Adaptive Dose-Ranging Designs with Two Efficacy Endpoints

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AptivSolutions℠
Accelerating the Possibilities

OUTLINE

1. Motivational CIAS study
2. Adaptive design
3. Operating characteristics
4. Comparison with a conventional design
5. Conclusion

Goals of Clinical Development

- Cognitive impairment is a core symptom of schizophrenia
- A successful CIAS therapy holds the promise of improving overall patient outcomes
- No products currently exist for effectively treating CIAS
- Subjects are clinically stable DSM-IV schizophrenia patients on concurrent anti-psychotics
- The study drug will be administered as an adjunctive therapy

Regulatory Requirements

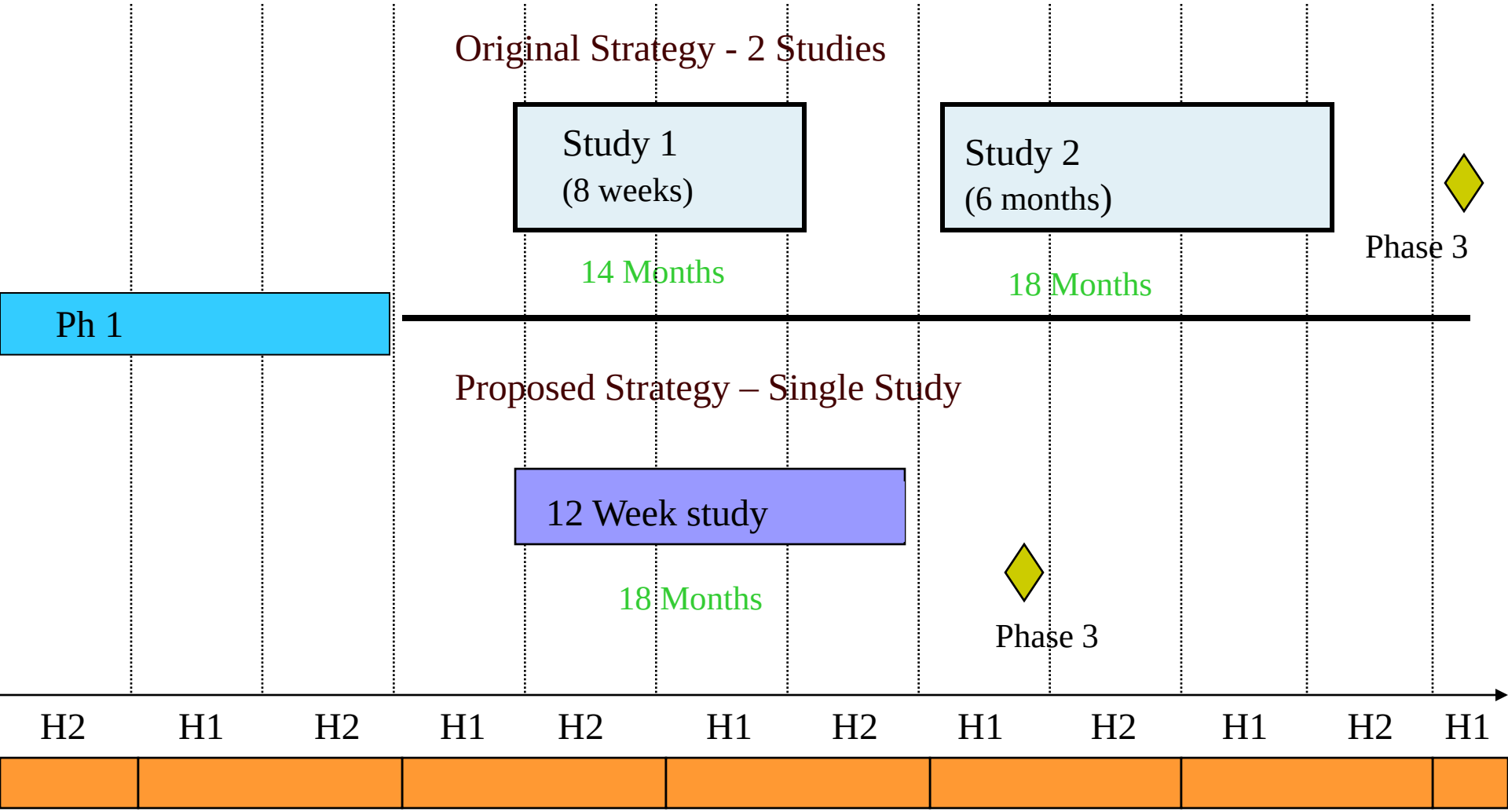
- No formal regulatory guideline exist, however, close cooperation has been taking place among Pharma, the FDA, and academia (in U.S.)*
- The Phase III study should:
  - Be of 6 months of treatment duration
  - Show a clinically meaningful effect of 0.5 SD both in cognition and functional capacity; a 1 SD effect on cognition alone is sufficient
  - Cognition measure: MCCB -- MATRICS Consensus Cognitive Battery composite endpoint
  - Functional Capacity Measure: UPSA-B -- UCSD Performance-based Skills Assessment Brief was recommended as the best measure

* Schizophr Bull. 2010 Jul 13. [Epub ahead of print]

The FDA-NIMH-MATRICS Guidelines for Clinical Trial Design of Cognitive-Enhancing Drugs: What Do We Know 5 Years Later?

Buchanan RW, Keefe RS, Umbricht D, Green MF, Laughren T, Marder SR.

Revised Phase 2 Strategy



Relative Advantages: Revised vs Original Strategies

Revised Strategy	**Original Strategy**
Faster – Phase 3 start 22 months earlier	**Replication of effect on cognition**
Cost savings – 5 M vs 10 M	**Greater evidence of long-lasting effect**

Revised strategy risk mitigation: Phase 3 studies to involve 6 month treatment, interim analysis + DSMB

Key Elements of the Study

- Goal: A SINGLE phase II study for proof of concept and dose finding to proceed to phase III
- Randomized, parallel group comparison of 6 study drug doses and Placebo
- Treatment Duration: 12 weeks (sufficient predictive value for decision of whether to proceed to Phase III)
  - Rationale: Functional capacity measures should show rapid effects, similar to cognition measures
- Co-primary endpoints:
  - Change from baseline at W12 for
    - MCCB composite for cognition
    - UPSA-B for functional capacity

Conventional Design

- Fixed equal allocation across 3 active doses + placebo
- 70 subjects per arm; total sample size (SS) 280 subjects
- Go to Phase III Decision:
  - One of the doses achieves an observed mean effect greater than 0.3 relative to placebo on both endpoints
  - The smallest dose that achieves this threshold is the “target” dose
- Risk control: for a given dose
  - Probability Go Decision $\geq$ 0.8 when both endpoints true effects are 0.5
  - Probability Go Decision $\leq$ 0.2 when both endpoints true effects are 0.2

Adaptive Design

- Response-adaptive allocation across 6 active doses + placebo
- Stopping rules (futility only)
- Early signal to start preparing for Phase III (does not involve stopping this study)
- Dose-Response modeling based on Normal Dynamic Linear Model with non informative priors
- Longitudinal modeling of endpoints to predict from earlier time points (W1, W4, W8)
- Drop out rate 25% (uniform throughout the treatment period)

Normal Dynamic Linear Model

- A piece-wise linear model
- Smoothed transitions in the dose-response slope across the doses
- Does not restrict the shape of the dose response curve
- Developed for analysis and forecasting of time series data
  - West and Harrison (1997). *Bayesian Forecasting and Dynamic Models*
- First used for adaptive dose-ranging studies
  - Berry, Mueller, Grieve, …, Krams (2002). *Adaptive Bayesian designs for dose-ranging drug trials.*

Normal Dynamic Linear Model

- The NDLM is defined with the following assumptions:

$$Y_{di} = \theta_d + \varepsilon_{di}, \qquad \varepsilon_{di} \sim N(0, \sigma^2)$$

$$\theta_d \sim N(\mu_{0d}, \nu_{0d}^2) \qquad \text{if } d \text{ is the first dose included in the NDLM}$$

$$\theta_d \sim N(\theta_{d-1}, \tau_{d-1}^2) \qquad \text{otherwise}$$

$$\tau_d^2 = \tau^2 (v_{d+1} - v_d).$$

- The prior distribution for the "drift" parameter and the error term in the NDLM are

$$\tau^2 \sim IG\left(\frac{\tau_n}{2}, \frac{\tau_\mu^2 \tau_n}{2}\right) \qquad \sigma^2 \sim IG\left(\frac{\sigma_n}{2}, \frac{\sigma_\mu^2 \sigma_n}{2}\right)$$

Longitudinal Model in the Design

- For each dose and each time point *t*

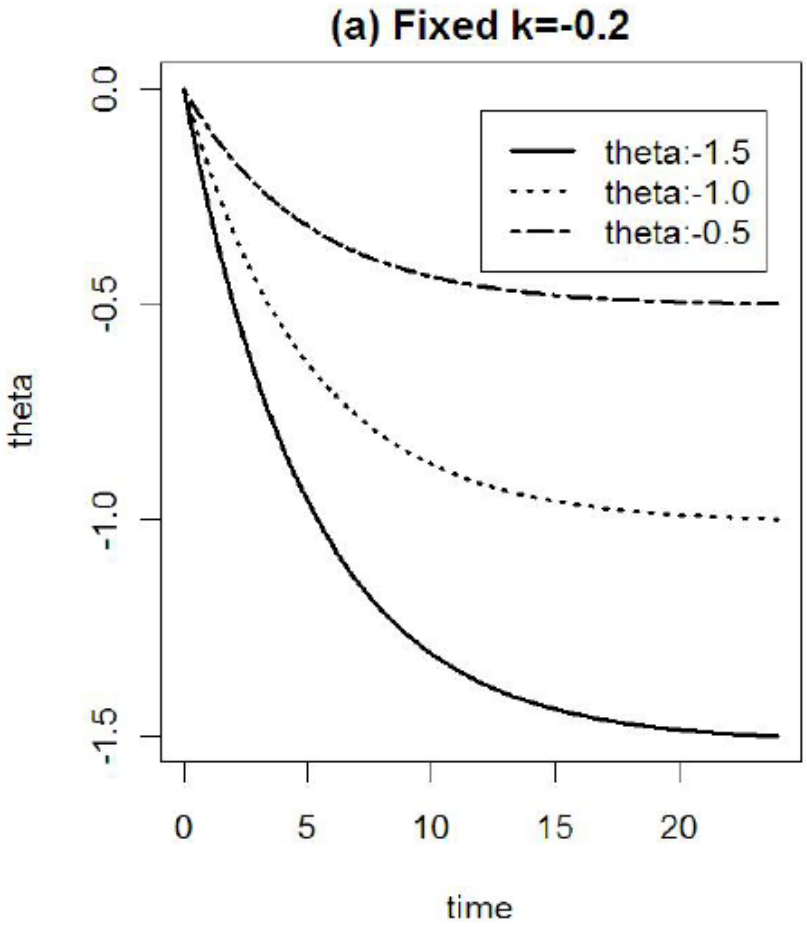
$$Y_T \mid Y_t \sim N(\alpha_t + \beta_t Y_t, \lambda_t^2)$$

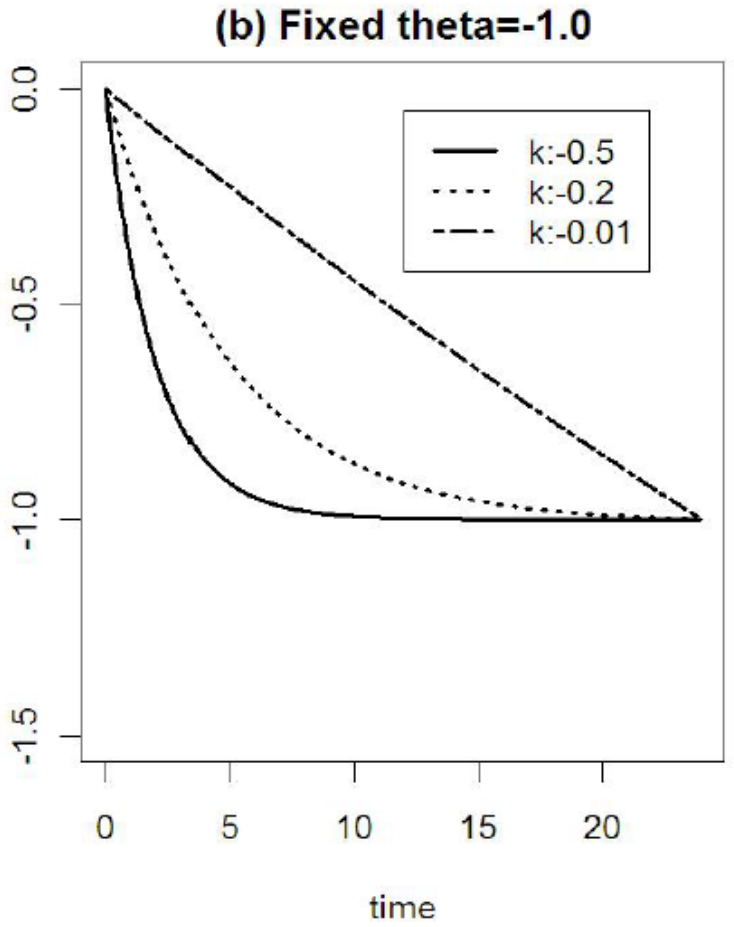
- with priors

$$\begin{aligned} \alpha_t &\sim N(\alpha_0, \sigma_\alpha^2) \\ \beta_t &\sim N(\beta_0, \sigma_\beta^2) \\ \lambda_t^2 &\sim IG\left(\frac{\lambda_n}{2}, \frac{\lambda_\mu^2 \lambda_n}{2}\right) \end{aligned}$$

Longitudinal Model

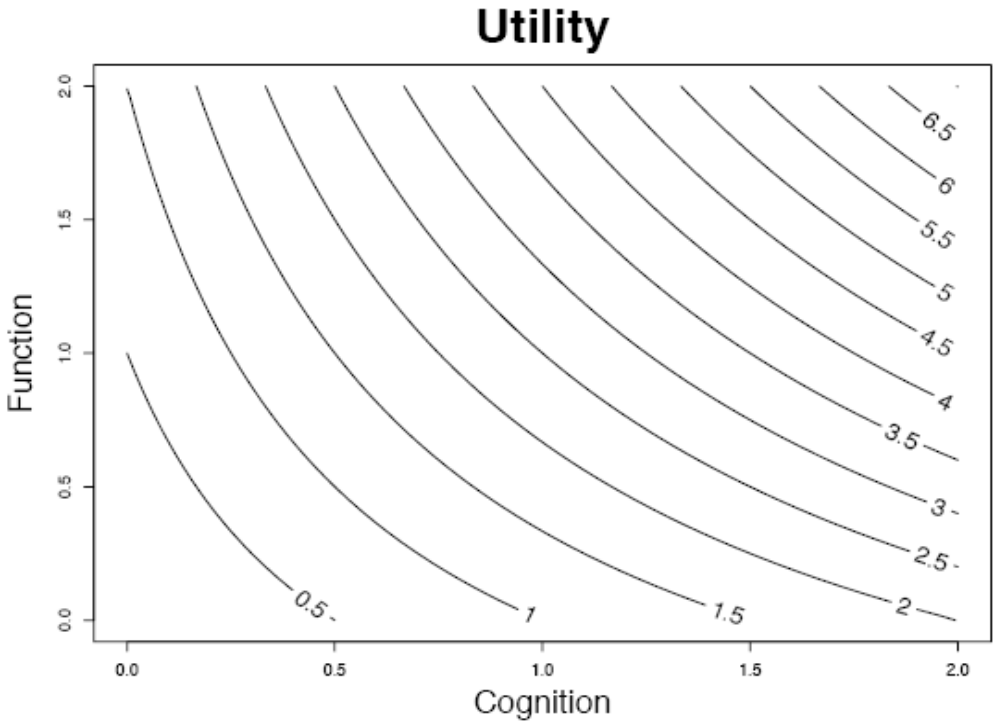
$$Y_{dit} = (\theta_d + s_{di} + \varepsilon_{dit})\frac{1 - e^{k_d t}}{1 - e^{k_d T}}, \quad s_{di} \sim N(0, \sigma_s^2), \quad \varepsilon_{dit} \sim N(0, \sigma^2)$$





Utility Index

- Utility index is an elegant and efficient way of imposing ordering in the multi-dimensional space.
- Simple to calculate and interpretation is straightforward
- The utility at each dose is calculated as:
- U = C + F/2 + C*F
  - C = Effect Size (Mean/SD) on cognition
  - F = Effect Size (Mean/SD) on function



Parameters of Adaptive Design

- Maximum 300 subjects
- Design Targets:
  - MUD – Maximum Utility Dose
  - MED – Minimum Efficacy Dose (U=0.5)
- Allocation Rule
  - Equal allocation of 10 subjects/dose initially
  - Allocation to placebo set to at least 20%, but no more than the maximum enrolling dose at any stage
  - Allocation ratios are updated at interim analyses every 2 weeks:

$$w_d \propto \frac{V(\theta_d)}{n_d + 1} \Pr(d = MUD)$$

Parameters of Adaptive Design

- No stopping for success
- "Trigger Phase 3 Preparation" signal is built-in
  - Pr (U @ MUD > 0.5) > 90% at the IA following 150, 230, 300 subjects have been accrued
- Stopping rule for futility:
  - Pr (U @ MUD > 0.5) < 7.5% with at least 100 subjects
- Go/No-Go decision (based on Final Data)
  - Go if Pr (U @ MUD > 0.5) > 70%
  - Failure if Pr (U @ MUD > 0.5) < 7.5%
  - Inconclusive (Open) otherwise

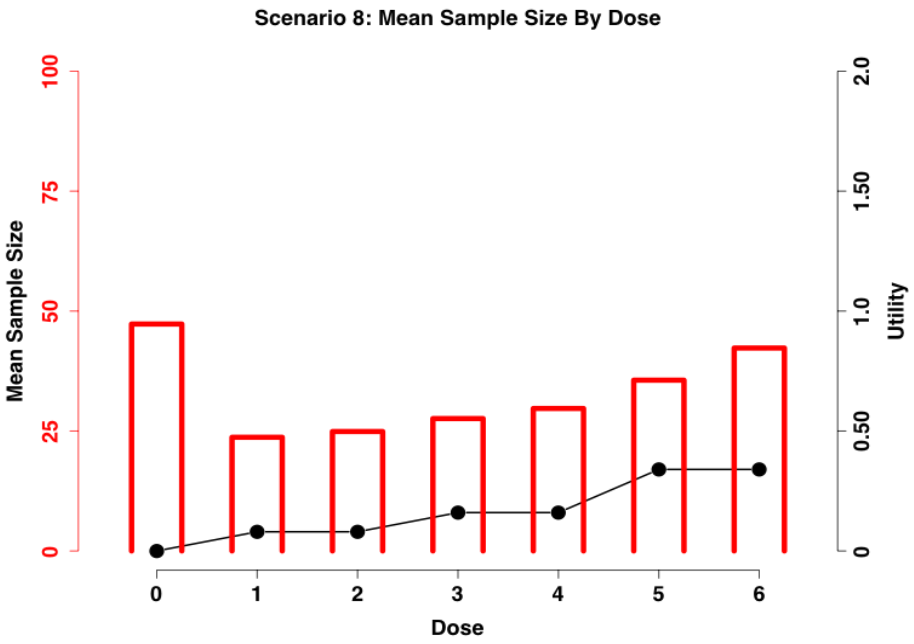
Examples: Scenario 2

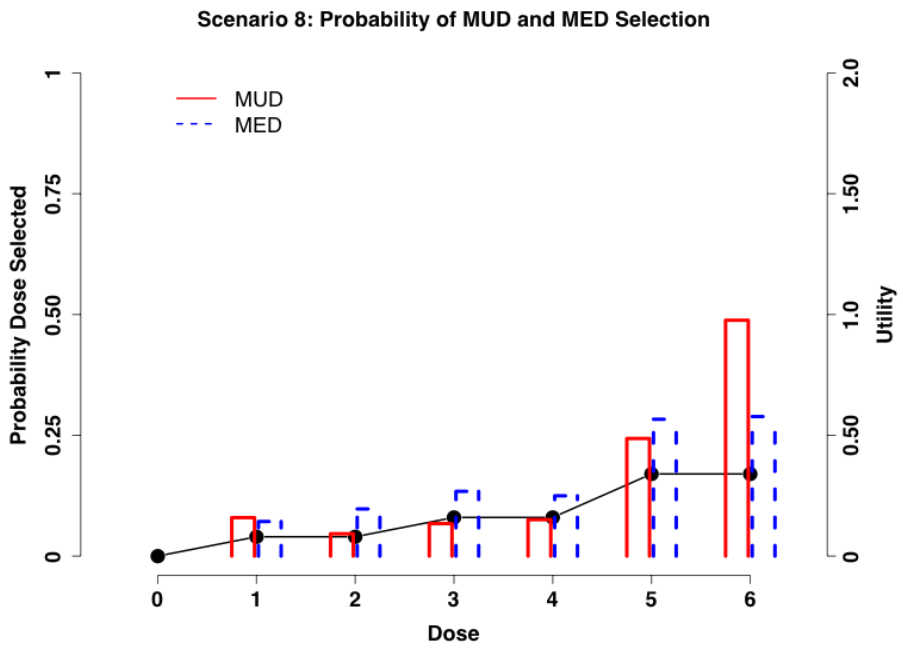
Dose	0	1	2	3	4	5	6
Cognition	**0**	**0.05**	**0.05**	**0.1**	**0.1**	**0.2**	**0.2**
Func. Cap	**0**	**0.05**	**0.05**	**0.1**	**0.1**	**0.2**	**0.2**
Utility	**0.00**	**0.08**	**0.08**	**0.16**	**0.16**	**0.34**	**0.34**

		Complete Data			
		Go	Open	Fail.	Total
End Accr.	Cap	**6**	**44.7**	**2.2**	**52.9**
	Futil.	**0.02**	**16.9**	**30.2**	**47.1**
	Total	**6**	**61.6**	**32.4**	

- **Mean SS (SD): 231 (84)**
- **Enroll to the maximum: 52.9%**
- **Futility stop for 47.1% of the time**
- **Declare Go 6%**
- **Open 61.6%**
- **Futility declared 32.4% of the time**

OC: Scenario 2





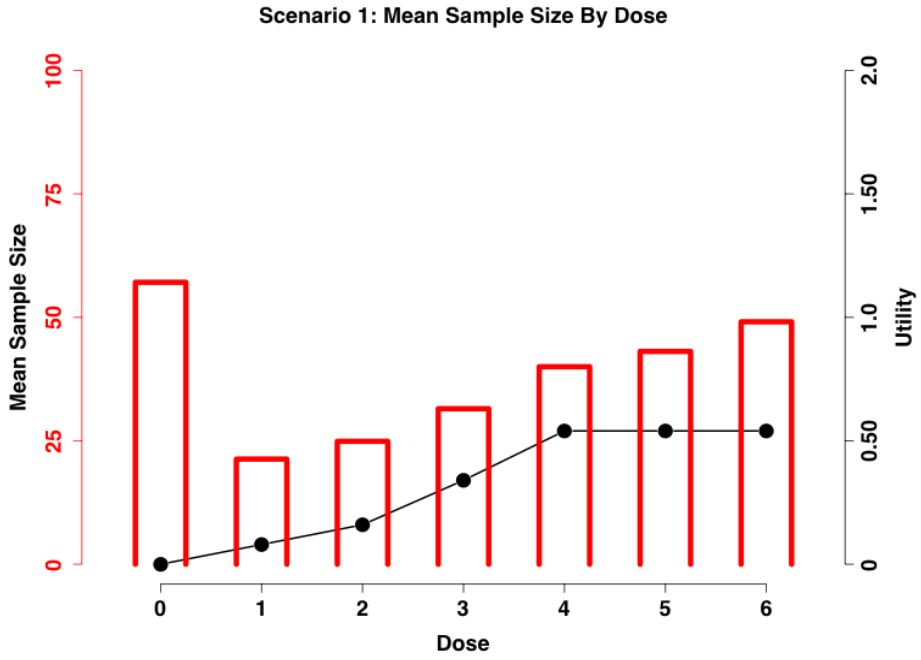
OC: Scenario 3

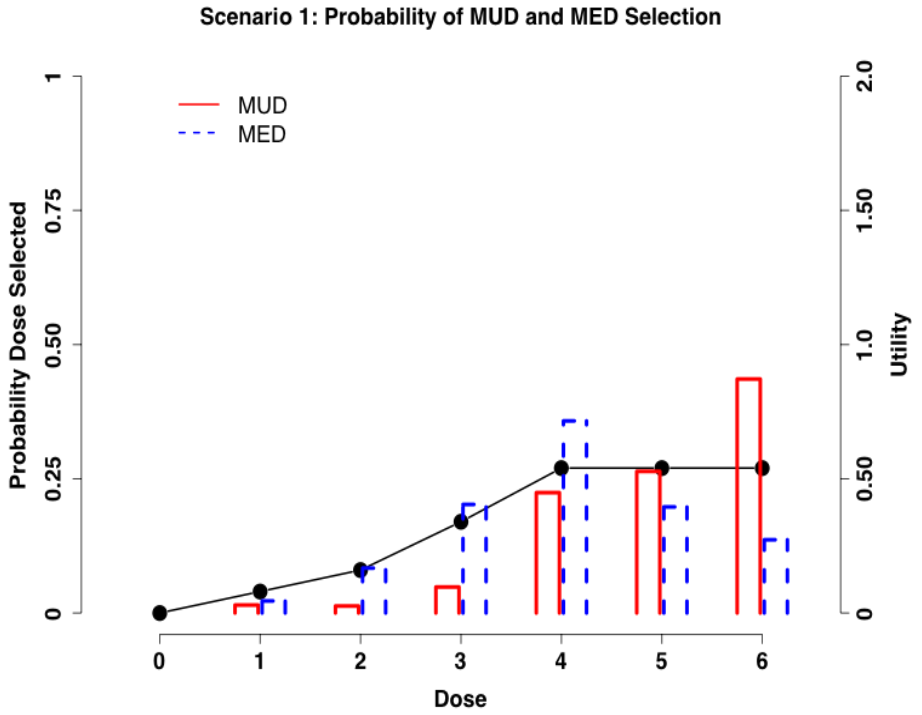
Dose	0	1	2	3	4	5	6
Cognition	**0**	**0.05**	**0.1**	**0.2**	**0.3**	**0.3**	**0.3**
Func. Cap	**0**	**0.05**	**0.1**	**0.3**	**0.3**	**0.3**	**0.3**
Utility	**0.00**	**0.08**	**0.16**	**0.34**	**0.54**	**0.54**	**0.54**

		Complete Data			
		Go	Open	Fail.	Total
End Accr.	Cap	**29**	**49**	**0.5**	**78.5**
	Futil.	**0.02**	**10**	**11**	**21**
	Total	**29**	**59**	**11.8**	

- **Mean SS (SD): 267 (68)**
- **Enroll to the maximum: 78.5%**
- **Futility stop for 21% of the time**
- **Declare Go 29%**
- **Open 59%**
- **Futility declared 11.8% of the time**

OC: Scenario 3





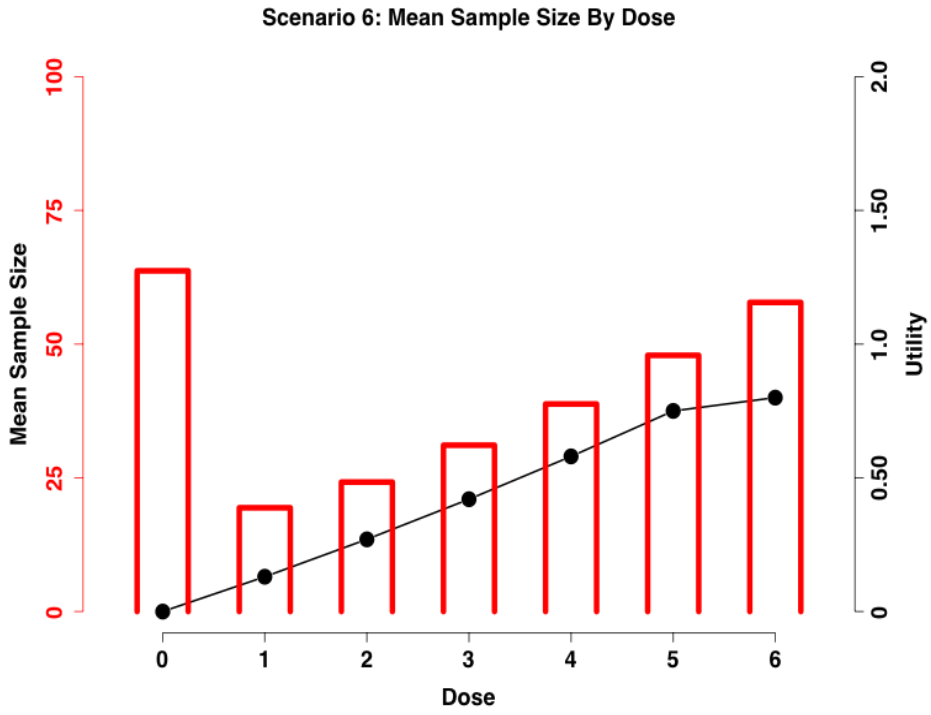
OC: Scenario 5

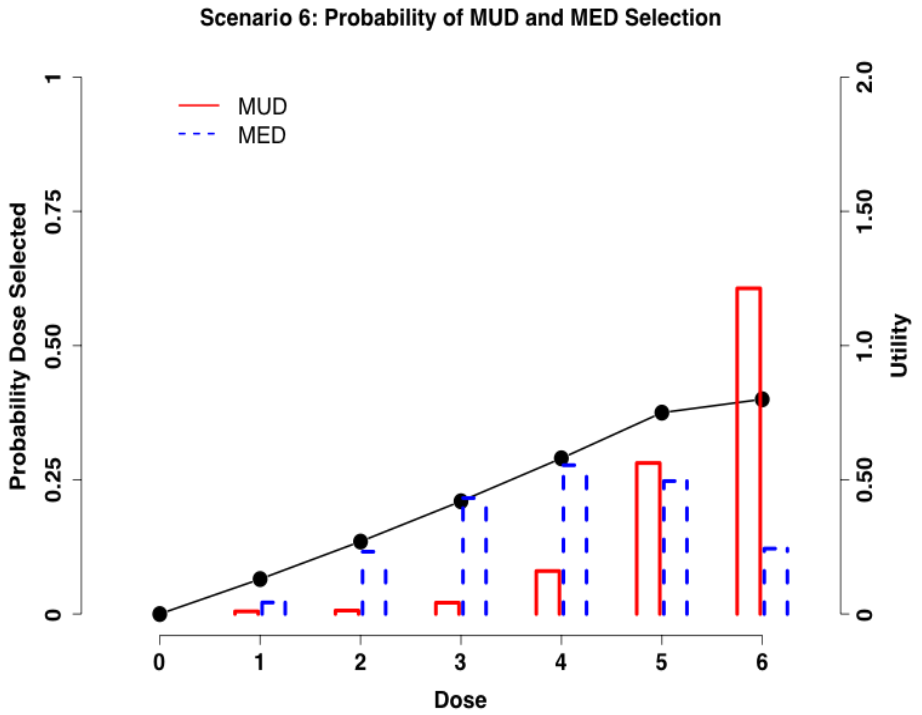
Dose	0	1	2	3	4	5	6
Cognition	**0**	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.5**
Func. Cap	**0**	**0.05**	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**
Utility	**0.00**	**0.13**	**0.27**	**0.42**	**0.58**	**0.75**	**0.80**

		Complete Data			
		Go	Open	Fail.	Total
End Accr.	Cap	**59**	**31**	**0.1**	**90**
	Futil.	**0.02**	**6**	**4**	**10**
	Total	**59**	**37**	**4**	

- **Mean SS (SD): 283 (52)**
- **Enroll to the maximum: 90%**
- **Futility stop for 10% of the time**
- **Declare Go 59%**
- **Open 37%**
- **Futility declared 4% of the time**

OC: Scenario 5





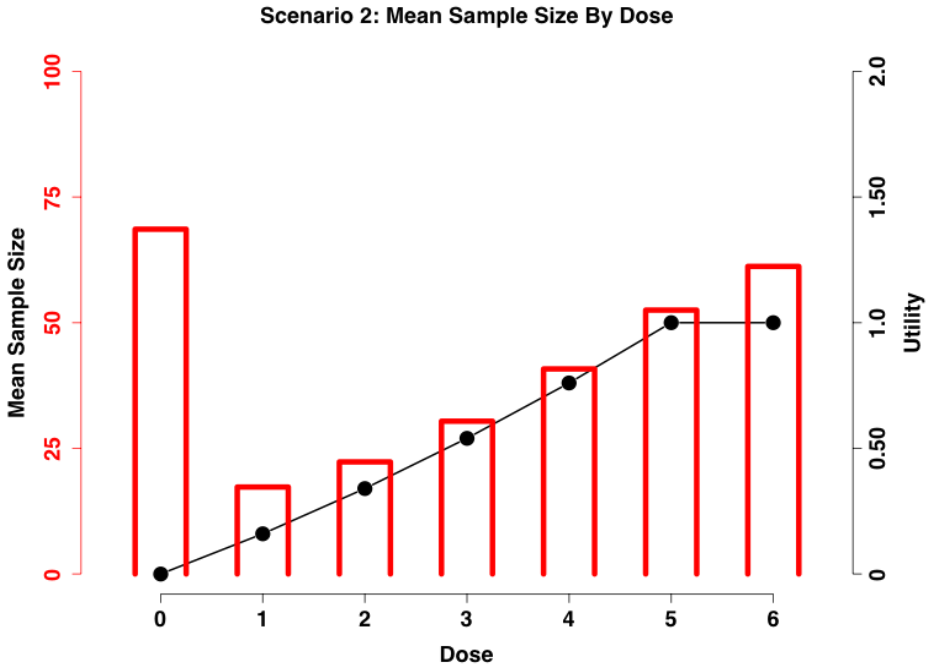
OC: Scenario 6

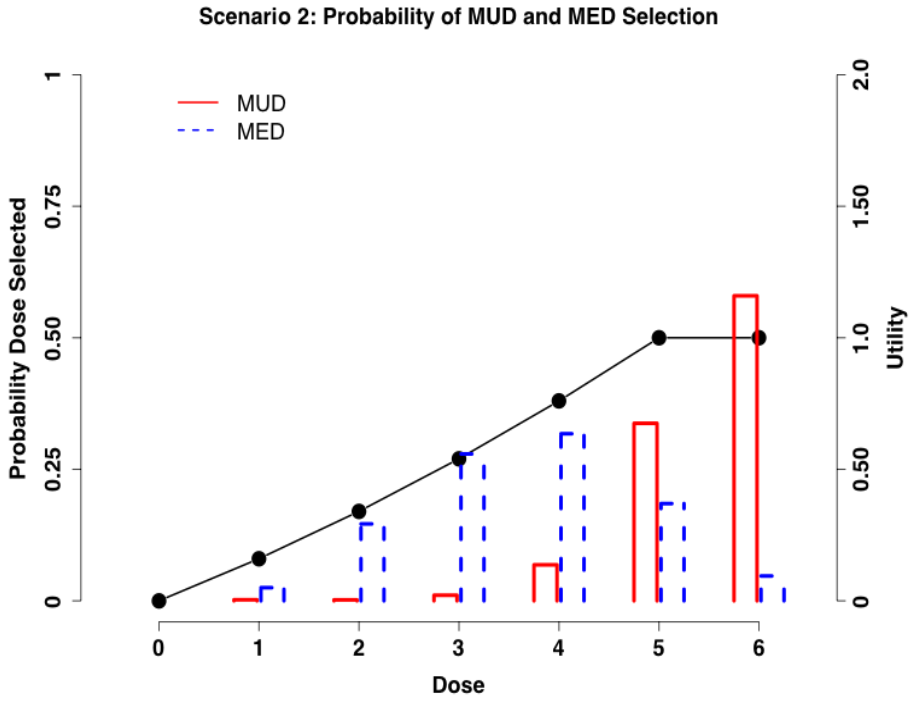
Dose	0	1	2	3	4	5	6
Cognition	0	0.1	0.2	0.3	0.4	0.5	0.5
Func. Cap	0	0.1	0.2	0.3	0.4	0.5	0.5
Utility	0.00	0.16	0.34	0.54	0.76	1.00	1.00

		Complete Data			
		Go	Open	Fail.	Total
End Accr.	Cap	83	13	0	96
	Futil.	0.02	2.5	1.4	4
	Total	83	15.5	1.4	

- **Mean SS (SD): 293 (35)**
- **Enroll to the maximum: 96%**
- **Futility stop for 4% of the time**
- **Declare Go 83%**
- **Open 15.5%**
- **Futility declared 1.4% of the time**

OC: Scenario 6





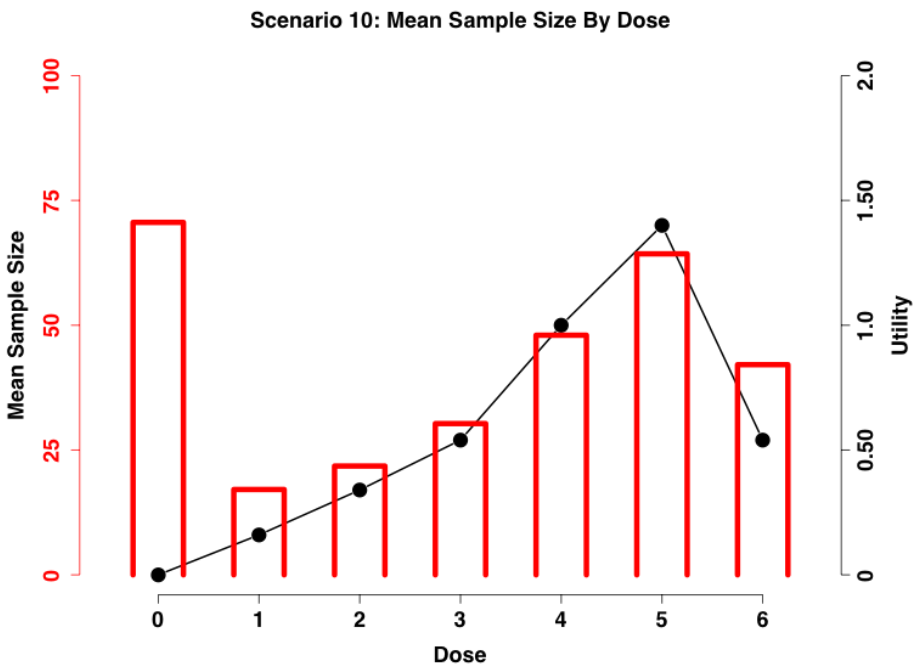
OC: Scenario 10

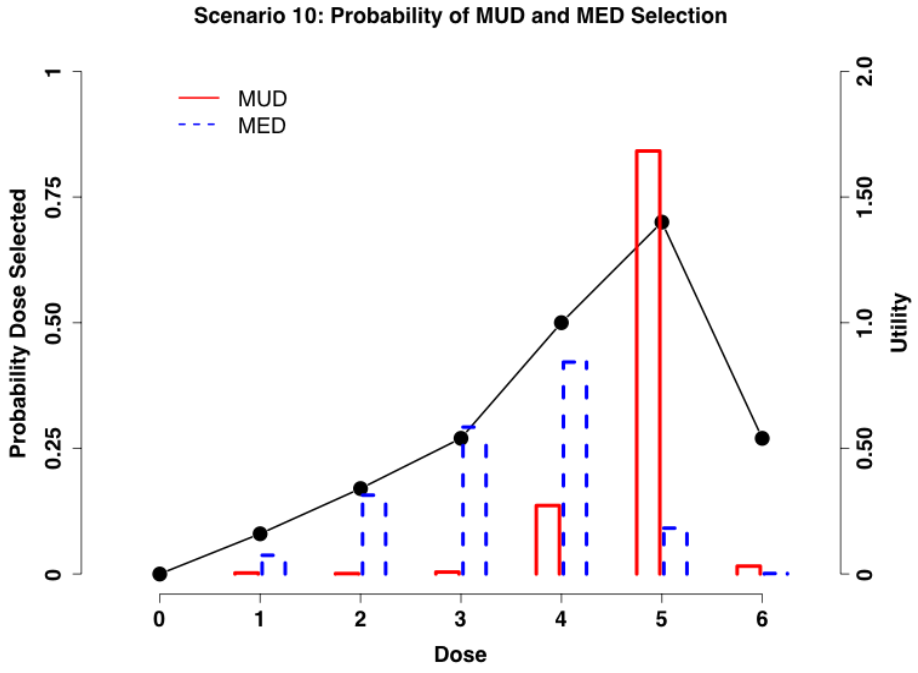
Dose	0	1	2	3	4	5	6
Cognition	**0**	**0.1**	**0.2**	**0.3**	**0.5**	**0.65**	**0.3**
Func. Cap	**0**	**0.1**	**0.2**	**0.3**	**0.5**	**0.65**	**0.3**
Utility	**0.00**	**0.16**	**0.34**	**0.54**	**1.00**	**1.40**	**0.54**

		Complete Data			
		Go	Open	Fail.	Total
End Accr.	Cap	**91**	**6**	**0**	**97**
	Futil.	**0**	**2**	**1**	**3**
	Total	**91**	**8**	**1**	

- **Mean SS (SD): 294 (32)**
- **Enroll to the maximum: 97%**
- **Futility stop for 3% of the time**
- **Declare Go 91%**
- **Open 8%**
- **Futility declared 1% of the time**

OC: Scenario 10





Fixed vs. Adaptive Design - Comparison

				Traditional design (3 doses + Pbo)		Adaptive Design (6 doses + Pbo)			
Sc. #	Cogn.	Func	Util @ MUD	SS	Success	Average SS	Success	Futility Stop	Trigger Ph. III
				(Complete)	(%)	(Enroll)	(%)	(%)	(%)
1	0.0	0.0	0.00	280	0.2	170	0.08	85.5	0.1
2	0.2	0.2	0.34	280	9.0	231	6.0	47.1	2.8
3	0.3	0.3	0.54	280	46.8	267	28.9	21.5	13.9
4	0.5	0.0	0.50	280	2.3	262	22.2	25.1	10.2
5	0.5	0.3	0.80	280	47.5	283	58.9	10.2	34.5
6	0.5	0.5	1.00	280	93.5	293	83.1	4.0	61.2
7	0.7	0.7	1.54	280	99.9	299	98.5	0.6	93.4
8	1.0	0.0	1.00	280	2.4	298	92.9	1.4	75.0
9	0.0	1.0	0.5	280	2.2	278	31.8	14.7	15.6
10	*0.65*	*0.65*	*1.4*	280	88.6	294	91.0	3.2	73.5

Conclusion

- Team needed to trade-off additional burden of running a flexible design vs. answering research questions more efficiently
  - The cost savings and more importantly, the improvement in the efficiency of decision making, as shown in previous slides, was sufficient enough for the team to decide in favor of the adaptive design
- Adaptive design enables the evaluation of greater number of doses in general
- The advantage is amplified in this CNS learn study where we cannot easily assume a monotonic dose response on either endpoint
- No additional cost to add futility and early GO evaluation criteria
- Outperforms the fixed design across all scenarios considered

Acknowledgement

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