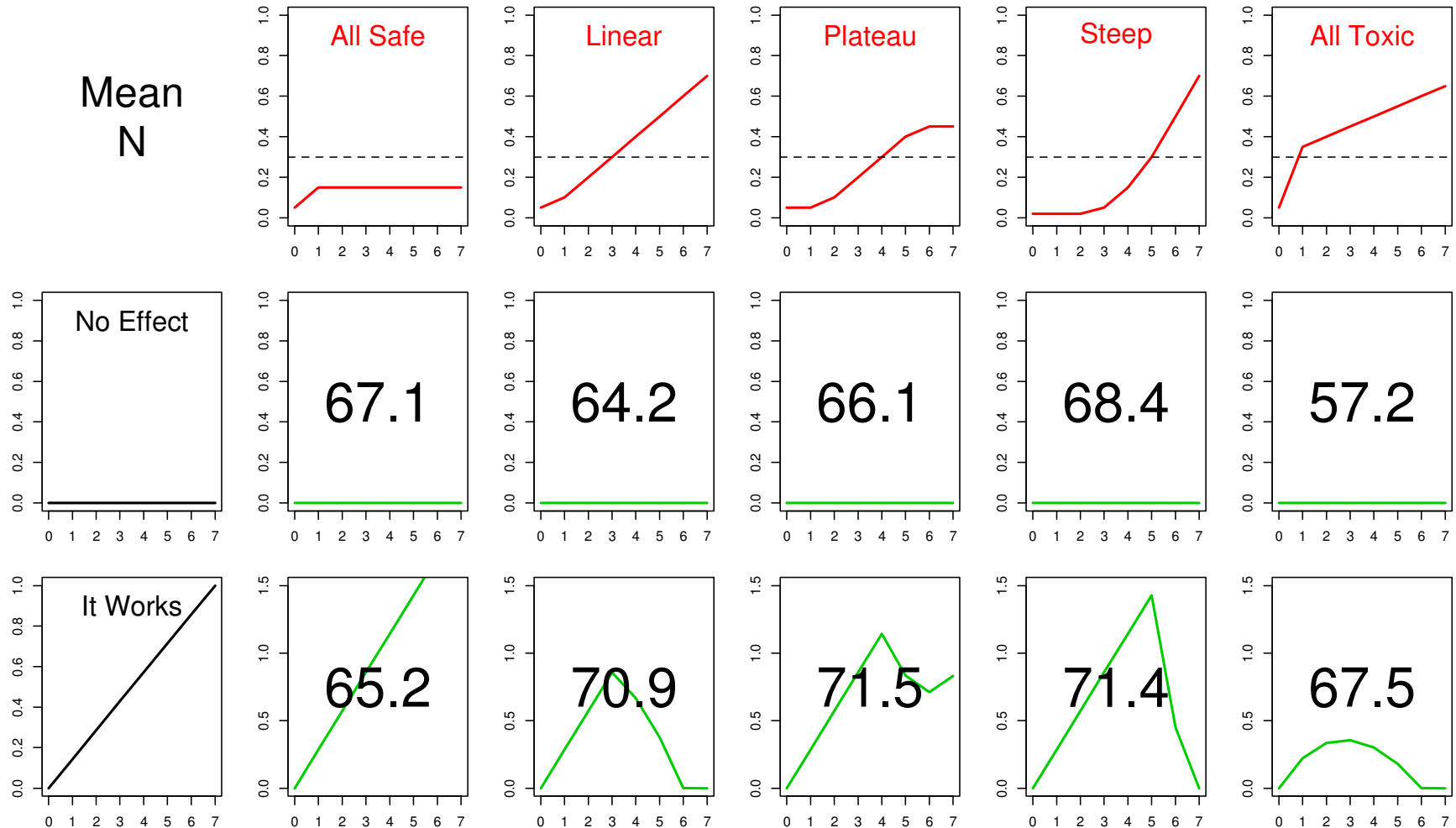


# Design 3: Operating Characteristics

POWER

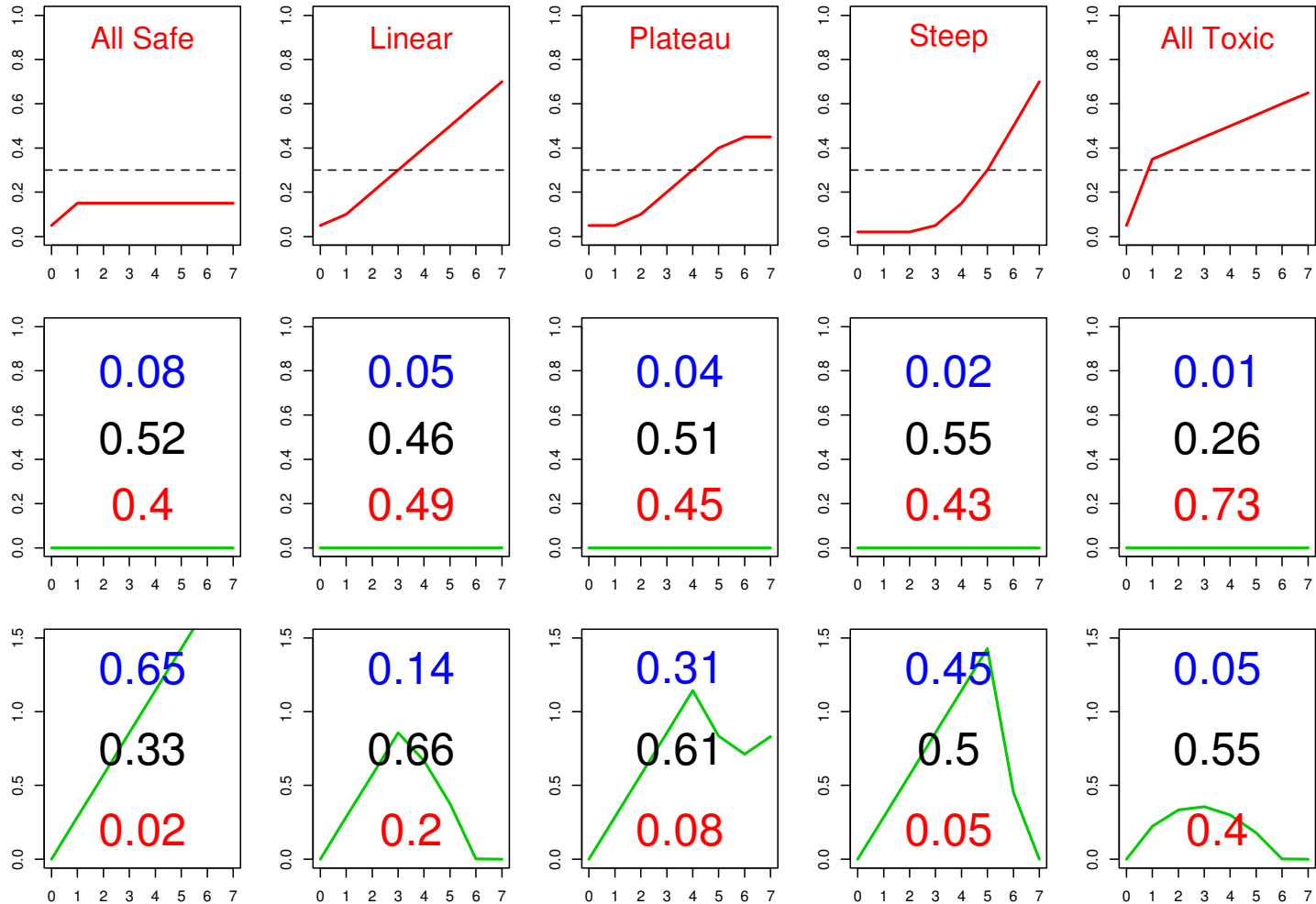


# Design 3: Operating Characteristics



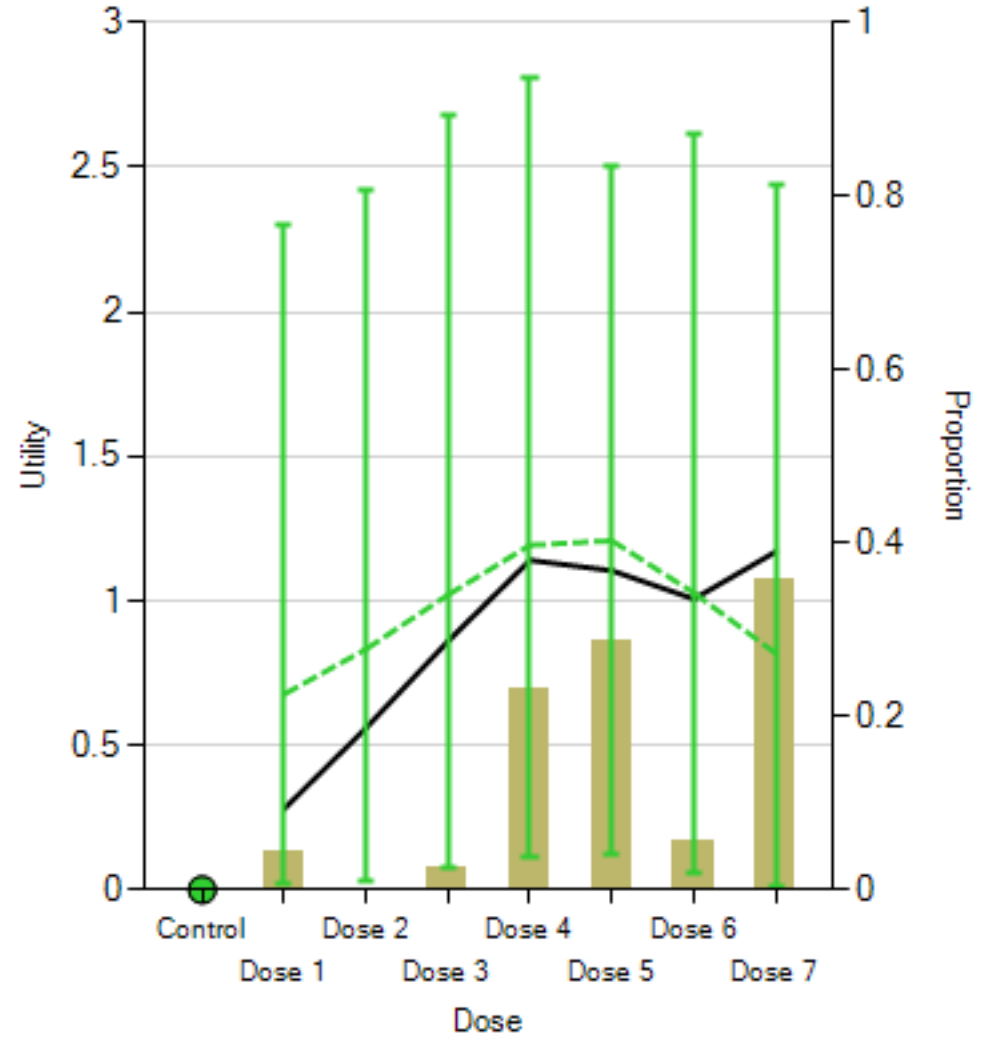
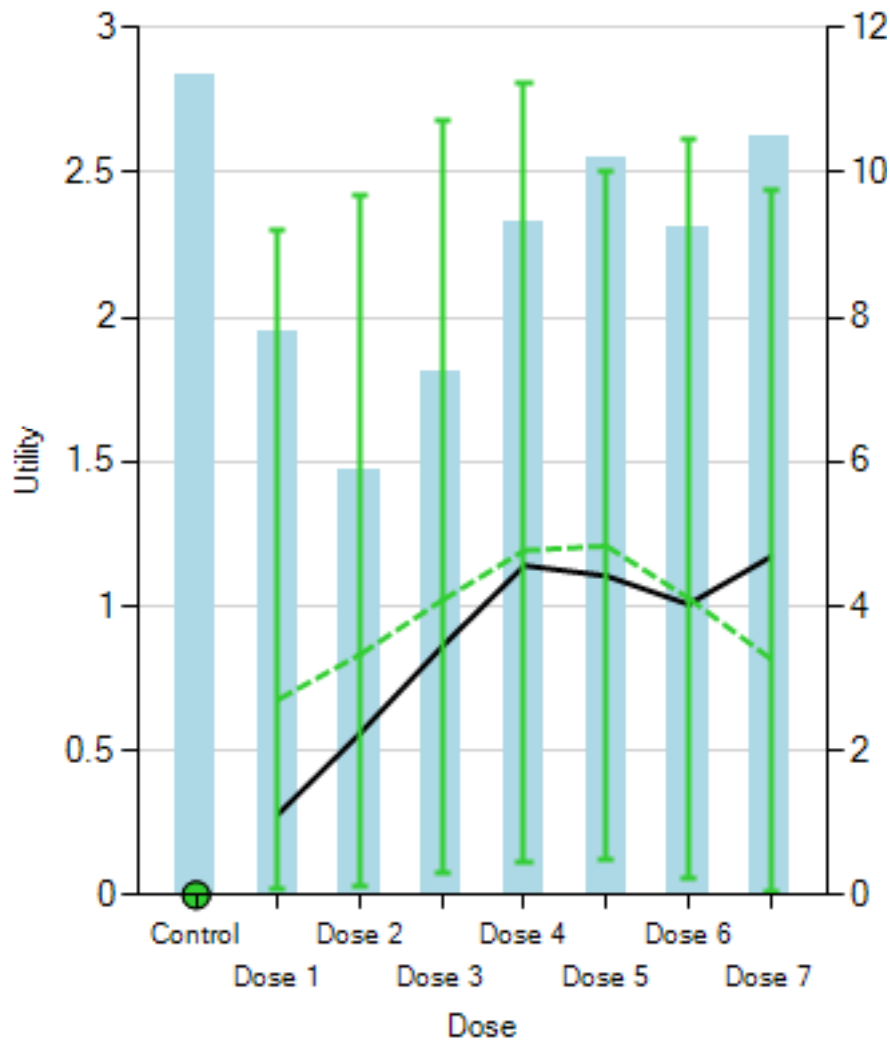
# Design 3: Operating Characteristics

Early  
Success  
Max  
Futility



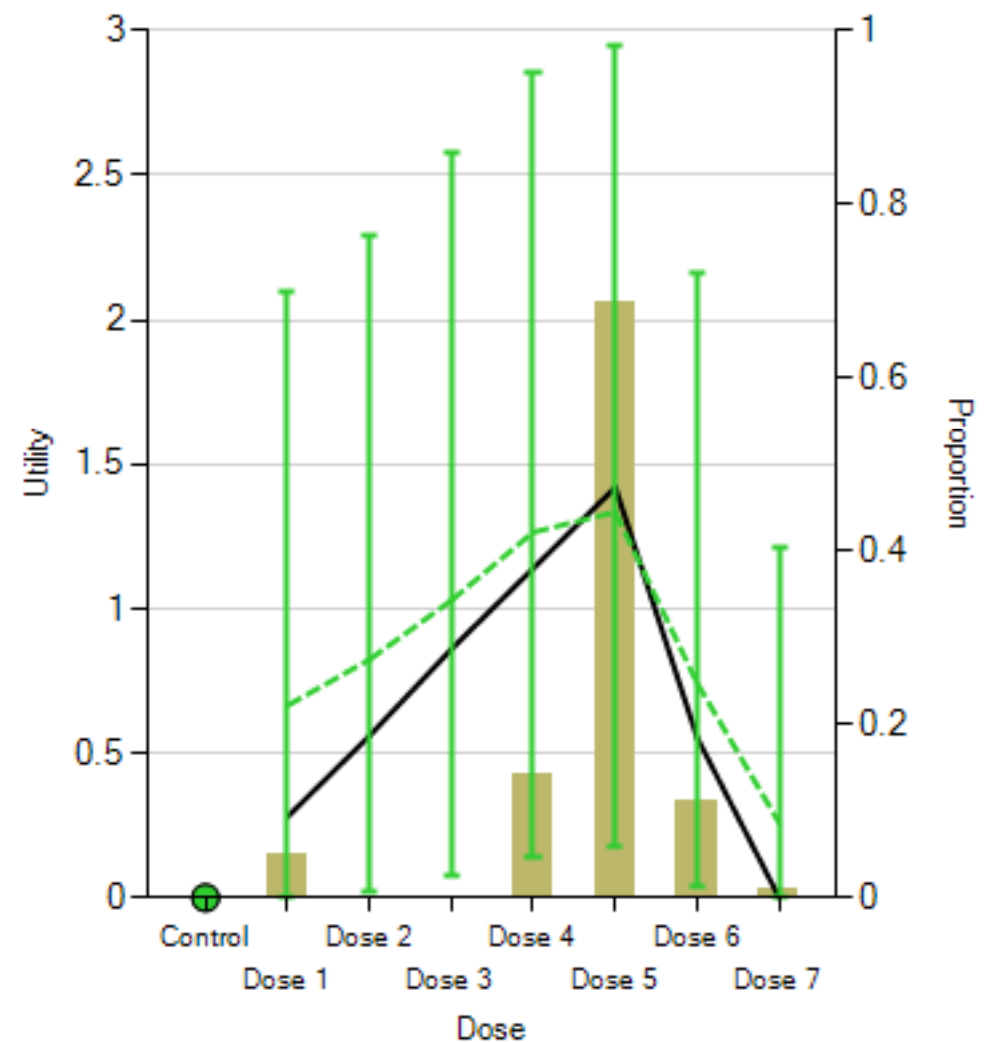
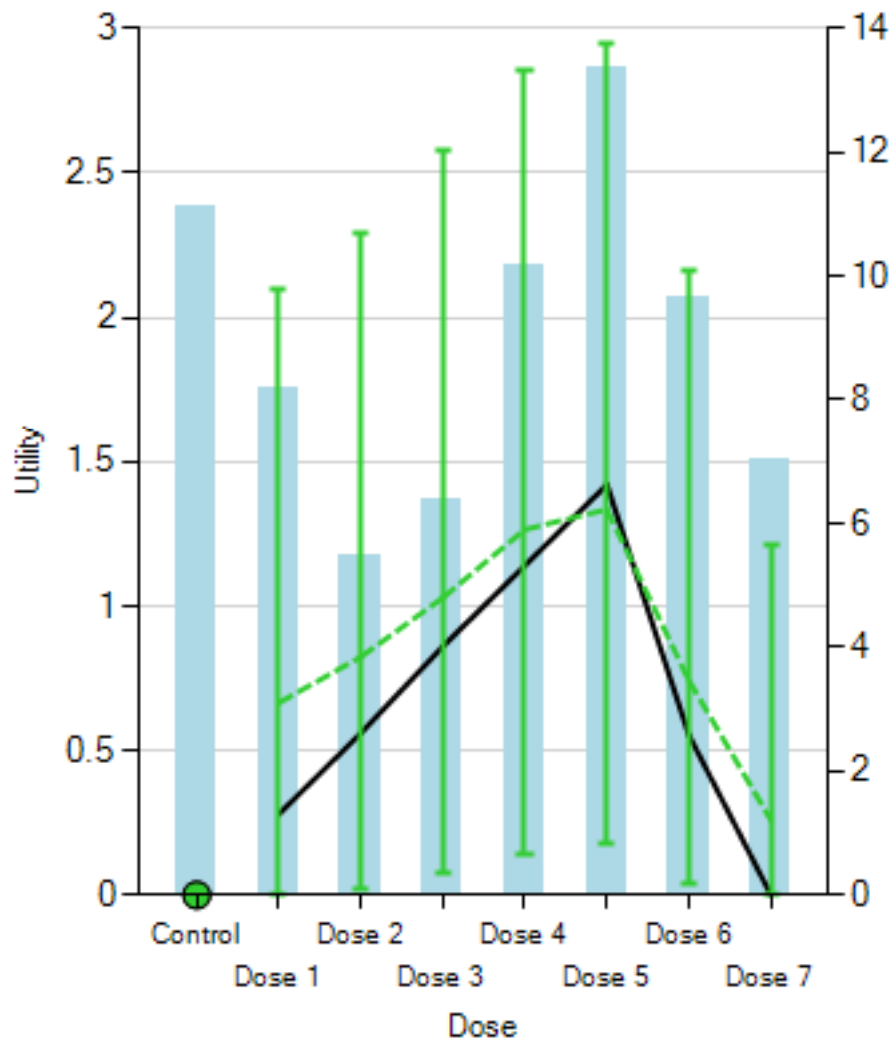
# Sample Size & Max Utility Dose

Efficacy: Works      Safety: Plateau



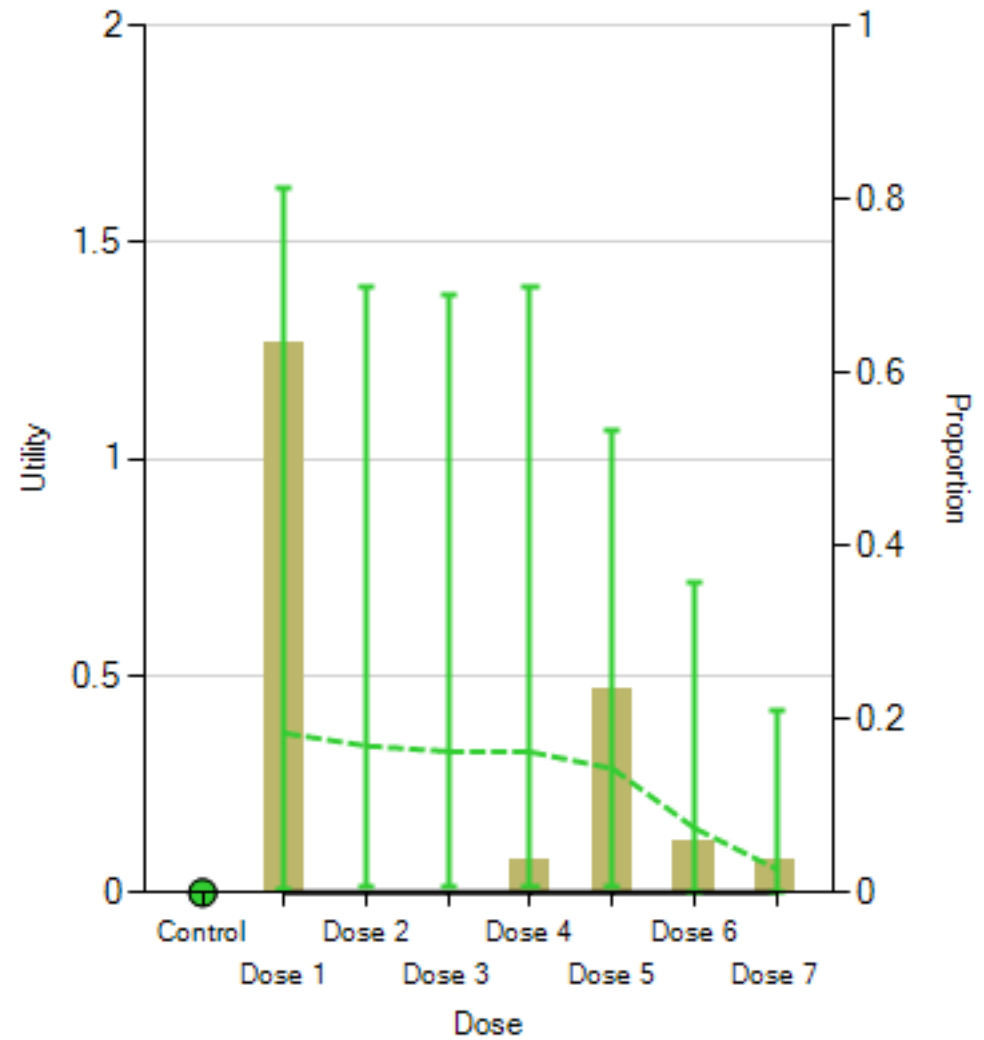
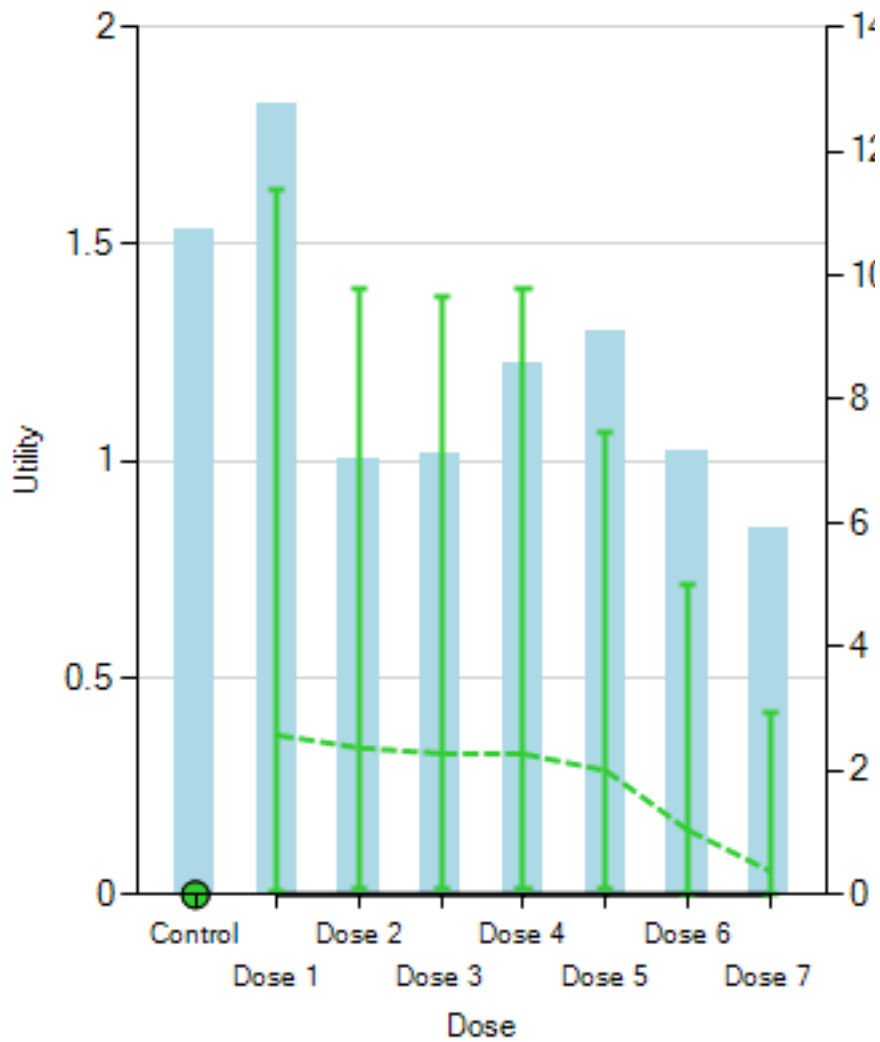
# Sample Size & Max Utility Dose

Efficacy: Works      Safety: Steep



# Sample Size & Max Utility Dose

Efficacy: No Better      Safety: Plateau



Contenten.....



# Future Work

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- Longer follow-up for efficacy –
  - 26 week efficacy endpoint
  - Use 4-wk outcomes in a longitudinal model of efficacy
- Phase I/II
  - add a futility look at end of phase I
  - add safety monitoring
- Phase II dose finding
  - more fully elicit a utility function
  - consider starting only with 3 low doses and ‘opening higher doses’ as appropriate