Regulatory-Industry Statistics Workshop

From Small Data to Big Data, from RCT to RWE, the Impact of Statistics
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Washington Marriott Wardman Park

Efficient drug development with master protocols integrating platform design, adaptive randomization, early stopping for futility and/or efficacy, and information borrowing in the Bayesian framework

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MD Anderson Cancer Center
Making Cancer History®

Success Rates for Drug Development

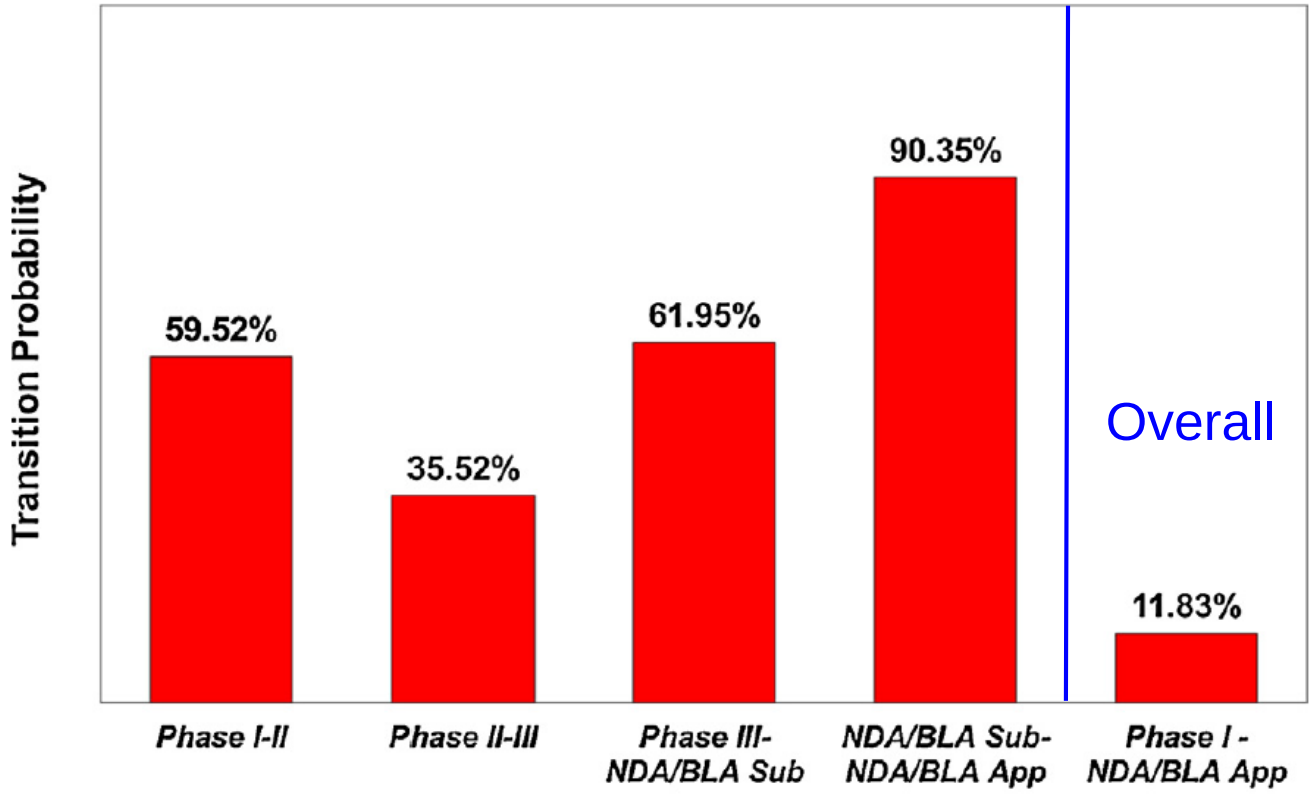


Fig. 1. Estimated phase transition probability and overall clinical approval success rates for self-originated new molecular entity (NME) and new therapeutically significant biologic entity (NBE) investigational compounds first tested in humans anywhere from 1995 to 2007.

J.A. DiMasi et al. / Journal of Health Economics 47 (2016) 20–33

Cost for Drug Development

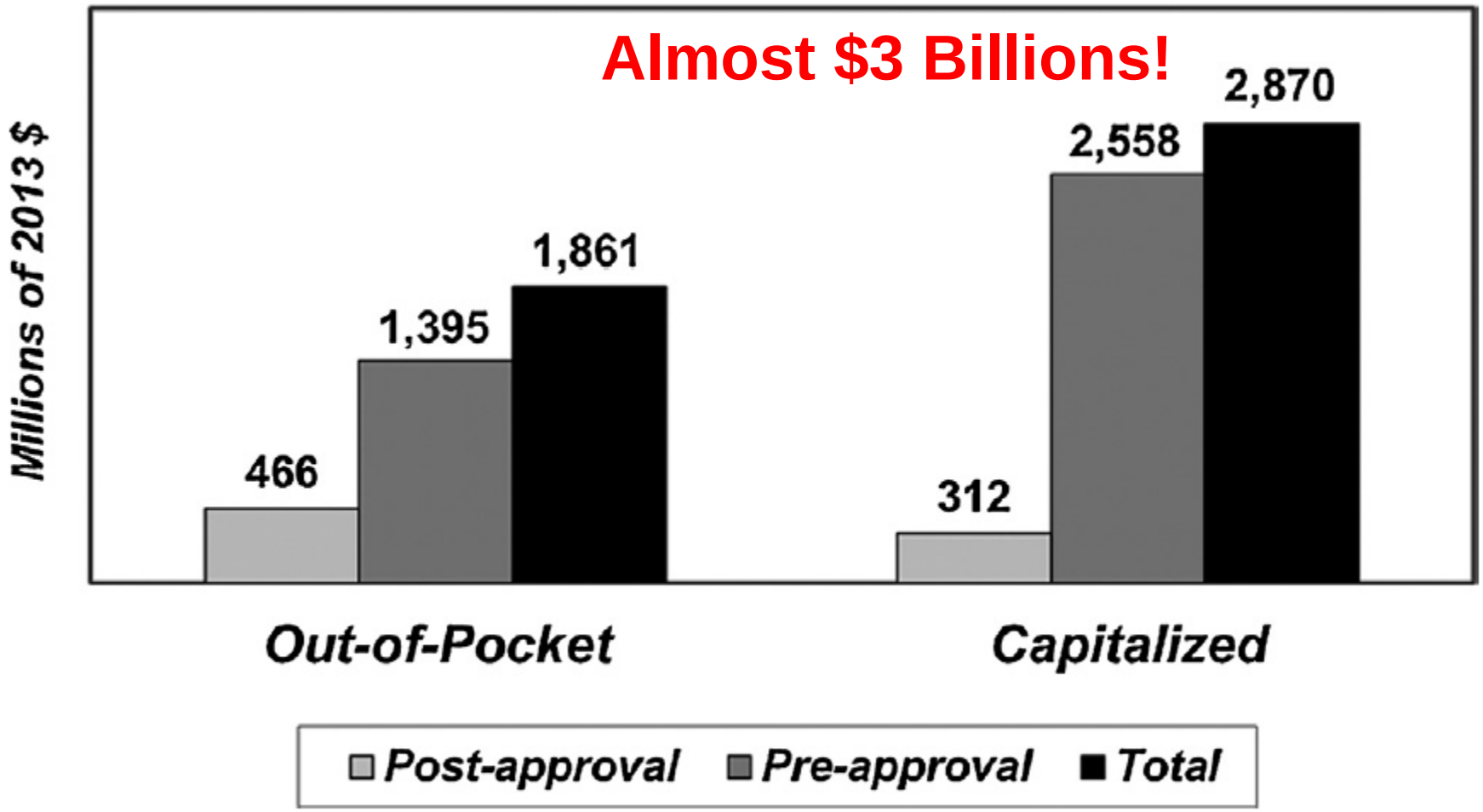


Fig. 4. Out-of-pocket and capitalized total cost per approved new drug for new drugs and for improvements to existing drugs.

J.A. DiMasi et al. / Journal of Health Economics 47 (2016) 20–33

How can we do better?

- Current status
  - One drug, one study population, one trial at a time.
  - Discrete-phase drug development
    - Phase I → Phase II → Phase III
  - Equal randomization
  - Infrequent interim monitoring
  - Limited use of all available information
    - No borrowing from historical data (external, outside of the trial)
    - No borrowing across subgroups (internal, within the trial)

How can we do better? Solutions

- Current status
  - One drug, one study population, one trial at a time.
  - Discrete-phase drug development
    - Phase I → Phase II → Phase III

Master Protocol: Umbrella, basket, platform trials

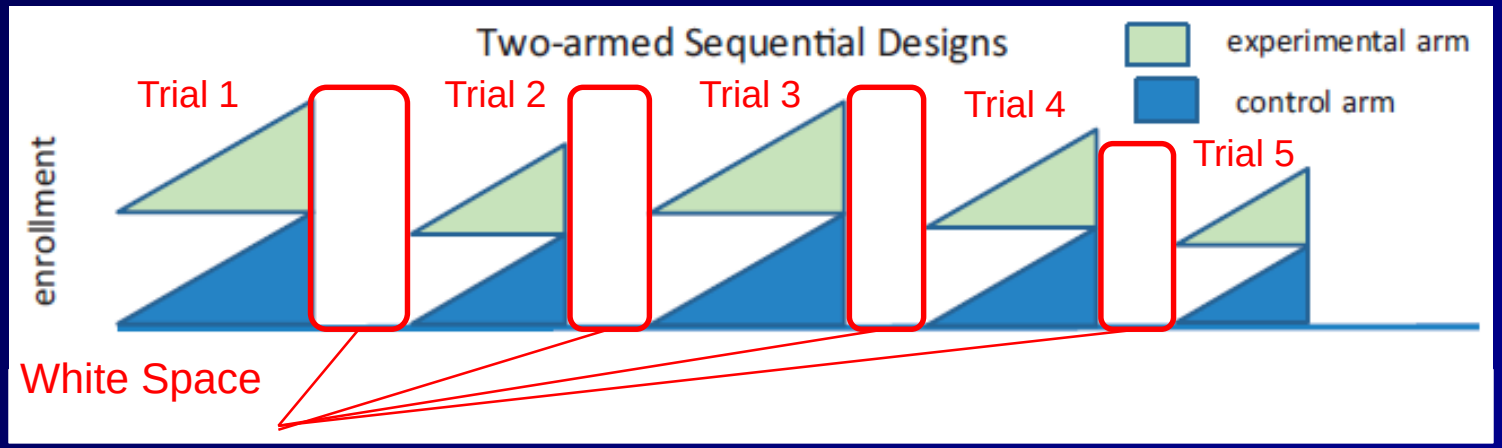
  - Equal randomization → Adaptive randomization
  - Infrequent interim monitoring → More interim analyses: Early stopping for toxicity, futility, efficacy
  - Limited use of all available information
    - No borrowing from historical data (external, outside of the trial) → Bayesian modeling with informative priors
    - No borrowing across subgroups (internal, within the trial) → Bayesian hierarchical model, Cluster hierarchical model

Multiple-Arm Platform Design

- Biological knowledge advances in a lightning speed
- Many new agents and many more combination therapies are needed to be evaluated
- Only a small fraction of the drugs are tested in clinical trials and the success rate is *very* low
- How can we do better?
  - Screen multiple agents simultaneously
  - Include a control arm in a randomized study
  - Early stopping for futility and/or efficacy via posterior or predictive probability
  - Control type I error with multiple testings
  - **Outcome adaptive randomization**

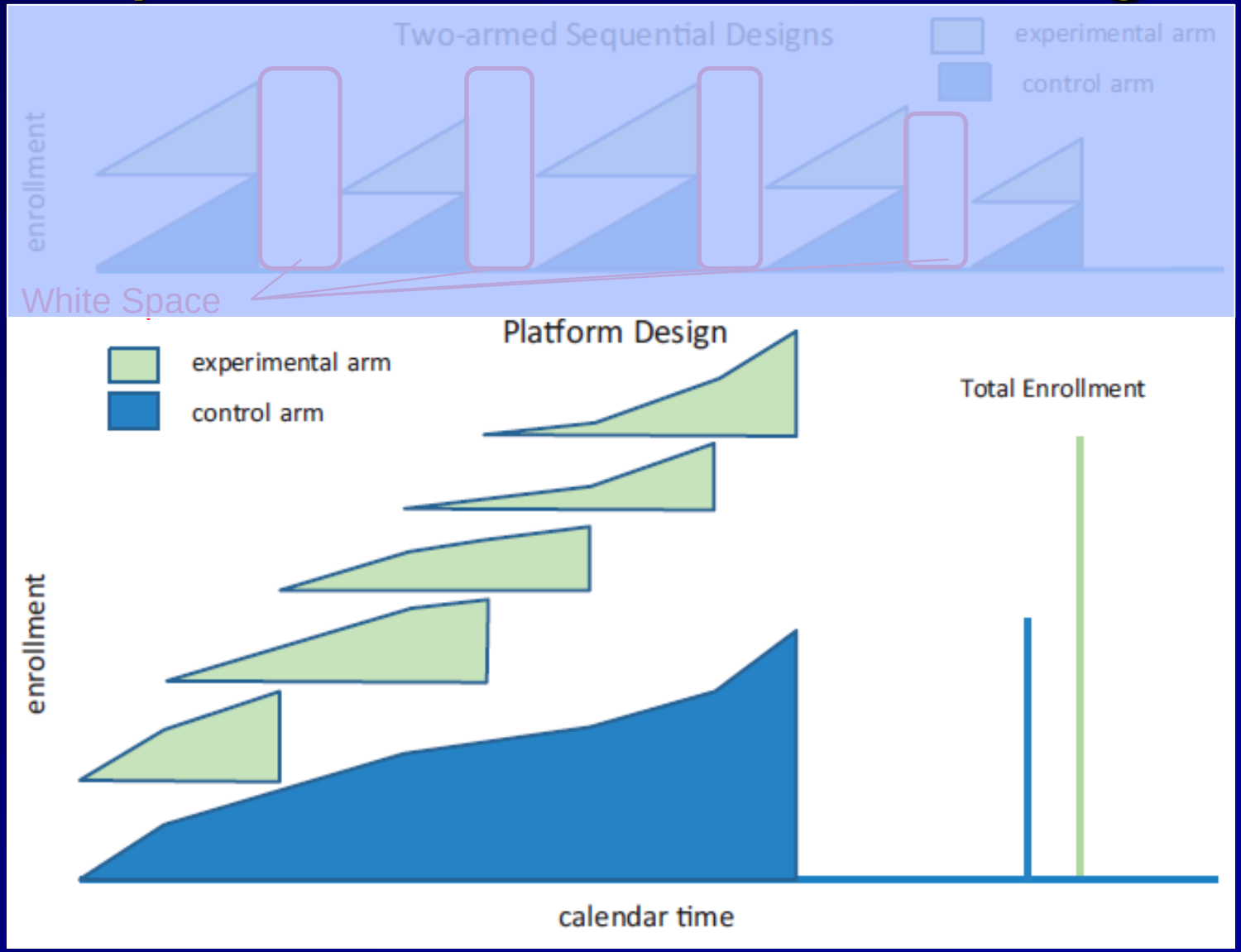
Hobbs, B.P., Chen, N., Lee, J.J. **Controlled multi-arm platform design using predictive probability** (2018) *Statistical Methods in Medical Research*, 27 (1), pp. 65-78.

Sequential vs. Platform Designs



Each shape depicts a study arm. The horizontal axis represents calendar time. Increases in the direction of the vertical axes represent increasing enrollment. The randomized two-arm approach necessitates that the standard of care therapy is repeated five times. The platform design enables consolidation of the control arms as well as seamless incorporation of novel investigational agents and as they emerge. This reduces redundancy and enhances efficiency.

Sequential vs. Platform Designs



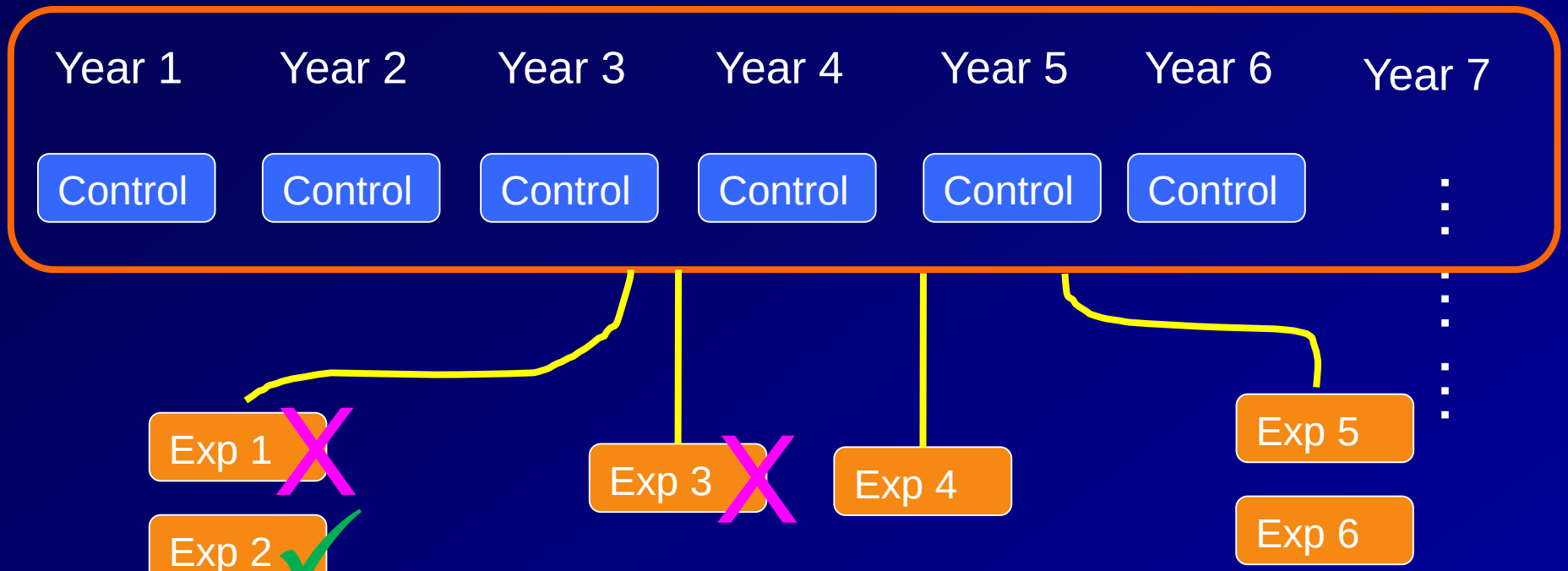
Each shape depicts a study arm. The horizontal axis represents calendar time. Increases in the direction of the vertical axes represent increasing enrollment. The randomized two-arm approach necessitates that the standard of care therapy is repeated five times. The platform design enables consolidation of the control arms as well as seamless incorporation of novel investigational agents and as they emerge. This reduces redundancy and enhances efficiency.

Conceptual Schema of the Platform Design

Drop Bad Drug — Exp 1, Exp 3

Graduate Good Drug — Exp 2

Control: Backbone of the Platform



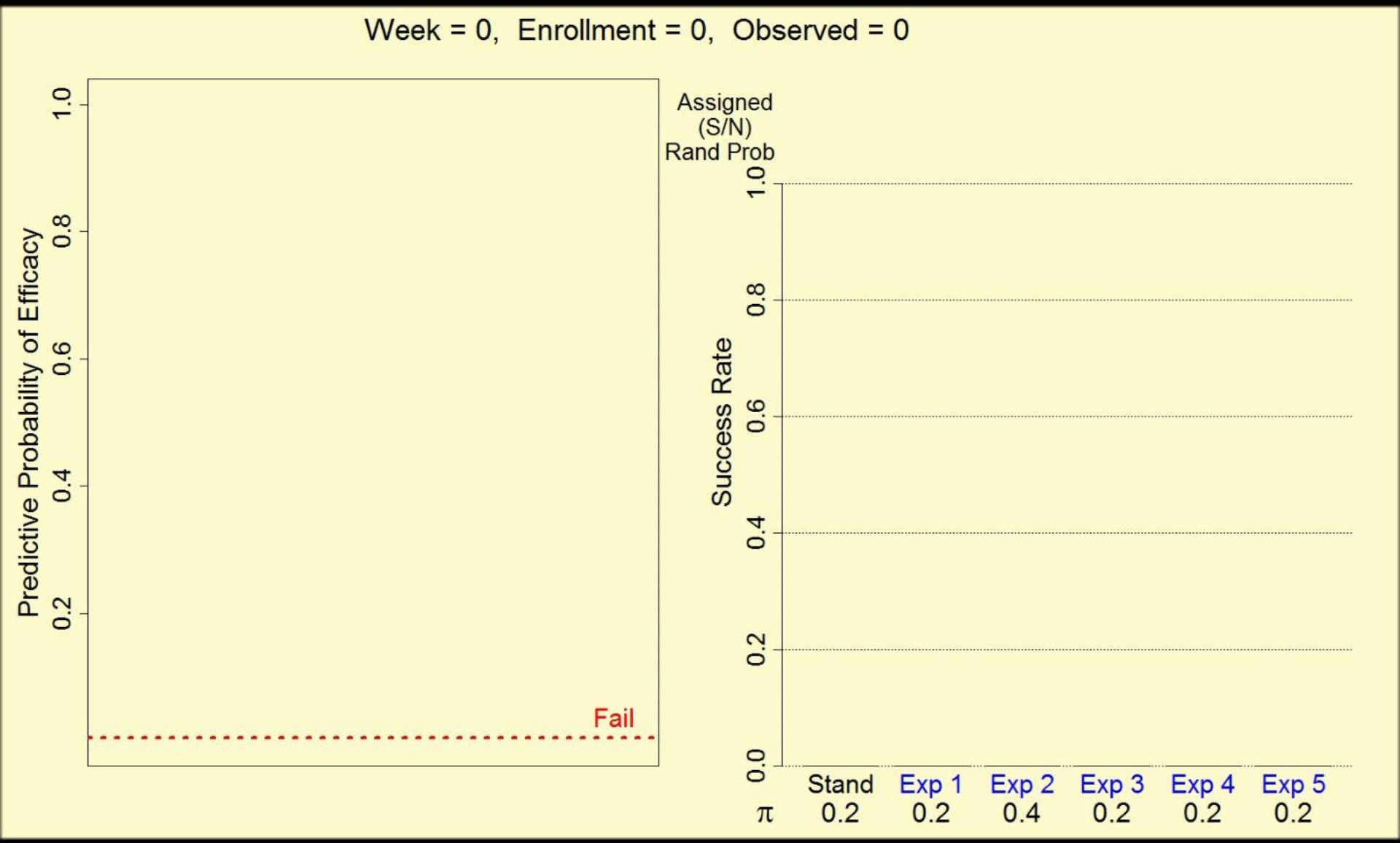
Experimental Treatments: Modules

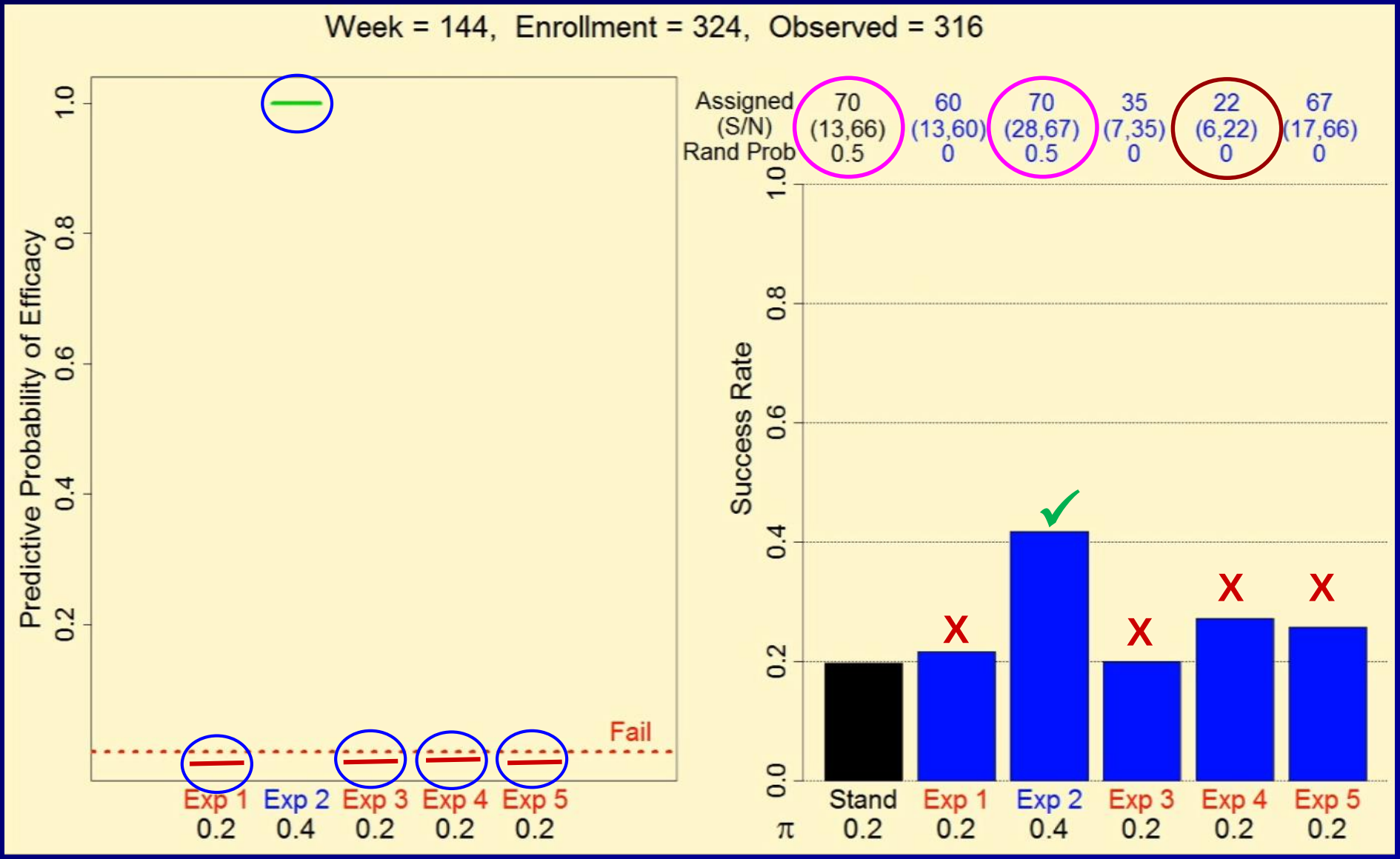
Example: Design Assumptions

- One control arm with p=0.2
- Maximum 5 experimental arms with N_{max} = 70 /each
- Power for detecting a 2-fold increase in the response rate for exactly one experimental therapy (p=0.4) when the other four experimental therapies are equivalent to control (p=0.2) at ≥ 0.8.
- Controls the familywise type I error rate at ≤ 0.10
- Therapeutic response was evaluated 4 weeks following therapy
- Calibrate the design parameters to control type I and type II errors

Hobbs, B.P., Chen, N., Lee, J.J. **Controlled multi-arm platform design using predictive probability** (2018) *Statistical Methods in Medical Research*, 27 (1), pp. 65-78.

Video 1: Platform Trial with ER: p_0=0.2, p_2=0.4, $p_1 = p_3 = p_4 = \theta_5$=0.2




Week = 144, Enrollment = 324, Observed = 316
Predictive Probability of Efficacy
1.0
0.8
0.6
0.4
0.2
Fail
Exp 1 Exp 2 Exp 3 Exp 4 Exp 5
0.2 0.4 0.2 0.2 0.2
Assigned
(S/N)
Rand Prob
70 (13,66) 0.5
60 (13,60) 0
70 (28,67) 0.5
35 (7,35) 0
22 (6,22) 0
67 (17,66) 0
Success Rate
1.0
0.8
0.6
0.4
0.2
0.0
X
X
X
Stand Exp 1 Exp 2 Exp 3 Exp 4 Exp 5
π 0.2 0.2 0.4 0.2 0.2 0.2

Operating Characteristics: Multi-arm Platform Design When All Experimental Arms Starts at the Same Time

Scenario		True response rate	Average no. patients assigned	Average no. patients respond	Probability selected for phase III	Probability none selected for phase III	Average total sample size	Average total duration (in years)
0	control	0.2	62.4	12.5	-	0.906	304	2.53
	exp. 1-5	0.2	48.3	9.7	0.026			
1	control	0.2	69.3	13.9	-	0.189	330	2.75
	exp. 1-4	0.2	47.9	9.6	0.024			
	exp. 5	0.4	69.0	27.6	0.809			
2	control	0.2	69.9	14.0	-	0.078	350	2.92
	exp. 1-3	0.2	47.5	9.5	0.022			
	exp. 4-5	0.4	69.1	27.6	0.802			
3	control	0.2	70.0	14.0	-	0.01	350	
	exp. 1	0.1	30.3	3.0	0.00			
	exp. 2	0.2	47.5	9.5	0.028			
	exp. 3	0.3	62.9	18.9	0.312			
	exp. 4	0.4	69.2	27.7	0.815			
	exp. 5	0.5	69.9	35.0	0.982			

~40% Saving from sequential design

Operating Characteristics: Comparing Sequential Design, Platform Design, and Platform Design with Delayed Entry

Design property	Design	Scenario 0	1	2	3
Proportion of patients assigned to arm with success rate $\pi \geq 0.3$	Sequential two-arm trials	0	0.13	0.24	0.36
	Platform	0	0.21	0.39	0.58
	Platform with delayed entry	0	0.20	0.37	0.52
Mean trial response rate	Sequential two-arm trials	0.20	0.23	0.25	0.27
	Platform	0.20	0.24	0.28	0.31
	Platform with delayed entry	0.20	0.24	0.27	0.30

22%↑

15%↑

Platform Design with Bayesian Adaptive Randomization

- Start with one control and multiple experimental arms
- Apply equal randomization (ER) or adaptive randomization (AR)
- Calculate the predictive probability or posterior probability of each experimental treatment being better than the control
  - Sufficiently low: Drop the treatment
  - Sufficiently high: Graduate the treatment
  - Otherwise, continue patient enrollment until reach N_{max}
- A perpetual, drug screening platform
  - Write a protocol with the “backbone” infrastructure
  - Add new treatments whenever needed
  - Amend the protocol by adding new treatments

PLBARPOSIM: Platform Design

- Max Arms = 6, no control group
  - True response rate (θ): 0.2, 0.3, 0.4, 0.2, 0.3, 0.4
  - Reference response rate = 0.3
- Number of Active Arms = 3
- N_{max} =180
  - For each arm: n_{min} = 15, n_{max} = 30
- Adaptive randomization

$$Prob(AR\ to\ Arm\ i) = Prob(Arm\ i\ is\ the\ best)^{\tau} / \sum_{k=1}^{K} Prob(Arm\ k\ is\ the\ best)^{\tau},\ \tau=1$$

- Early stopping rules and final analysis
  - Stopping for futility if Prob(θ < 0.3) > 0.95
  - Stopping for efficacy if Prob(θ > 0.3) > 0.95
  - Final efficacy claim if Prob(θ > 0.3) > 0.9

Video 2: Platform Trial with BAR: θ_1=0.2, θ_2=0.3, θ_3=0.4, θ_4=0.2, θ_5=0.3, θ_6=0.4

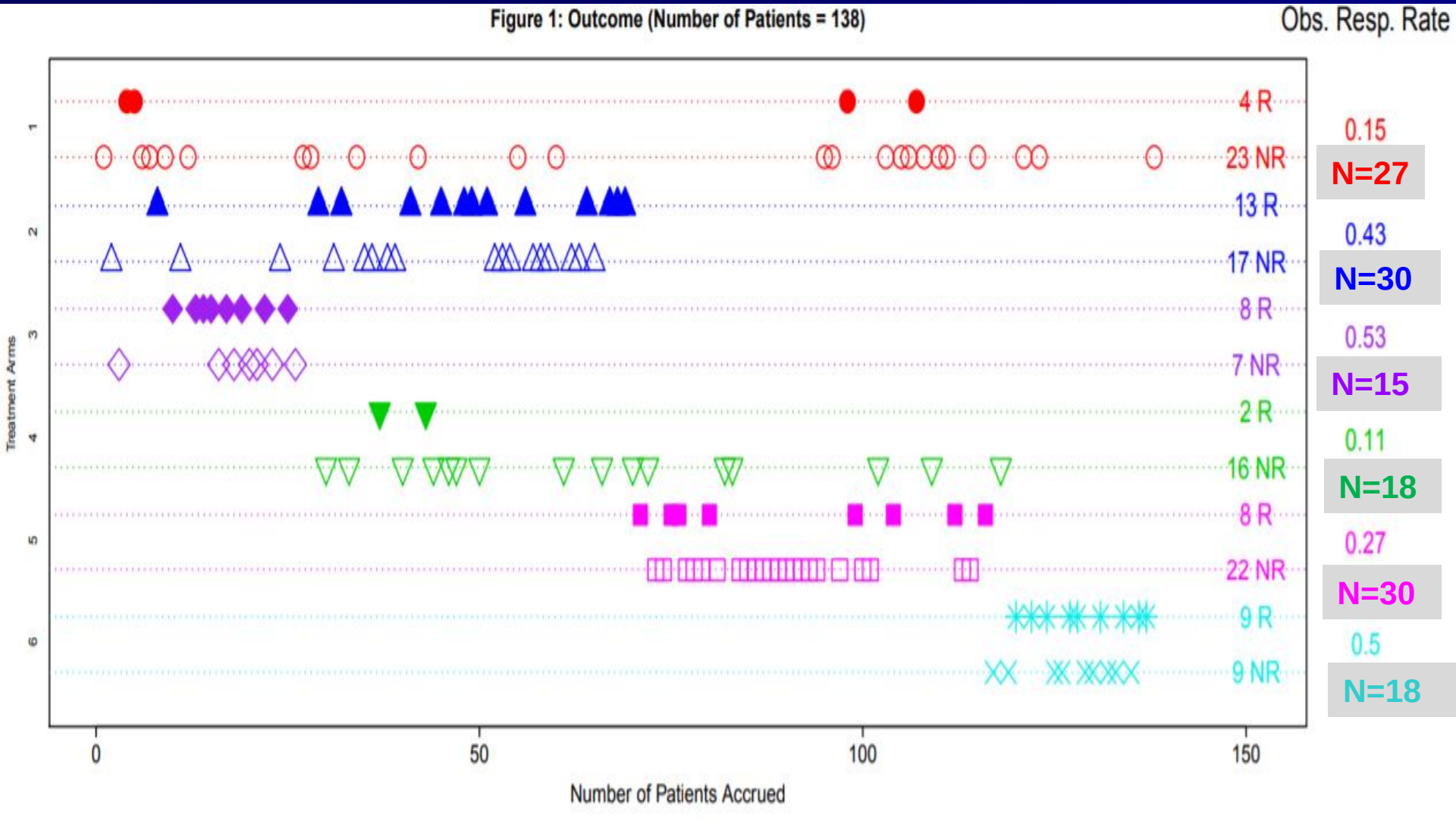


Figure 1: Outcome (Number of Patients = 138)
Obs. Resp. Rate
4 R
23 NR
13 R
17 NR
8 R
7 NR
2 R
16 NR
8 R
22 NR
9 R
9 NR
0.15
N=27
0.43
N=30
0.53
N=15
0.11
N=18
0.27
N=30
0.5
N=18
Treatment Arms
1
2
3
4
5
6
0
50
100
150
Number of Patients Accrued

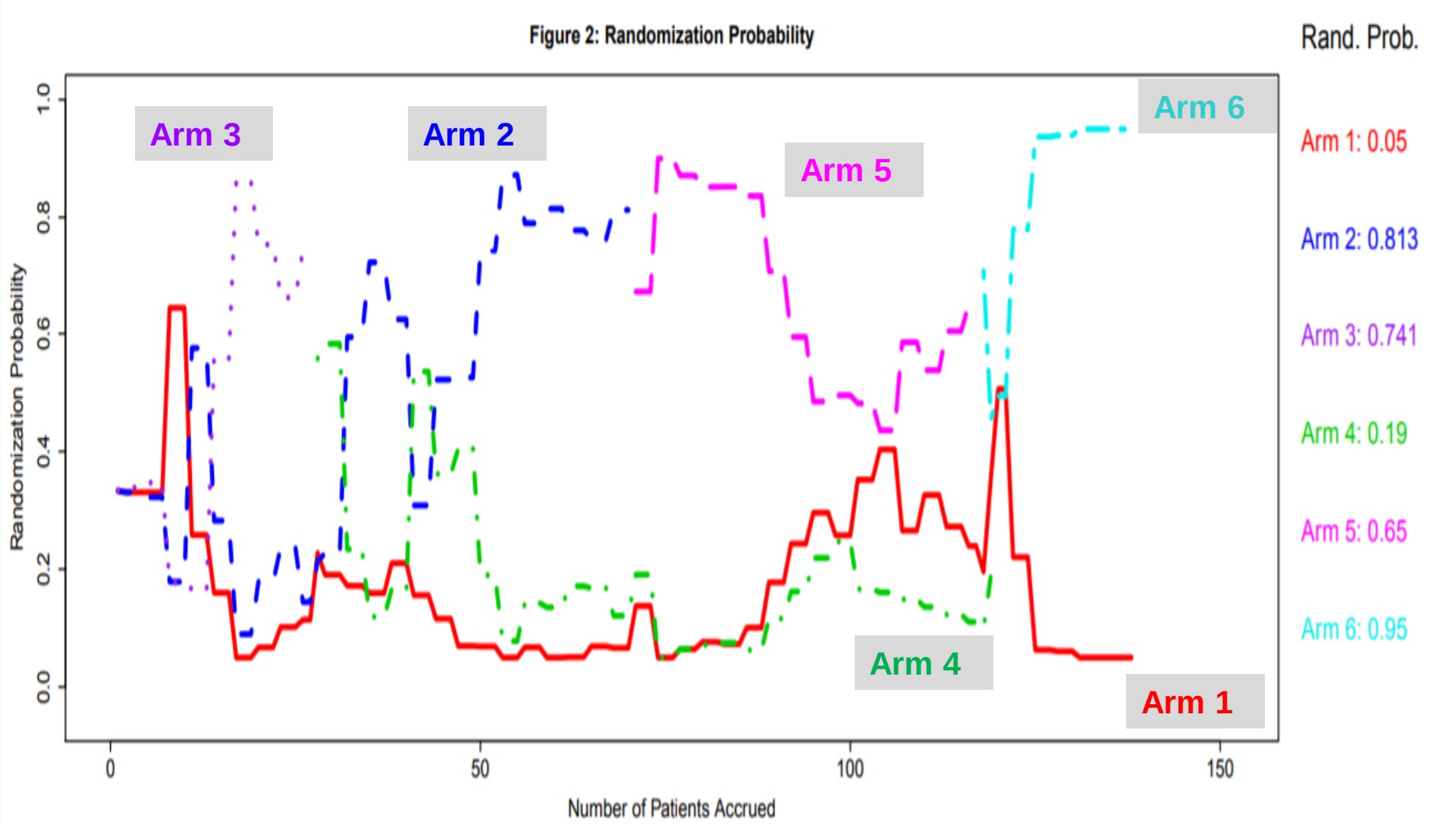
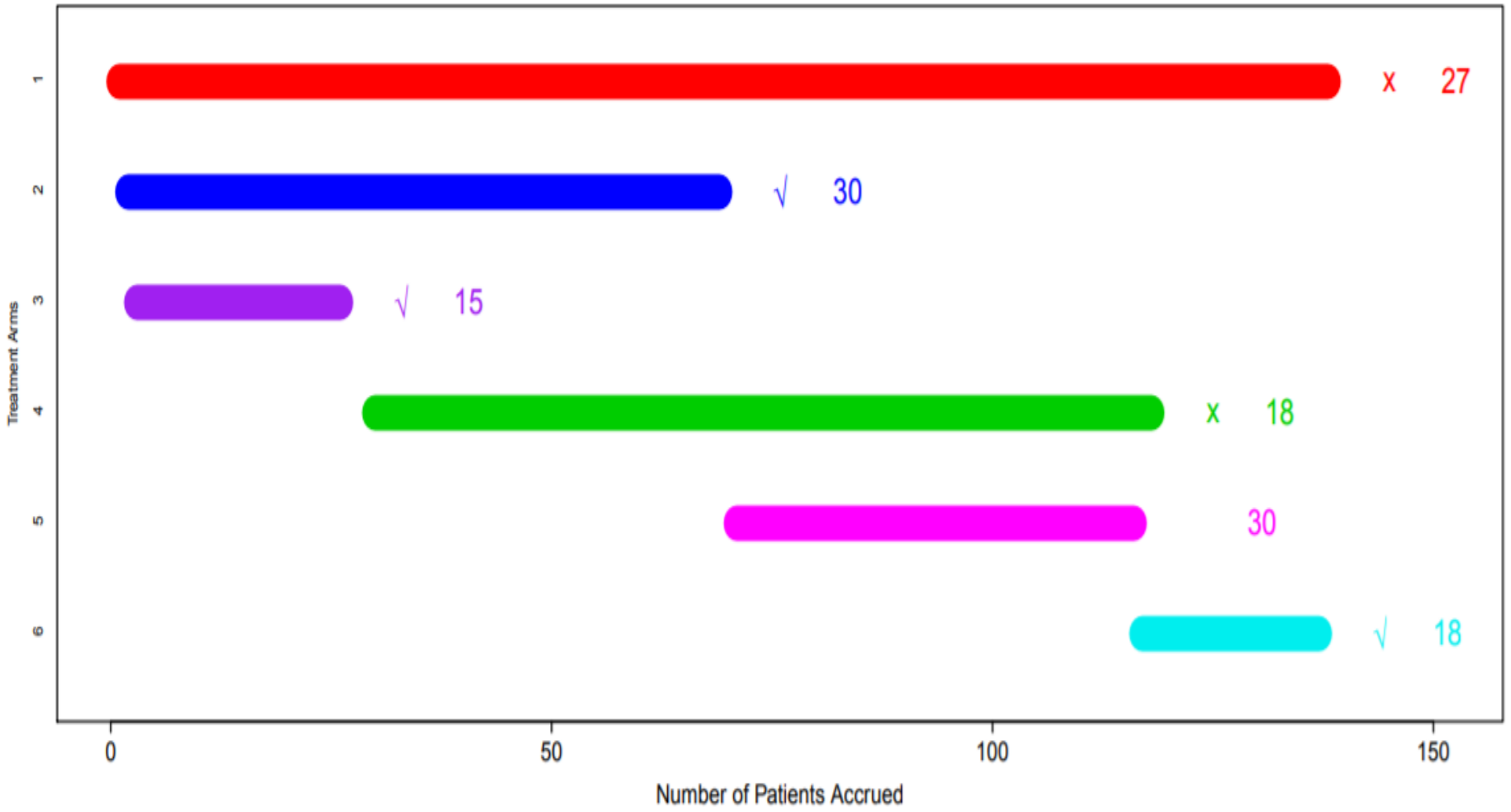


Figure 2: Randomization Probability
Rand. Prob.
Arm 1: 0.05
Arm 2: 0.813
Arm 3: 0.741
Arm 4: 0.19
Arm 5: 0.65
Arm 6: 0.95
Arm 3
Arm 2
Arm 5
Arm 6
Arm 4
Arm 1
Randomization Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Number of Patients Accrued

Figure 3: Accrual Timeline (Number of Patients = 138)



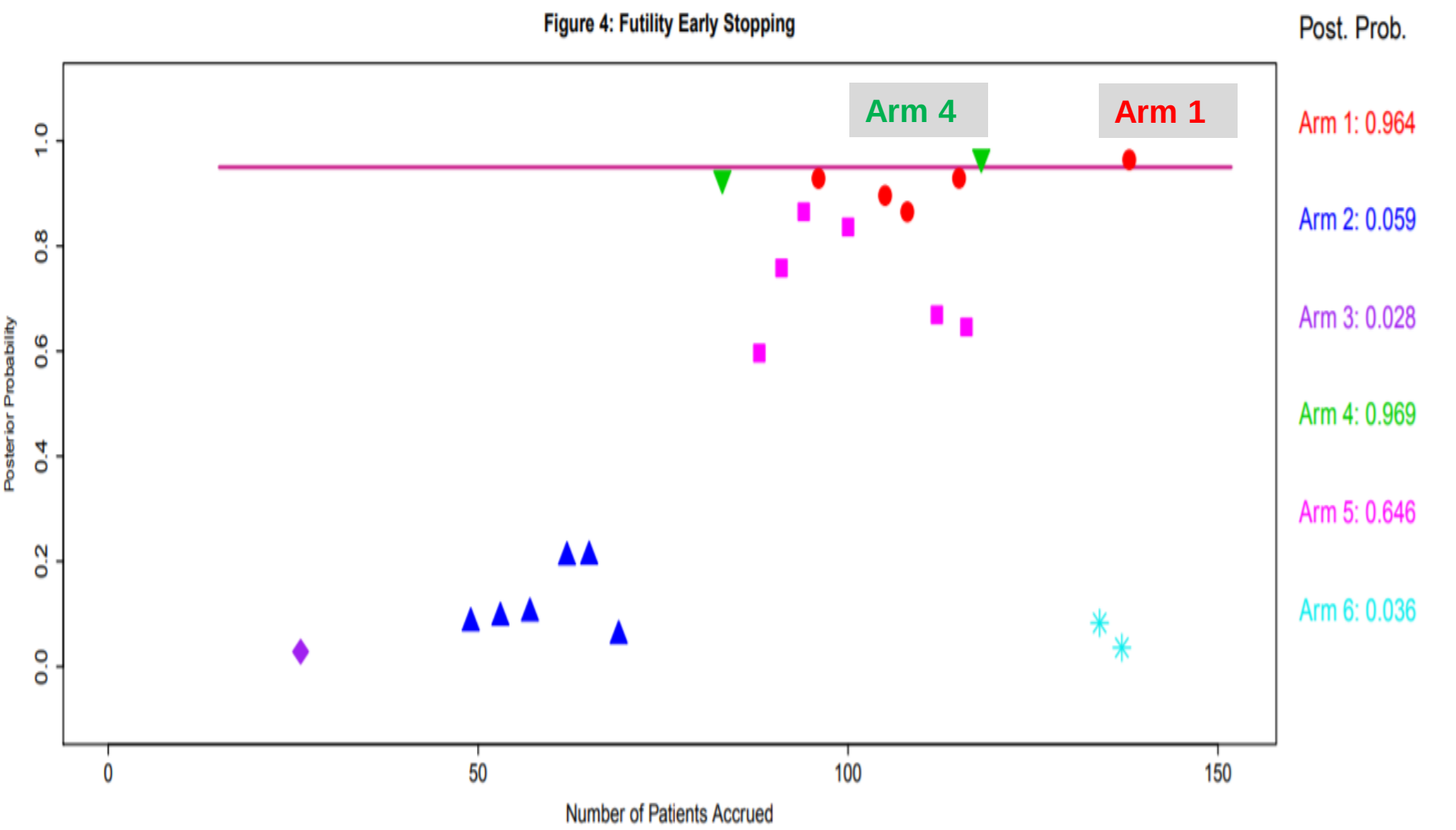


Figure 4: Futility Early Stopping
Post. Prob.
Arm 4
Arm 1
Arm 1: 0.964
Arm 2: 0.059
Arm 3: 0.028
Arm 4: 0.969
Arm 5: 0.646
Arm 6: 0.036
Posterior Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Number of Patients Accrued

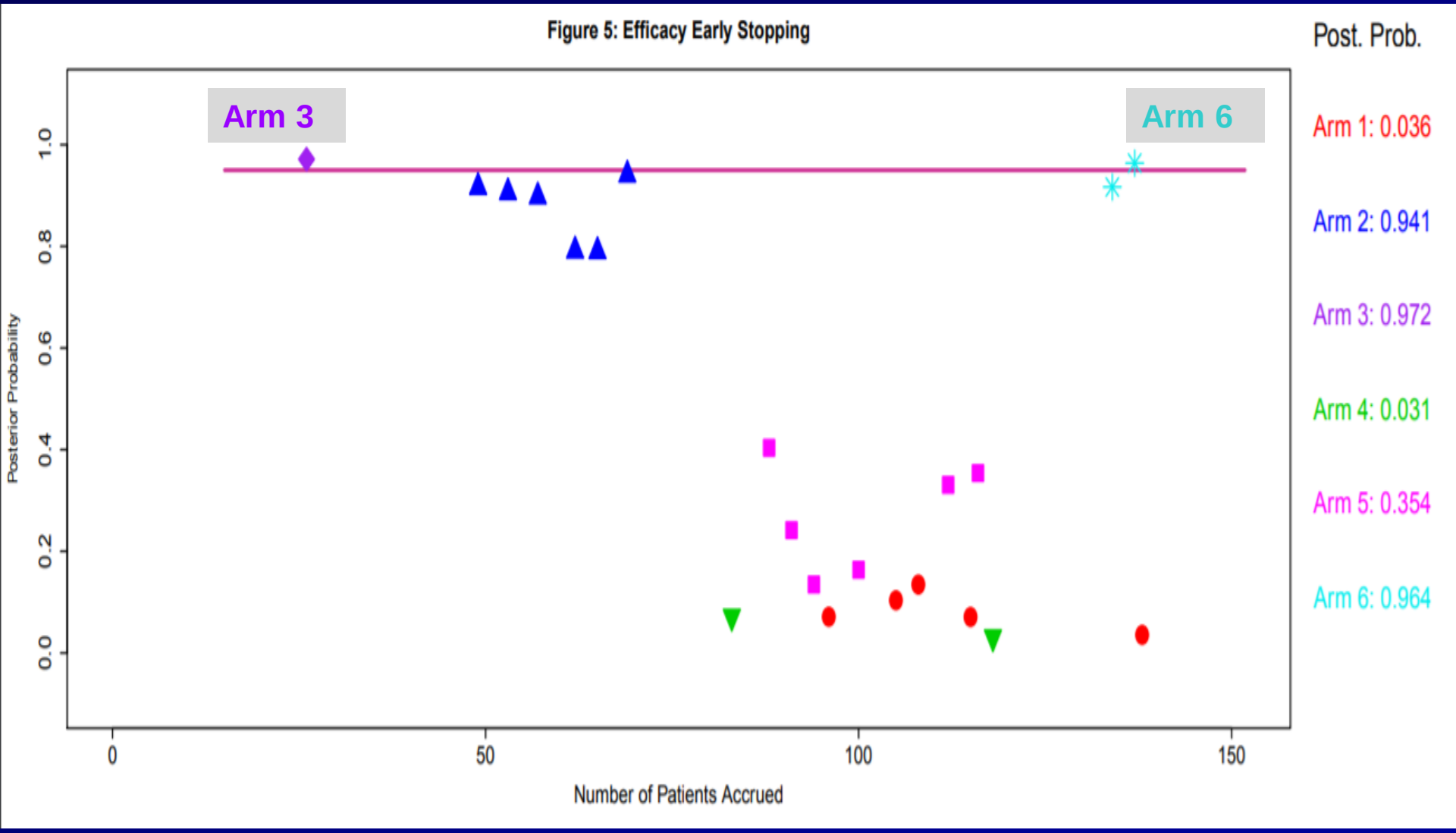


Figure 5: Efficacy Early Stopping
Arm 3
Arm 6
Post. Prob.
Arm 1: 0.036
Arm 2: 0.941
Arm 3: 0.972
Arm 4: 0.031
Arm 5: 0.354
Arm 6: 0.964
Posterior Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Number of Patients Accrued

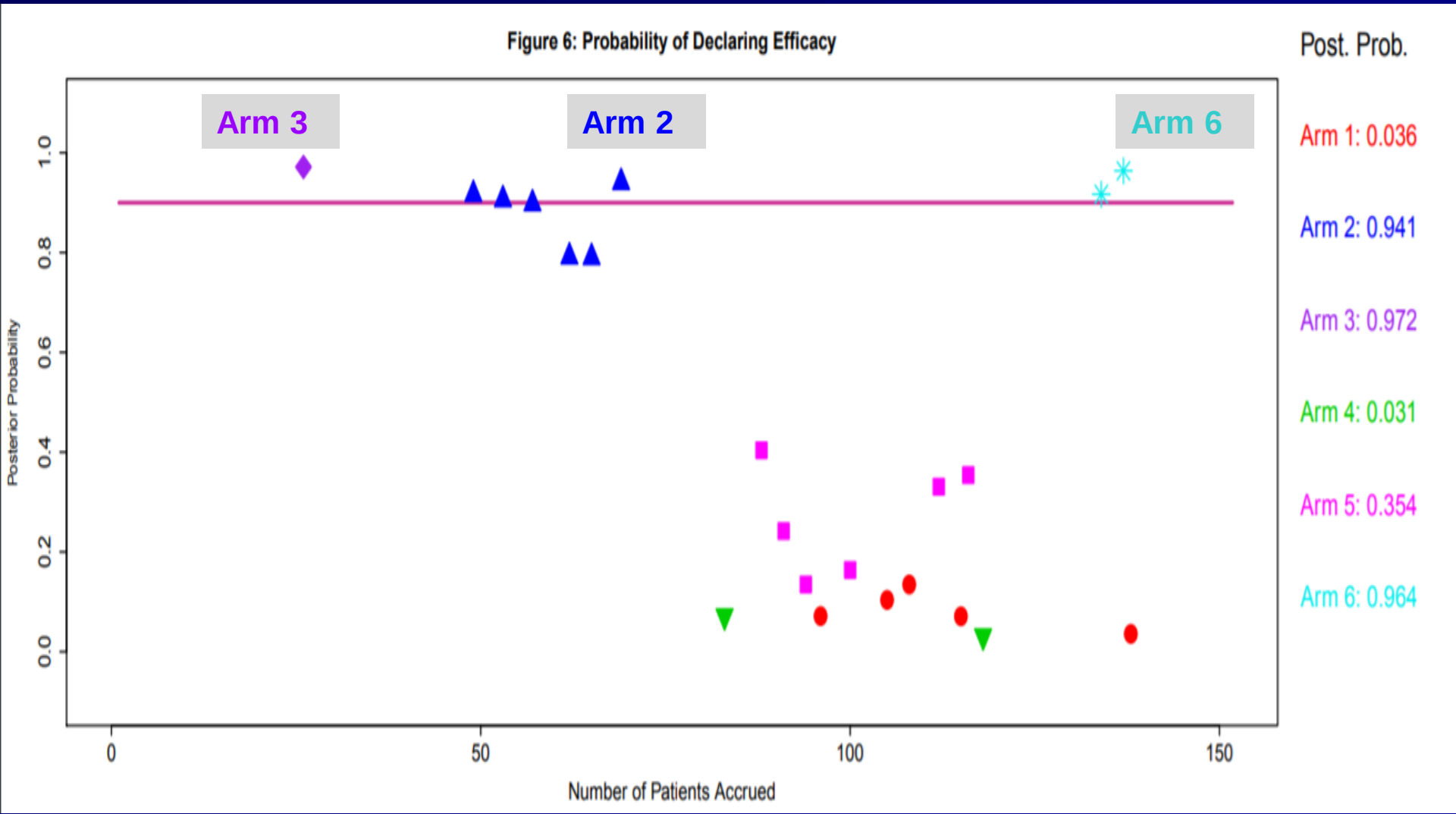


Figure 6: Probability of Declaring Efficacy
Arm 3
Arm 2
Arm 6
Post. Prob.
Arm 1: 0.036
Arm 2: 0.941
Arm 3: 0.972
Arm 4: 0.031
Arm 5: 0.354
Arm 6: 0.964
Posterior Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Number of Patients Accrued

PLBARPO: Input for Platform Design

Operating Characteristics Input

Input Parameter	Input Value
Trial Name (Optional)	
With Control Arm	FALSE
Control Arm Option	FALSE
Maximum Number of Arms	6
Number of Active Arm	3
Equal Prior for All Arms	TRUE
Prior distribution for theta:Beta(a,b) a	0.5
Prior distribution for theta:Beta(a,b) b	0.5
True Response Rate	0.2 , 0.3 , 0.4 , 0.2 , 0.3 , 0.4
Minimum number of patients per arm before early stopping rule applies	15
Maximum number of patients per arm	30
Maximum total number of patient in the trial	180
Input Cohorts Manually	FALSE
Cohort size for Interim Analysis	3
Cohorts for Interim Analysis: (separate by a comma)	
Randomization Method	AR
Adaptive Randomization Cohort Size	3
AR Method	BARCP
Adaptive Randomization Tuning Parameter/Allocation Function Parameter	1
Allocation Function Parameter	
Minimum Randomization Probability for each testing arm	0.05

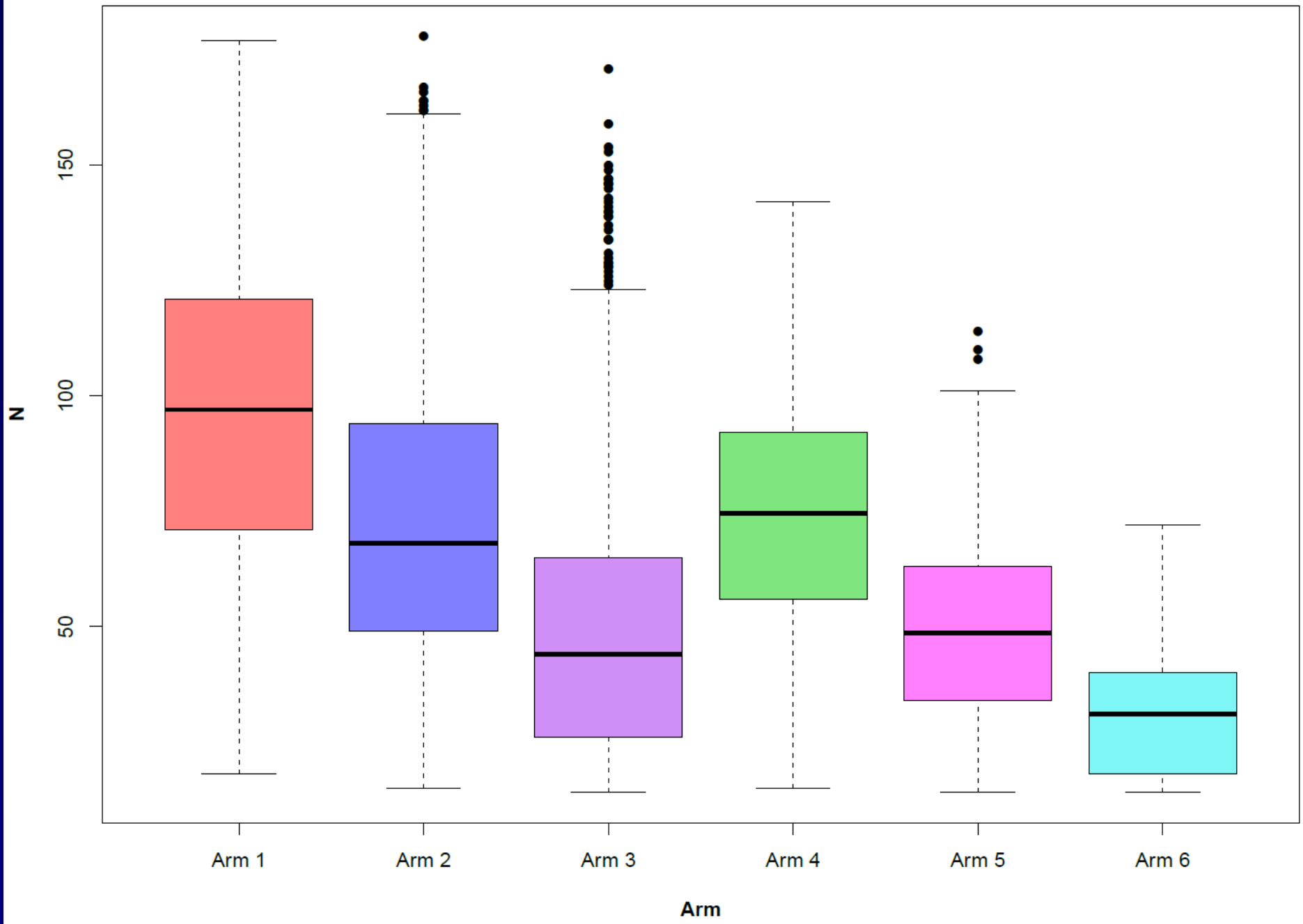
Operating Characteristics Input (Continued)

Input Parameter	Input Value
Minimum Randomization Probability for each testing arm	0.05
Number of Simulations for calculating AR	10000
Number of Simulated Trials	1000
Seed	2000
Early Stopping for Futility	TRUE
Reference response rate for futility monitoring	0.3
Probability confidence threshold for futility stopping	0.9
Early Stopping for Efficacy	TRUE
Reference response rate for efficacy monitoring	0.3
Probability confidence threshold for claiming efficacy early	0.9
Reference response rate for final decision	0.3
Probability confidence threshold for claiming efficacy	0.8
Auto Generated Graph Parameters	TRUE
Color	red,blue,purple,green3,magenta,cyan2
Line Type	1,2,3,4,5,6
Point Symbol	1,2,3,4,5,6

Table OC1: Overall Summary

Arm	Resp.Rate	Prob.Fut.Stop	Prob.Eff.Stop	Prob.Declare.Eff	Avg.N.Patients	Avg.N.Resp	Obs.Resp.Rate	Arm.Usage
1	0.2	0.613	0.022	0.023	22.44	4.472	0.1993	1
2	0.3	0.202	0.187	0.223	25.191	7.523	0.2986	1
3	0.4	0.036	0.531	0.645	22.485	9.003	0.4004	1
4	0.2	0.611	0.019	0.022	22.542	4.473	0.1984	1
5	0.3	0.215	0.201	0.253	24.942	7.451	0.2987	1
6	0.4	0.033	0.547	0.646	22.269	8.952	0.402	1

Figure OC3: Distribution of the Accrual Interval



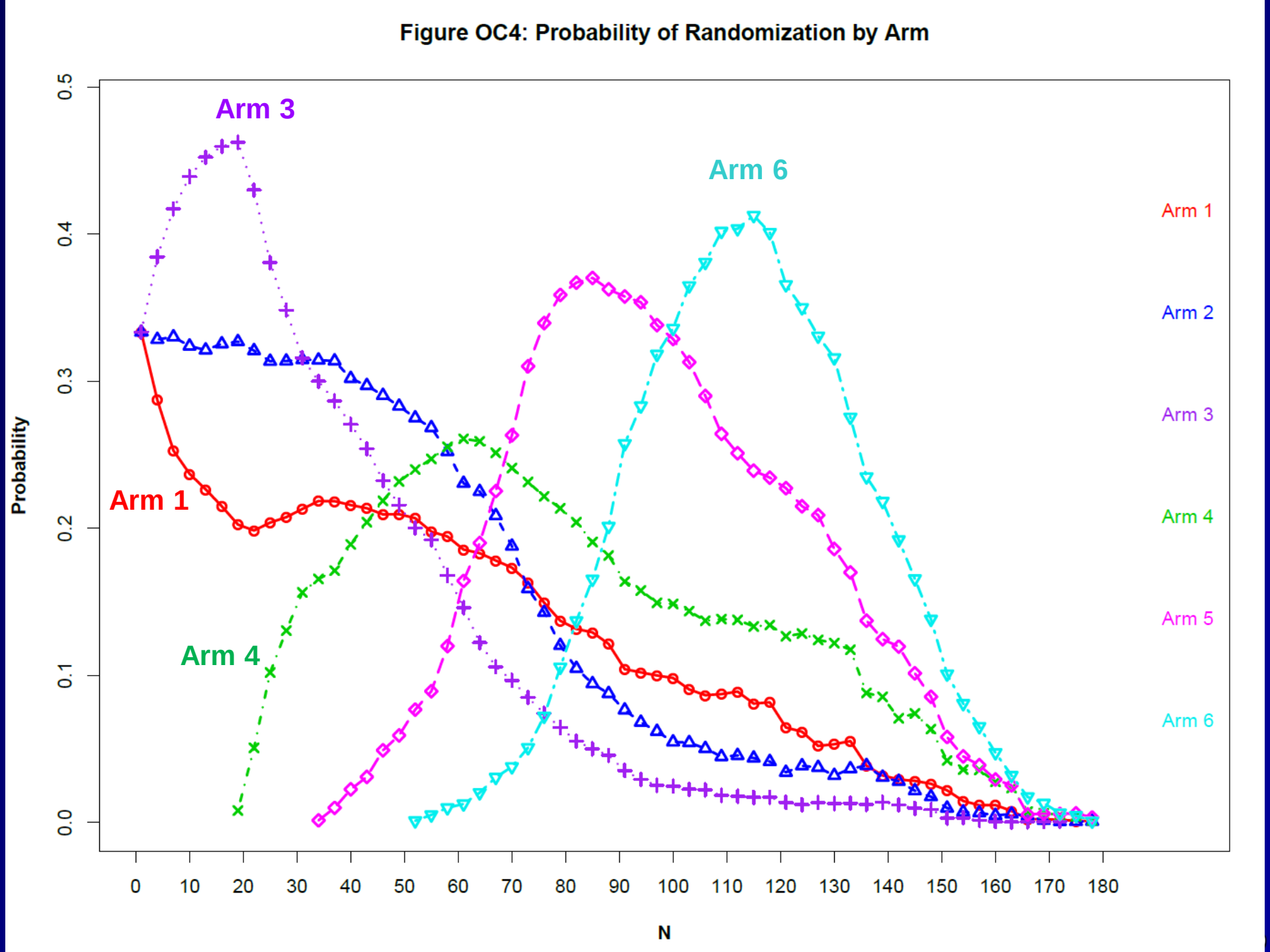


Figure OC4: Probability of Randomization by Arm
Arm 3
Arm 6
Arm 1
Arm 4
Arm 1
Arm 2
Arm 3
Arm 4
Arm 5
Arm 6
Probability
0.0
0.1
0.2
0.3
0.4
0.5
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
N

Figure OC5: Early Stopping Due to Futility

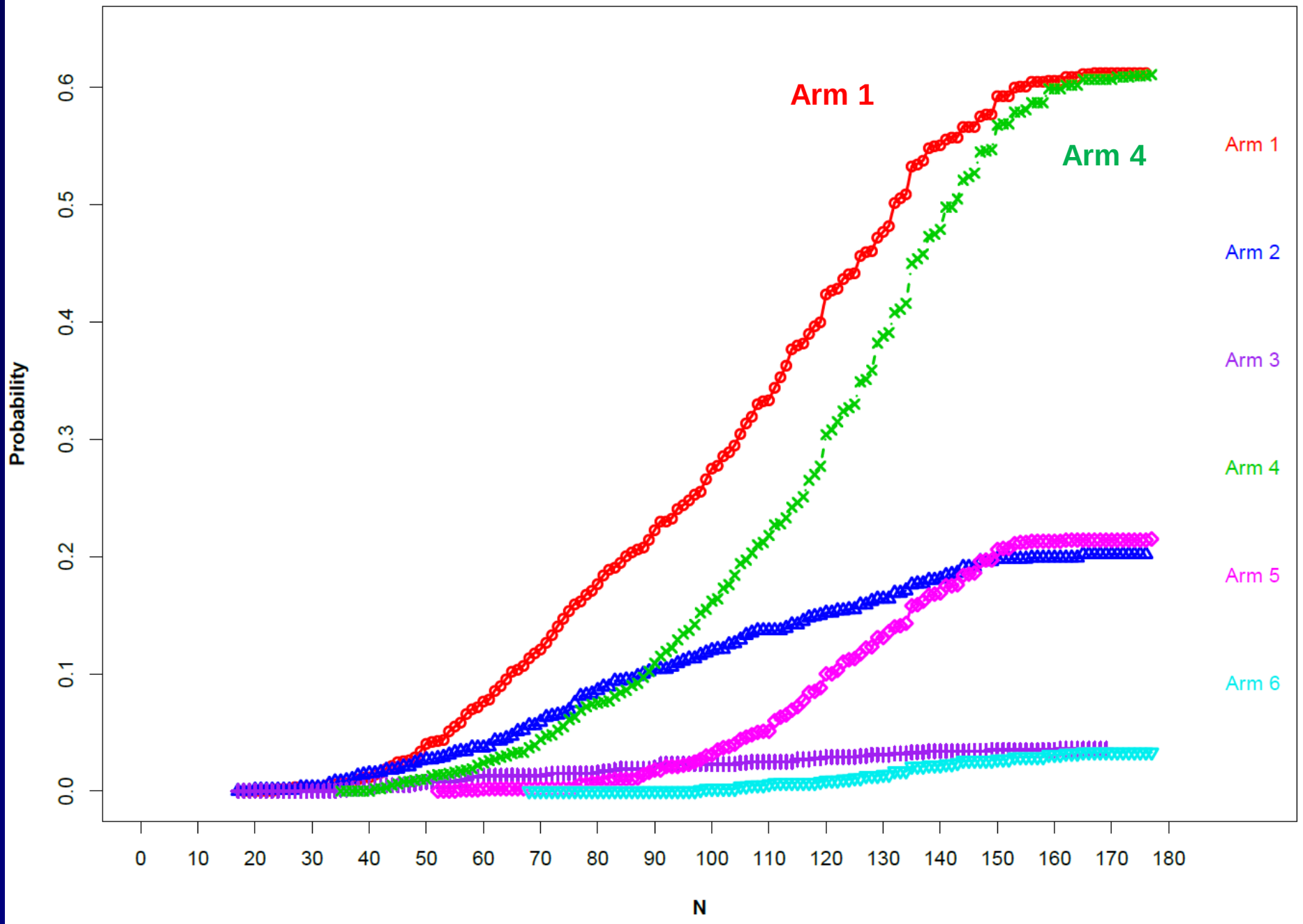
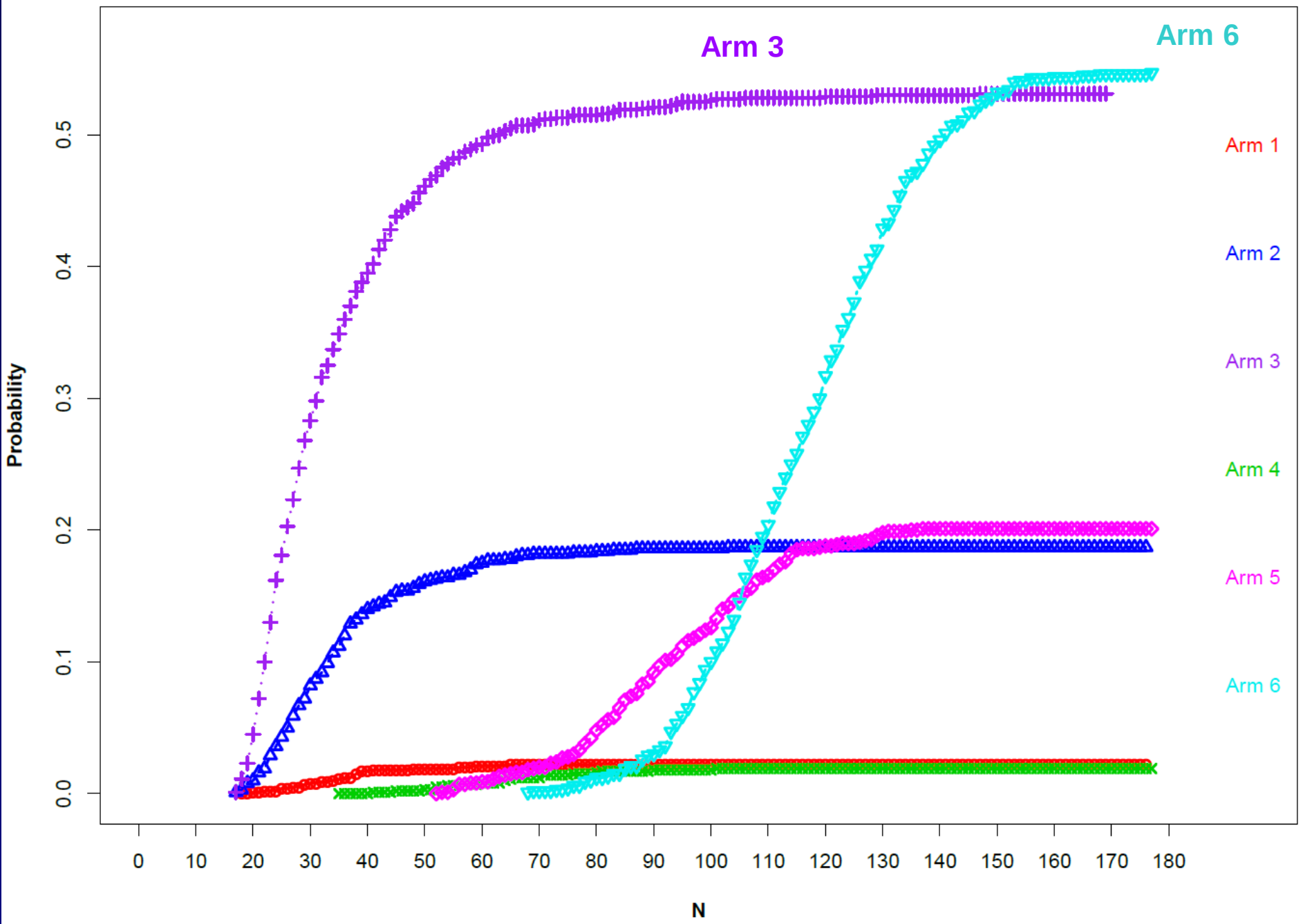


Figure OC6: Early Stopping Due to Efficacy



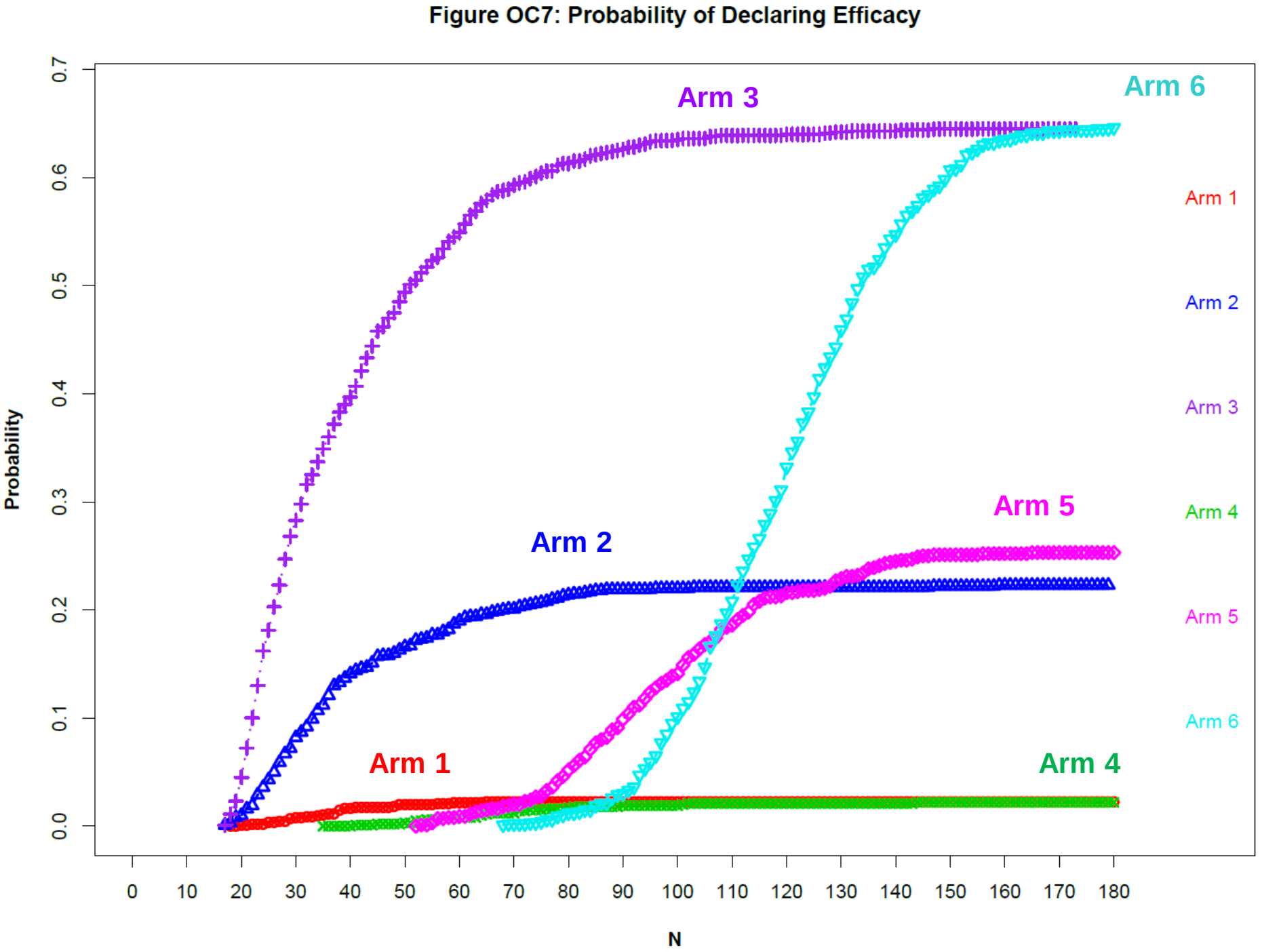


Figure OC7: Probability of Declaring Efficacy
Probability
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
N
Arm 3
Arm 6
Arm 2
Arm 5
Arm 1
Arm 4
Arm 1
Arm 2
Arm 3
Arm 4
Arm 5
Arm 6

Bayesian Hierarchical Model (BHM) for Basket Designs

- Clinical Trials often have subgroups
  - Different histology subtypes in breast cancer/lung cancer/sarcoma
  - One drug in multiple diseases or multiple drugs in a single disease
  - Multi-regional studies
- How do we analyze data?
  - Treat each subgroup separately
    - Do not use information efficiently
  - Combine all subgroups into one group
    - Not all groups are the same (iid assumption is too strong and may not hold in most cases)
- Bayesian hierarchical model can borrowing information across subgroups under the exchangeability assumption.
  - More borrowing when subgroups are more like and less borrowing when subgroups are more different. (nice!)
  - But, what to do if the subgroups are not exchangeable?

An Illustrative Example

- Suppose we run a clinical trial with one drug in 5 subgroups.
- The primary endpoint is binary: Response or No Response. We are interested in estimating the response rate, p
- We want to know whether the drug works or not in each subgroup
- We observe the following outcome:
  - (number of responses/n): 1/15, 2/18, 3/10, 7/15, 8/20
  - Estimated response rate: 0.07, 0.11, 0.30, 0.47, 0.40
- Can we apply Bayesian hierarchical model to borrow information across subgroups? How?

Bayesian Hierarchical Model – BLN (Binomial, Logit, Normal)

- There are m groups.
- Observe the number of successes for each group:

  $y_i \sim Bin(p_i, n_i), i = 1, \ldots, m$
- Take a logit transformation on p_i and let

  $\log(p_i/(1\text{-}p_i)) = \theta_i$
- Assume θ_i are exchangeable and $\theta_i \sim N(\mu, \sigma^2) = N(\mu, \tau^{-1})$, where $\tau = \sigma^{-2}$ is the precision parameter
- Assume the hyper-prior for $\mu \sim N(\mu_0, {\tau_0}^{-1})$, and
- Assume the hyper−prior for $\tau \sim Gamma\ (\Gamma_a, \Gamma_b)$
- Compute the posterior distribution for
  - p_i under no borrowing with the prior for $p_i \sim Beta(a_0, b_0)$
  - p_i under the BHM model described above
  - p under the $i.i.d.$ model with $p_i = p$
  - p under the BHM model with $p = 1/(1 + \exp(-\mu))$

Weak Borrowing

Parameters for BHM

Hyper Prior for overall mean, mu:

μ_0 | τ_0

0 | 0.000001

Hyper Prior for precision of mu, tau:

Γ_a | Γ_b

0.01 | 10

Prior distribution for ρ_i :Beta(a_0 ,b_0)

a_0 | b_0

0.001 | 0.001

Credible Interval (1- α) x 100%: α

0.2

WinBUGS Settings

Burnin | Iter

1000 | 10000

Sample Information

Number of Groups

5

Number of Success for Each Group *(separate by a comma)*

1,2,3,7,8

Sample Size for Each Group *(separate by a comma)*

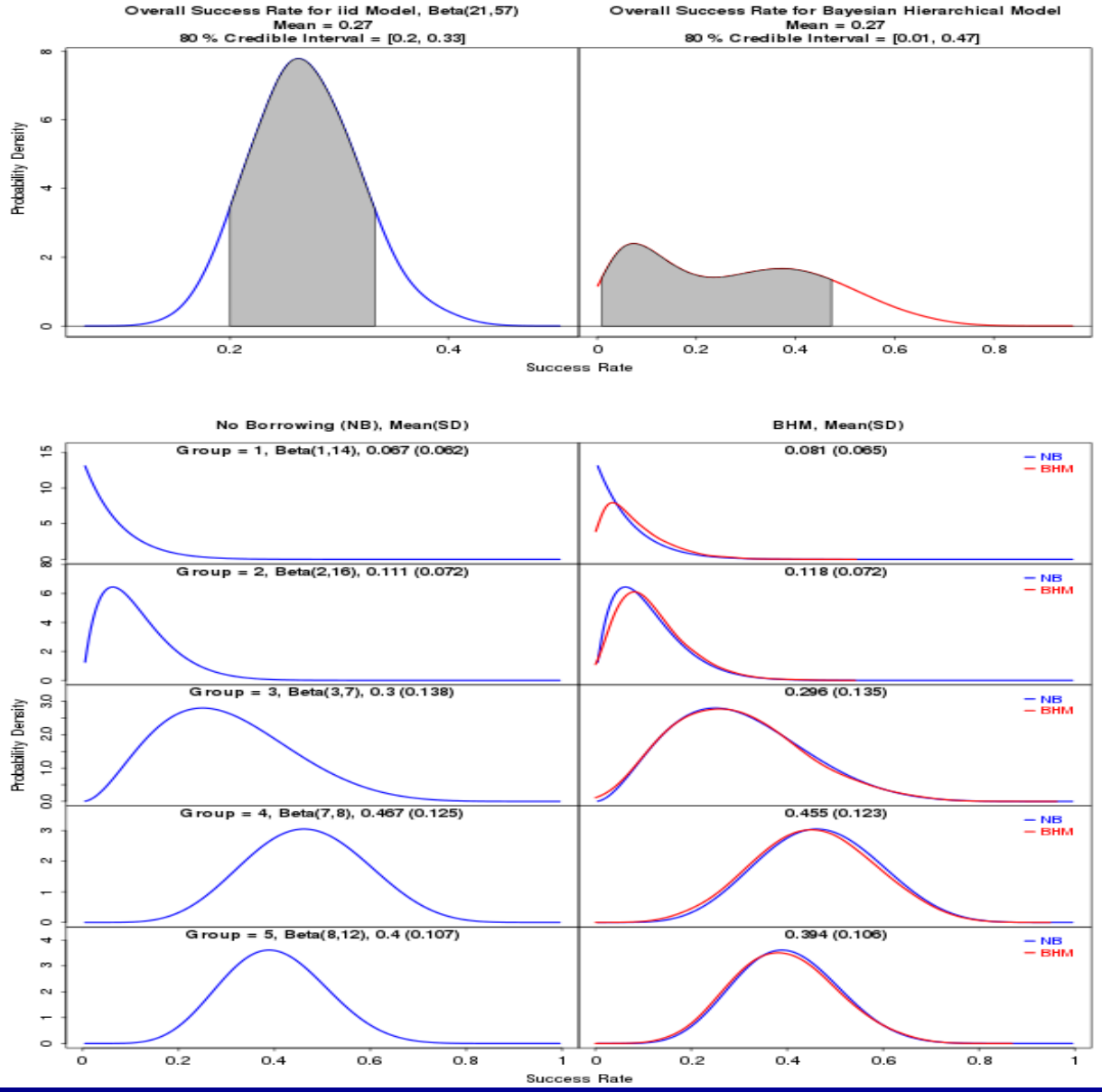
15,18,10,15,20

Calculate

Edit | Start Over

Data: 1/15, 2/18, 3/10, 7/15, 8/20

BHM - Binomial Data | Support Document



Strong Borrowing

Parameters for BHM

Hyper Prior for overall mean, mu:

μ_0 0

τ_0 0.000001

Hyper Prior for precision of mu, tau:

Γ_a 10

Γ_b 0.01

Prior distribution for ρ_i :Beta(a_0 ,b_0)

a_0 0.001

b_0 0.001

Credible Interval (1- α) x 100%: α

0.2

WinBUGS Settings

Burnin 1000

Iter 10000

Sample Information

Number of Groups

5

Number of Success for Each Group *(separate by a comma)*

1,2,3,7,8

Sample Size for Each Group *(separate by a comma)*

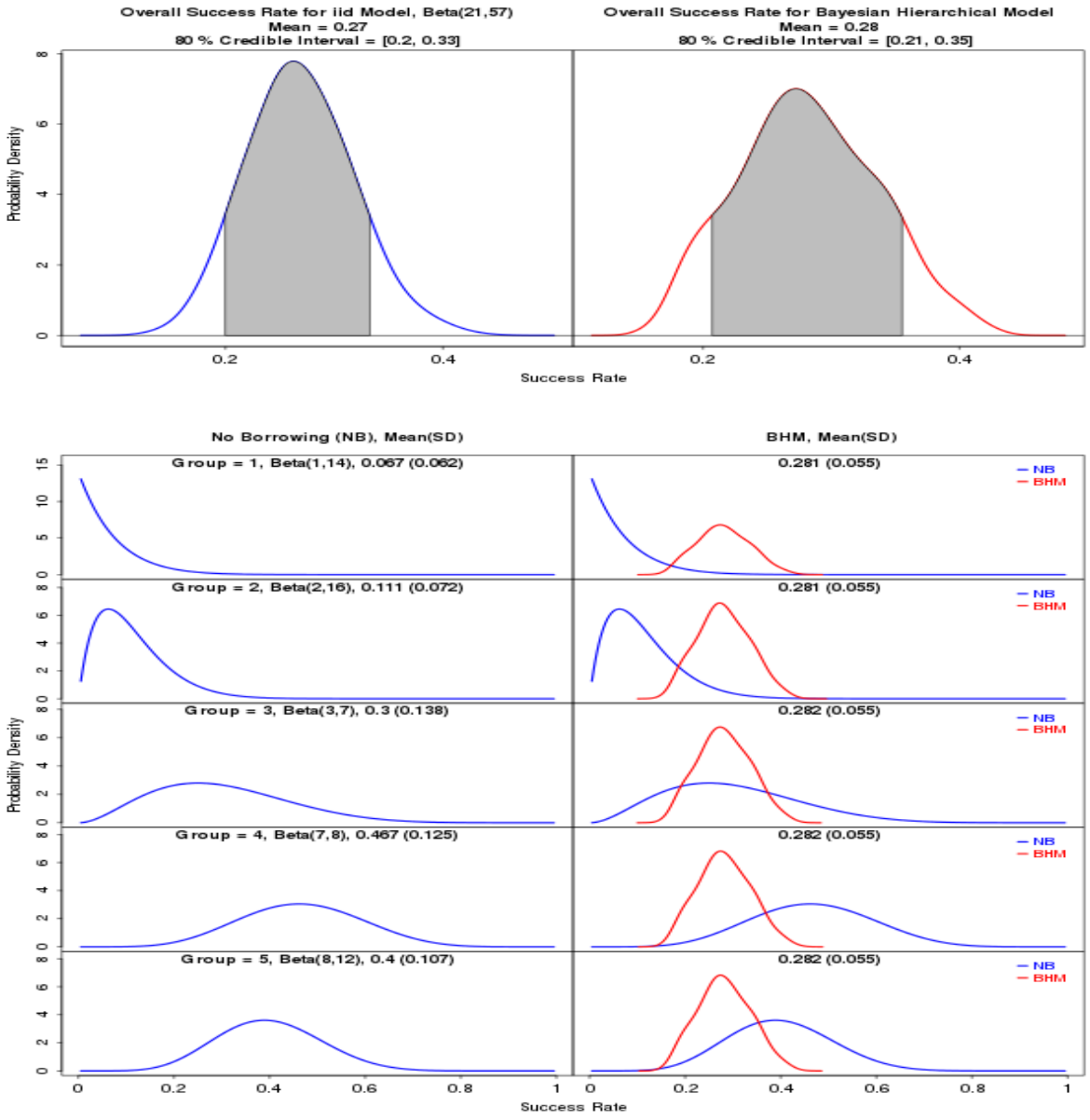
15,18,10,15,20

Calculate

Edit Start Over

Data: 1/15, 2/18, 3/10, 7/15, 8/20

BHM - Binomial Data | Support Document



Moderate Borrowing

Parameters for BHM

Hyper Prior for overall mean, mu:

μ_0 0 τ_0 0.000001

Hyper Prior for precision of mu, tau:

Γ_a 0.01 Γ_b 0.1

Prior distribution for p_i :Beta(a_0 ,b_0)

a_0 0.001 b_0 0.001

Credible Interval (1- α) x 100%: α

0.2

WinBUGS Settings

Burnin 1000 Iter 10000

Sample Information

Number of Groups

5

Number of Success for Each Group *(separate by a comma)*

1,2,3,7,8

Sample Size for Each Group *(separate by a comma)*

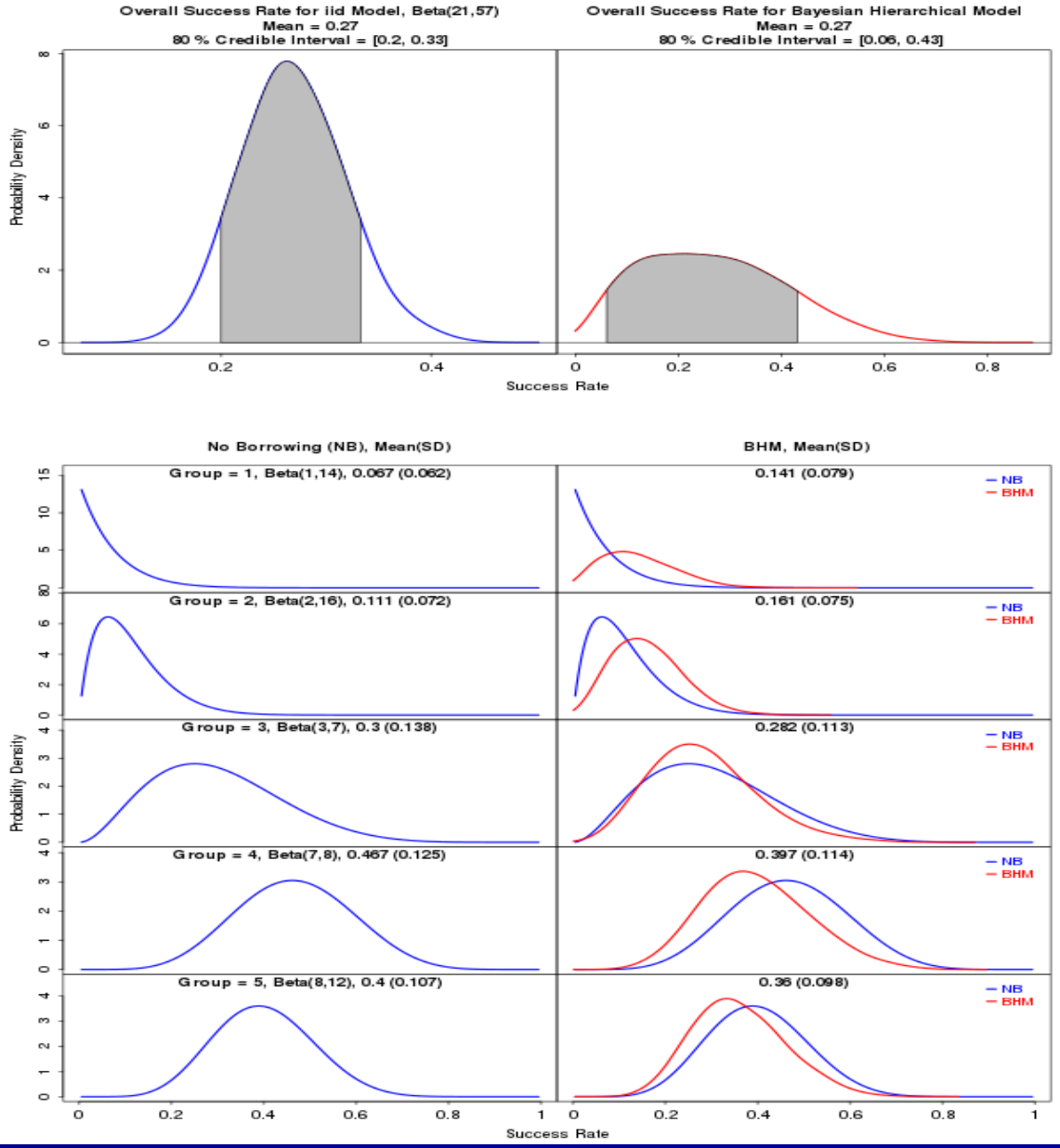
15,18,10,15,20

Calculate

Edit Start Over

Data: 1/15, 2/18, 3/10, 7/15, 8/20

BHM - Binomial Data Support Document



Bayesian Classification and Information Sharing (BaCIS)

- Traditional Bayesian hierarchical models do not have subgroup classifications; thus, information is shared across all subgroups.
- When the subgroups have very different outcomes, placing all subgroups in one pool and borrowing information across all subgroups can result in substantial bias.
- BaCIS allows *smart borrowing* which borrows across "similar" subgroups and does not borrow across "dissimilar" ones. BaCIS yields better operating characteristics across a wide range of scenarios with high statistical power while controlling type I error rate.

Chen, N. and Lee, J. J. Bayesian hierarchical classification and information sharing for clinical trials with subgroups and binary outcomes, Biometrical Journal 2019.

Model Specification

- In a Phase II clinical trial with a binary endpoint, assume that there are *K* subgroups. For each subgroup, there are n_i patients with a response rate p_i. The number of responses:

$$Y_i \sim Binomial(n_i, p_i), i = 1, \ldots, K.$$

- Taking the hypothesis testing framework, subgroups are classified into two clusters: drug works or drug does not work.

- Subsequently, information sharing takes place within subgroups in the same cluster, but not across different clusters.

- Two-step approach:
  - Step 1: Classification (Model 1)
  - Step 2: Information Sharing within each cluster (Model 2)

Step 1: Classification (Model 1)

Outcome

$$Y_i \sim Binomial(n_i, p_i)$$
$$logit(p_i) = \eta_i$$
$$\eta_i \sim Normal(\gamma_{I_i}, \tau_1)$$

Classification with Latent Variables

$$I_i = 1, if\ \theta_i < 0$$
$$I_i = 2, if\ \theta_i \geq 0$$
$$\theta_i \sim Normal(0, \tau_2)\ i=1,\ldots,K$$

ϕ_1: Low Response Rate
ϕ_2: High Response Rate

$$\gamma_j \sim logit(\phi_j)\ \ j=1,\ldots,2$$

Mimicking Hypothesis Testing Framework: $H_0: p_i \leq \phi_1$ vs $H_1: p_i > \phi_1$

Subgroup i is classified into Cluster 1 if $Prob(\theta_i > 0) > \theta_c$ or Cluster 2 otherwise. $\theta_c = 1 - \frac{1}{1+\exp\{-\frac{2\Delta_r}{\phi_2-\phi_1}\}}$, where $\Delta_r = (\frac{\sum Y_i}{\sum n_i} - \frac{\phi_1+\phi_2}{2})$.

θ_c is determined adaptively. When the overall observed response rate is closer to the average of ϕ_1 and ϕ_2, Δ_r is closer to 0. Thus θ_c is closer to 0. When the overall observed response rate is large, Δ_r is large, θ_c becomes small. Thus, more subgroups are classifed into the high response rate cluster (Cluster 2) and vice versa.

Step 2: Subgroup Borrowing within Each Cluster Using Bayesian Hierarchical Model (Model 2)

Outcome

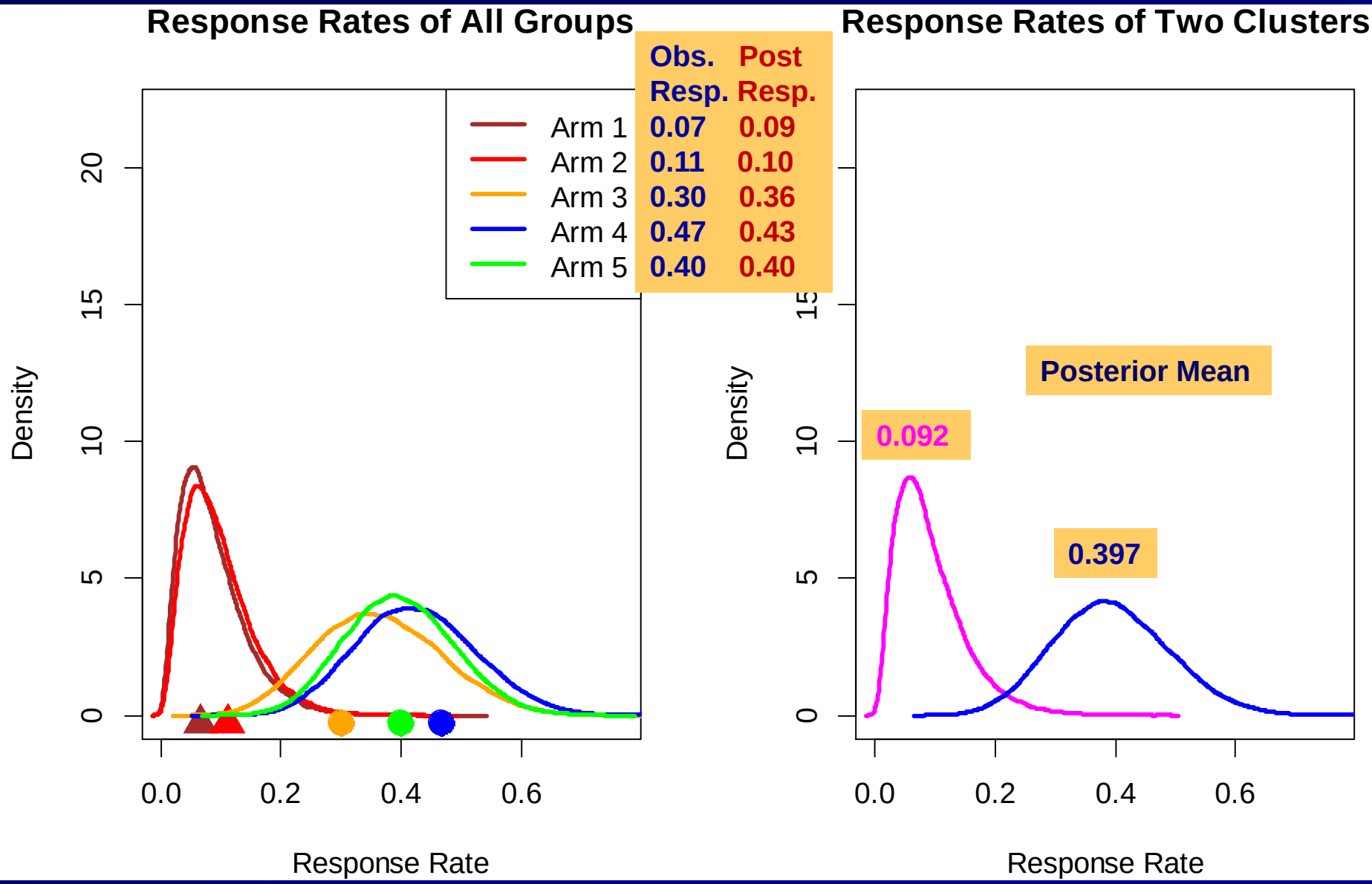
$$Y_i \sim Binomial(n_i, p_i)$$
$$logit(p_i) = \eta_i$$
$$\eta_i \sim Normal(\mu, \tau_3)$$

Hyper Prior

$$\mu \sim Normal(\mu_0, \tau_4)$$
$$\tau_4 \sim \text{Gamma}(\alpha, \beta)$$
$$\mu_0 = logit(\phi)$$

An R-Package: bacistool is available.

Posterior Distributions of Response Rates



Posterior distributions of (a) response rates of all treatment arms, and (b) response rates of two clusters with outcomes of (1/15, 2/18, 3/10, 7/15, 8/20).

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By Quantitative Research Computing at MD Anderson Cancer Center

This is free software that can be used for:

- Designing and conducting clinical trials in the medical field
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Url	Last Modified Date	Software Name	Brief Description
	2019-04-09	Platform Design of Bayesian Adaptive Randomization with Posterior Probability	A multi-arm platform design with Bayesian adaptive randomization and efficacy monitoring via posterior probability for binary outcomes. The design allows futility and/or efficacy early stopping with or without a control group. The application provides design operating characteristics and can be used for study conduct. Number of concurrent arms and maximum number of arms can be specified.
	2019-04-05	Bayesian Adaptive Randomization and Efficacy Monitoring with Posterior Probability	A multi-arm design with Bayesian adaptive randomization and efficacy monitoring via posterior probability for binary outcomes. The design allows futility and/or efficacy early stopping with or without a control group. The application provides design operating characteristics and can be used for study conduct.
	2019-04-01	Platform Design of Bayesian Adaptive Randomization with Posterior Probability Simulator	Simulating one trial at a time for the multi-arm platform design with Bayesian adaptive randomization and efficacy monitoring via posterior probability for binary outcomes. The design allows futility and/or efficacy early stopping with or without a control group. Animation is provided to illustrate how a trial evolves over time. Number of concurrent arms and maximum number of arms can be specified.
	2019-03-29	Bayesian Adaptive Randomization and Efficacy Monitoring with Posterior Probability – A Simulator	Simulating one trial at a time for the multi-arm design with Bayesian adaptive randomization and efficacy monitoring via posterior probability for binary outcomes. The design allows

https://biostatistics.mdanderson.org/softwareOnline/

http://trialdesign.org

Clinical Trial Design Software

Filter by: ALL | PHASE I | PHASE II | PHASE I-II | BASKET & PLATFORM | SAMPLE SIZE CALCULATION | EDUCATION

Instructions: To access the software online click the red circle or the title. To download a desktop version, click the download arrow. To expand software description, mouse over the description.

BO

BOIN Suite

Bayesian optimal interval (BOIN) designs provide a novel platform to design phase ***more...***

CRM

CRM & BMA-CRM

The continual reassessment method (CRM) is a model-based dose-finding approach ***more...***

KB

Keyboard Design

The keyboard design provides an upgrade to the modified toxicity probability ***more...***

TTK

Time-to-Event Keyboard

The time-to-event keyboard design can handle toxicity data that are pending due ***more...***

S2S

Simon's Two Stage Design

The Simon's two stage design is a commonly used phase II design. It controlls type 1 ***more...***

BOP

Bayesian Optimal Phase 2 (BOP2) Design

The Bayesian optimal phase II (BOP2) design is a flexible Bayesian design that allows ***more...***

TOP

Time-to-Event Bayesian Optimal Phase II Trial Design

The time-to-event Bayesian Optimal Phase II (TOP) design is a flexible and efficient design for phase II clinical trials. ***more...***

PP

Bayesian Efficacy Monitoring with Predictive Probability

Bayesian efficacy monitoring with options of early futility ***more...***

DL

Bayesian Phase 2 Design with Delayed Outcomes

One practical impediment in adaptive phase II trials is that outcomes must be observed soon enough ***more...***

TM

Bayesian Toxicity Monitoring

Bayesian toxicity monitoring for evaluating drug safety.

PO

Bayesian Efficacy Monitoring with Posterior Probability

Bayesian efficacy monitoring with options of early futility and/or efficacy stopping using posterior probability.

OBD

Find Optimal Biological Dose for Immunotherapy

Down for maintenance. Sorry for the inconvinience.

CBH

Calibrated Bayesian Hierarchical Model Design

Bayesian hierarchical modeling has been proposed to adaptively borrow

BST

Bayesian Latent Subgroup Design for Basket Trials

The innovation of the BLAST design is that it adaptively clusters cancer types

PAS

Bayesian Drug Combination Platform Trial Design with Adaptive Shrinkage

ComPAS provides a flexible Bayesian

http://trialdesign.org

Summary (1)

- Traditional clinical trial design: One trial, one drug at a time, discrete phase, infrequent interim analyses approach is inefficient, expensive, and results in high failure rate
- Master protocol / platform designs can
  - Study multiple drugs and populations in one trial.
  - Eliminate white space between trials in separate phases
  - Frequent monitor toxicity and efficacy
  - Drop bad arms by early stopping for futility
  - Graduate good arms by early stopping for efficacy
  - Add new arms
  - Assign more patients to more effective treatments by adaptive randomization
  - Continuously learn and improve in a perpetual trial

Summary (2)

- Basket Designs can
  - Evaluate the drug effect in multiple subgroups.
- Bayesian hierarchical model can
  - Borrow information from all available data (external and internal to the trial) to increase efficiency in evaluating treatment effect.
  - "Smart borrowing" allows borrowing among the "similar" subgroups and restrict borrowing across "dissimilar" groups by classifying the subgroups to clusters first, then, borrow within the clusters.
- Conduct more innovative trials to learn and to adapt so we can expedite progress.

Let's roll up our sleeves, implement novel designs, and make a difference!