In a Sea of Design Options Using Visualizations to Navigate a Variety of Options for a Platform Trial

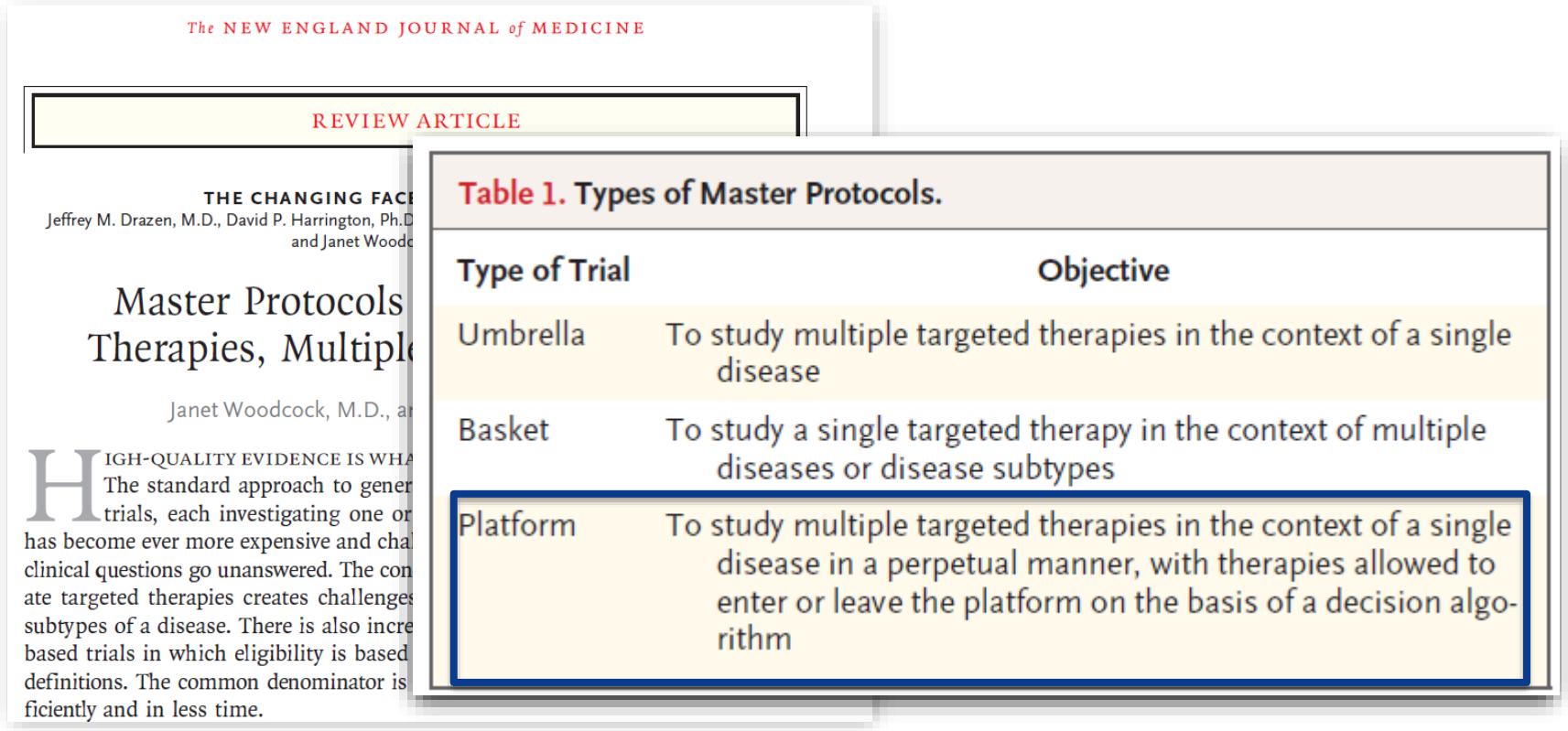
J. Kyle Wathen
Vice President of Scientific Strategy and Innovation
Cytel

Outline

- Introduction to platform trials
- ASA – DahShu IDSWG Workgroup – Useful Aids and “Tools”
- The ADAPPT – The **ADA**ptive **P**rostate Cancer **P**latform **T**rial – The Prostate Cancer Clinical Trial Consortium (PCCTC)
- Iterative process of designing a platform trial
    - Various visuals and tables to convey trial decisions and performance
    - Trade-offs to calibrate futility
    - Use of Bayesian predictive probabilities (BPP) to help guide futility
    - Further calibration of futility through the use of BPP and Shiny App
- Summary

Reference

- Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017 Jul 6;377(1):62-70. doi: 10.1056/NEJMra1510062. PMID: 28679092.



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D.
and Janet Woodc

Master Protocols
Therapies, Multipl

Janet Woodcock, M.D., a

HIGH-QUALITY EVIDENCE IS WHA
The standard approach to gener
trials, each investigating one or
has become ever more expensive and cha
clinical questions go unanswered. The con
ate targeted therapies creates challenges
subtypes of a disease. There is also incre
based trials in which eligibility is based
definitions. The common denominator is
ficiently and in less time.

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

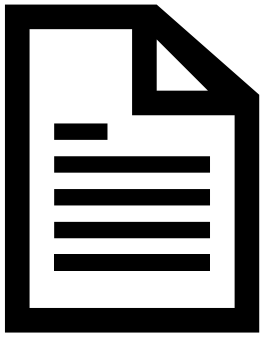
What is a Platform Trial?

An experimental infrastructure to evaluate multiple treatments and/or combinations of treatments in heterogeneous patient populations

- Not all interventions are included, or even known, at the start of the platform
- Pre-existing infrastructure for clinical operations and trial implementation
- Patient data can be shared to improve analysis

Protocol Organization

Master Protocol

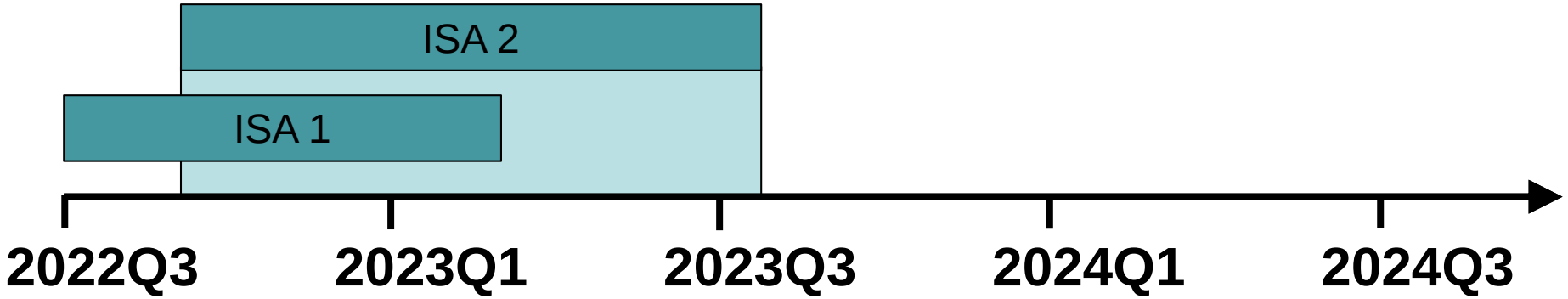


ISA 1 ISA 2 ISA 3

ISA = Intervention Specific Appendix
Contains experimental treatment(s) & matched control

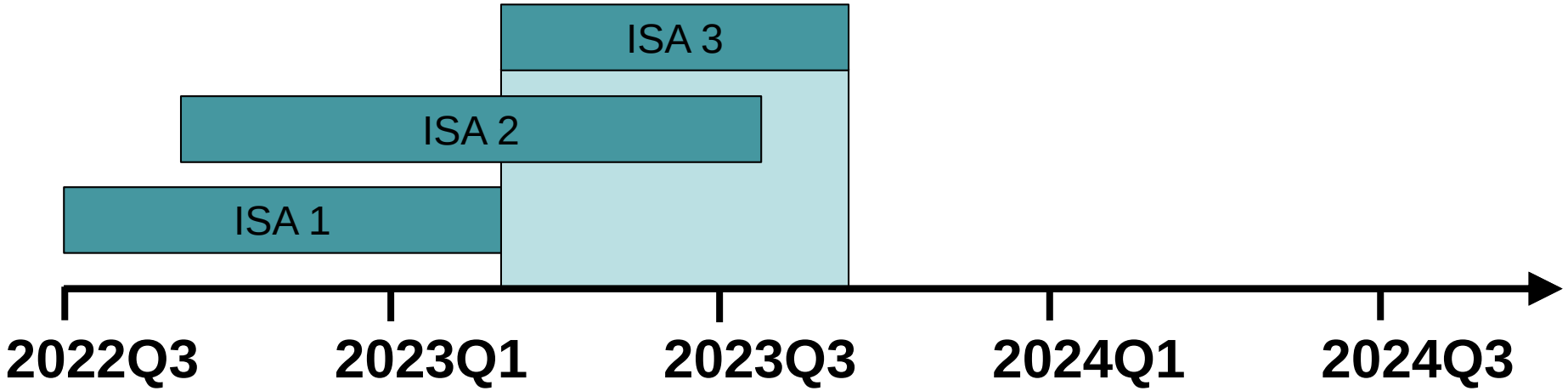
Example Platform – Adding New Treatments

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



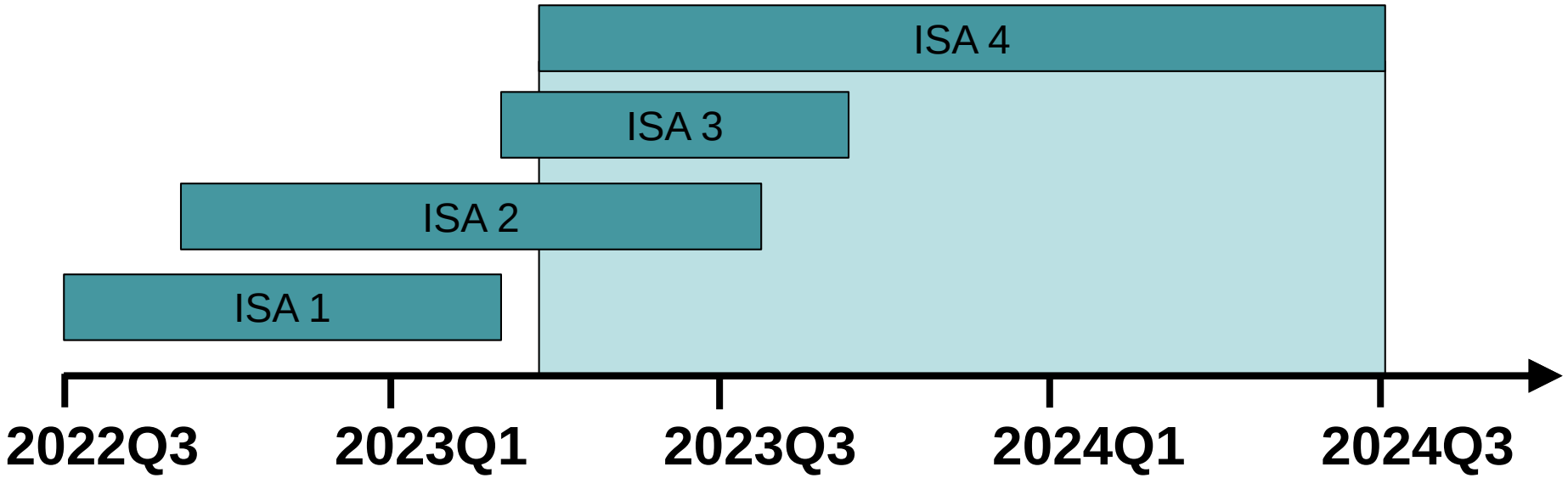
Example Platform – Adding New Treatments

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



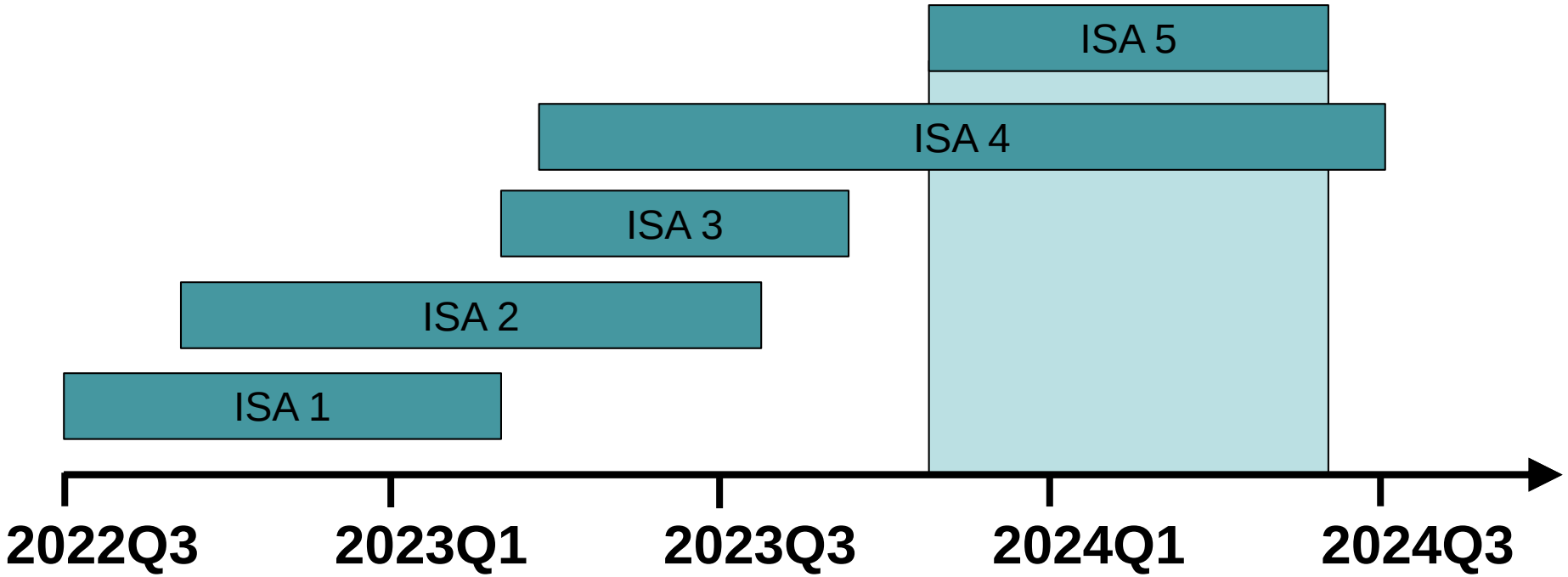
Example Platform – Adding New Treatments

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



Sharing Information Between ISAs?

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



Platform Trial In Practice

- Development of a master protocol should be done in a very pragmatic fashion
- Learning curve may be steep for a team or group when organizing a master protocol for the first time
- Similar experiences and approaches taken in various organizations and groups
- Utilize experience and wealth of knowledge available
- Avoid the assumption that master protocol is always the “best” approach, consider in stages using “Tools and Aids”

“Tools” and Aids

- To help determine if a master protocol is a good option, consider the following stages for Master Protocols (MP) planning

  - **Considering a MP - MP Score Card** – A set of questions that can be scored in a preliminary fashion to help determine if a master protocol is a good fit (little time investment)

  - **Assessing a MP - Master Protocol Quick Start Worksheet** – A list of more detailed questions that may require more input and knowledge about the trial under consideration (more time-consuming exercise)

  - **Implementing a MP - Simulation Plan and Report:** A formal write up of the details for simulating the trial and the desired output that will be obtained. Often good to outline the required improvement and/or performance that would is required to justify a master protocol (can be very time consuming)

Score Card – Considerations for MP

Tier 1 Evaluation			
Operational Assessment			
Sites	Same site network can be used to enroll to all modules	Sites may enroll to some but may not participate in all modules	Each module requires unique sites
Accrual	Opportunity to reduce sample size and/or competition with other studies	Oppurtunity to enroll a broader population, increase site, investigator, or patient engagment to enhance recruitment	Patients and investigators not supportive of MP approach
Screening	Same screening for all patients where most patients would be eligible for at least one module	Some modules would have unique screening requirements, a multi-step screening procedure may be needed.	Each module has unique screening requirements
Visit Schedules	Patients within each module can be assessed on the same visit schedule	Most visits the same, but some modules may need additional visits, or may skip some visits	Each module requires a different visit schedule
Endpoints	Same endpoints for each module	Most endpoints and assessments the same, but some modules may require an additional measure or two	Each module has unique assessments and endpoints
Study Duration	Study timelines are expected to be similar, data cuts can be batched	Can batch the read-out of most modules, while some may be earlier or later	Multiple study-read outs expected in sequence. Continous data clearning and reporting
Scoring Guidance	*The degree of similarity and combineablity across the modules will dictate the amount of possible operational efficiency possible. Modules should be as consistent as possible to be able to condense trial infrastructure. Some areas of efficiency should be found in the areas above to proceed with a Master Protocol concept*		

Score Card – Considerations for MP

Tier 2 Evaluation			
Complexity and Study Integrity			
Randomization	Not required or same control arm is applicable across all modules	Some similar, but some different control arms	Each module requires a different control treatment
Blinding	Not necessary, or is required but all drugs have same route of administration	Different routes of administration but feasible to either have placebos or matched placebos	Different routes of adminstration where placebos are not feasible and possible placebo or no-cebo effects
Read-Out ,Reporting, Data Sharing	Independent modules so one module will not impact the integrity of another module. All assets company owned so cross-asset comparisons and data sharing not a concern.	Data is shared across modules. Need a data sharing and communication plan in place to protect study integrity	Data is shared across modules and not all assets are company owned. Sensitivities around cross-asset comparisons, data ownership, and data sharing
Regulatory Review Issues	Early phase study where regulatory concerns are expected to be minimal/adressable	Anticipate regulatory hurdles in some countries	Confirmatory study in which regulatory interactions will be challenging
Cross-Team Communication Plans (e.g. Regulatory and Safety			
Ways of Working	Time, resourcing, and stakeholder support	Limited time, resourcing, and/or stakeholder support	Other development plans are mature and limited resources and support for additional design work
Scoring Guidance	*Evaluate these areas for the ability to manage and mitigate any issues. Weight the complexity and study integrity issues with the operational efficiencies expected from Tier 1*		

Score Card – Considerations for MP

Tier 3 Evaluation			
Statistical Efficiency Assessment			
Shared Control	Randomized comparisons where each module would have the same control arm	Randomized comparisons where at least some modules would use the same control	Single arm trials, or where each earch module would require a unique control arm
Borrowing	Clinical reason for borrowing across modules for efficacy and/or safety	Modules are considered independent, but the same endpoints and analysis is used for all so batching is possible	Modules are independent and endpoints and analyses are unique
Scientific Advantages	Reduced screen failure to enroll more rare patient groups that cannot be studied stand-alone	Unified data collection strategy could support additional translational learnings	Not applicable
Scoring Guidance	*This tier evaluates additional statistical advantages. These are not a minimum requirements, but may add to the exected benefits of the master protocol approach*		

Transition from Considering to Assessing a MP

Master Protocol QuickStart Worksheet
Single Indication / Multi-Asset

Master Protocol (MP) Information

When stating the MP objective regarding asset strategy/development, consider aspects such as

- Will the MP be used to assess POC for each asset that is included in an ISA
- Will the assets be compared across ISAs

When describing other MP goals, examples may include:

- Reduce placebo sample size
- Share information across assets
- Establish framework for operational efficiencies

Table 1: MP Indication of Interests and Objective(s)

Indication	
MP Objective	
Other MP Goals	
Known studies in this indication	

Using the studies in Table 1: MP Indication of Interests and Objective(s), fill in Table 2: Design Elements of Existing Studies of Interest with information on the study design to determine common elements. Columns may be removed if not applicable and columns may be added (ex – washout; rescue) as needed.

Table 2: Design Elements of Existing Studies of Interest

Study Name	Patient Population	Goal/Objective	Primary Endpoint(s)	Key Secondary Endpoints	Control	Sample Size (per arm)	Target Efficacy	Period 1 Duration	Period 2 Duration	Follow-up Duration

Based on the information collected in Table 2: Design Elements of Existing Studies of Interest, specify in Table 3: Information Common to Existing Studies of Interest, the design elements that are common among them

Table 3: Information Common to Existing Studies of Interest

Information Common to Studies	
Patient Population (High Level I/E criteria)	
Primary Endpoint(s)	
Key Secondary Endpoints	
Control	
Sample size (per arm)	
Indication Target Efficacy or CSF:	
Indication Study Duration: Induction	
Indication Study Duration: Maintenance	
Indication Study Duration: Follow-up	

Intervention Specific Appendix (ISA) Information

Provide the names of the assets and key design elements. Note in the final column design elements for the asset that deviate from what was specified in Table 3: Information Common to Existing Studies of Interest.

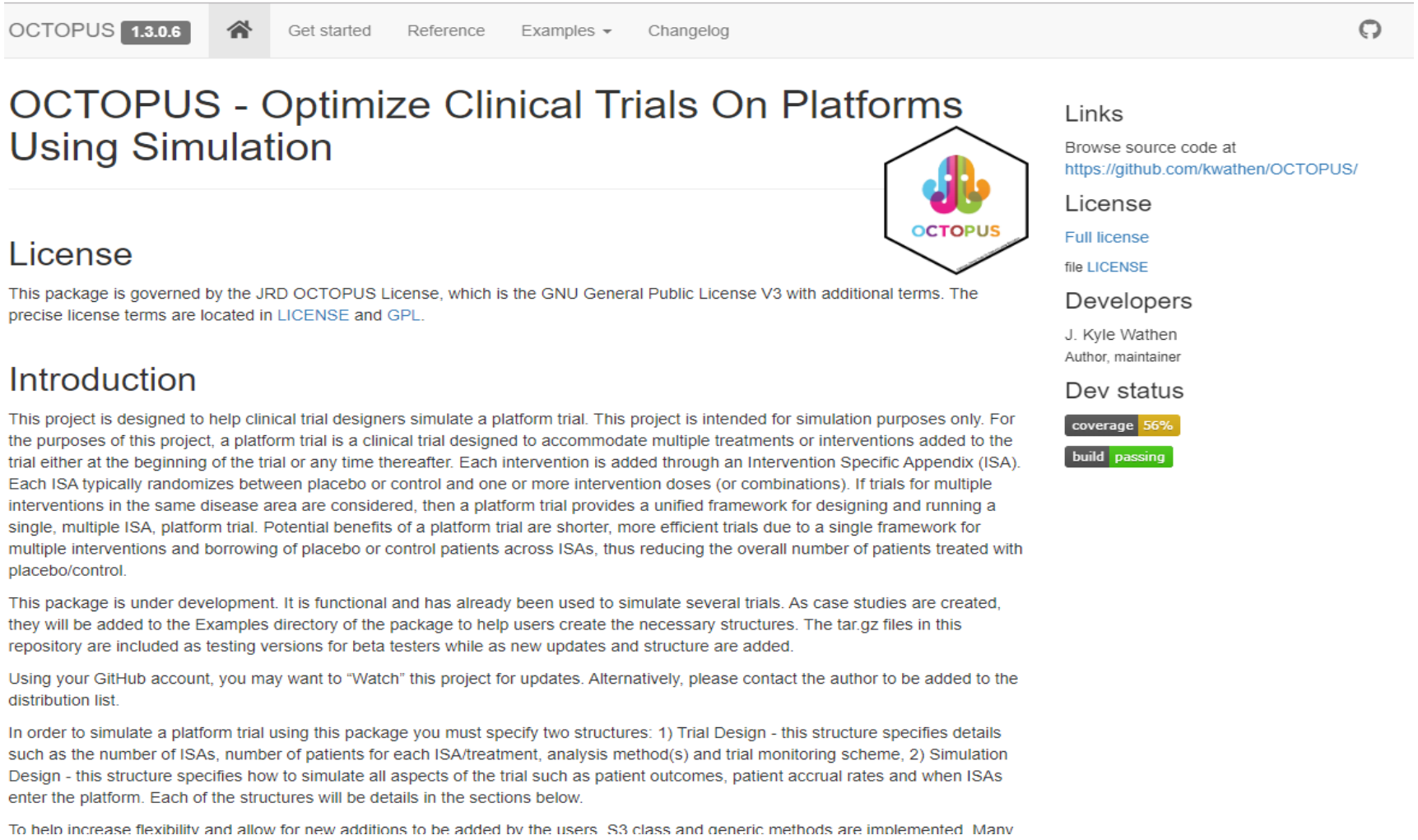
Table 4: Design Elements of Interest by Asset

Asset	**Phase** (2a, 2b, 3)	**Goal** (POC, DF, Confirm)	**Expected FPV**	**Study Duration**	**Route of Administration**	**Dosing Frequency**	**Estimated FPV**	**Control**	**Sample Size (per arm)**	**Deviations from MP**

Transition from Assessing a MP to Implementing a MP

Open Source Software - GitHub Page

https://github.com/kwathen/OCTOPUS



OCTOPUS 1.3.0.6 | Get started | Reference | Examples | Changelog

OCTOPUS - Optimize Clinical Trials On Platforms Using Simulation

License

This package is governed by the JRD OCTOPUS License, which is the GNU General Public License V3 with additional terms. The precise license terms are located in LICENSE and GPL.

Introduction

This project is designed to help clinical trial designers simulate a platform trial. This project is intended for simulation purposes only. For the purposes of this project, a platform trial is a clinical trial designed to accommodate multiple treatments or interventions added to the trial either at the beginning of the trial or any time thereafter. Each intervention is added through an Intervention Specific Appendix (ISA). Each ISA typically randomizes between placebo or control and one or more intervention doses (or combinations). If trials for multiple interventions in the same disease area are considered, then a platform trial provides a unified framework for designing and running a single, multiple ISA, platform trial. Potential benefits of a platform trial are shorter, more efficient trials due to a single framework for multiple interventions and borrowing of placebo or control patients across ISAs, thus reducing the overall number of patients treated with placebo/control.

This package is under development. It is functional and has already been used to simulate several trials. As case studies are created, they will be added to the Examples directory of the package to help users create the necessary structures. The tar.gz files in this repository are included as testing versions for beta testers while as new updates and structure are added.

Using your GitHub account, you may want to "Watch" this project for updates. Alternatively, please contact the author to be added to the distribution list.

In order to simulate a platform trial using this package you must specify two structures: 1) Trial Design - this structure specifies details such as the number of ISAs, number of patients for each ISA/treatment, analysis method(s) and trial monitoring scheme, 2) Simulation Design - this structure specifies how to simulate all aspects of the trial such as patient outcomes, patient accrual rates and when ISAs enter the platform. Each of the structures will be details in the sections below.

To help increase flexibility and allow for new additions to be added by the users, S3 class and generic methods are implemented. Many

Links

Browse source code at https://github.com/kwathen/OCTOPUS/

License

Full license

file LICENSE

Developers

J. Kyle Wathen

Author, maintainer

Dev status

coverage 56%

build passing

R Package + Project Specific Files

OCTOPUS Package		Project Specific
Core components Built on generic functions Tested Generalized functions from projects Community driven development in future versions	+	Define trial design element Define simulation design element Define any project specific functions

Key Advantages – Tested code, reuse general parts, speed up development, learn across projects, project details remain in the project specific files, extendable, generic concepts can be moved from projects to package

Allowed for easy exploration of designs including client provided Winbugs model for analysis and customization to fine the need of client

Initial Design

- Fixed design
  - Value of a control arm vs using historical data
- Binary outcome at 6 months
  - Also had two other outcomes under consideration with longer outcome window
- Understand borrowing of control patient data from earlier ISAs or historical data, and risks associated with it
- Understand the impact of having treatments start at different times
- Understand timelines of when things would occur

Statistical Model

For simplicity, ignore ISA

X ~ Binary(π_i) for i = C (Control) or E (Experimental)

Priors

π_c ~ Beta(a, b); Vary amount of prior data utilized

Non-informative π_c ~ Beta(0.15, 0.85);

Reflect prior response rate of 15%

π_E ~ Beta(0.15, 0.85); Assume prior response rate is same C/E

Decision Criteria

Assuming a Minimal Acceptable Value (MAV) decisions are based on

$p = Pr(\pi_E - \pi_c > MAV \mid data) > P_U$ → E is better than C

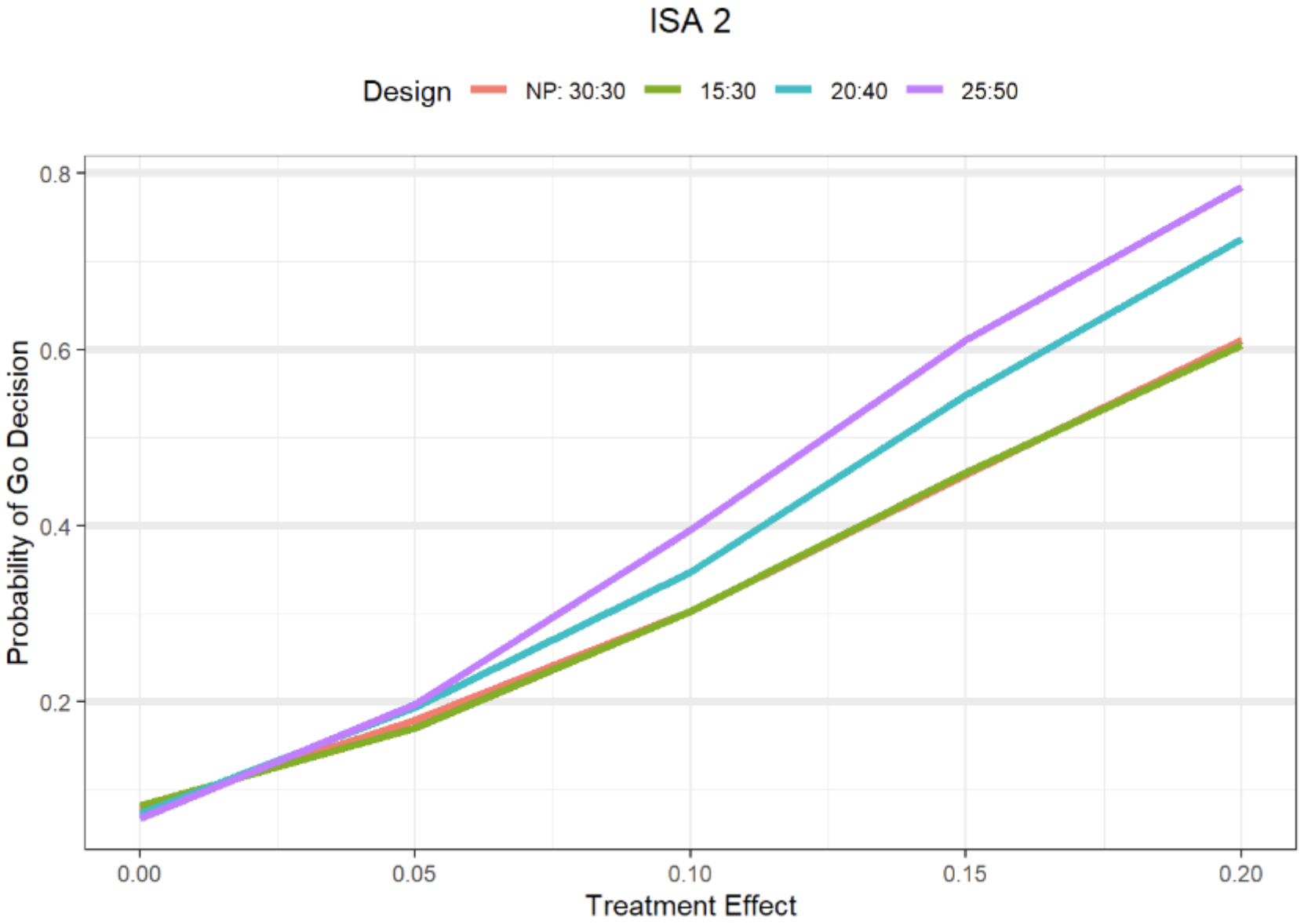
Use MAV = 0 for decision making but may also be interested in MAV = 0.2

Trial Design – An Iterative Process
Starting with a Fixed Design

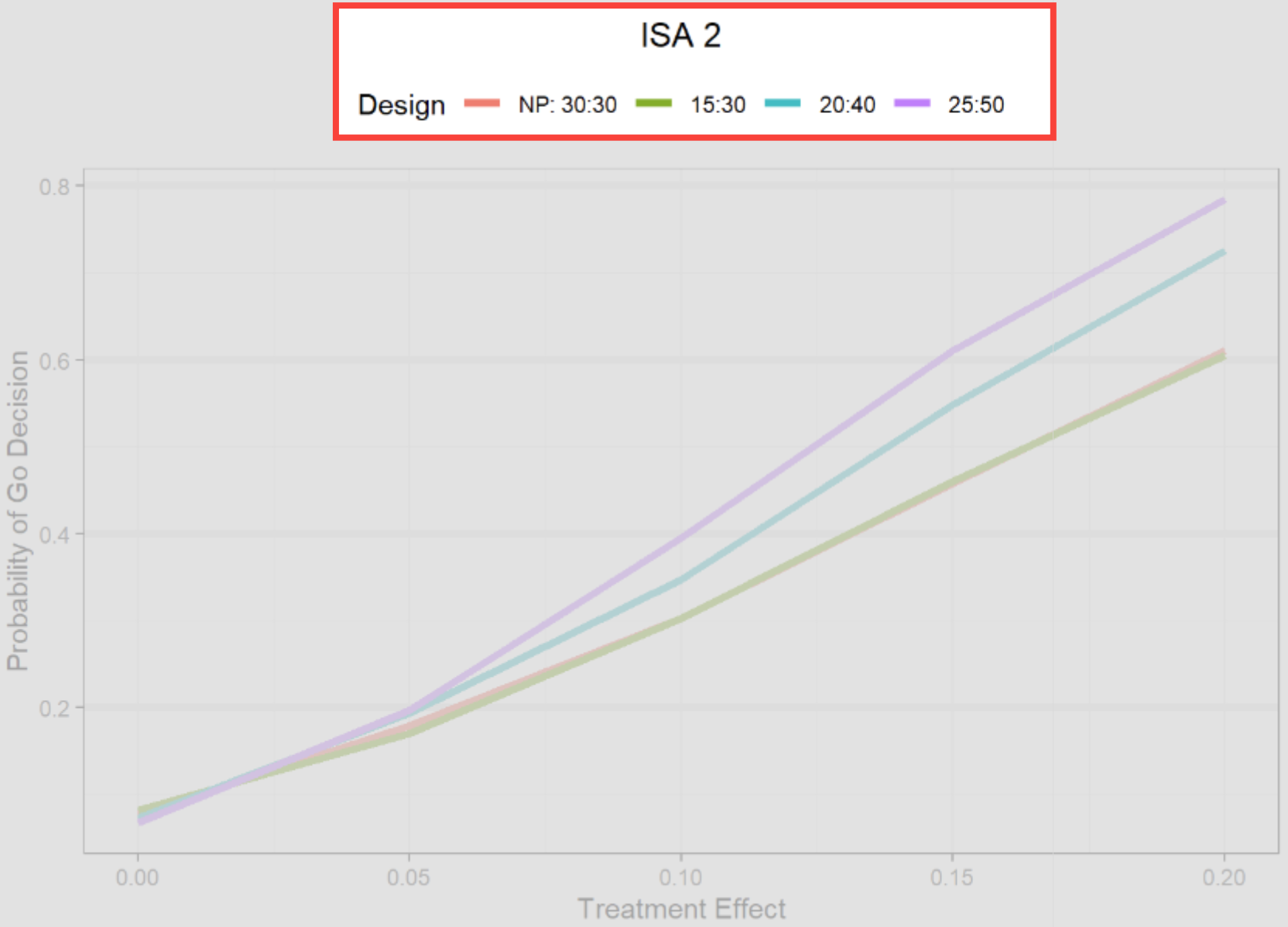
- **Design 1**
  - *ISA1*- Borrowing: No Borrowing, # Patients on Control:30, # Patients on Treatment:30, Max # to borrow: 0
  - *ISA2*- Borrowing: No Borrowing, # Patients on Control:30, # Patients on Treatment:30, Max # to borrow: 0
  - *ISA3*- Borrowing: No Borrowing, # Patients on Control:30, # Patients on Treatment:30, Max # to borrow: 0
- **Design 2**
  - *ISA1*- Borrowing: Share Controls, # Patients on Control:15, # Patients on Treatment:30, Max # to borrow: 15
  - *ISA2*- Borrowing: Share Controls, # Patients on Control:15, # Patients on Treatment:30, Max # to borrow: 15
  - *ISA3*- Borrowing: Share Controls, # Patients on Control:15, # Patients on Treatment:30, Max # to borrow: 15
- **Design 3**
  - *ISA1*- Borrowing: Share Controls, # Patients on Control:20, # Patients on Treatment:40, Max # to borrow: 20
  - *ISA2*- Borrowing: Share Controls, # Patients on Control:20, # Patients on Treatment:40, Max # to borrow: 20
  - *ISA3*- Borrowing: Share Controls, # Patients on Control:20, # Patients on Treatment:40, Max # to borrow: 20
- **Design 4**
  - *ISA1*- Borrowing: Share Controls, # Patients on Control:25, # Patients on Treatment:50, Max # to borrow: 25
  - *ISA2*- Borrowing: Share Controls, # Patients on Control:25, # Patients on Treatment:50, Max # to borrow: 25
  - *ISA3*- Borrowing: Share Controls, # Patients on Control:25, # Patients on Treatment:50, Max # to borrow: 25

Explanation of Borrowing:
First two ISAs would begin the at the start of platform and borrowing patients is done first from concurrent ISAs then most recent as needed. Done to prioritize use of concurrent patients

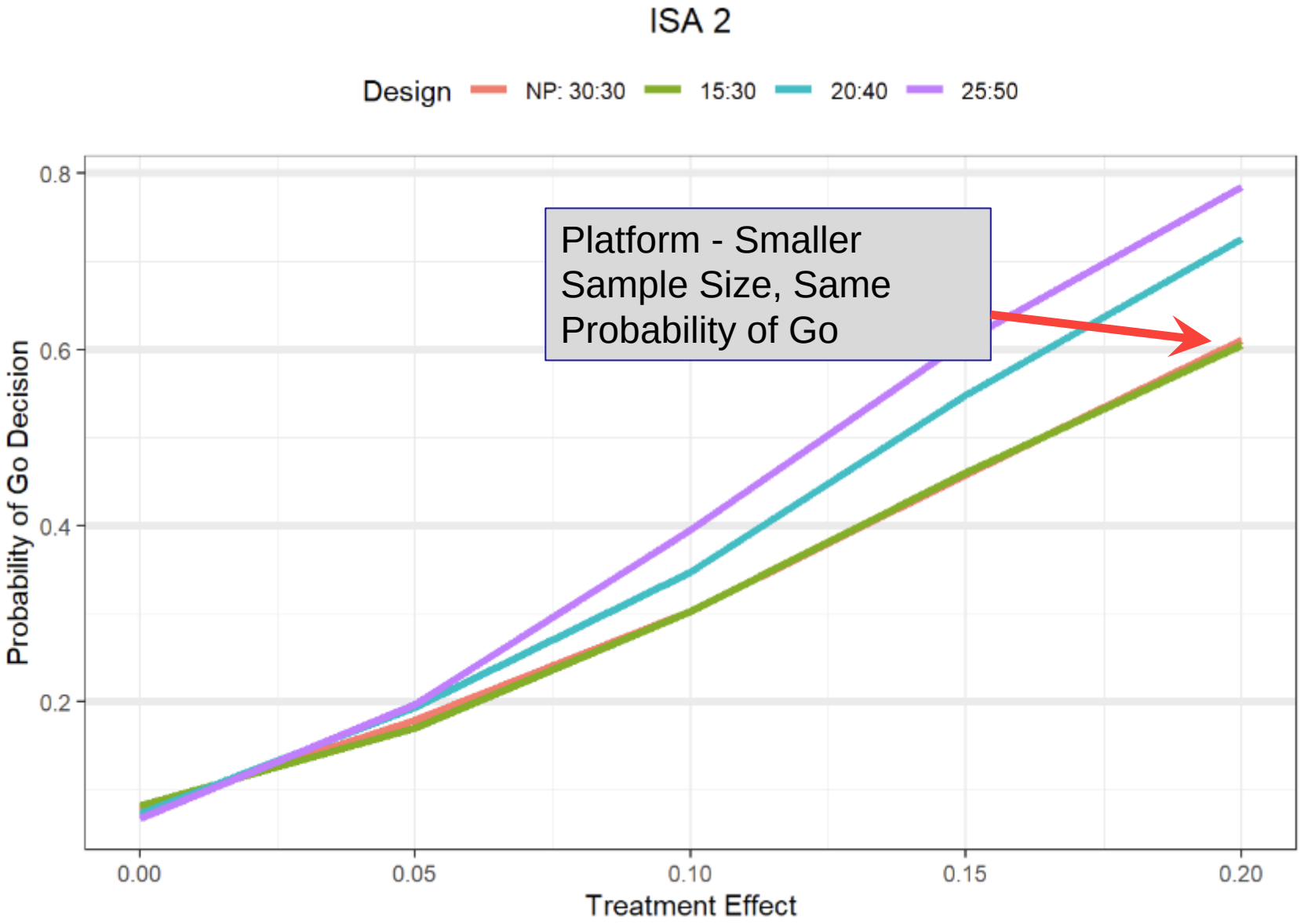
Probability of Making a Go Decision



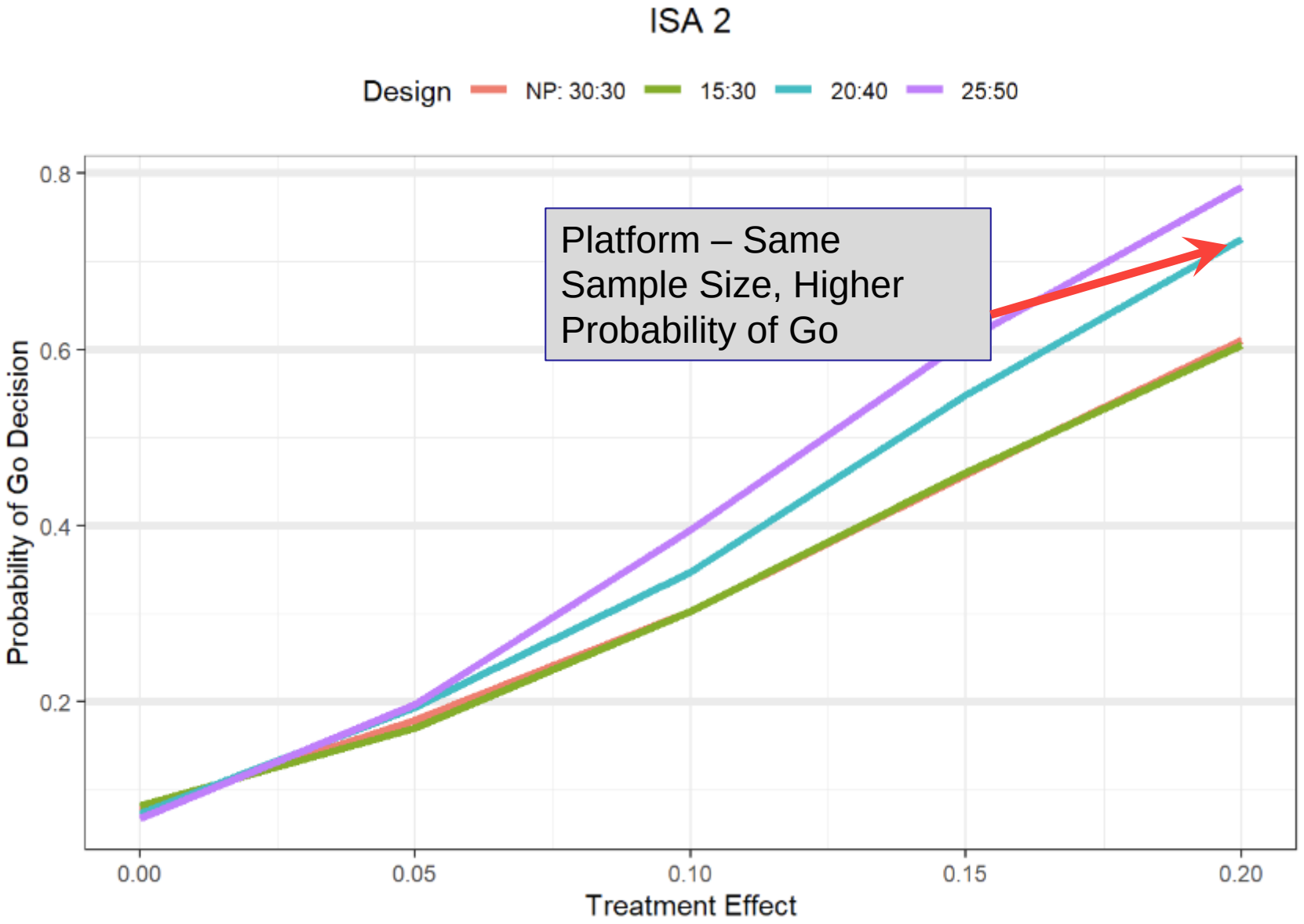
Probability of Making a Go Decision



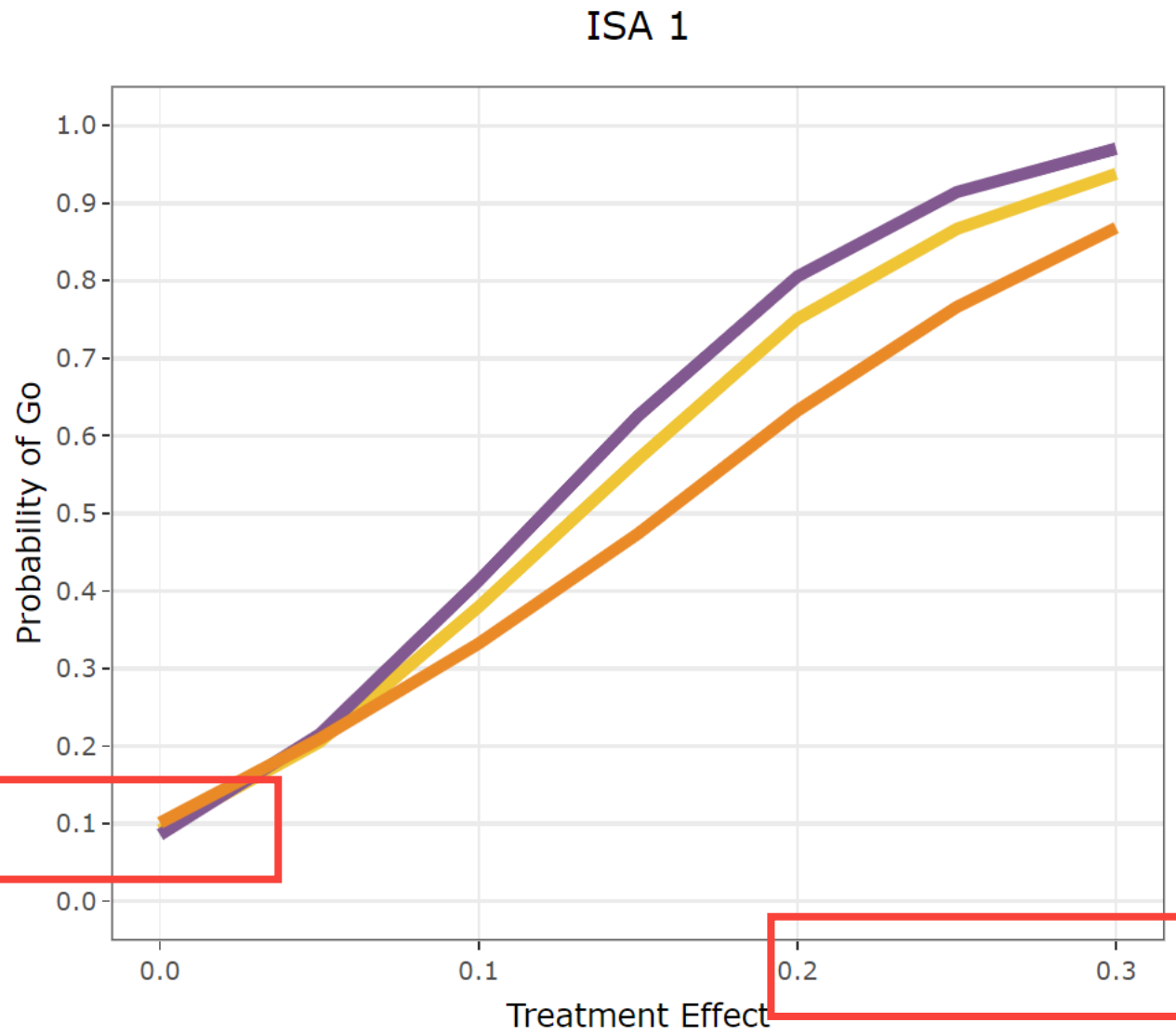
Probability of Making a Go Decision



Probability of Making a Go Decision



Sample Size Comparison



Design
20:40:20
25:50:25
NP: 30:30:0

Adding the number of "borrowed" patients

Futility?

Expanded treatment effect

Interim Analysis for Futility

For simplicity, ignore ISA

X ~ Binary(π_i) for i = C (Control) or E (Experimental)

Priors

π_c ~ Beta(0.15, 0.85); Vary amount of prior data utilized

Reflect prior response rate of 15%

π_E ~ Beta(0.15, 0.85); Assume prior response rate is same C/E

At Interim Analysis – Futility Decision

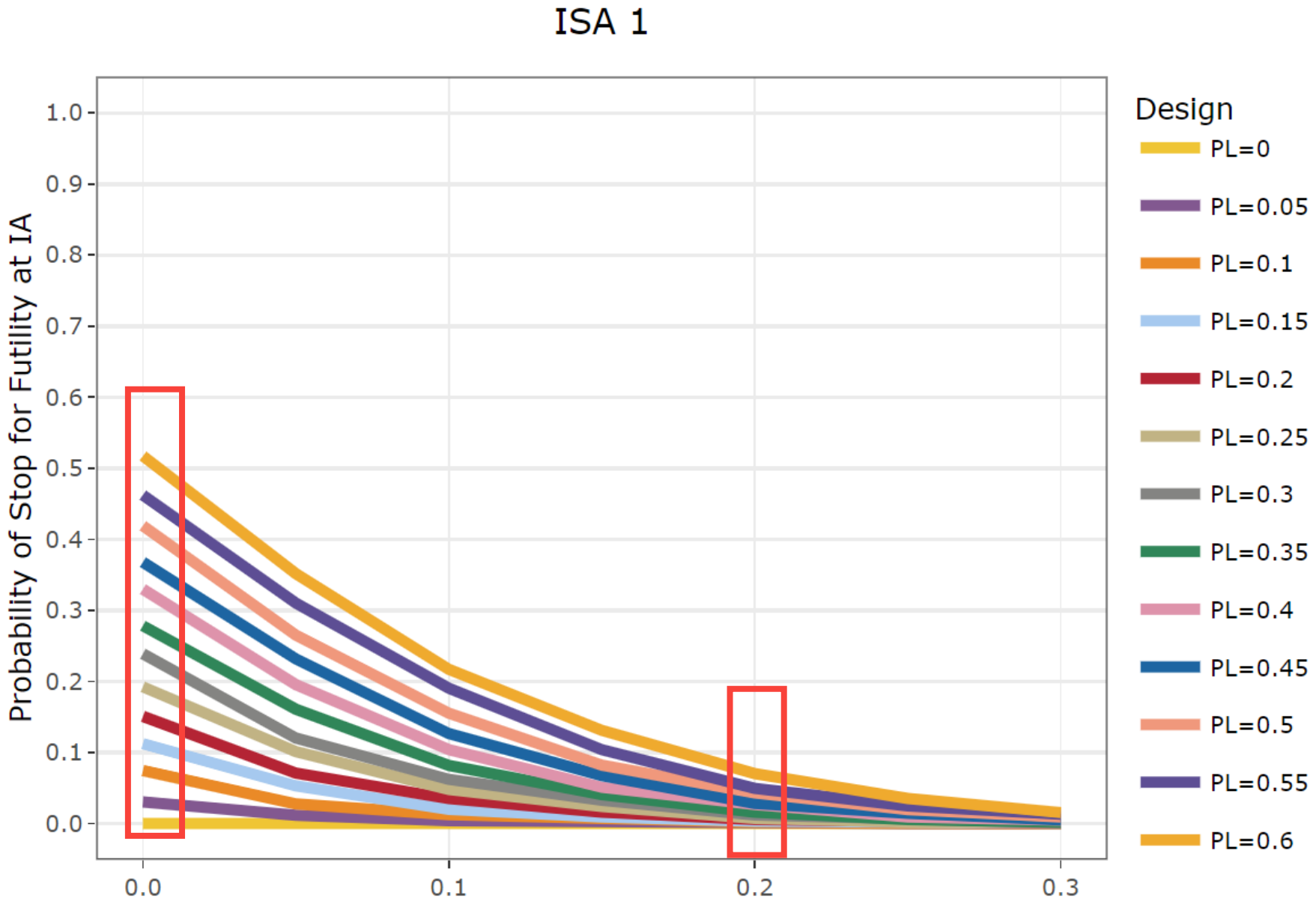
p = Pr(π_E - π_c > MAV | data) < P_L → E is UNLIKELY better than C → Stop for futility

At Final Analysis Decision Criteria

p = Pr(π_E - π_c > MAV | data) > P_U → E is better than C

Interim Analysis for Futility – Probability of Go

Probability of Futility at IA



Visuals Can Make it Difficult to Convey Trade-off

Trade-off Futility vs Go Probability

PL	Prob No Go @ IA when Trt. Eff. = 0	Prob Go by FA when Trt. Eff. = 0.2
0.05	0.030	0.754
0.10	0.074	0.746
0.15	0.112	0.742
0.20	0.151	0.751
0.25	0.192	0.742
0.30	0.239	0.734
0.35	0.278	0.744
0.40	0.330	0.748
0.45	0.368	0.740
0.50	0.419	0.736
0.55	0.462	0.734
0.60	0.517	0.729

What does this mean to individual trials?

Interactive Plot Example

Trial Index:
4

PL:
0.6

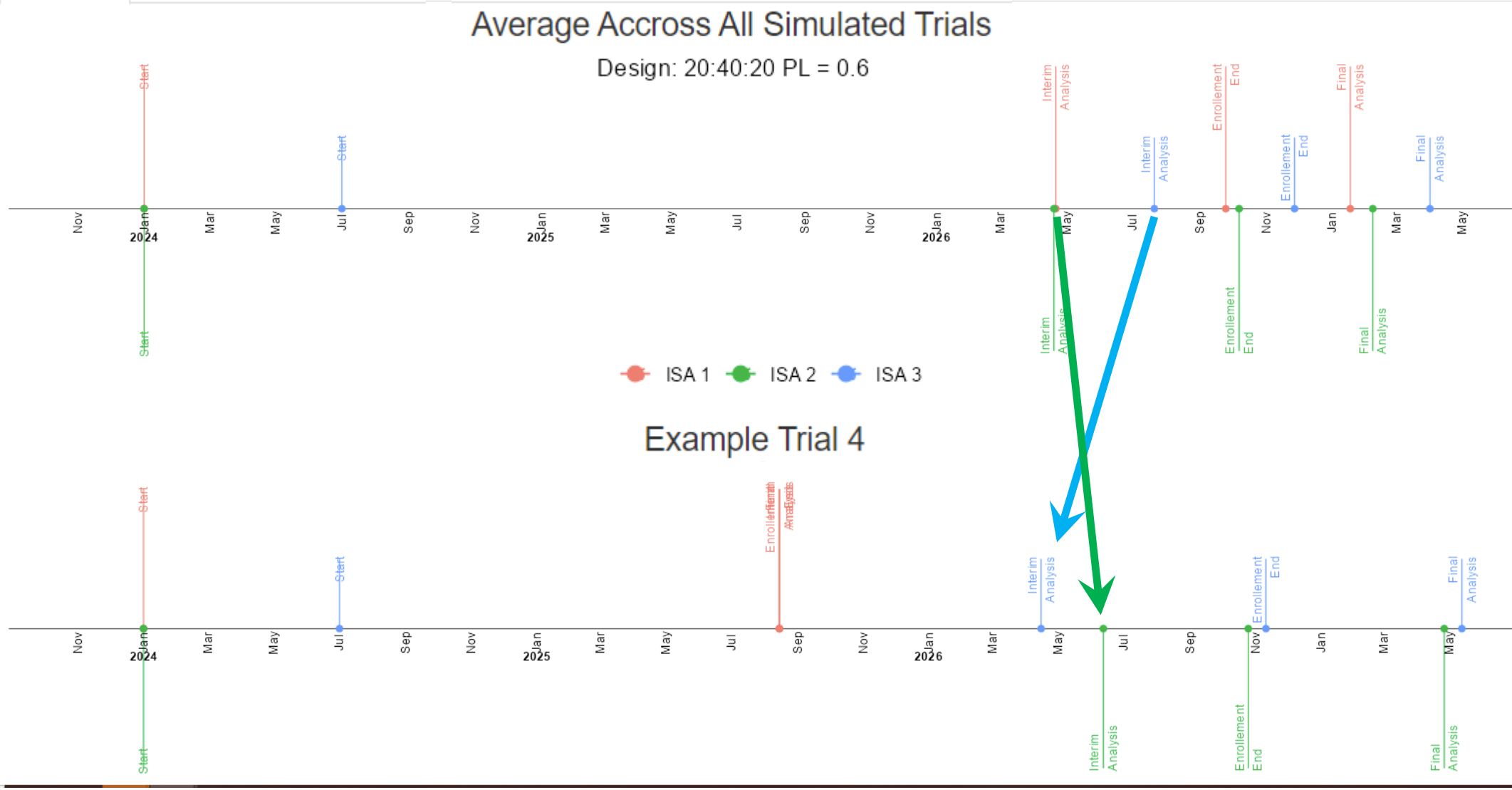
Treatment Effect:
0.1

Sample Size:
20:40:20

Plot

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Timeline | ISA 1 | ISA 2 | ISA 3



Interactive Plot Example

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Trial Index:
4

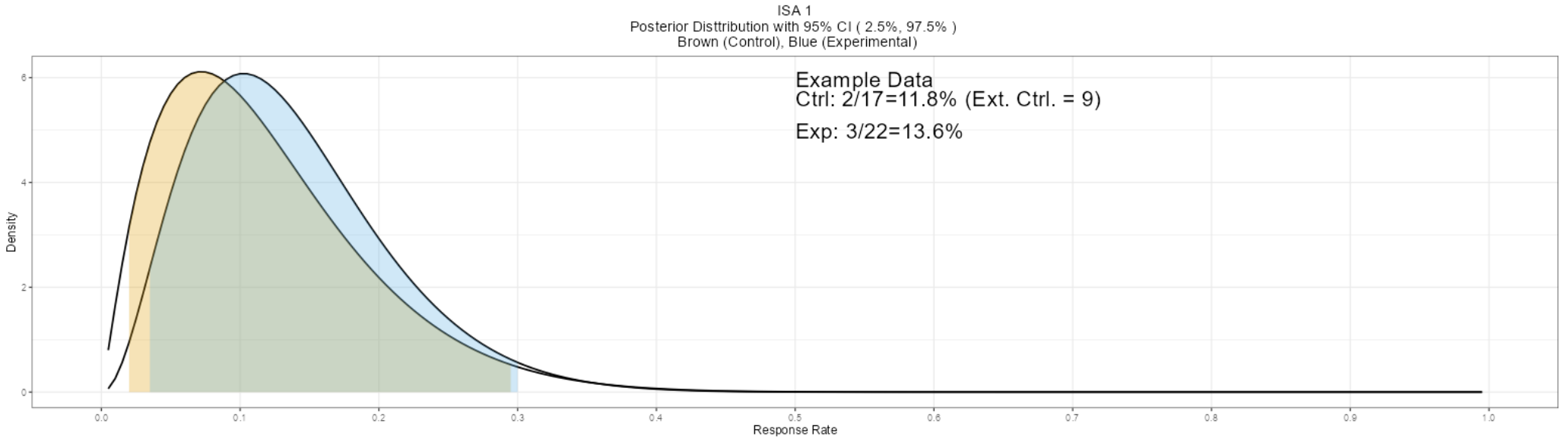
PL:
0.6

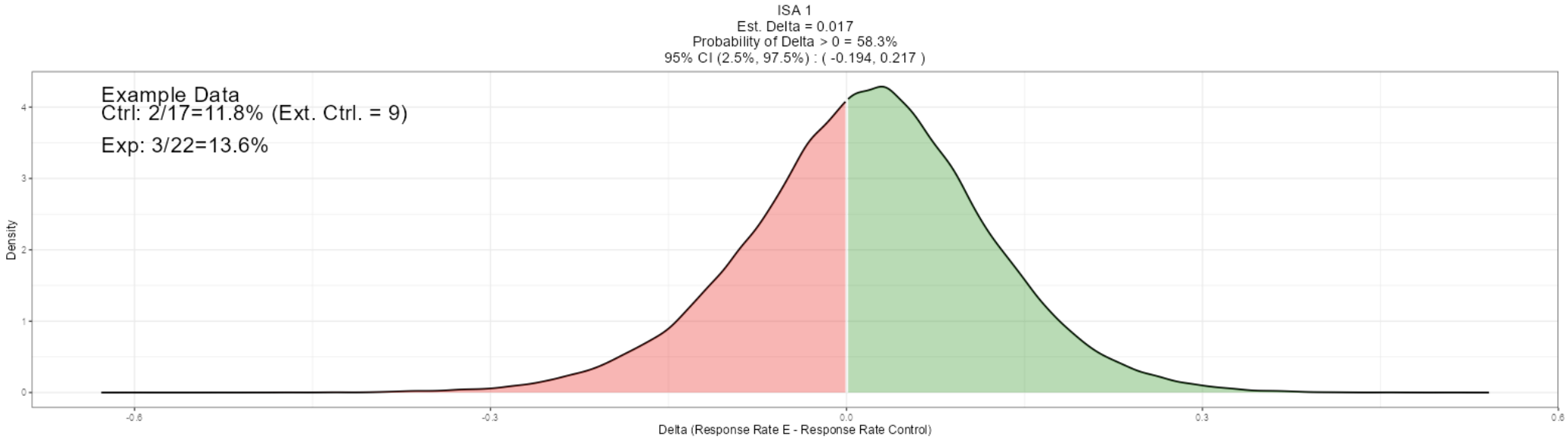
Treatment Effect:
0.1

Sample Size:
20:40:20

Plot

Timeline | ISA 1 | ISA 2 | ISA 3





Interactive Plot Example

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Timeline | ISA 1 | ISA 2 | ISA 3

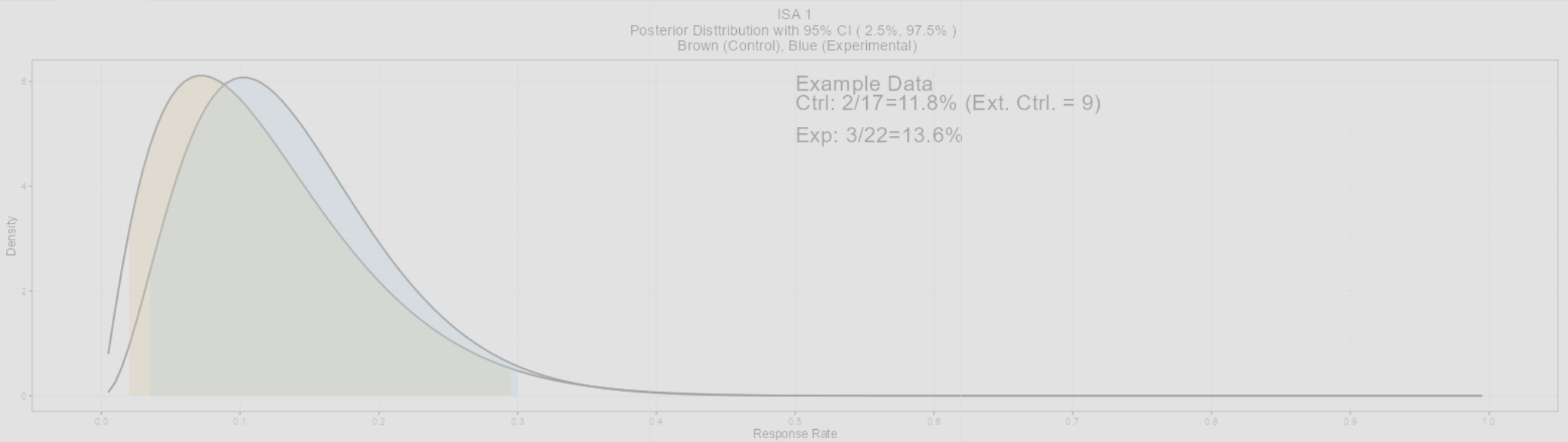
Trial Index: 4

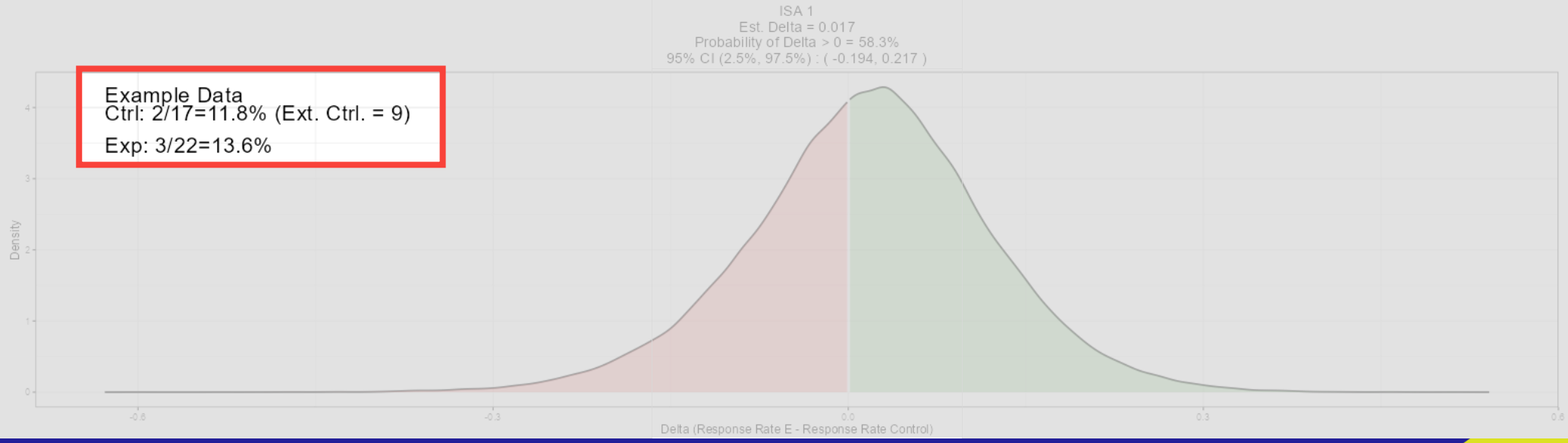
PL: 0.6

Treatment Effect: 0.1

Sample Size: 20:40:20

Plot





Interactive Plot Example

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Timeline | ISA 1 | ISA 2 | ISA 3

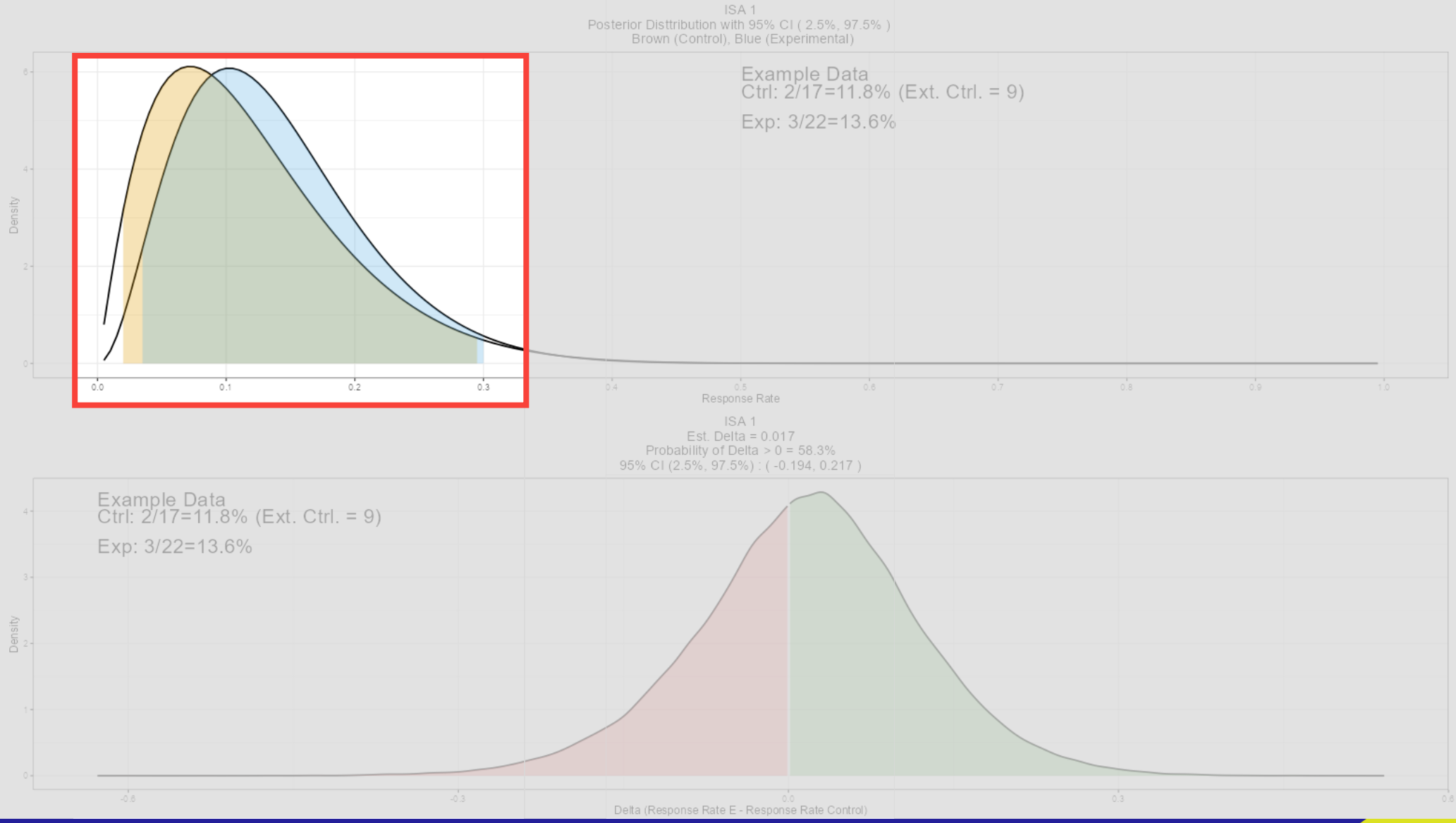
Trial Index: 4

PL: 0.6

Treatment Effect: 0.1

Sample Size: 20:40:20

Plot



Interactive Plot Example

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Timeline | ISA 1 | ISA 2 | ISA 3

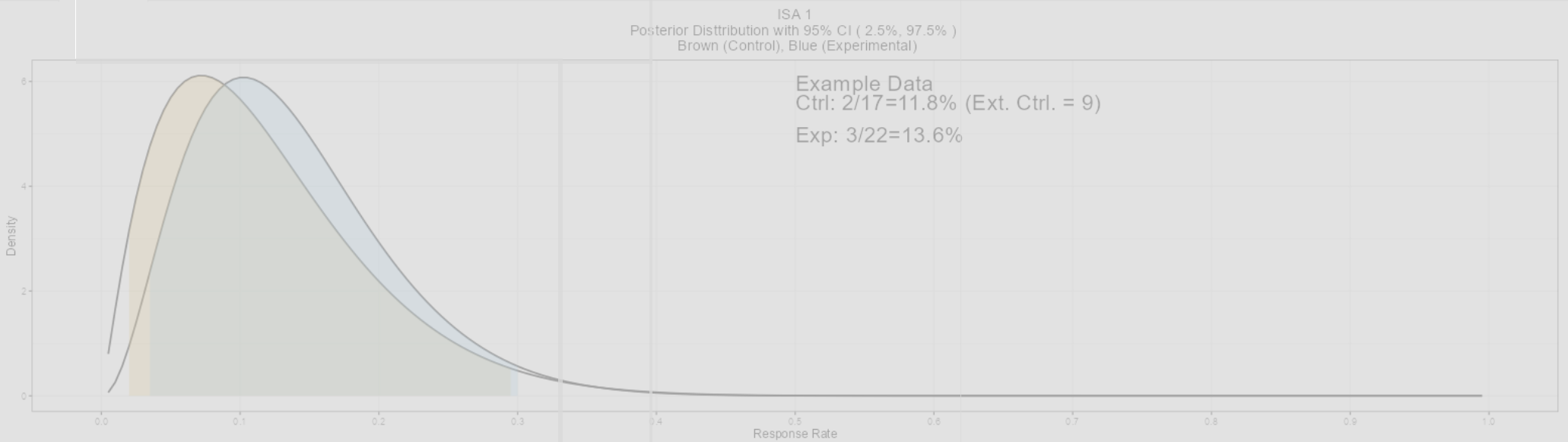
Trial Index: 4

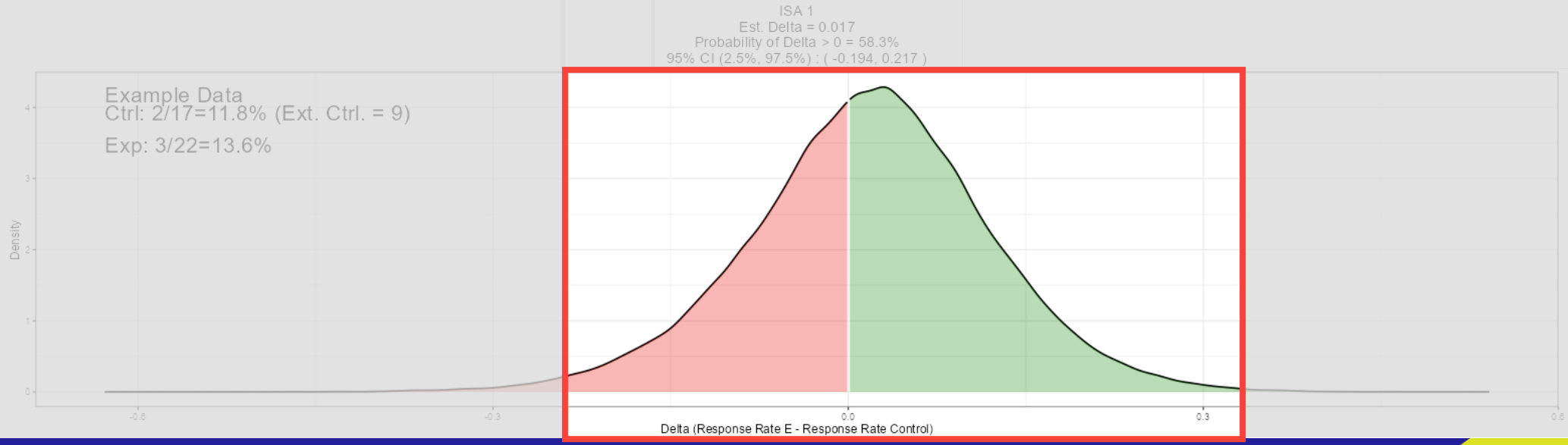
PL: 0.6

Treatment Effect: 0.1

Sample Size: 20:40:20

Plot





Interactive Plot Example

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Timeline | ISA 1 | ISA 2 | ISA 3

Trial Index: 4

PL: 0.6

Treatment Effect: 0.1

Sample Size: 20:40:20

Plot

Interactive Plot Example

Sample Size: 20:40:20 Trt Eff = 0.1, PL = 0.6

Timeline | ISA 1 | ISA 2 | ISA 3

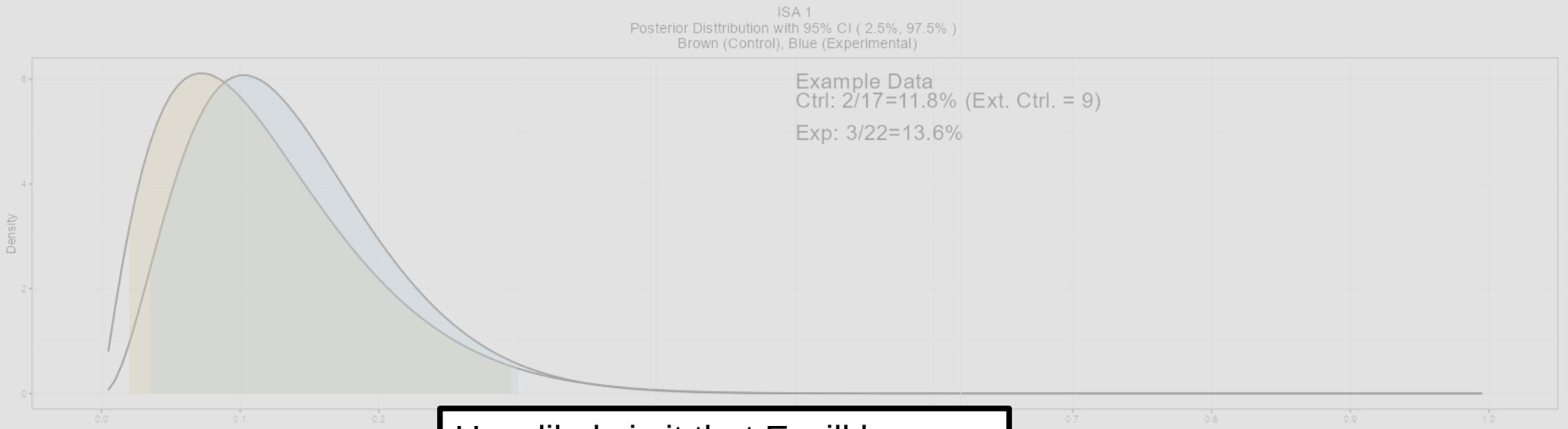
Trial Index: 4

PL: 0.6

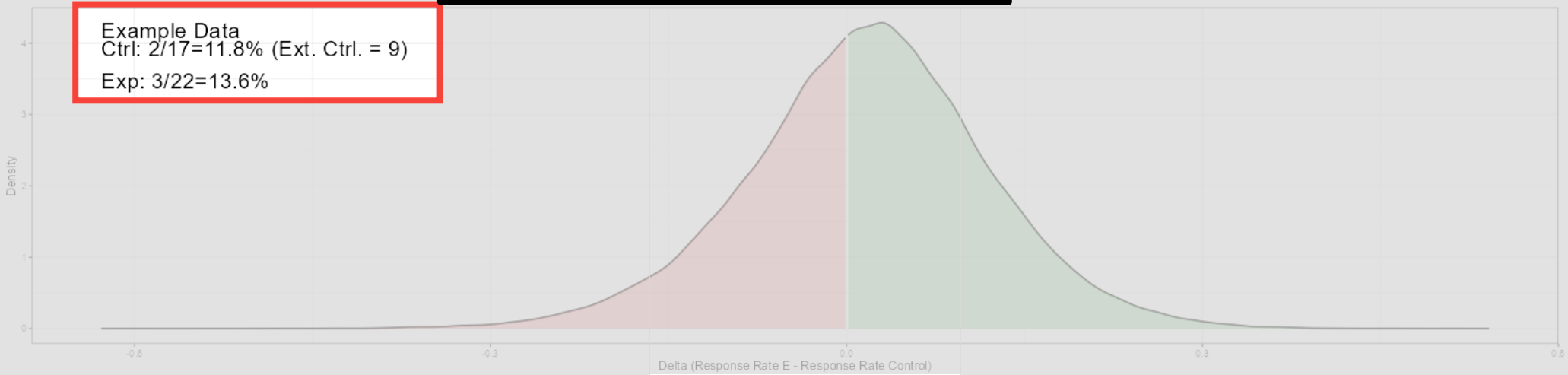
Treatment Effect: 0.1

Sample Size: 20:40:20

Plot



How likely is it that E will be selected as superior at the end?



Bayesian Predictive Probabilities

Current Data: Control (2/17) – N = 13 remaining
Experimental (3/22) – N = 8 remaining

		Experimental			
		0/8	**1/8**	**…**	**8/8**
Control	**0/13**	C: 2/30; E: 3/30	C: 2/30; E: 4/30	…	C: 2/30; E: 11/30
	1/13	C: 3/30; E: 3/30	C: 3/30; E: 4/30	…	C: 3/30; E: 11/30
	…	**…**	…	…	…
	13/13	C: 16/30; E: 3/30	C: 16/30; E: 4/30	…	C: 16/30; E 11/30

Each Cell Compute: $p_{i,j} = Pr(\pi_E - \pi_c > MAV \mid data)$, i = # responses on C, j = # responses on E
If $p_{i,j} > P_U$ → Compute likelihood using Beta-Binomial distribution as $p'_{i,j}$
Otherwise $p'_{i,j} = 0$
→ Predictive probability of success is the sum of $p'_{i,j}$

Futility Elicitation

Priors for Prediction

Control

a	b
12.77	72.4

Experimental

a	b
5.03	9.34

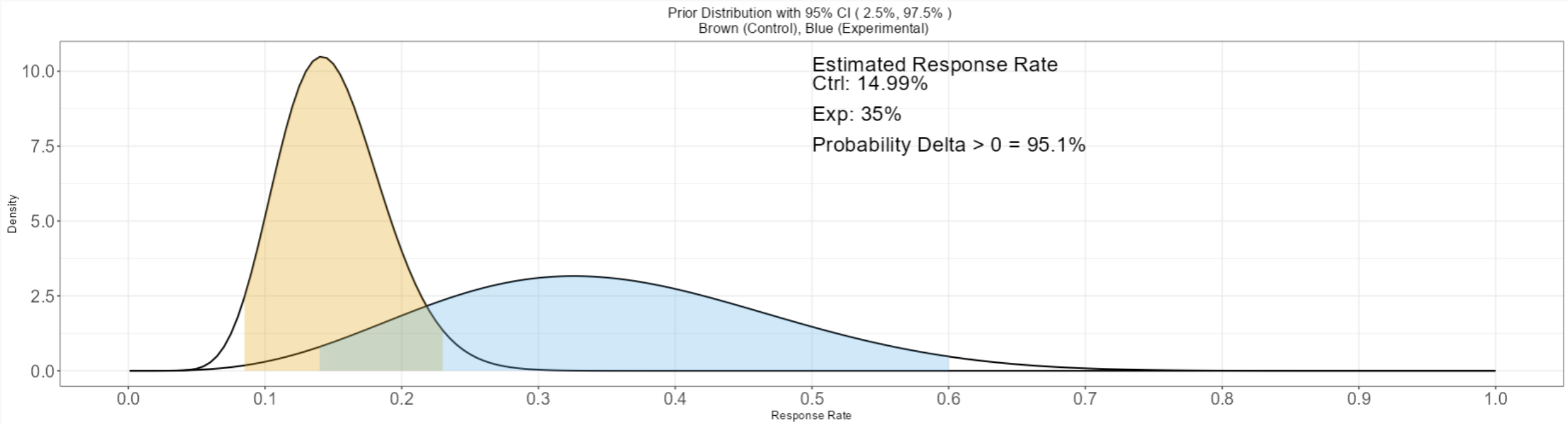
Observed Data

Observed Probability Experimental Response Rate is Greater than Control?

0.99

Start Back

Priors for Prediciton



Example Trial 7490

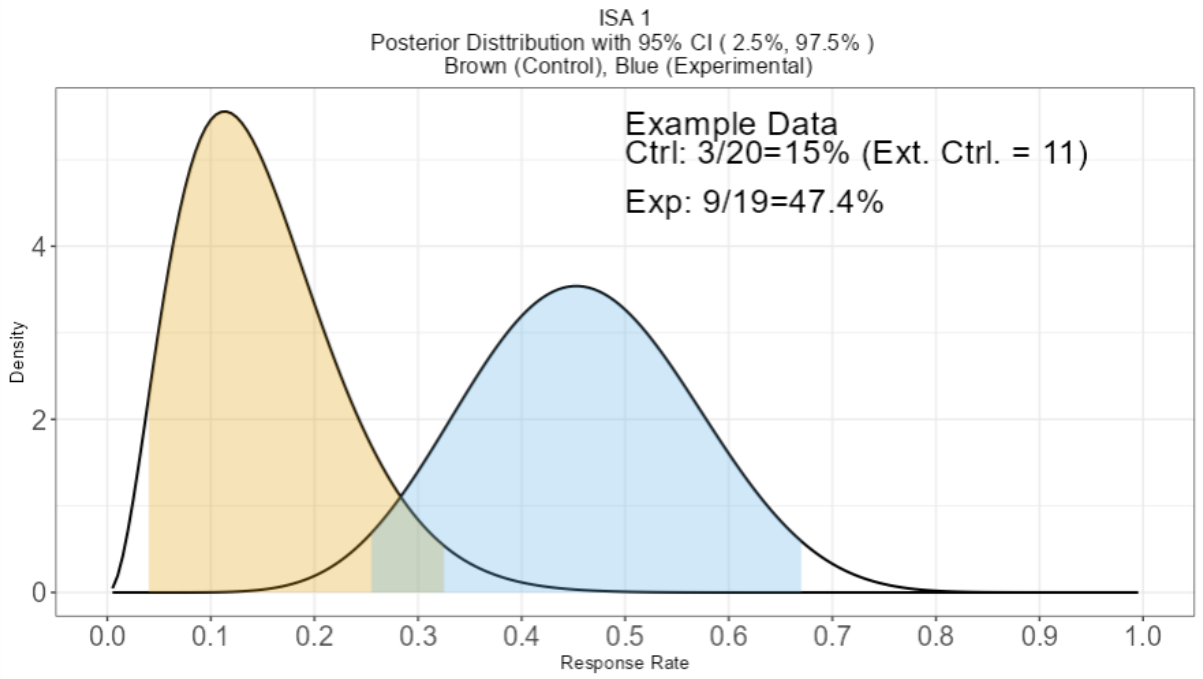
In the example trial the observed data are (Number of Responses / Number of Patients):

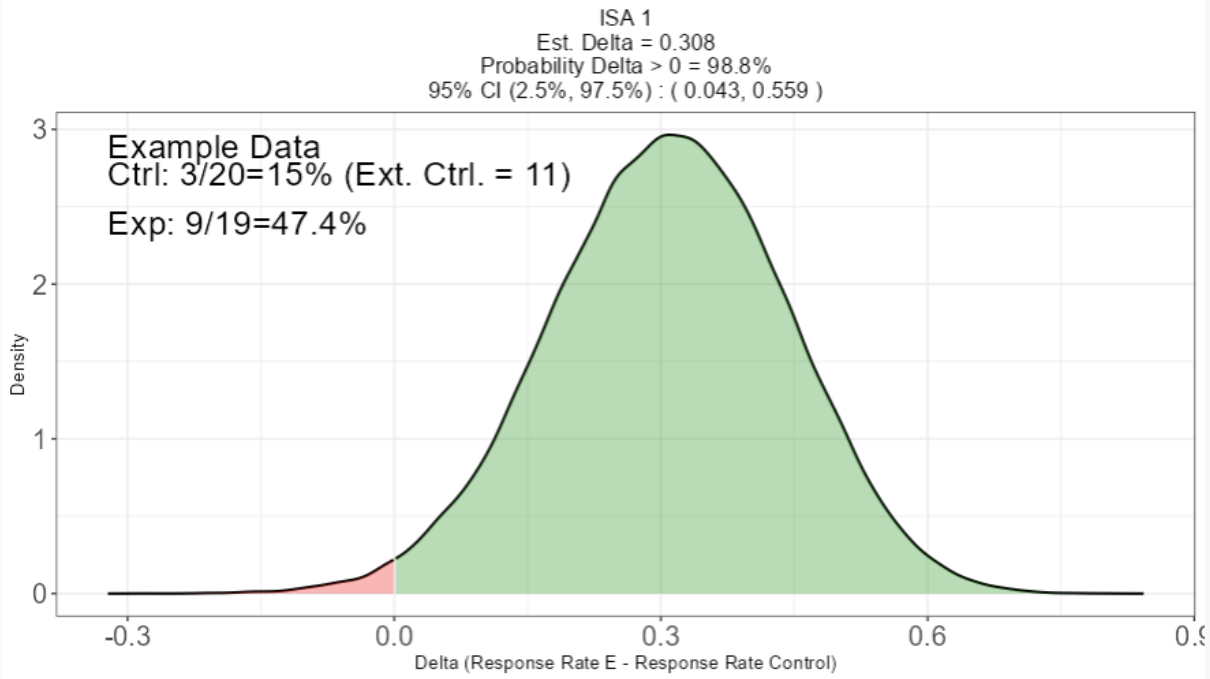
Control Arm: 3/20 = 15% (Borrowed Controls = 11)
Experimental Arm: 9/19 = 47.4%

Bayesian Calculations
Estimated difference (E-S) in response rate (95% CI): 0.308 (0.043, 0.559)
Probability that the response rate on E is greater than S: 98.8%

The likelihood that E will be declared superior to S at the end of the ISA is
With the analysis prior: 93.8%
With the prior provided above: 94.6%

Given the example trial data at the interim analysis shown below, would you stop for futility? Yes No





Example Trial 2530

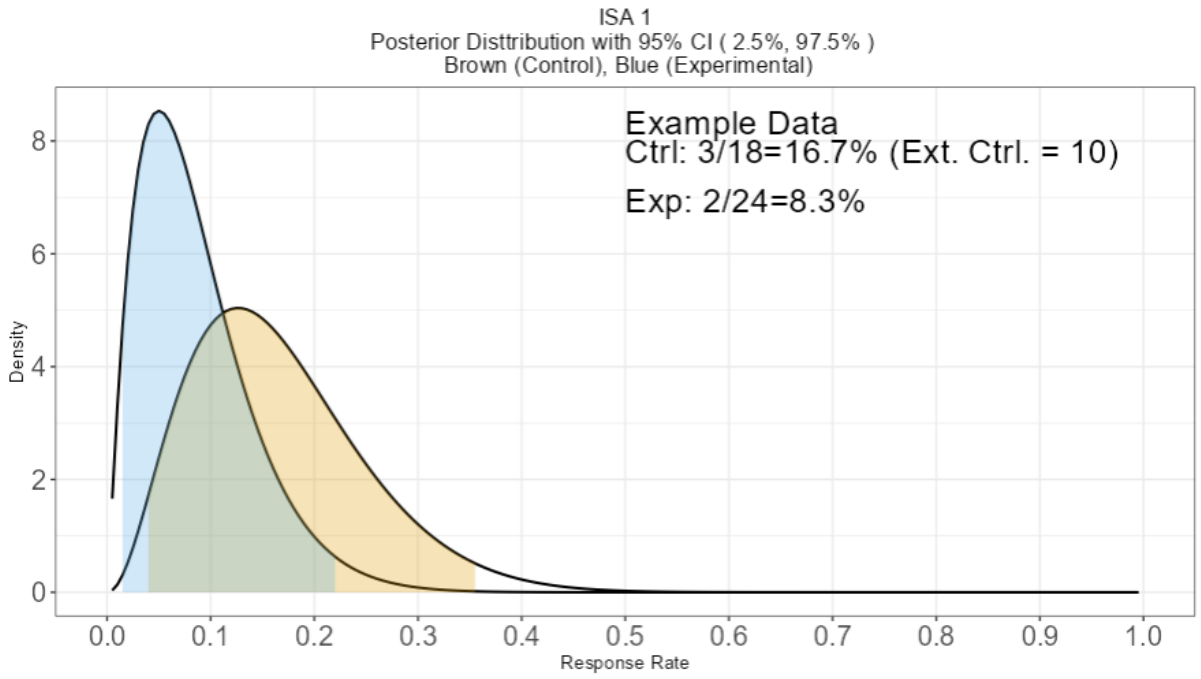
In the example trial the observed data are (Number of Responses / Number of Patients):

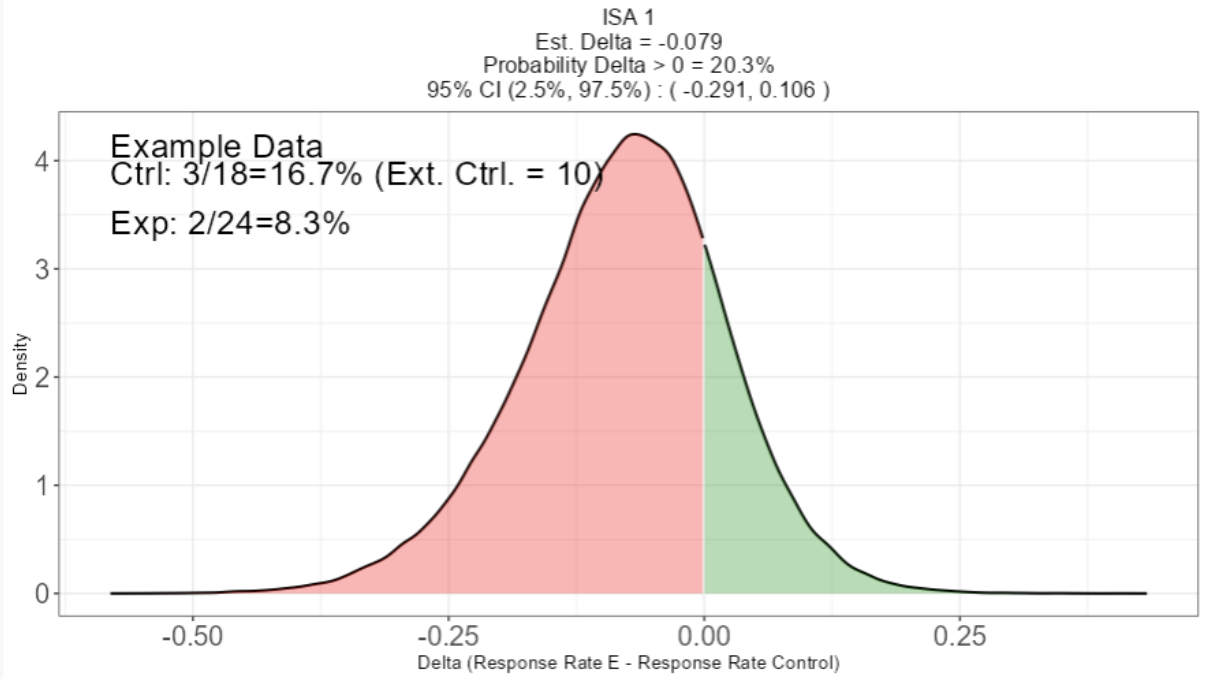
Control Arm: 3/18 = 16.7% (Borrowed Controls = 10)
Experimental Arm: 2/24 = 8.3%

Bayesian Calculations
Estimated difference (E-S) in response rate (95% CI): -0.079 (-0.291, 0.106
Probability that the response rate on E is greater than S: 20.3%

The likelihood that E will be declared superior to S at the end of the ISA is
With the analysis prior: < 1%
With the prior provided above: 0.6%

Given the example trial data at the interim analysis shown below, would you stop for futility? Yes No





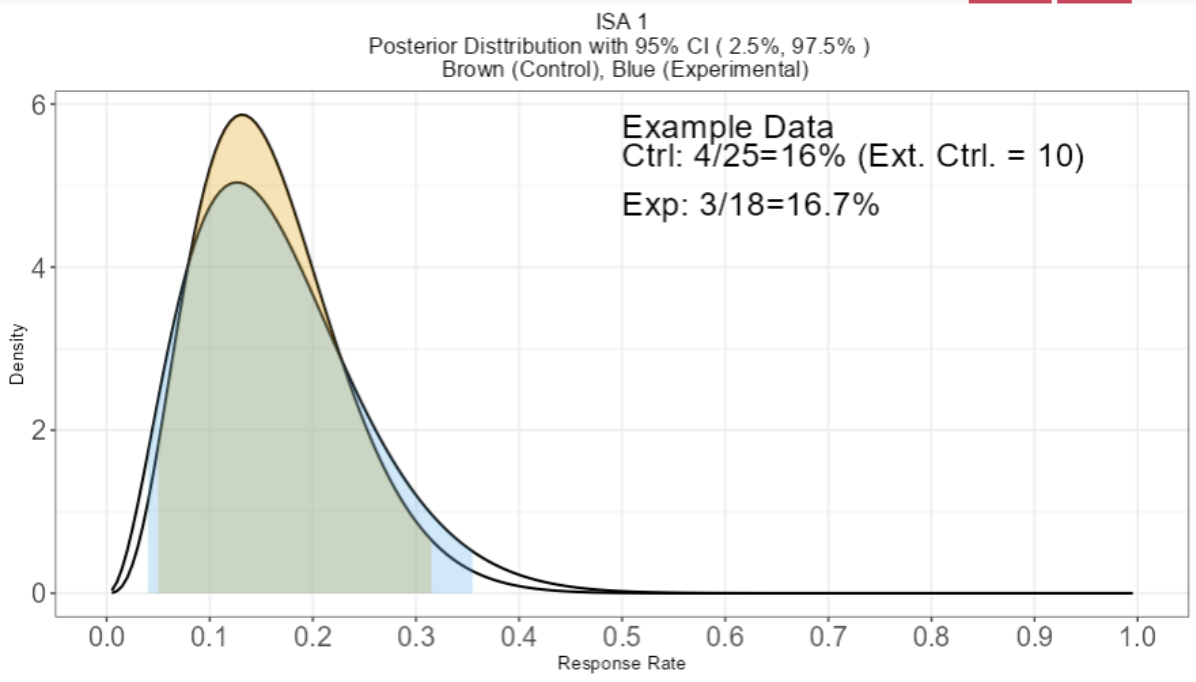
Example Trial 27801

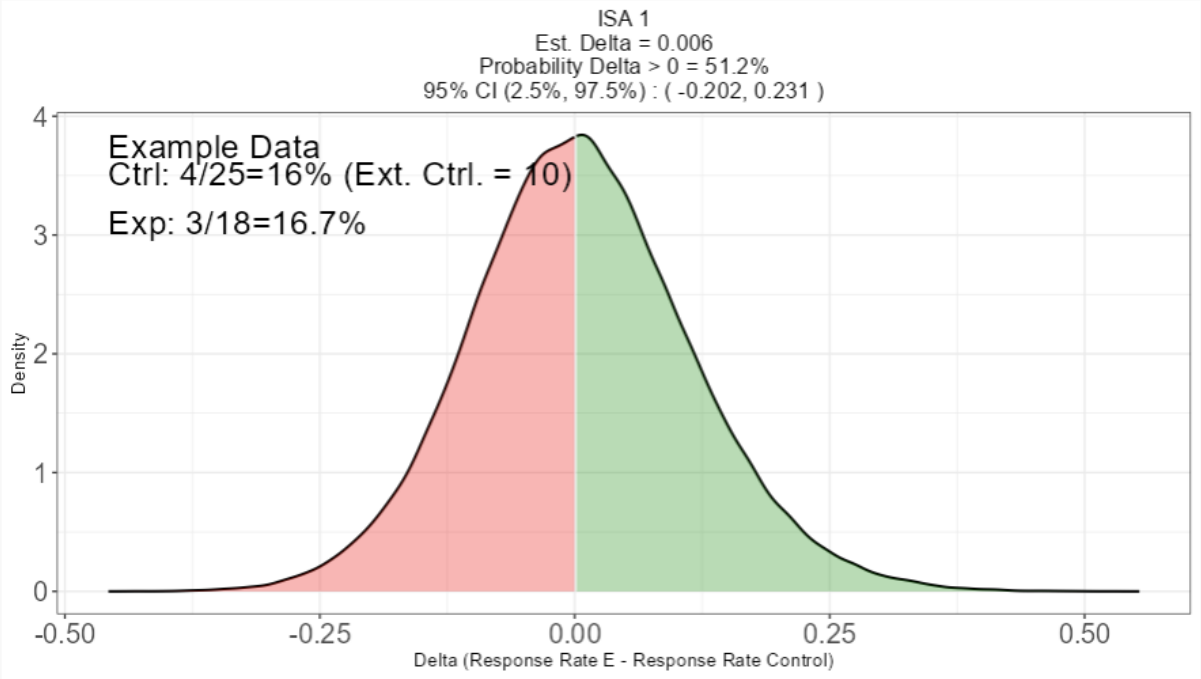
In the example trial the observed data are (Number of Responses / Number of Patients):
Control Arm: 4/25 = 16% (Borrowed Controls = 10)
Experimental Arm: 3/18 = 16.7%

Bayesian Calculations
Estimated difference (E-S) in response rate (95% CI): 0.006 (-0.202, 0.231)
Probability that the response rate on E is greater than S: 51.2%

The likelihood that E will be declared superior to S at the end of the ISA is
With the analysis prior: 4.3%
With the prior provided above: 10.9%

Given the example trial data at the interim analysis shown below, would you stop for futility? Yes No





Summary

- Platform studies can be difficult to design
- Beginning with score card and quick start worksheet can help identify potential issues and provide input to simulation plan
- OCTOPUS – simulations running quickly by leveraging exiting R code
- Walking through trade-offs can lead to additional calculations that are useful – Predictive Probabilities
- Walking through example trials can demonstrate potential data sets that the team may encounter at an interim analysis allowing for checking for agreement between design recommendations based on analysis and the team decision
- Variety of visuals, tables, example trial walk through, and shiny app helped to improve communication and team understanding

Thank You!
Kyle.Wathen@Cytel.com