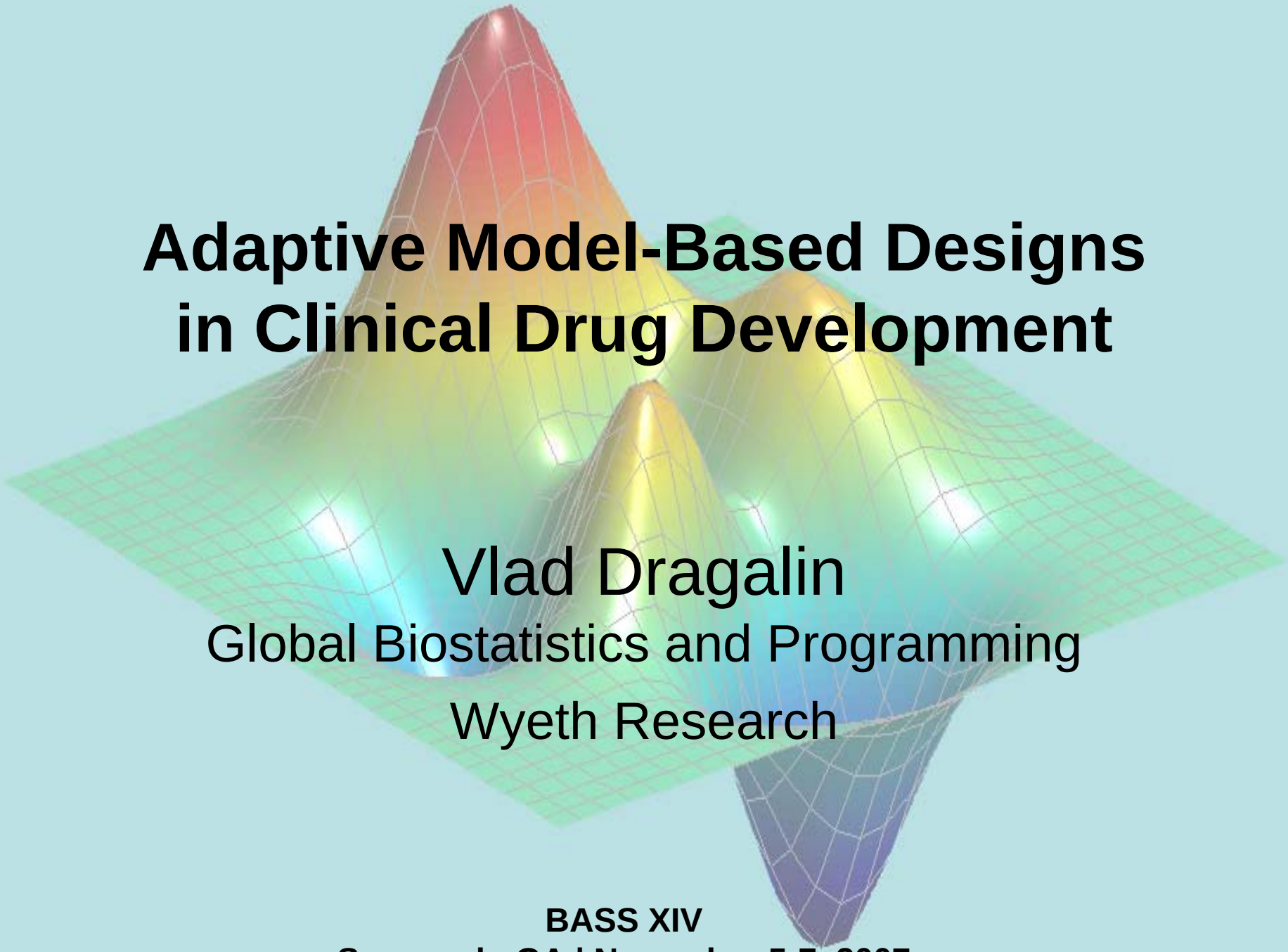

Adaptive Model-Based Designs in Clinical Drug Development

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Global Biostatistics and Programming
Wyeth Research

BASS XIV
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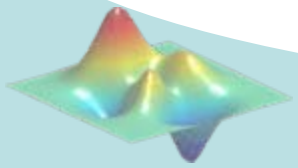
Outline

- Definition and general structure of adaptive designs
- Landscape of adaptive designs in drug development
- Achieving the goals
- Three case studies to exemplify capabilities/limitations
- Future prospects



Definition

Adaptive Design

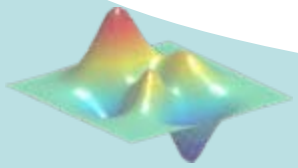
- uses accumulating data to decide on how to modify aspects of the study
- without undermining the *validity* and *integrity* of the trial

Validity means

- providing correct statistical inference (such as adjusted p-values, unbiased estimates and adjusted confidence intervals, etc)
- assuring consistency between different stages of the study
- minimizing operational bias

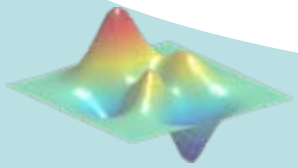
Integrity means

- providing convincing results to a broader scientific community
- preplanning, as much as possible, based on intended adaptations
- maintaining confidentiality of data



General Structure

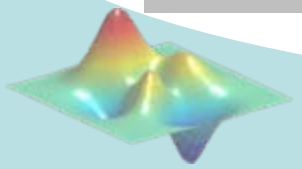
- An adaptive design requires the trial to be conducted in several stages with access to the accumulated data
- An adaptive design may have one or more rules:
  - **Allocation Rule**: how subjects will be allocated to available arms
  - **Sampling Rule**: how many subjects will be sampled at next stage
  - **Stopping Rule**: when to stop the trial (for efficacy, harm, futility)
  - **Decision Rule**: the final decision and interim decisions pertaining to design change not covered by the previous three rules
- At any stage, the data may be analyzed and next stages redesigned taking into account all available data



Classification

Achieving the goals

- The objective of a clinical trial may be either
  - to target the MTD or MED or to find the therapeutic range
  - or to determine the OSD (Optimal Safe Dose) to be recommended for confirmation
  - or to confirm efficacy over control in Phase III clinical trial
- This clinical goal is usually determined by
  - the clinicians from the pharmaceutical industry
  - practicing physicians
  - key opinion leaders in the field, and
  - the regulatory agency

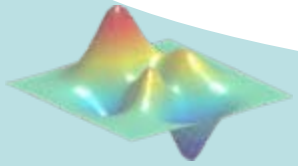


Achieving the goals

- Once agreement has been reached on the objective, it is the statistician's responsibility to provide the appropriate design and statistical inferential structure required to achieve that goal

- There are plenty of available designs on statistician’s shelf
- The greatest challenge is their implementation

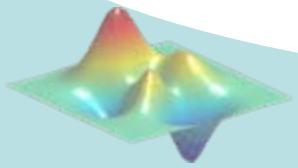
- Adaptive designs have much more to offer than the rigid conventional parallel group designs in clinical trials



Critical Path Opportunity

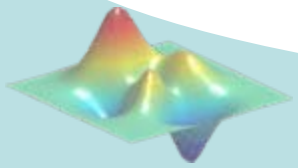
- Model-based approaches to integrating knowledge and improving drug development decision making
  - Dose-response (exposure-response) modeling
  - Efficacy-toxicity response modeling
  - Drug combination modeling
  - Drug and disease modeling

- Exploration of innovative, alternative clinical trial designs using models
  - Adaptive dose finding
  - Enrichment approaches
  - Randomized withdrawal studies



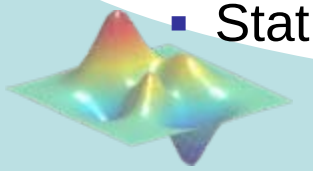
Case Study 1

- Gold pass compound XXX
  - lead indication in Psychiatry (anxiety & depression)
  - secondary indications in Neuropathic pain, RLS & FMS
- Objectives : To establish superiority of XXX dose(s) versus placebo
  - Confirm efficacy (and durability of response)
    - 8 week treatment, but expect treatment effect at 2 weeks
    - correlation between early and late treatment effects
  - Establish safety profile
  - Establish dose-response
- Strategic Aim:
  - pivotal quality to potentially support registration



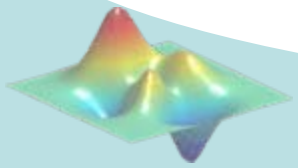
Study Designs

- Last thing we want is to get to the end only to discover
  - no doses are effective OR
  - we missed obtaining a significant result because our original assumptions were too optimistic
- Standard Dose Ranging Design
  - known entity, but lacks flexibility
- Adaptive Design
  - Potential savings in terms of both resource and time if there are clear signs that the compound does not work
  - Allows for addition of more patients to a promising dose
    - Protects against underestimate of variance
  - Potential to get to decision quicker, e.g. 5 - 9 months
  - Full data package on doses of interest
  - Statistical validity maintained

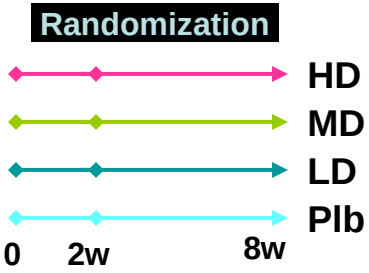


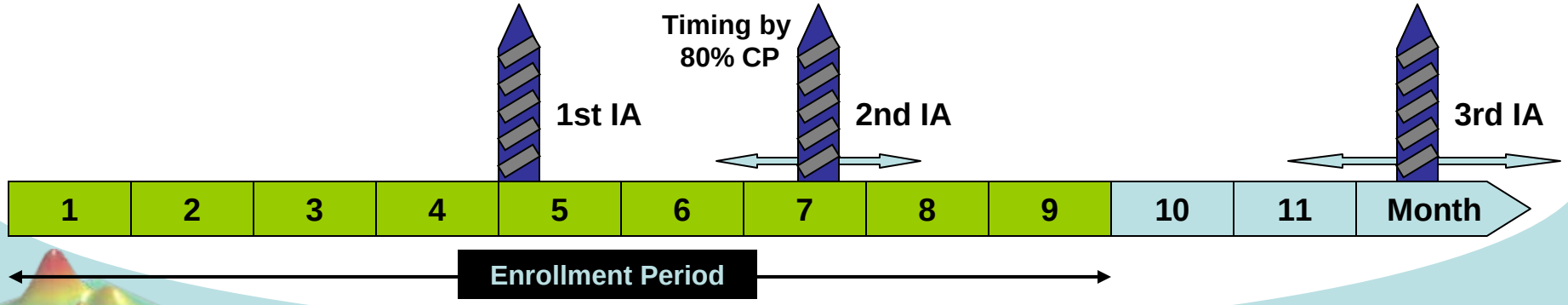
Details of the Design

Primary Endpoint:	**PI-NRS change from Baseline at 8thW of treatment**
Primary Goal:	**Comparison of three doses (LD, MD, HD) with Plb**
Target Difference:	**1.3 units**
STDeviation:	**2.1 units**
Type I error:	**α = 0.05 (adjustment for multiplicity α = 0.05/3 = 0.017)**
Power:	**90%**
Traditional Dsgn:	**4 parallel groups - 72 patients/per arm (total 288)**
Adaptive Dsgn:	**3 stage inverse-normal combination test**
Efficacy Bndry:	**O'Brien-Fleming type**
	nominal levels: (0.0006, 0.014, 0.047)
Futility Bndry:	**nominal levels: (0.5, 0.5)**
Inflation Factor:	**1.025 - maximum 75 patients/arm**

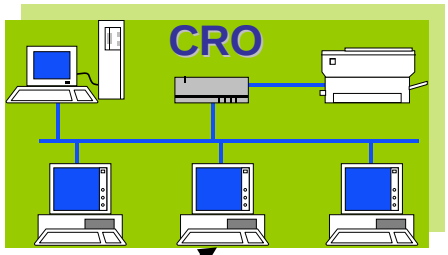


1st Stage


Randomization
HD
MD
LD
Plb
0
2w
8w


Timing by
80% CP
1st IA
2nd IA
3rd IA
1
2
3
4
5
6
7
8
9
10
11
Month
Enrollment Period

1st Stage



Steering Committee

Randomization

HD
MD
LD
Plb

0 2w 8w

Decisions:

- Stop arm for futility
  - 49.5%
- Stop arm for efficacy
  - 2.9%
- Stop the study for futility
- Stop arm(s) for safety
- Determine Randomization
- Determine timing of 2nd IA (based on 80% Cond. Power)

1st Stage Data

Timing by 80% CP

1st IA

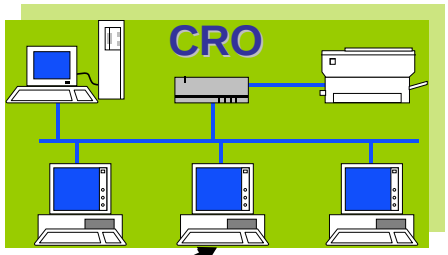
2nd IA

3rd IA

1 2 3 4 5 6 7 8 9 10 11 Month

Enrollment Period

2nd Stage



Steering Committee

Randomization

HD

MD

Plb

0 2w 8w

2nd Stage Data

1st Stage Data

Decisions:

- Stop arm for futility
  - 13.1%
- Stop arm for efficacy
  - 47.6%
- Stop the study for futility
- Stop arm(s) for safety
- Determine Randomization
- Determine timing of 3rd IA (based on 80% Cond. Power)

1st IA

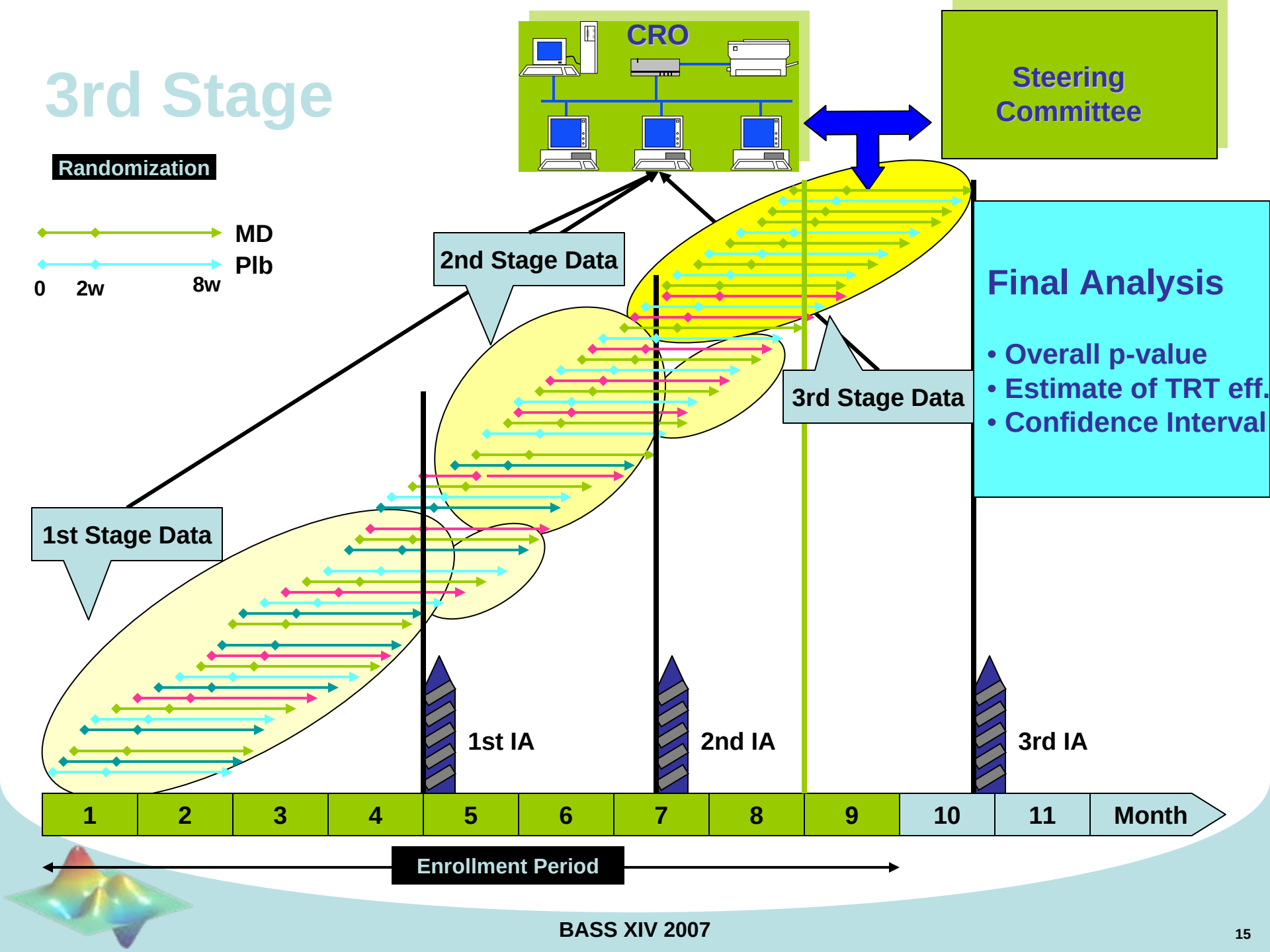
2nd IA

3rd IA

1 2 3 4 5 6 7 8 9 10 11 Month

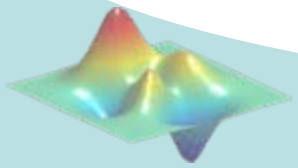
Enrollment Period

3rd Stage


CRO
Steering Committee
Randomization
MD
Plb
0
2w
8w
2nd Stage Data
3rd Stage Data
1st Stage Data
Final Analysis
• Overall p-value
• Estimate of TRT eff.
• Confidence Interval
1st IA
2nd IA
3rd IA
1
2
3
4
5
6
7
8
9
10
11
Month
Enrollment Period

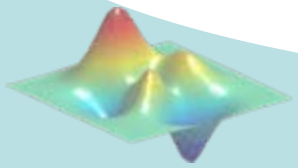
Case Study 2

- Phase II Study: Treatment of Acute Migraine during the Mild Headache Phase with YYY compound
  - **Allocation Rule:** according to CRM procedure
  - **Sampling Rule:** after each observation
  - **Stopping Rule:** for efficacy/futility
  - **Decision Rule:** update the model (one-parameter logistic regression)



Details of the Design

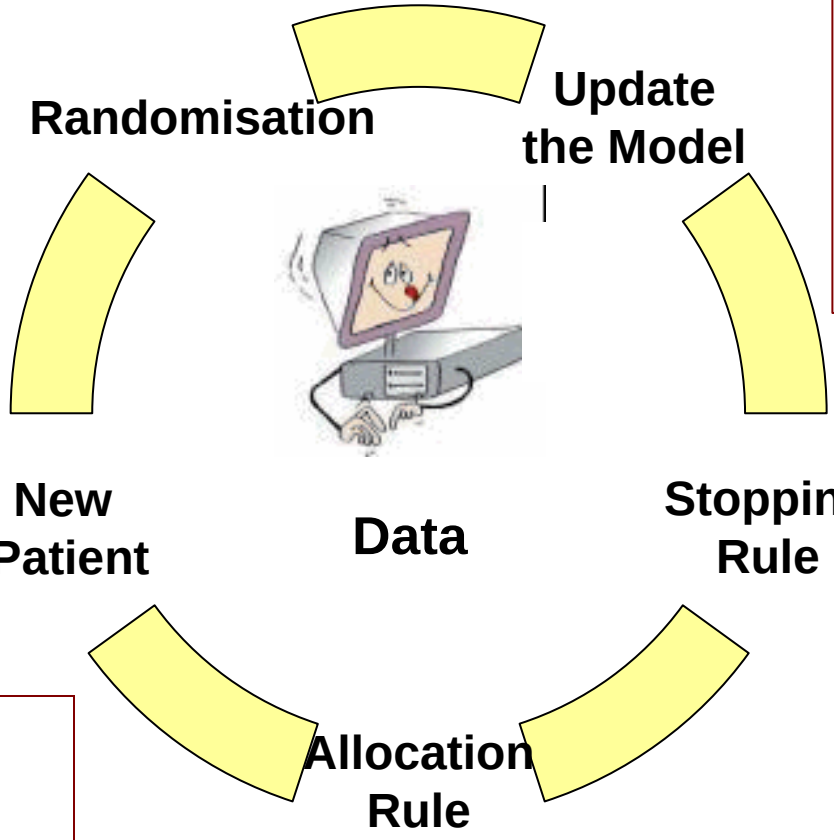
Primary Endpoint:	**Pain free by 2 hours after treatment**
Primary Goal:	**To identify the MED (60% of subjects reporting cessation of migraine pain by 2 hours)**
	To establish dose-response relationship of YYY when dosing during the mild phase of a migraine attack
Doses:	**[5, 15, 30, 60, 120, 180] mg of YYY and Plbo**
Max Number Patients:	**126 (feasibility considerations)**
Stopping for Efficacy:	**When 52 patients are treated at MED**
Stopping for Futility:	**After at least 39 patients are treated at Plbo and HD and the difference in proportions is less than 0.1**
Final Dose Response:	**The dose-response curve will be estimated using a four-parameter logistic regression**



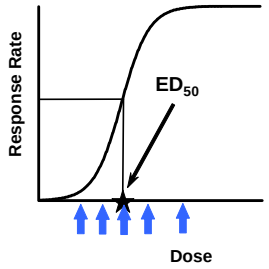
Adaptive Design Process

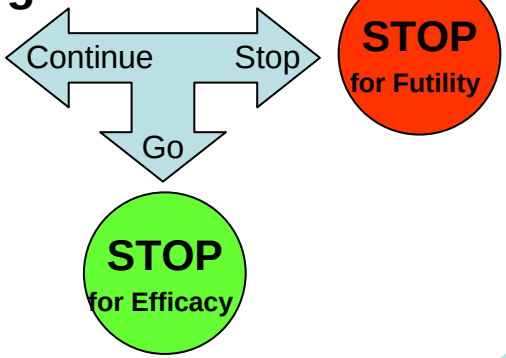
Patient is randomised
in blinded fashion to:
placebo (25%),
high dose (25%)
or “optimal” dose (50%)
[5, 15, 30, 60, 120, 180]mg

Site will fax IVRS system to:
- register patient
- confirm eligibility



Logistic Regression Model

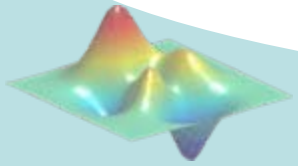




Continual Reassessment Method
chooses the “optimal” dose
that will optimise learning about the ED60

Logistical Challenges

- Continually adapting design:
  - requires continuous reassessment of response data
  - ability to update a statistical model and the randomisation on an ongoing basis
- Treatment of early/ mild migraine headache necessitates an outpatient study
- Need access to a system which can collect response data and update a statistical model to determine treatment allocation
- Patients will need to make the phone call to find out their treatment allocation **not** the sites
- Each patient will need to be provided with all **7** possible doses
- Patients will need to report back their response

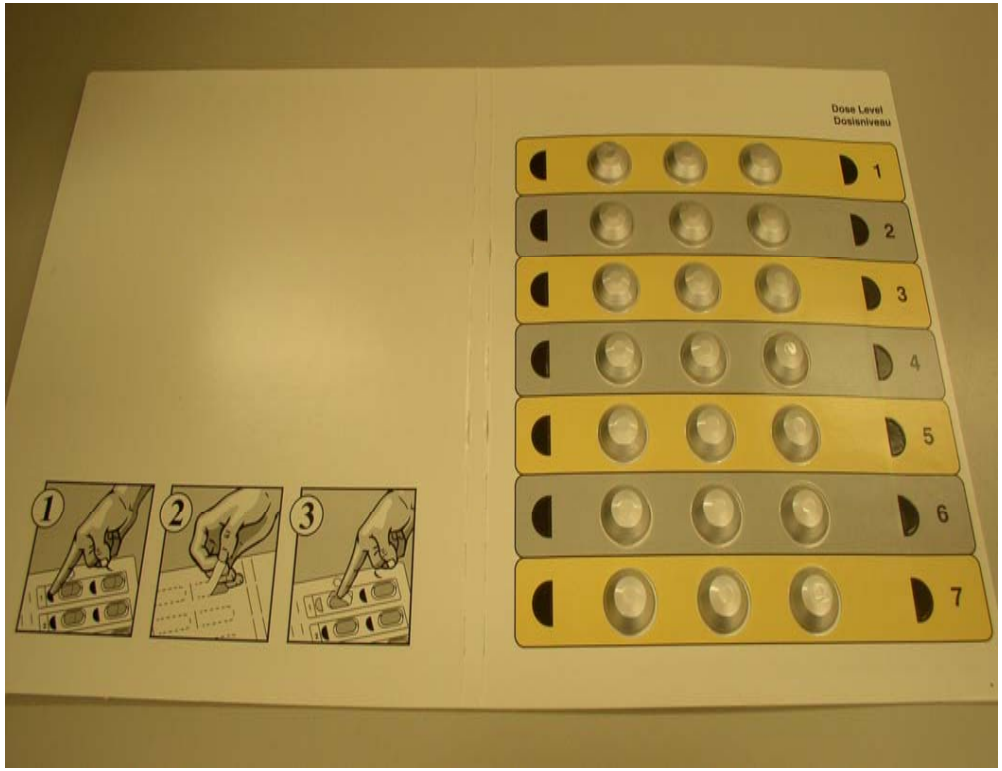


Study medication packs

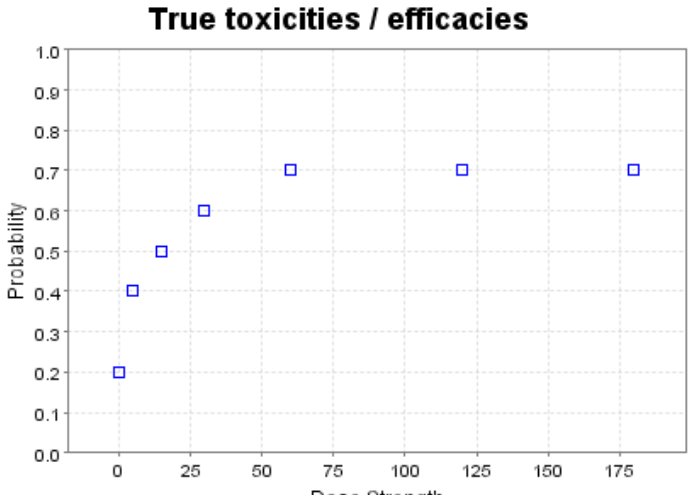
- 7 possible doses:

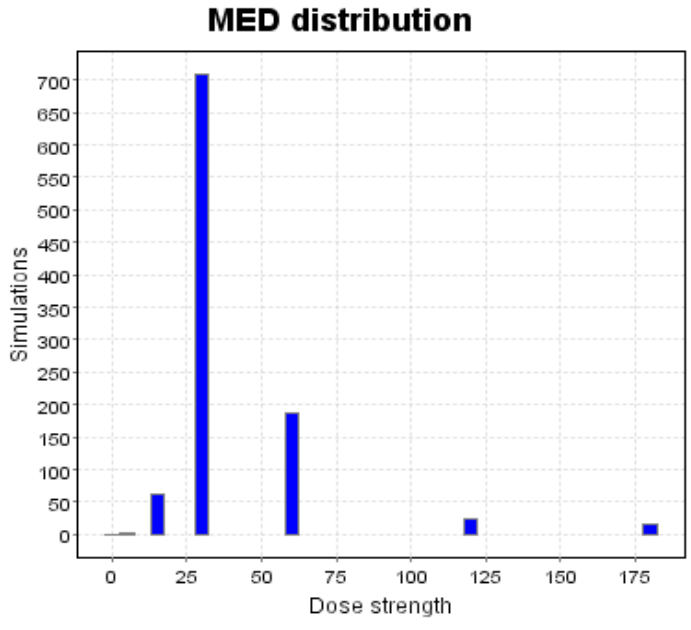
  [0, 5, 15, 30, 60, 120, 180]mg
- 4 possible tablet strengths:

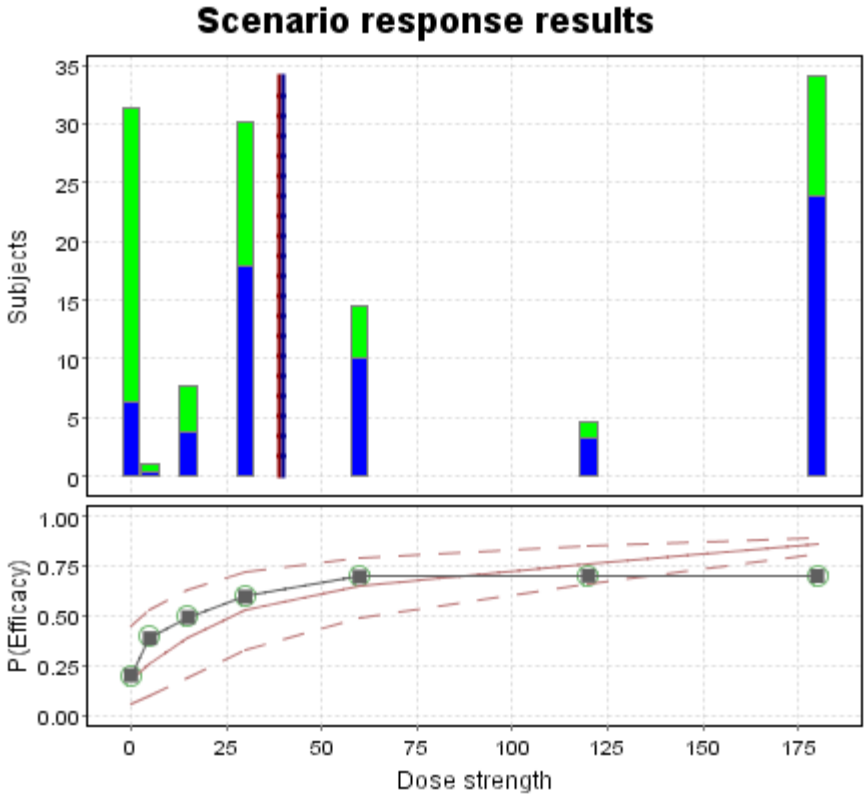
  Placebo, 5, 30 & 90 mg
- To provide all possible doses & double blind the study, each dose is made up of 3 tablets
- Outpatient study
  - patients need to be able to find the correct dose quickly
  - each dose requires each treatment pack



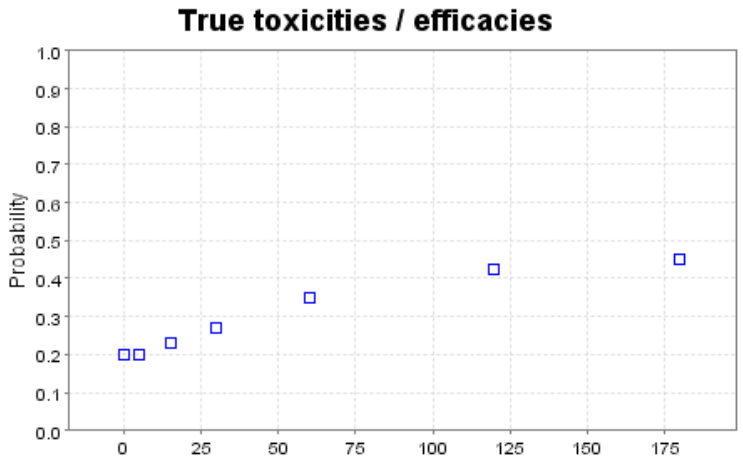
Simulation: Early Effect

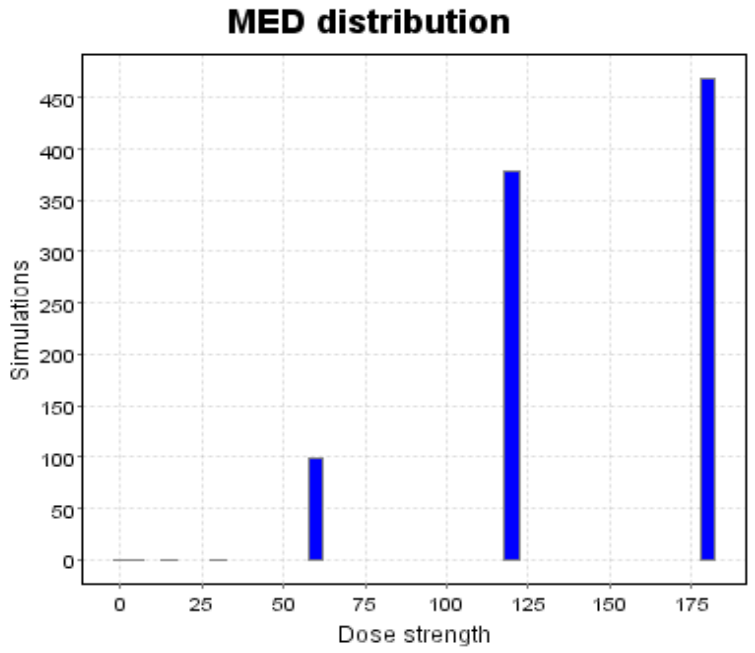


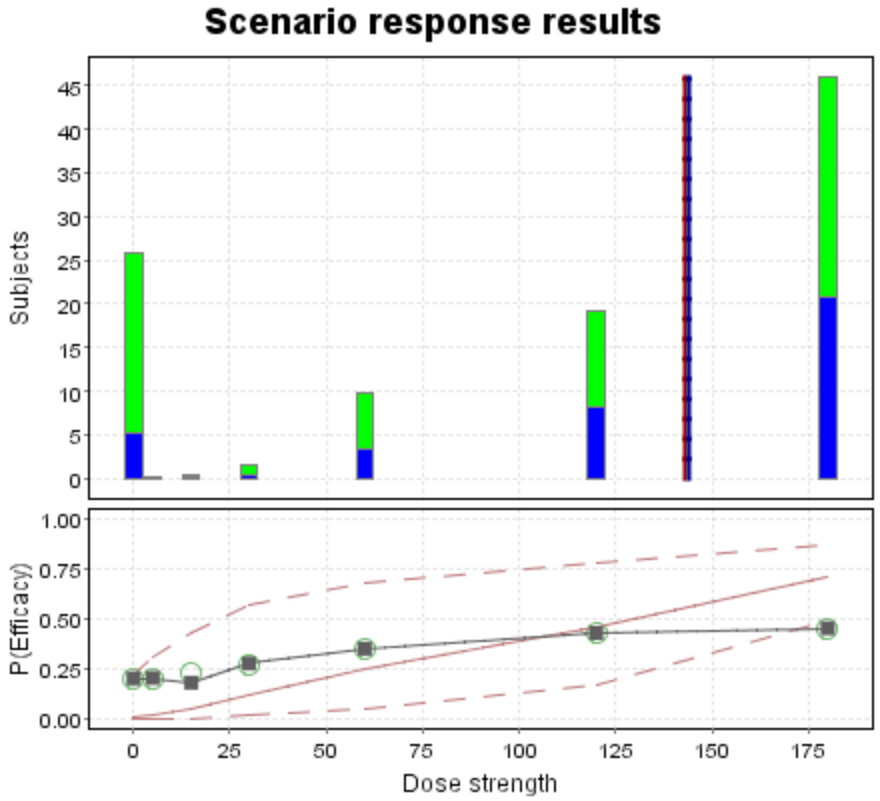




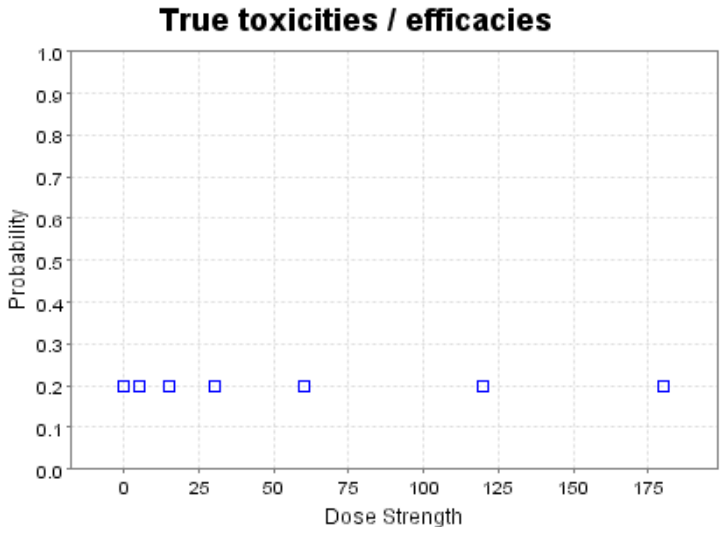
Simulation: Small Effect

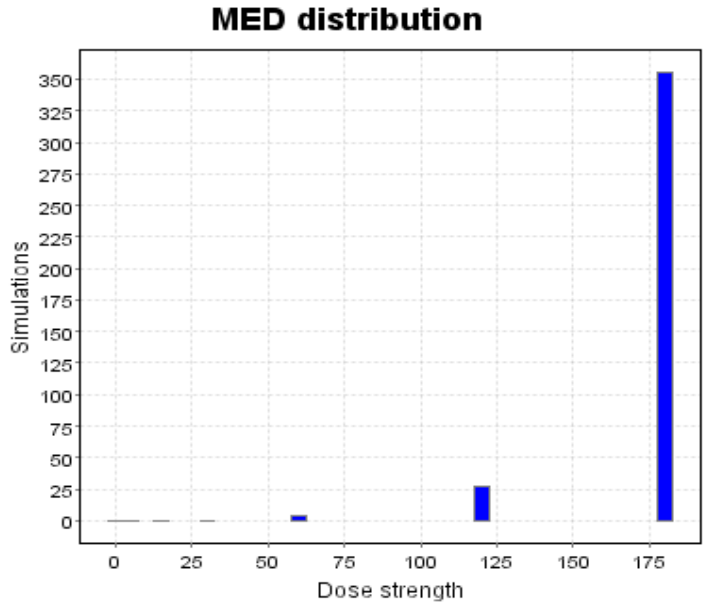


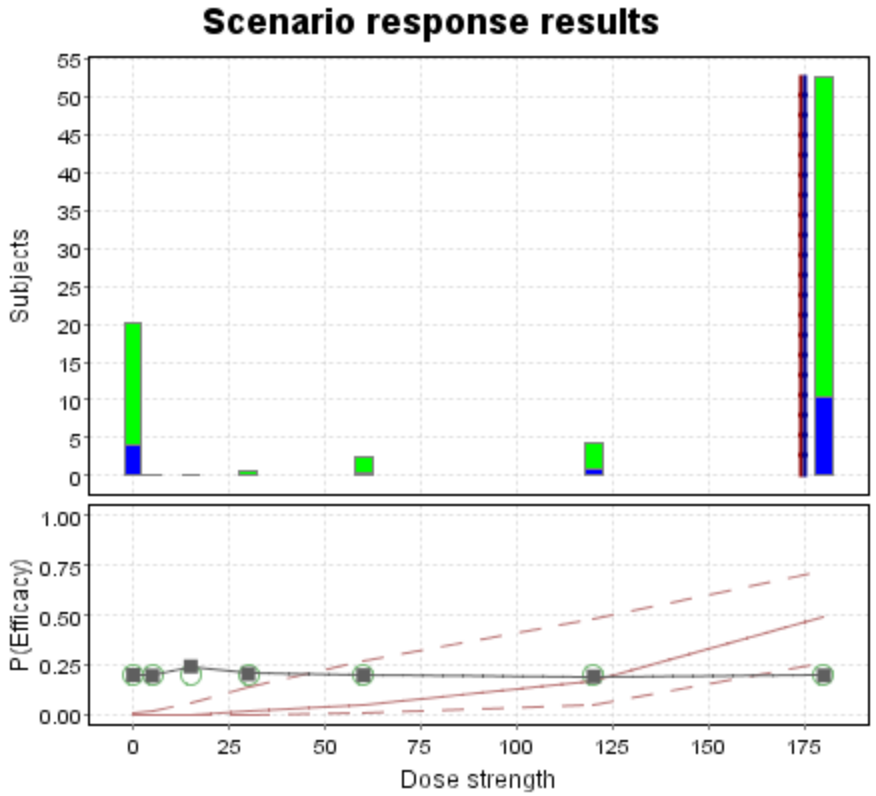




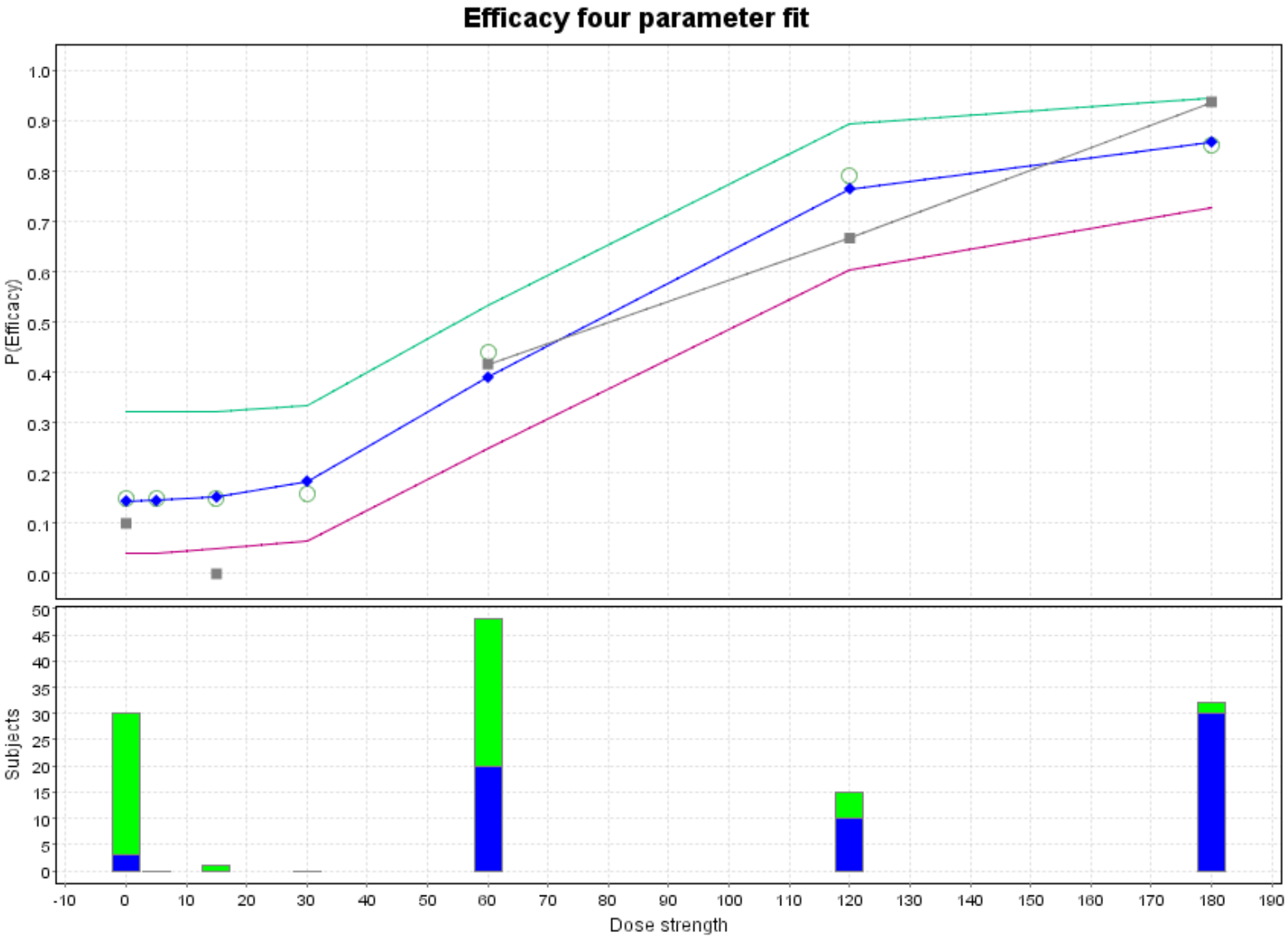
Simulation: Flat Dose Response





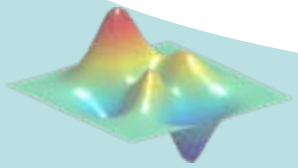


Simulated Dose Response



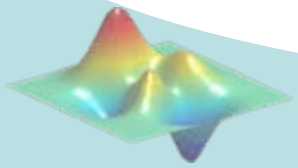
Case Study 3

- Dose-Ranging Study to evaluate the analgesic efficacy of a single dose of ZZZ in the treatment of acute pain associated with oral surgery
  - **Allocation Rule:** according to D-optimal design
  - **Sampling Rule:** three-stage rule
  - **Stopping Rule:** for lack of assay sensitivity/futility
  - **Decision Rule:** update the model (four-parameter logistic regression)



Details of the Design

Primary Endpoint:	**TOTPAR8 Score by 8 hours after treatment**
Primary Goal:	**To identify the ED80: the dose achieving 80% of the treatment effect of Ctrl versus Plbo**
	To establish dose-response relationship of ZZZ when dosing during the mild phase of a migraine attack
Doses:	**[150, 300, 450, 600, 750, 900] mg of ZZZ, Plbo and Ctrl**
Max Number Patients:	**180 (feasibility considerations): 30 sub/arm for 90% power at 8 units diff. in TOTPAR8, STD=10.7, α = 0.05**
Stopping for LAS:	**After 10 and 15 subjects are treated on Ctrl**
Stopping for Futility:	**After 10 and 15 subjects are treated on ZZZ 900mg using Pocock type boundary**
Final Dose Response:	**The dose-response curve will be estimated using a four-parameter logistic regression**



Adaptive Design Process

Stage I

TRT 900mg
TRT 750mg
TRT 600mg
TRT 450mg
TRT 300mg
TRT 150mg
Plbo
Ctrl

Stop Futility

IA I

Stop NAS

Total Ssize ~30:

10 pats/arm

Stage II

TRT 900mg
TRT 750mg
TRT 600mg
TRT 450mg
TRT 300mg
TRT 150mg
Plbo
Ctrl

Stop Futility

IA II

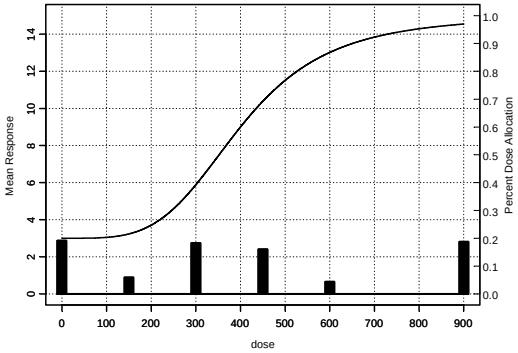
Stop NAS

Total Ssize ~ 65:

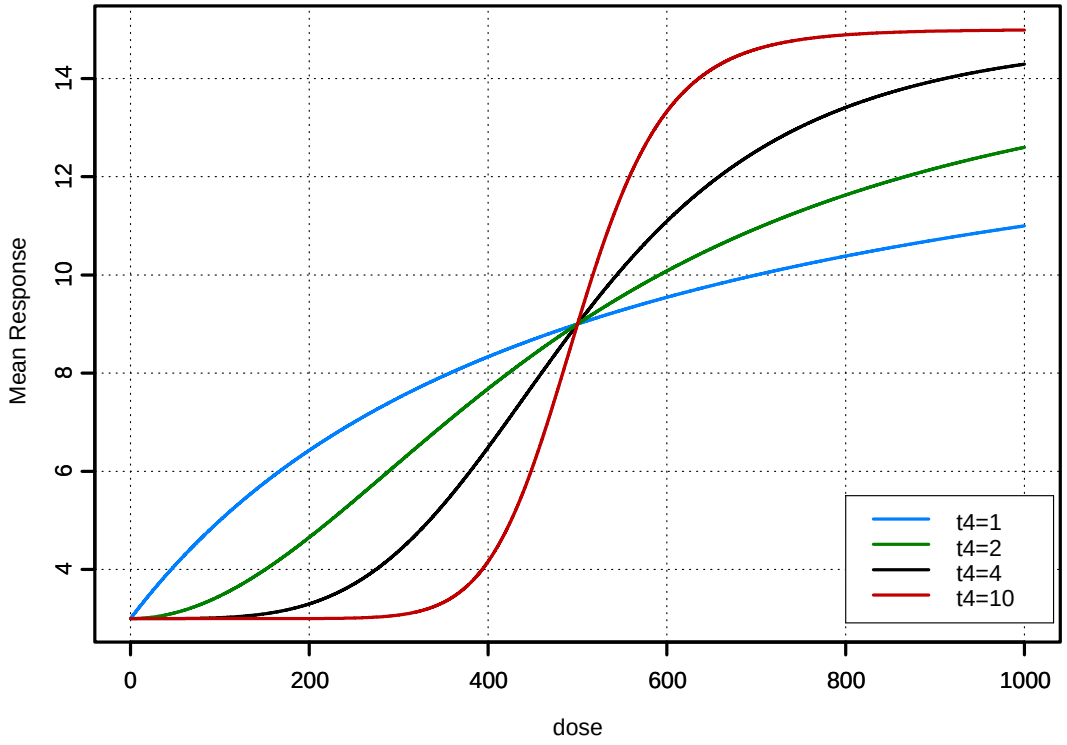
5:10 pats/arm

Stage III

- Fit the Model
- Find the D-Optimal Design
- Determine Sample Size



Primary Response: TOTPAR8



Four Parameter Logistic Model

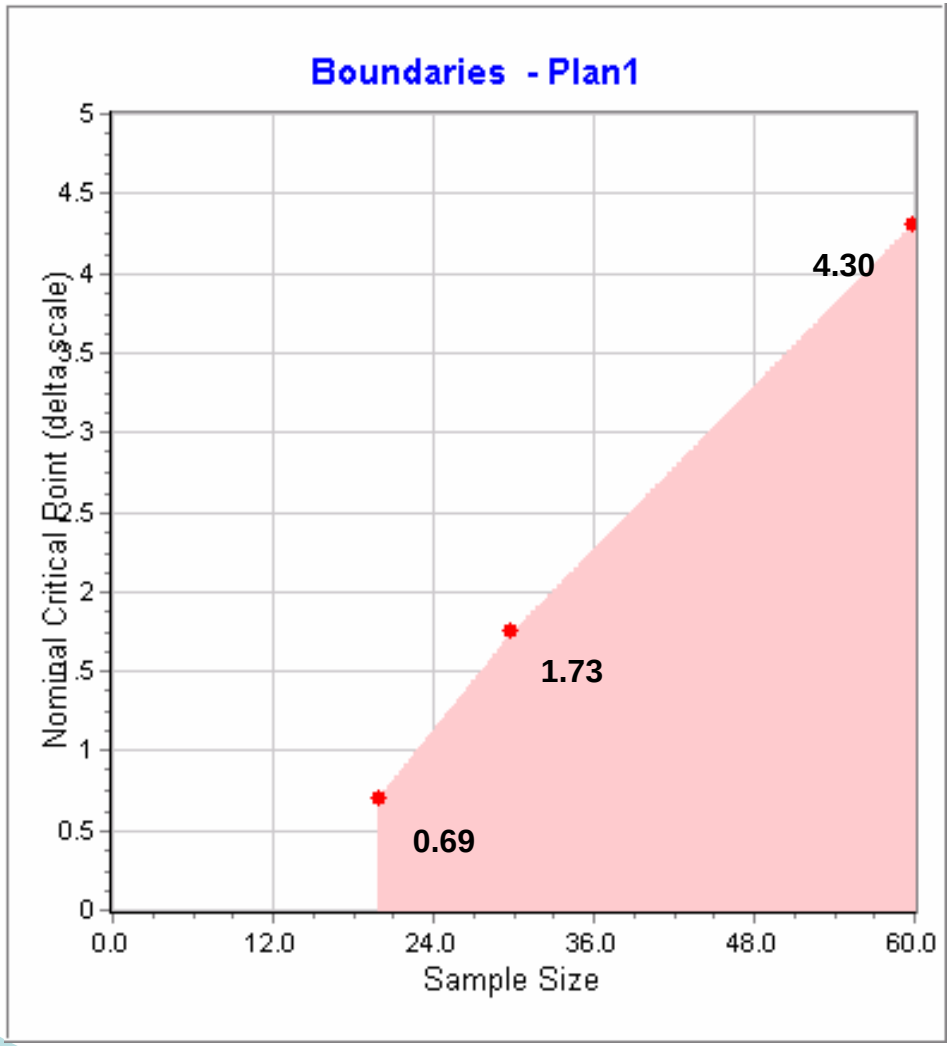
$$\mu(x) = \theta_1 + (\theta_2 - \theta_1)\frac{x^{\theta_4}}{x^{\theta_4} + \theta_3^{\theta_4}},$$

where

μ—the mean response,
x—dose,
θ_1—the minimum response,
θ_2—the maximum response,
θ_3—ED_{50},
θ_4—the slope parameter.

$\theta = (3,15,500,\theta_4)$

Boundaries for Early Stopping



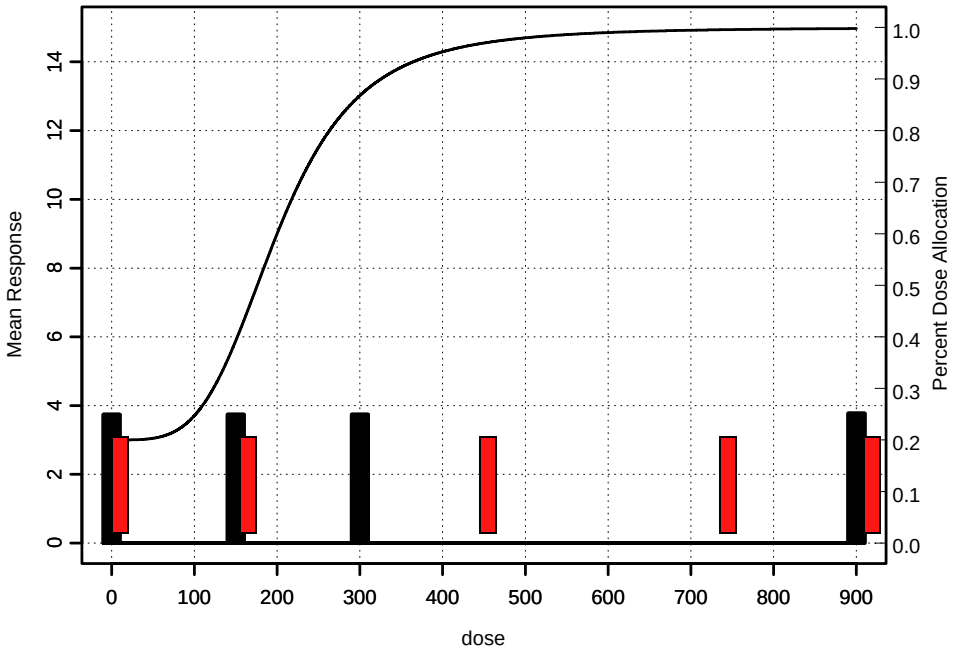
Pocock Type Boundary

For Assay Sensitivity
For Futility

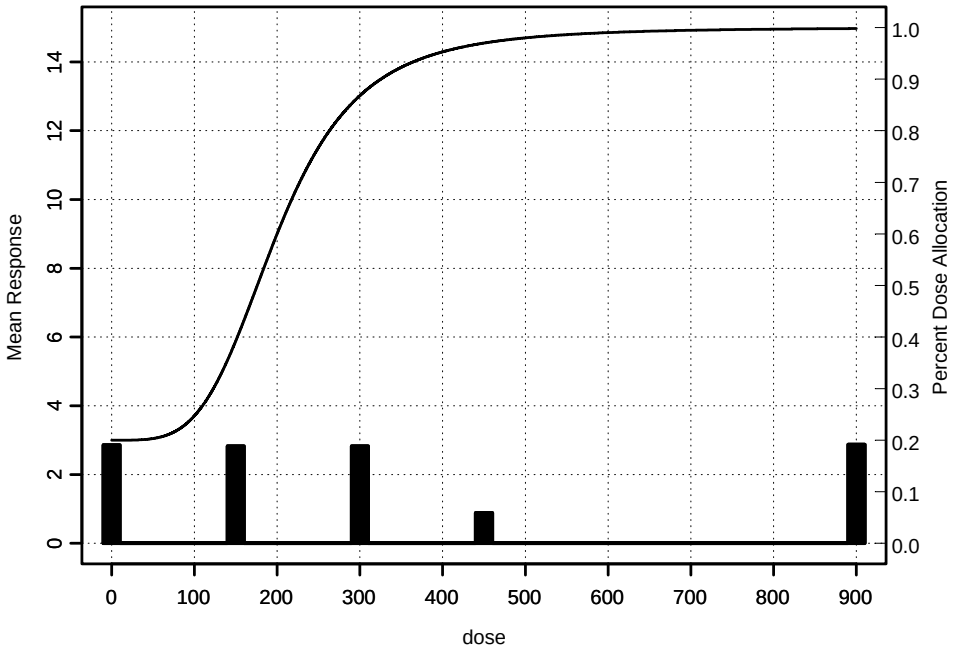
S.Size	Boundary Crossing Probabilities		
	Under H0	Under H1	Under H1/2
20	0.558	0.063	0.245
30	0.161	0.023	0.099
60	0.231	0.053	0.254

Simulation 1: Design

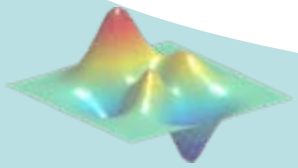
D-Optimal Design



Adaptive Design

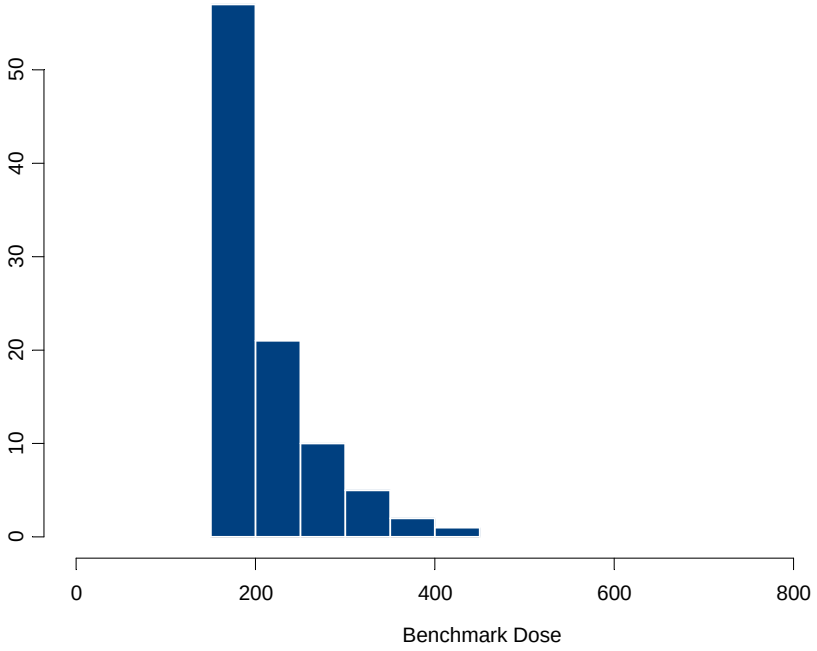


θ = (3,15,200,4)

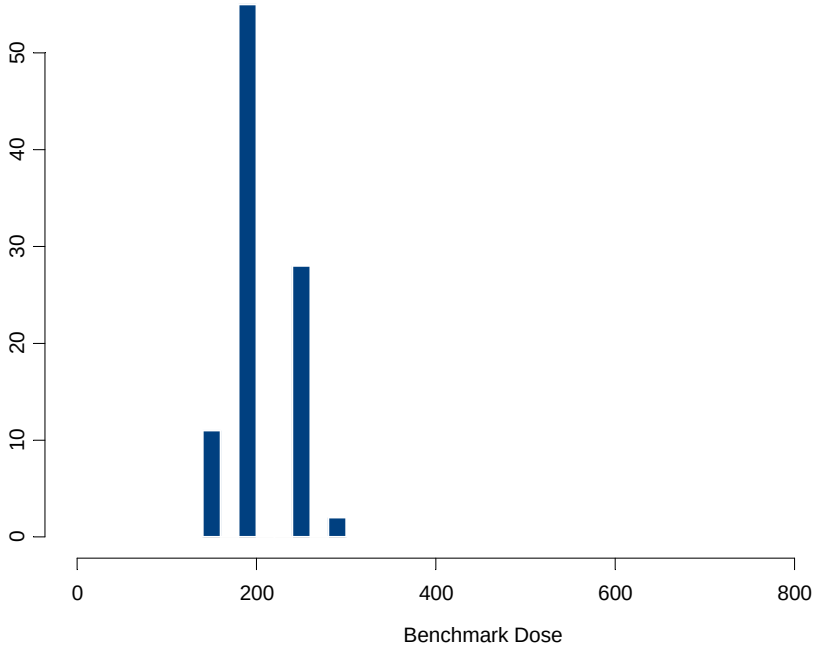


Simulation 1: Benchmark Dose Selection

Fixed Design



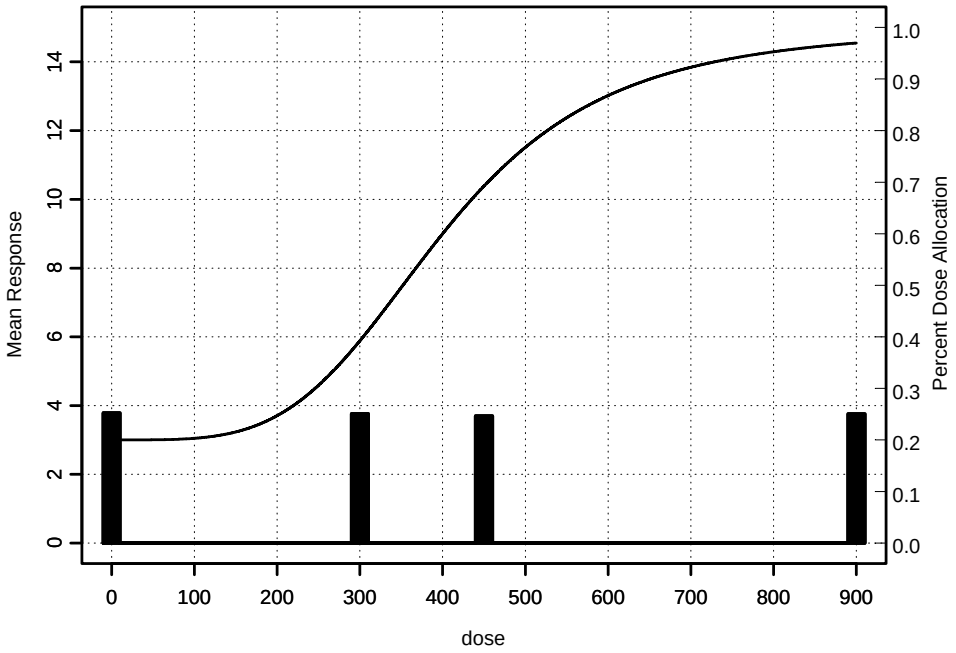
Adaptive Design



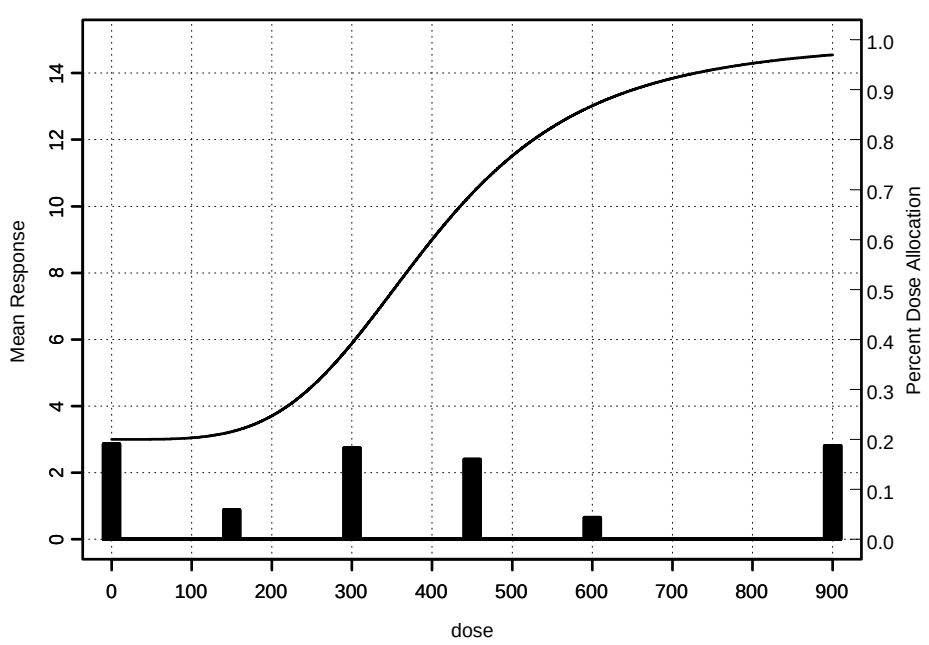
Design	S.Size	CI width	Efficiency
Fixed	180	138.02	1.734
Adaptive	163.44	115.63	1.680

Simulation 2: Design

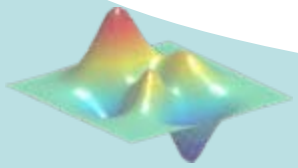
D-Optimal Design



Adaptive Design

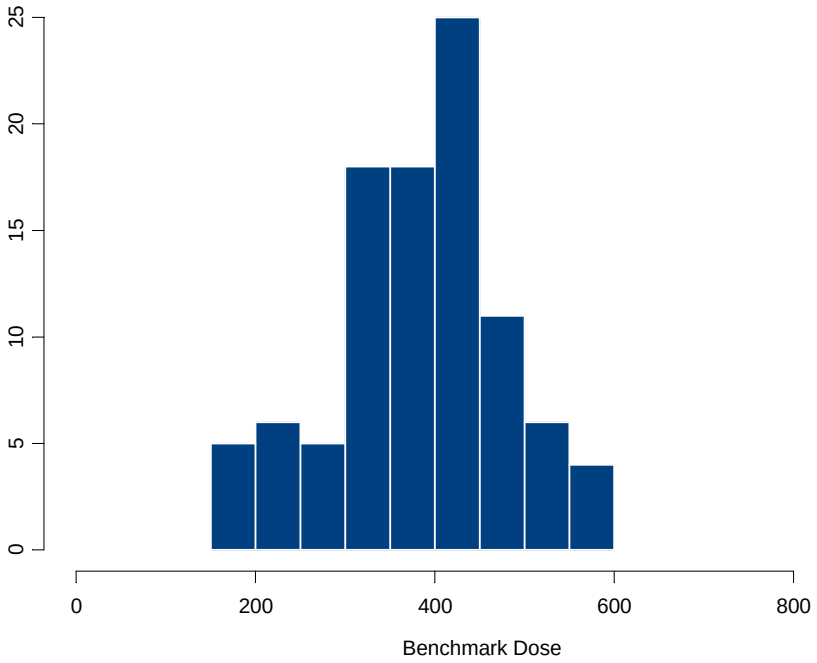


θ = (3,15,400,4)

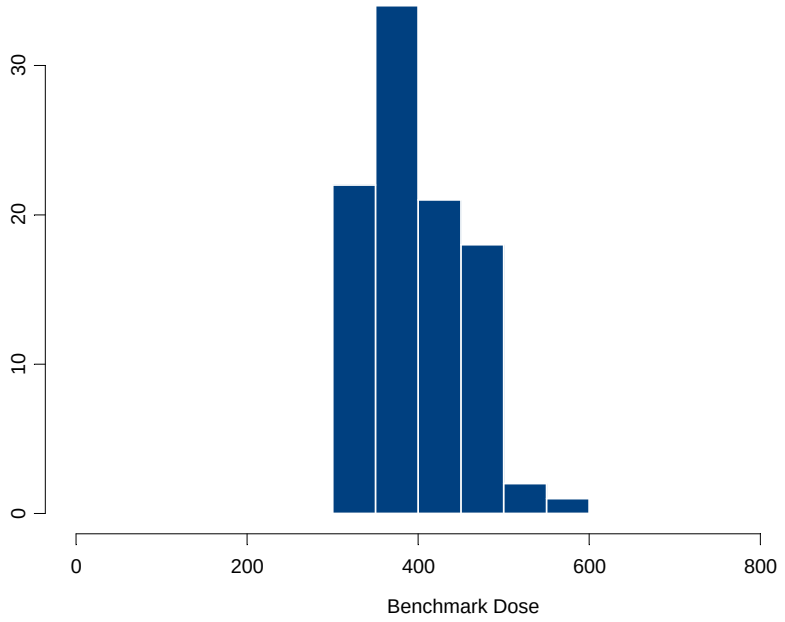


Simulation 2: Benchmark Dose Selection

Fixed Design



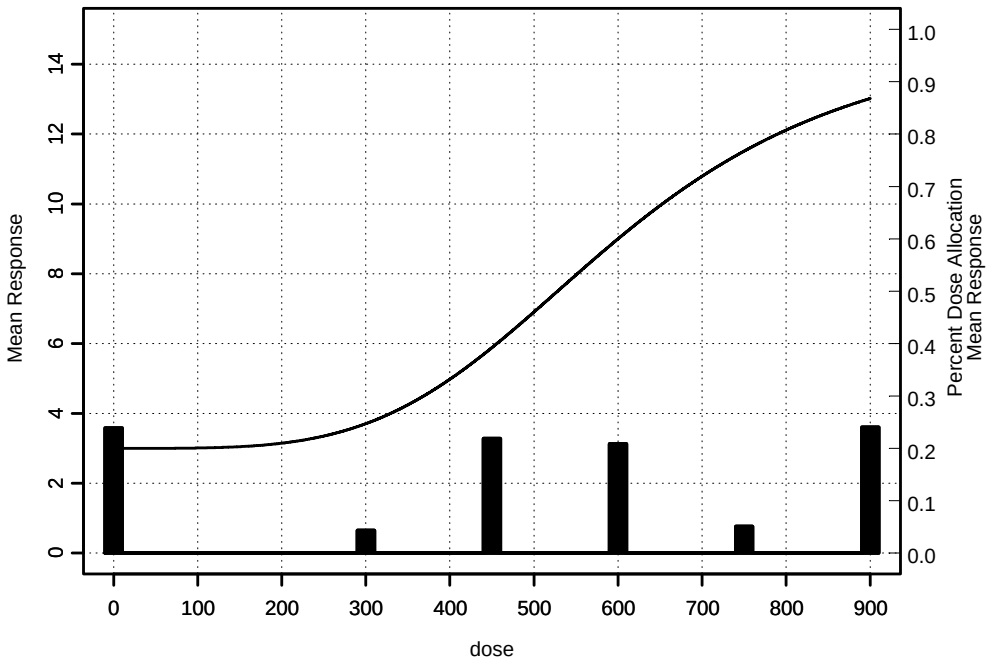
Adaptive Design



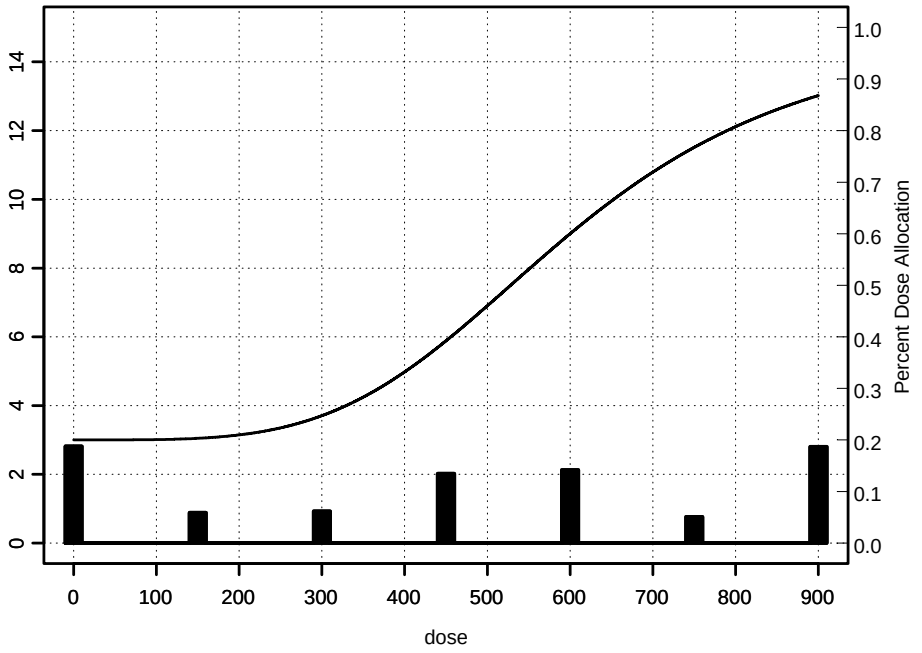
Design	S.Size	CI width	Efficiency
Fixed	180	248.98	1.799
Adaptive	167.19	200.51	1.750

Simulation 3: Design

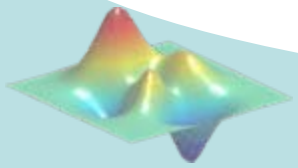
D-Optimal Design



Adaptive Design

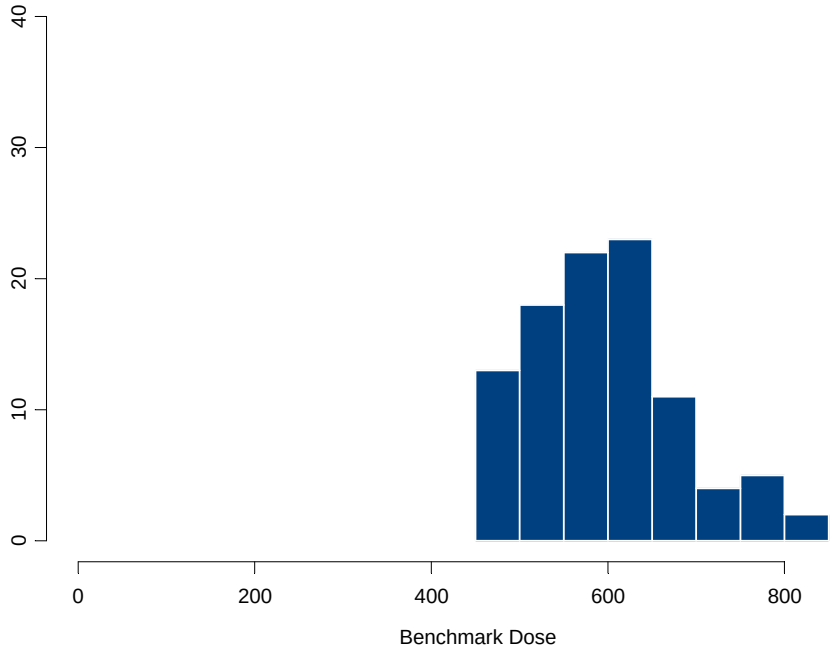


θ = (3,15,600,4)

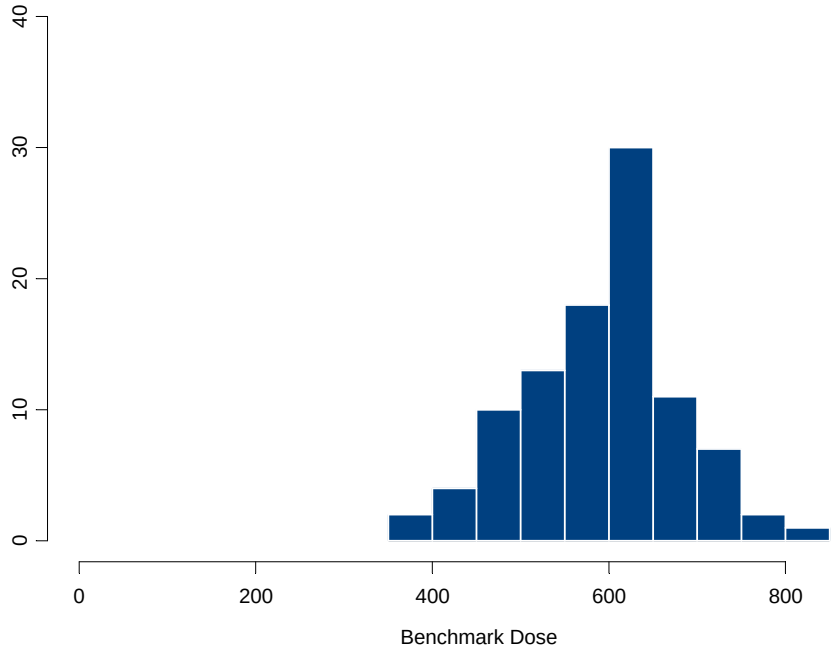


Simulation 3: Benchmark Dose Selection

Fixed Design



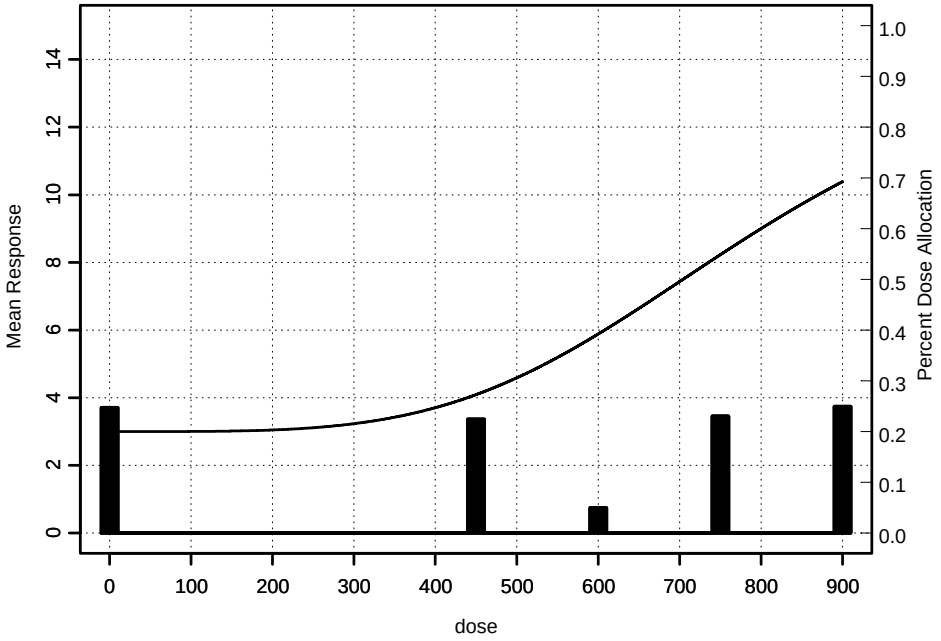
Adaptive Design



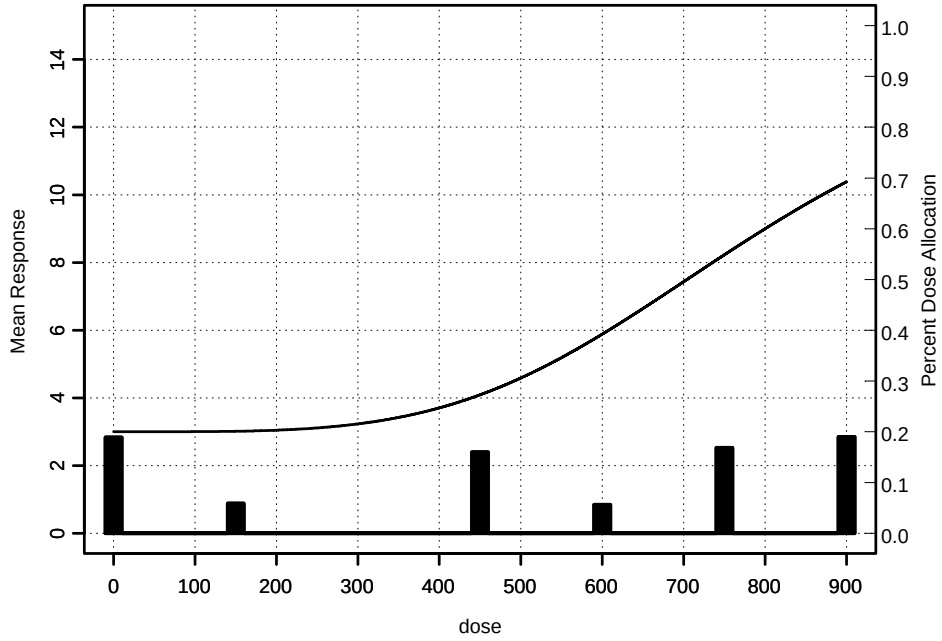
Design	S.Size	CI width	Efficiency
Fixed	180	297.96	1.139
Adaptive	166.95	286.22	1.100

Simulation 4: Design

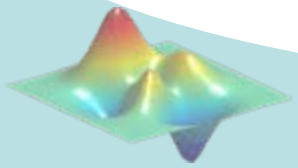
D-Optimal Design



Adaptive Design

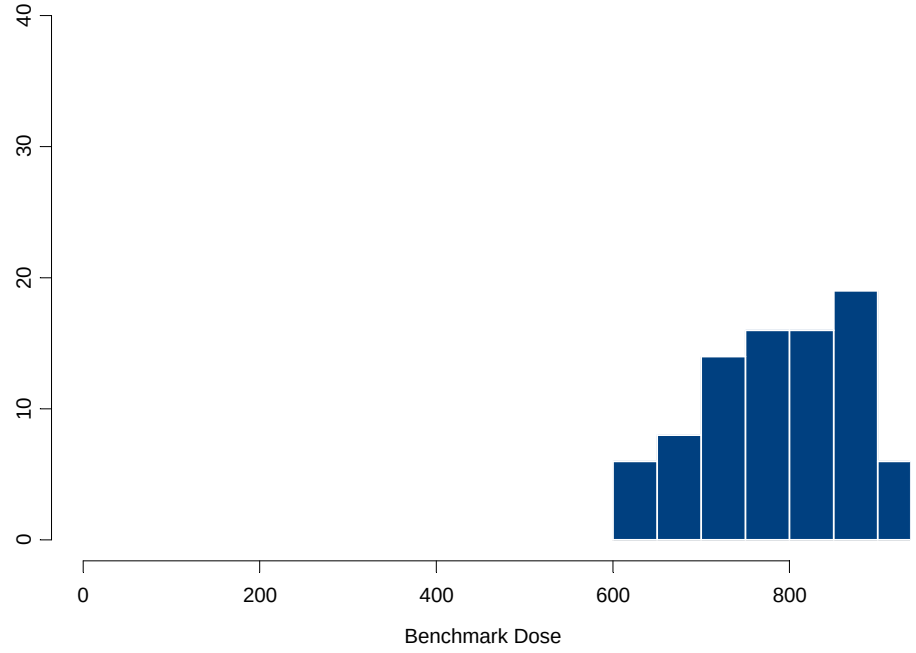


$\theta = (3,15,800,4)$

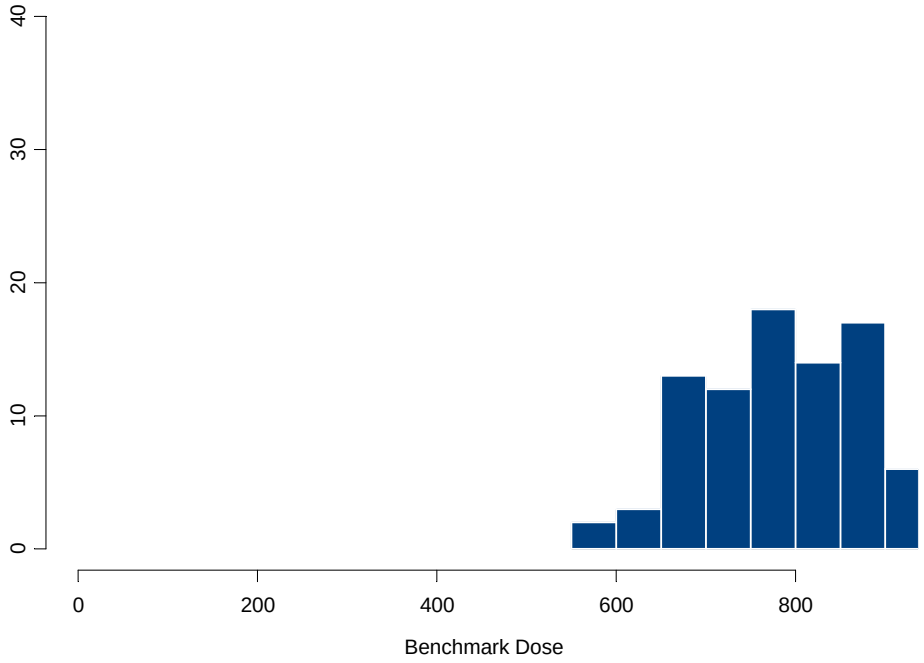


Simulation 4: Benchmark Dose Selection

Fixed Design



Adaptive Design



Design	S.Size	CI width	Efficiency
Fixed	180	310.75	1.065
Adaptive	160.41	298.39	1.05

Future prospects

- Adaptive Designs
  - Should be a part of a *"new product development toolkit"*
  - Provide a more ethical treatment of patients in the trials
  - Have the potential to improve the quality, speed and efficiency of drug development
- Implementing Adaptive Designs requires
  - Careful planning
  - Increased upfront work (simulations)
  - Integration of data capture, drug supply management, and interactive communication system