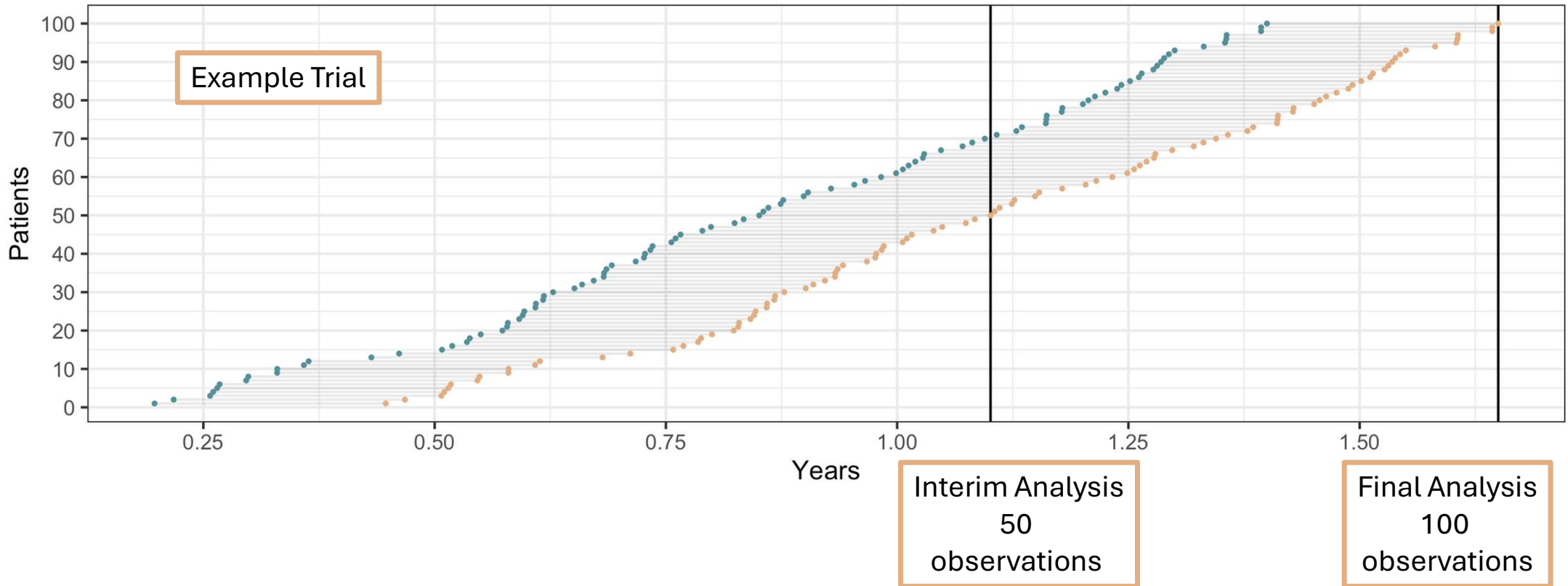


Forecasting with Confidence: Harnessing Predictive Probabilities in Adaptive Clinical Trial Design

Cora Allen-Savietta
Berry Consultants

*thanks to my co-authors
Joe Marion, Liz Lorenzi, Kert Viele, & Scott Berry*

Predicting Future Outcomes from Current Data



Given 50 observed patients, what is the probability of success at 100?

What do current data show?

	posterior probability	conditional power	predictive probability
Assumptions	incorporates prior information	frequentist calculation, no priors	incorporates prior information
Information	currently observed data	currently observed data	currently observed data
Goal	summarizes current information + prior	predicts trial success assuming a precise future treatment effect	predicts trial success based on a distribution of possible future treatment effects

Given observed interim data, how likely is a win if all future data show an assumed treatment effect?

	posterior probability	conditional power	predictive probability
Assumptions	incorporates prior information	typically frequentist, no priors	incorporates prior information
Information	currently observed data	currently observed data	currently observed data
Goal	summarizes current information + prior	predicts trial success assuming a single future treatment effect	predicts trial success based on a distribution of possible future treatment effects

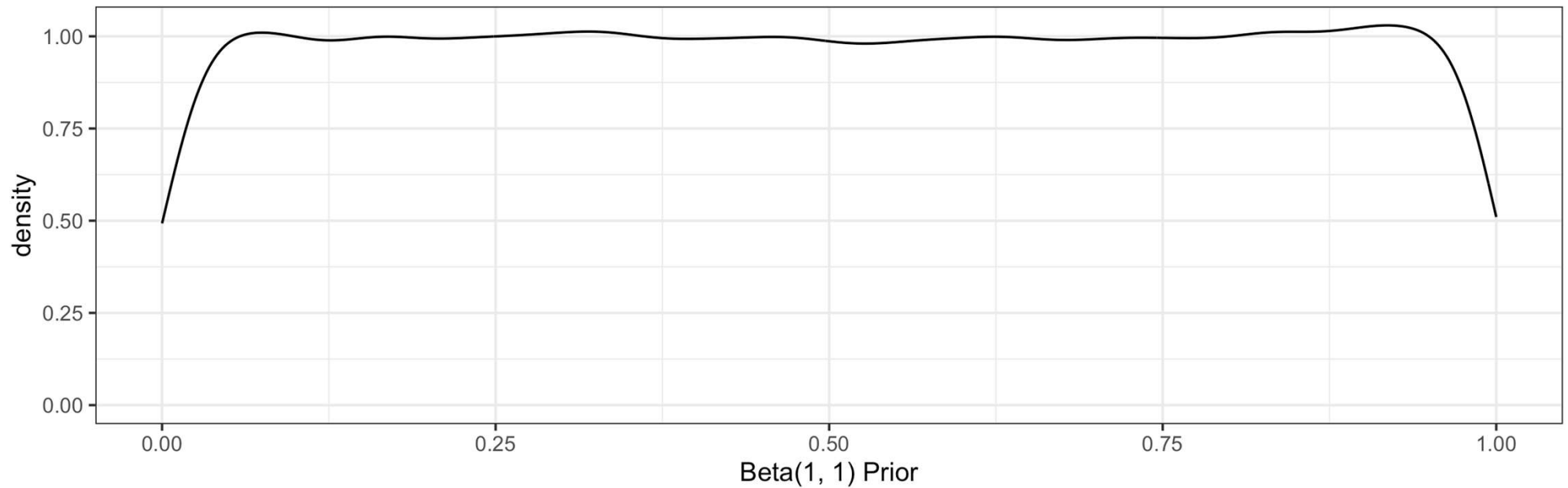
Given the observed data and distribution of treatment effects, how likely is a win?

	posterior probability	conditional power	predictive probability
Assumptions	incorporates prior information	typically frequentist, no priors	incorporates prior information
Information	currently observed data	currently observed data	currently observed data
Goal	summarizes current information + prior	predicts trial success assuming a precise future treatment effect	predicts trial success based on a distribution of possible future treatment effects

Computing Predictive Probabilities – Closed Form

centered at prior estimate

$$\theta \sim \text{Beta}(\alpha, \beta)$$



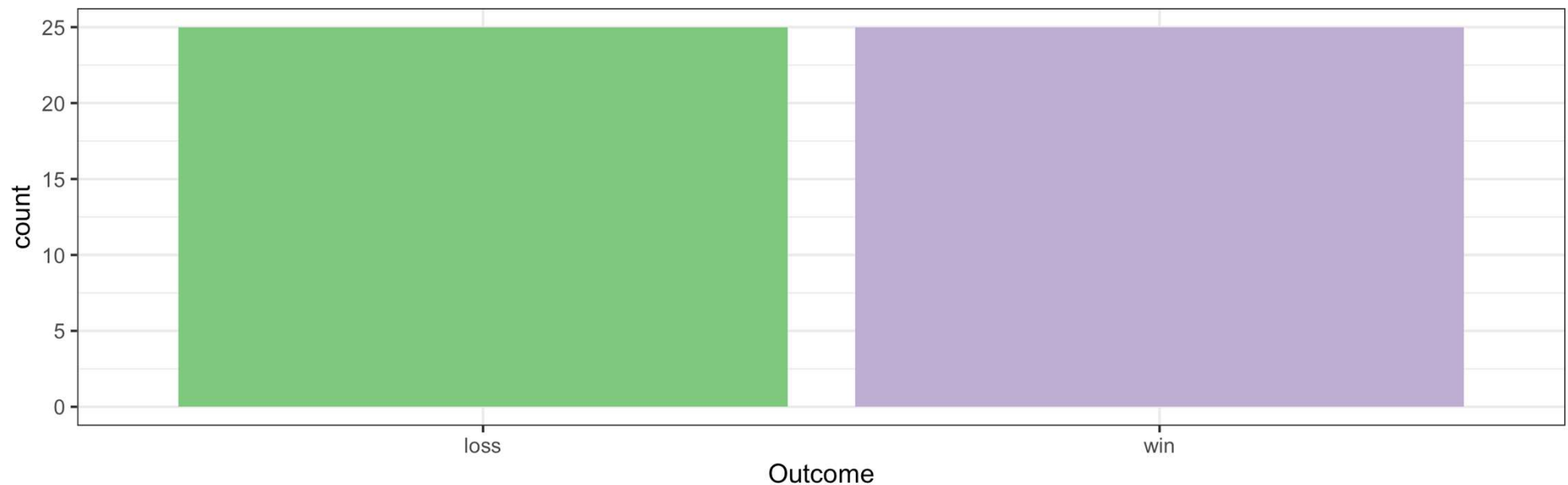
Computing Predictive Probabilities – Closed Form

centered at prior estimate

$$\theta \sim \text{Beta}(\alpha, \beta)$$

observed data at $N = 50$
25 wins, 25 failures

$$x_1 \sim \text{Binomial}(n_1, \theta)$$



Computing Predictive Probabilities – Closed Form

centered at prior estimate

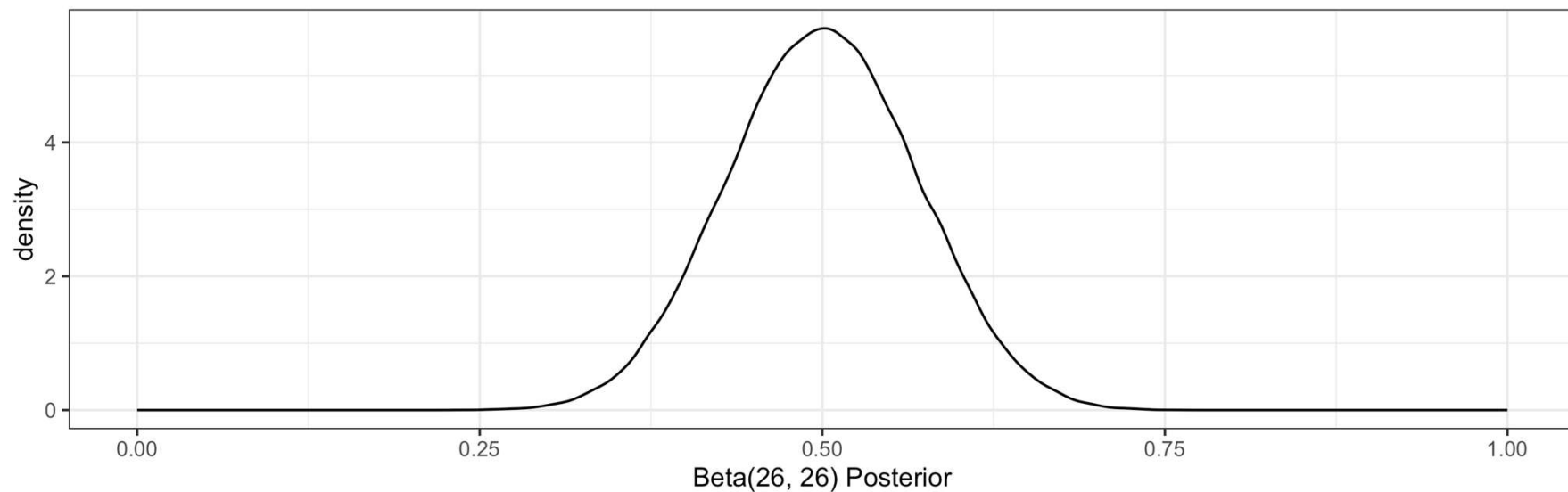
$$\theta \sim \text{Beta}(\alpha, \beta)$$

observed data at $N = 50$
25 wins, 25 failures

$$x_1 \sim \text{Binomial}(n_1, \theta)$$

posterior distribution

$$\theta | x_1, n_1 \sim \text{Beta}(\alpha + x_1, \beta + n_1 - x_1)$$



Computing Predictive Probabilities – Closed Form

centered at prior estimate

$$\theta \sim \text{Beta}(\alpha, \beta)$$

observed data at $N = 50$
25 wins, 25 failures

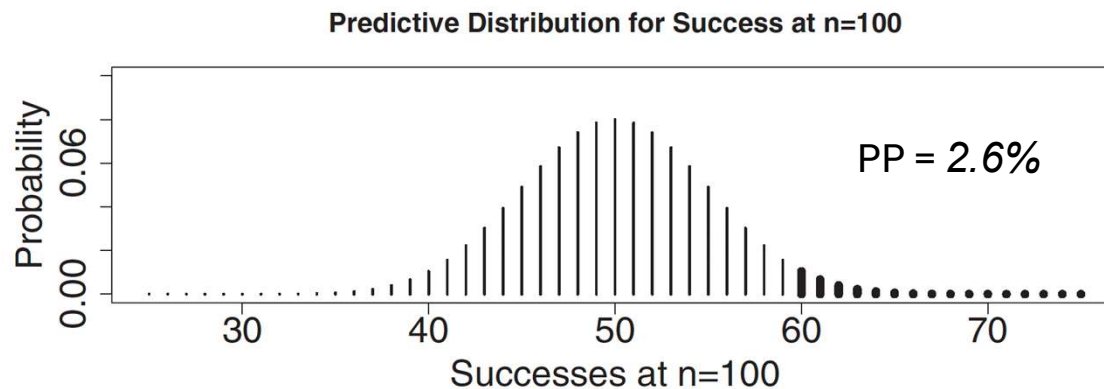
$$x_1 \sim \text{Binomial}(n_1, \theta)$$

posterior distribution

$$\theta | x_1, n_1 \sim \text{Beta}(\alpha + x_1, \beta + n_1 - x_1)$$

predictive distribution for
next n_2 observations

$$x_2 | n_1, \alpha + x_1, \beta + n_1 - x_1 \sim \text{Beta-Binomial}(n_2, \alpha + x_1, \beta + n_1 - x_1)$$

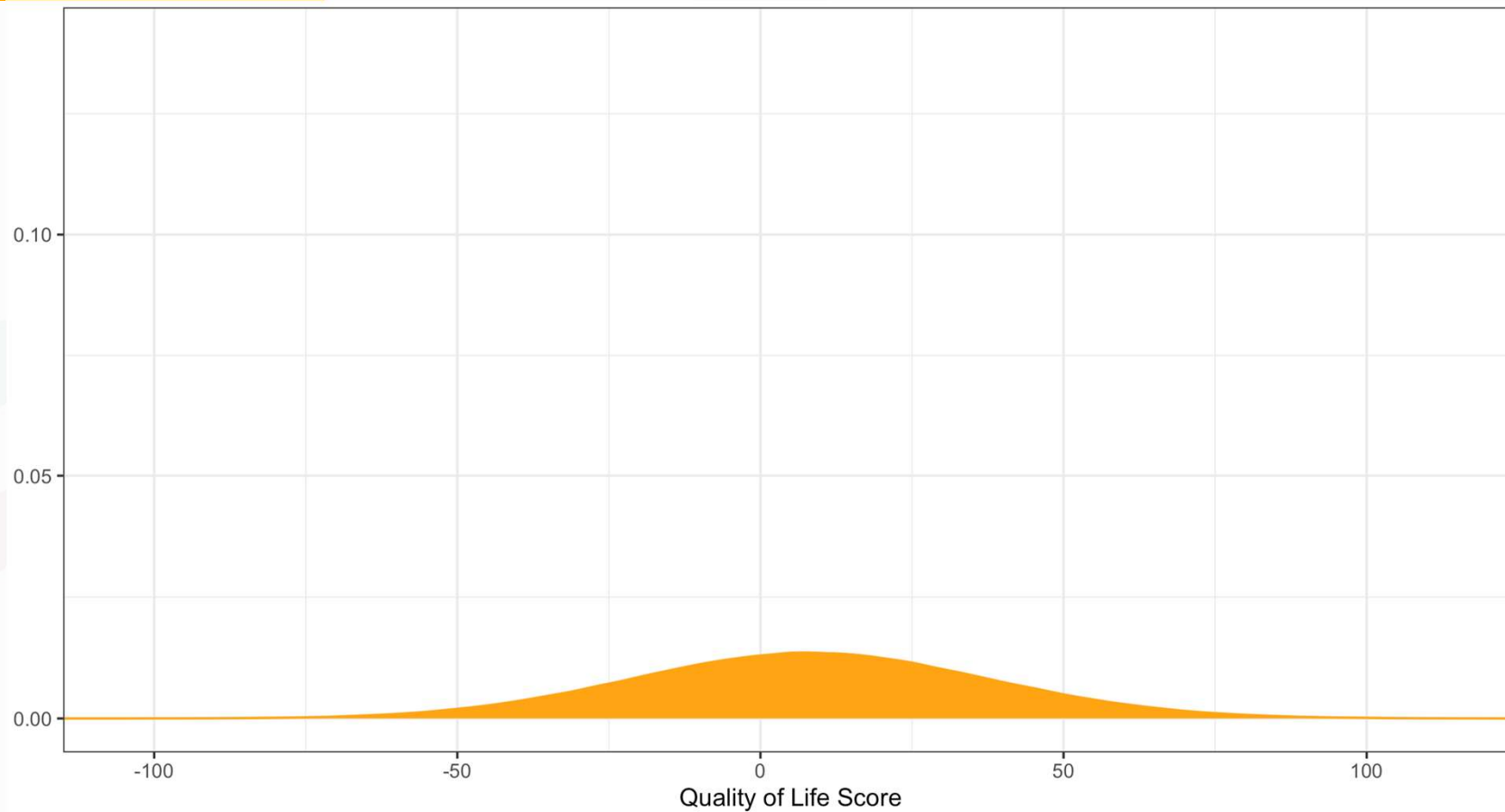


Bayesian Adaptive Methods for Clinical Trials. Berry et al. 2011

Calculating a Predictive Probability of Success: Monte Carlo Integration

prior information

- clinical expertise
- previous studies
- purposefully diffuse



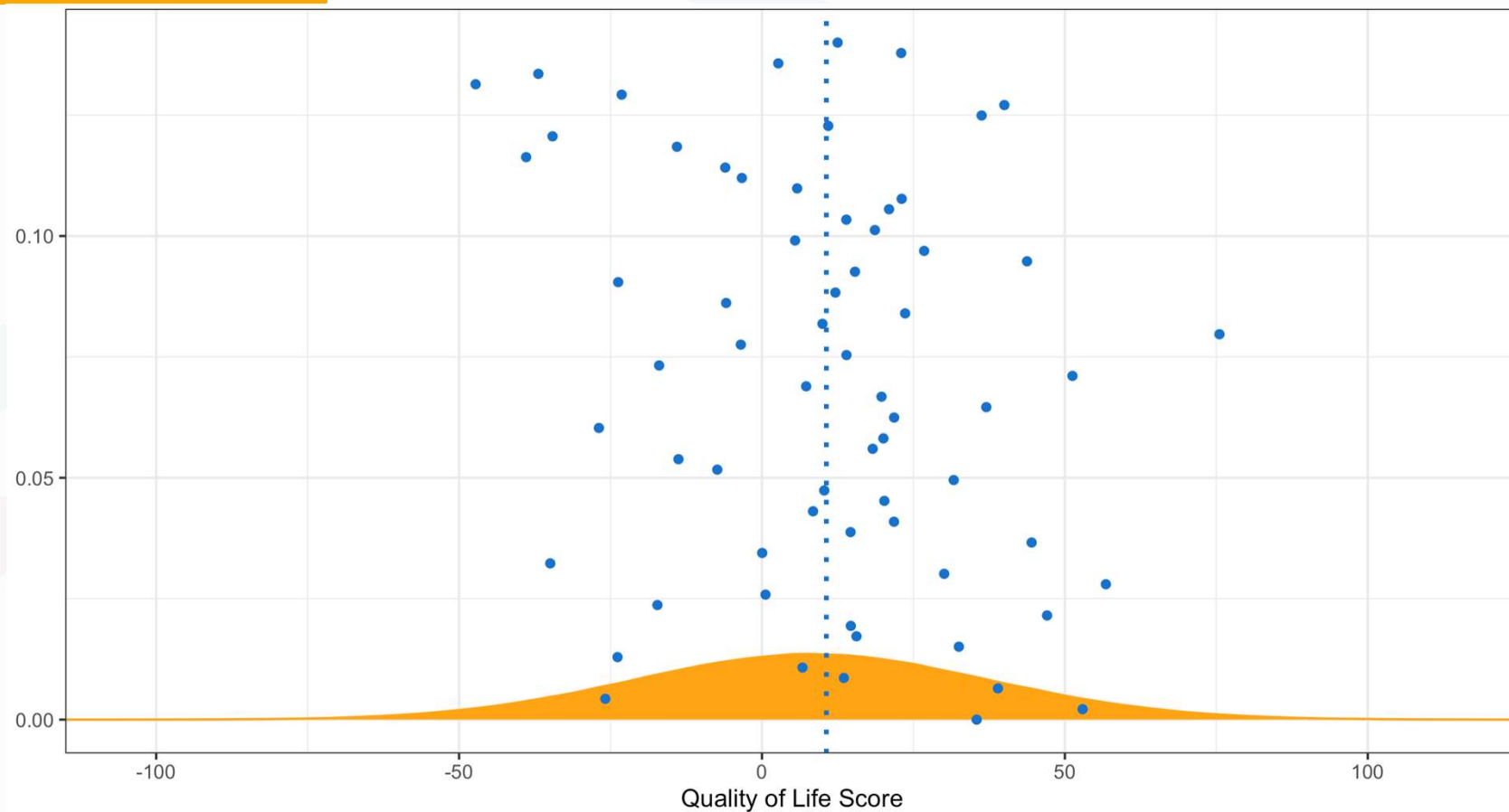
Calculating a Predictive Probability of Success

prior information

- clinical expertise
- previous studies
- purposefully diffuse

+

interim observed
data



Calculating a Predictive Probability of Success

prior information

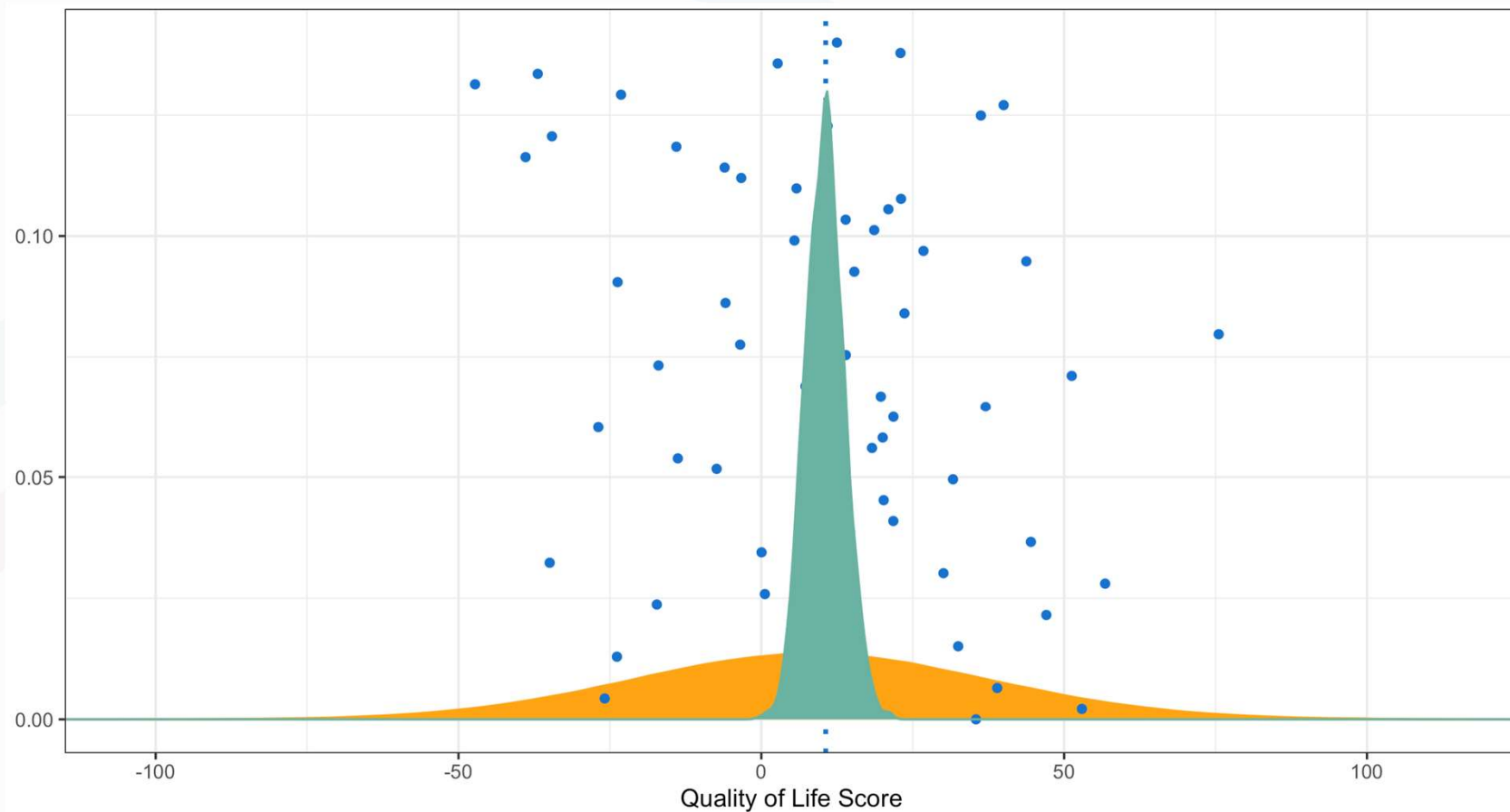
- clinical expertise
- previous studies
- purposefully diffuse

+

interim observed
data

=

posterior distribution
of the mean



Calculating a Predictive Probability of Success

prior information

- clinical expertise
- previous studies
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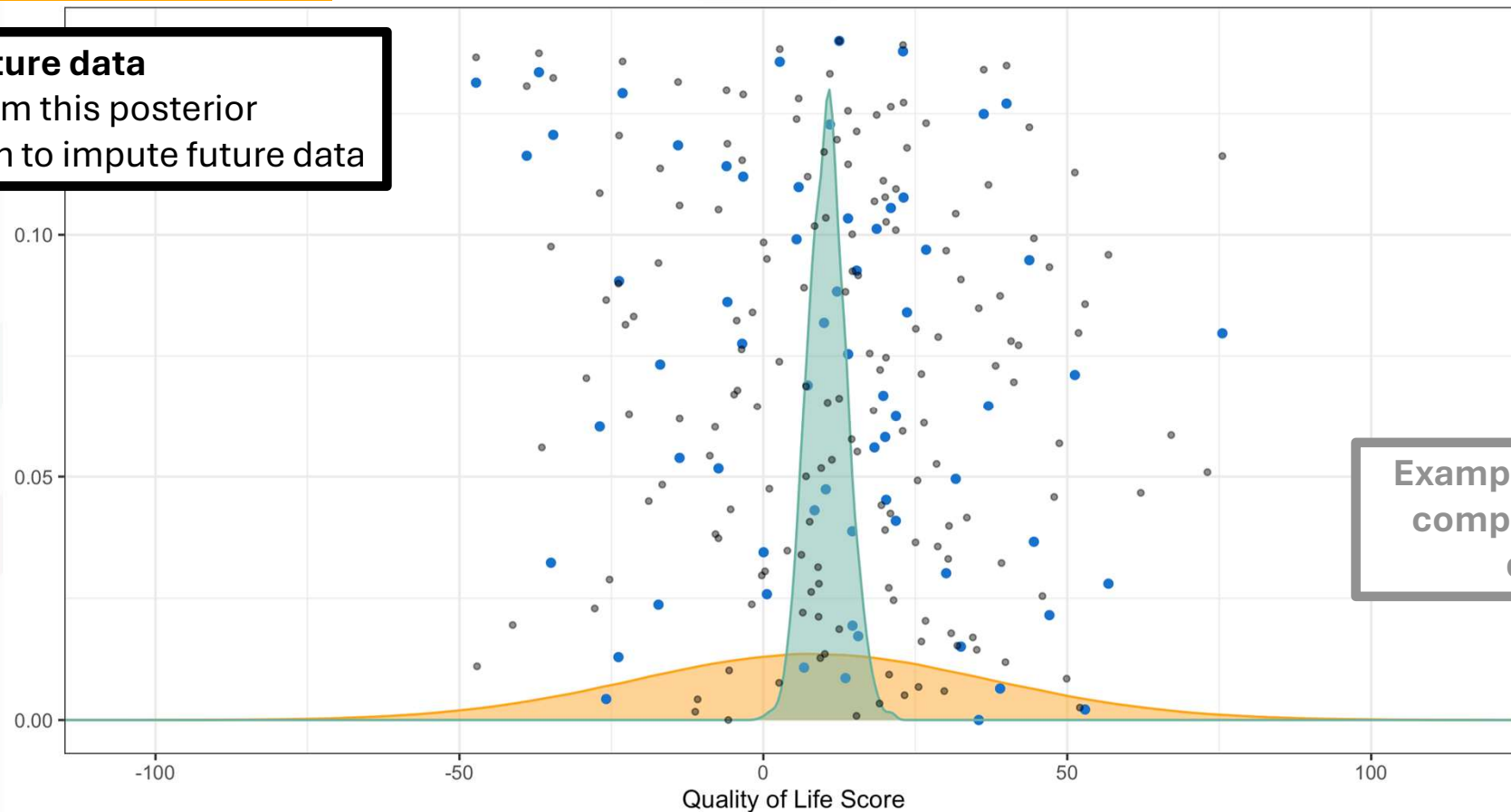
interim observed
data

=

posterior distribution
of the mean

impute future data

sample from this posterior
distribution to impute future data



Calculating a Predictive Probability of Success

prior information

- clinical expertise
- previous studies
- purposefully diffuse

+

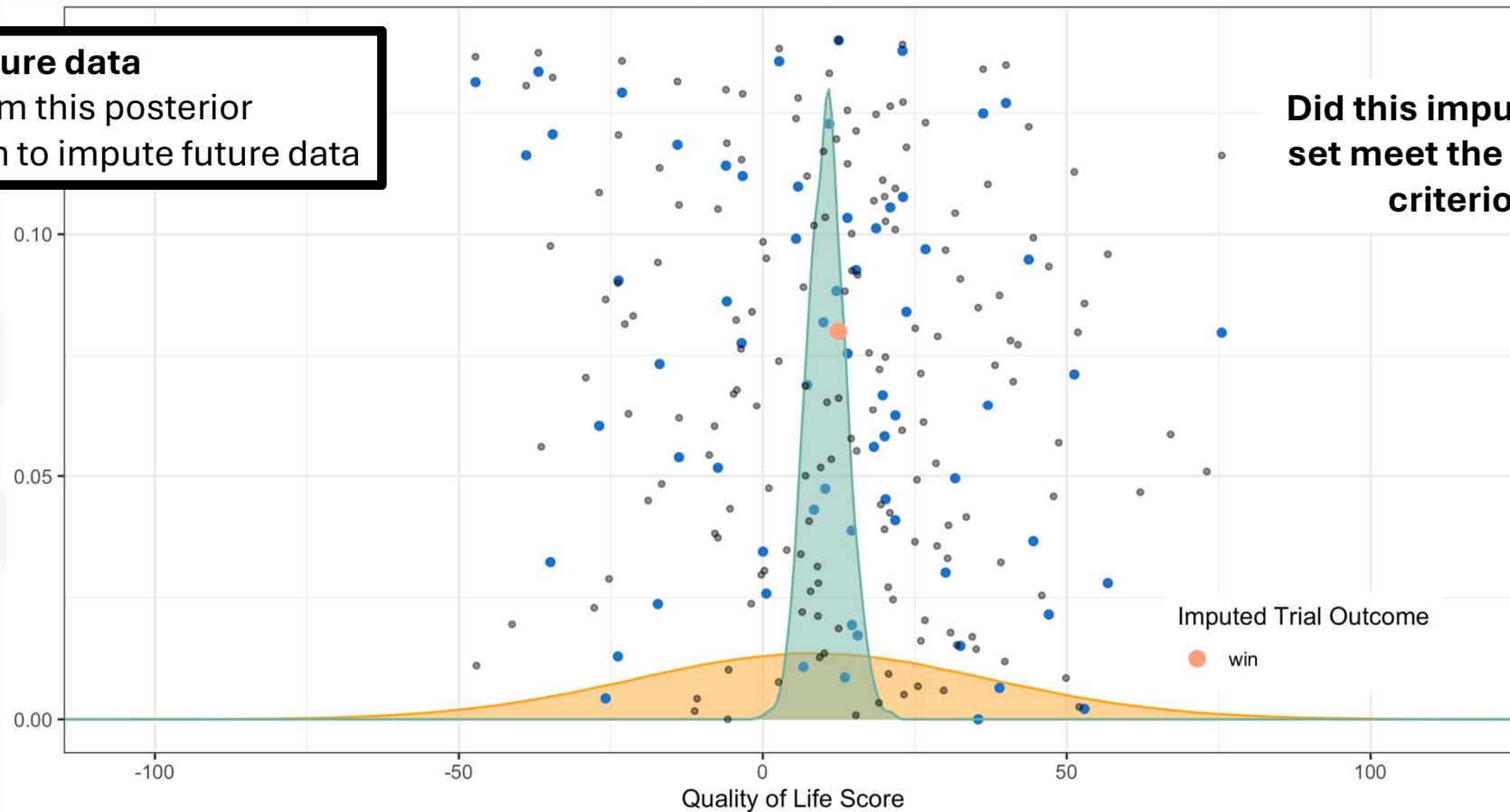
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posterior distribution
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Calculating a Predictive Probability of Success

prior information

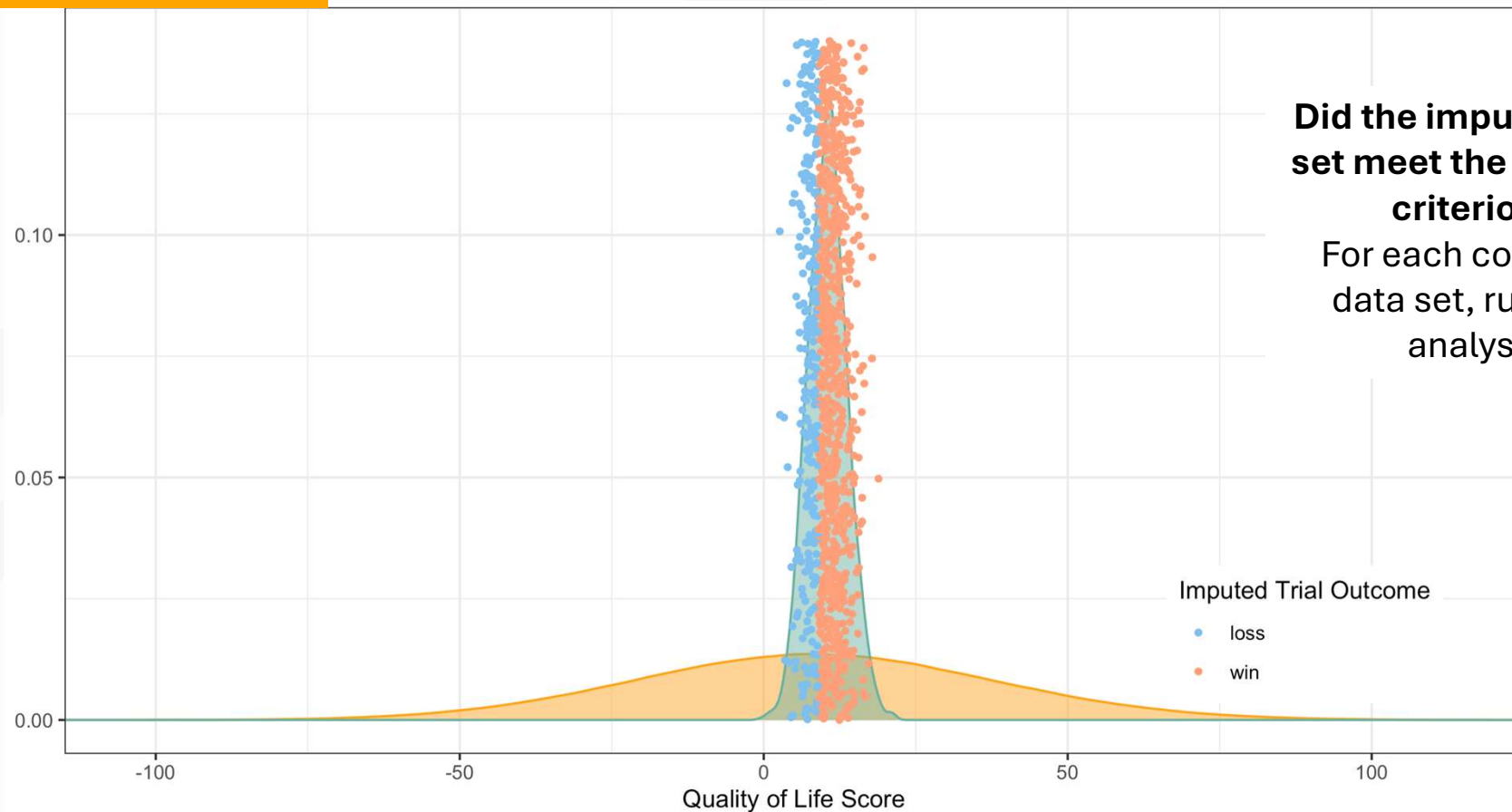
- clinical expertise
- previous studies
- purposefully diffuse

+

interim observed
data

=

posterior distribution
of the mean



**Did the imputed data
set meet the success
criterion?**

For each complete
data set, run final
analysis

Calculating a Predictive Probability of Success

prior information

- clinical expertise
- previous studies
- purposefully diffuse

+

interim observed
data

=

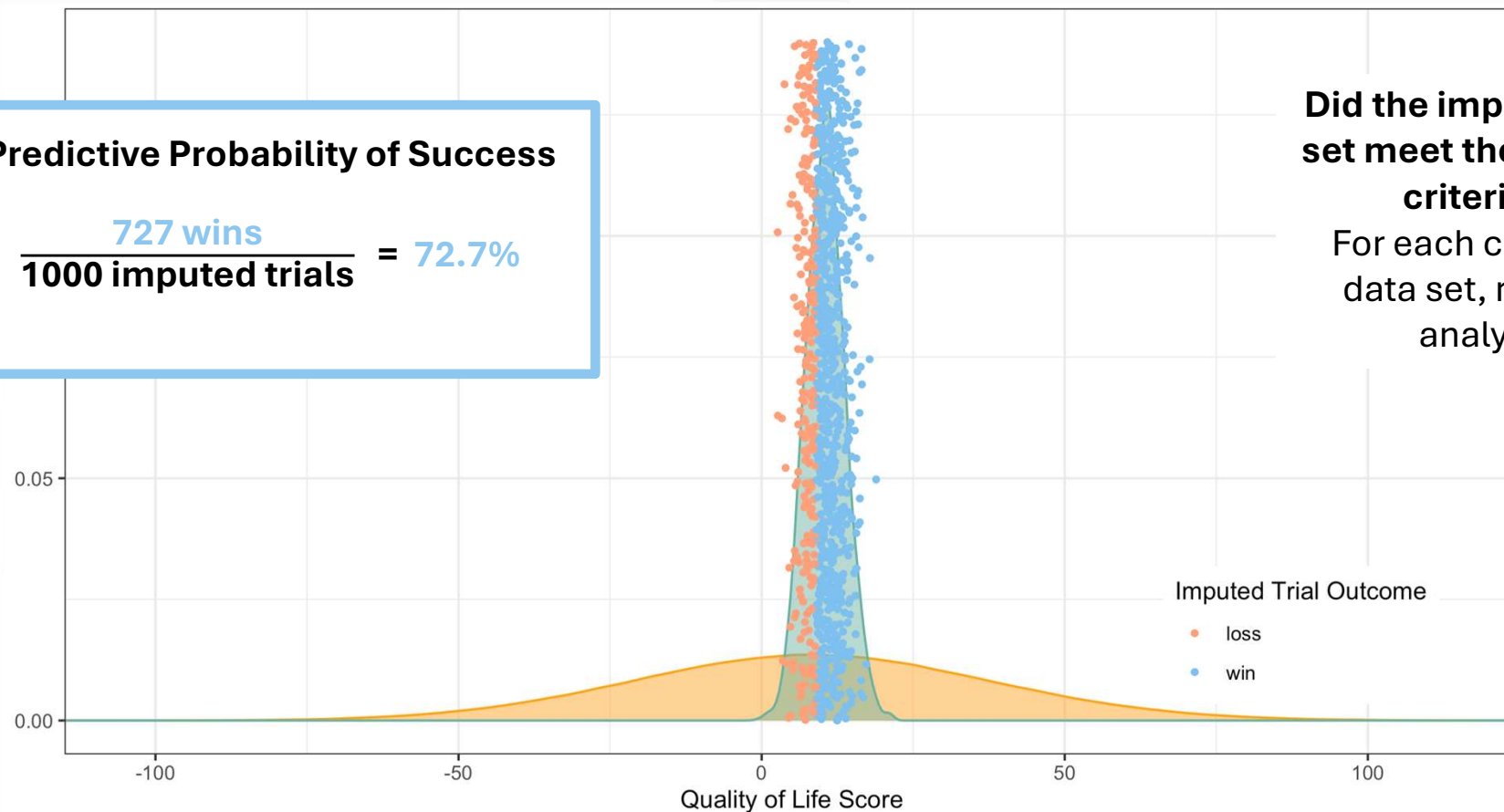
posterior distribution
of the mean

Predictive Probability of Success

$$\frac{727 \text{ wins}}{1000 \text{ imputed trials}} = 72.7\%$$

Did the imputed data
set meet the success
criterion?

For each complete
data set, run final
analysis



When would we need predictive probabilities?

- To choose a sample size at a prespecified interim analysis



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ORIGINAL ARTICLE



Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

Authors: Raul G. Nogueira, M.D., Ashutosh P. Jadhav, M.D., Ph.D., Diogo C. Haussen, M.D., Alain Bonafe, M.D., Ronald F. Budzik, M.D., Parita Bhuvra, M.D., Dileep R. Yavagal, M.D., Marc Ribo, M.D., Christophe Cognard, M.D., Ricardo A. Hanel, M.D., Cathy A. Sila, M.D., Ameer E. Hassan, D.O., Monica Millan, M.D., Elad I. Levy, M.D., Peter Mitchell, M.D., Michael Chen, M.D., Joey D. English, M.D., Qaisar A. Shah, M.D., Frank L. Silver, M.D., Vitor M. Pereira, M.D., Brijesh P. Mehta, M.D., Blaise W. Baxter, M.D., Michael G. Abraham, M.D., Pedro Cardona, M.D., Erol Veznedaroglu, M.D., Frank R. Hellinger, M.D., Lei Feng, M.D., Jawad F. Kirmani, M.D., Demetrius K. Lopes, M.D., Brian T. Jankowitz, M.D., Michael R. Frankel, M.D., Vincent Costalat, M.D., Nirav A. Vora, M.D., Albert J. Yoo, M.D., Ph.D., Amer M. Malik, M.D., Anthony J. Furlan, M.D., Marta Rubiera, M.D., Amin Aghaebrahim, M.D., Jean-Marc Olivot, M.D., Wondwossen G. Tekle, M.D., Ryan Shields, M.Sc., Todd Graves, Ph.D., Roger J. Lewis, M.D., Ph.D., Wade S. Smith, M.D., Ph.D., David S. Liebeskind, M.D., Jeffrey L. Saver, M.D., and Tudor G. Jovin, M.D., for the DAWN Trial Investigators* -40 [Author Info & Affiliations](#)

Published November 11, 2017 | N Engl J Med 2018;378:11-21 | DOI: 10.1056/NEJMoa1706442 | VOL. 378 NO. 1

STATISTICAL ANALYSIS

The adaptive trial design allowed for a sample size ranging from 150 to 500 patients. During interim analyses, the decision to stop or continue enrollment was based on a prespecified calculation of the probability that thrombectomy plus standard care would be superior to standard care alone with respect to the first primary end point. The enrichment trial design gave us the flexibility to identify whether the benefit of the trial intervention was restricted to a subgroup of patients with relatively small infarct volumes at baseline. The interim analyses, which included patients with available follow-up data at the time of the analysis, were prespecified to test for the futility, enrichment, and success of the trial.

When would we need predictive probabilities?

- To identify subgroups benefiting most from a treatment



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When would we need predictive probabilities?

- To **identify subgroups** benefiting most from a treatment



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ORIGINAL ARTICLE

Results led to an FDA expansion

FDA NEWS RELEASE

FDA expands treatment window for use of clot retrieval devices in certain stroke patients

<https://www.fda.gov/news-events/press-announcements/fda-expands-treatment-window-use-clot-retrieval-devices-certain-stroke-patients>

When would we want to use a predictive probability?

- To determine if additional data are likely to provide convincing evidence of a treatment effect. In other words, **should the trial stop for futility?**



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ORIGINAL ARTICLE



Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus

Authors: Jaideep Kapur, M.B., B.S., Ph.D., Jordan Elm, Ph.D., James M. Chamberlain, M.D., William Barsan, M.D., James Cloyd, Pharm.D., Daniel Lowenstein, M.D., Shlomo Shinnar, M.D., Ph.D., [+6](#), for the NETT and PECARN

Investigators* [Author Info & Affiliations](#)

Published November 27, 2019 | N Engl J Med 2019;381:2103-2113 | DOI: 10.1056/NEJMoa1905795

VOL. 381 NO. 22

When would we want to use a predictive probability?



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VOL. 381 NO. 22

Table S6. Computations of the futility analysis

Look	Predictive probability that an arm is identified as best / worst at maximum sample size*			Predictive probability that any arm Wins**
	Levetiracetam	Fosphenytoin	Valproate	
Analysis after 400 ^a Enrollment (N=384 unique subjects)				

* Maximum sample size was assumed to be 720 unique subjects for calculation of the predictive probabilities.

** This represents the sum of the predictive probabilities arm is best/worst at the maximum sample size for each of the 3 groups. If this sum is < 5%, the trial stops for futility.

Computing Bayesian Predictive Probabilities

Computing Bayesian Predictive Probabilities

Analytical Calculation

- Mathematical formula to directly calculate predictive probability
- Feasible when integral has closed form
- Very fast

Monte Carlo integration

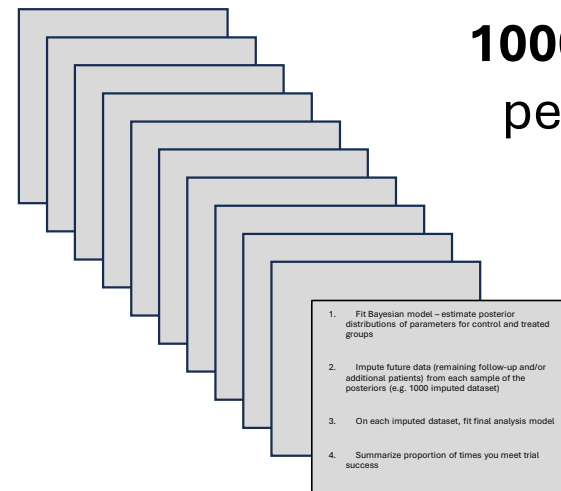
- if no closed form, requires Monte Carlo integration
- **Can become computationally restrictive**

Monte Carlo Integration for Bayesian Predictive Probabilities

1. Fit Bayesian model
2. Impute future data & fit final analysis model
3. Summarize % meeting trial success

Clinical trial simulations for operating characteristics...

Repeat
1000s of times
per scenario



Computing Bayesian Predictive Probabilities

Analytical Calculation

- Mathematical formula to directly calculate predictive probability
- Feasible when integral has closed form
- Very fast

Monte Carlo integration

- if no closed form, requires Monte Carlo integration
- **Can become computationally restrictive**

Approximation

- accurate
- simple and fast

Computing Bayesian Predictive Probabilities

Analytical Calculation

Monte Carlo integration

Approximation

fits easily into **both** frequentist and Bayesian designs
without burdensome computation

Predictive Probability Approximation

Interim analysis

Z_n

- n patients enrolled
- I_n Information
- p_n associated p -value

Predictive probability PP_N is probability null hypothesis is rejected if analysis performed at N patients

Rewrite final test statistic as weighted sum of Z_n and Z_{N-n}

$$Z_N \sqrt{I_N} = Z_n \sqrt{I_n} + Z_{N-n} \sqrt{I_N - I_n}$$

Assume uninformative prior distribution $\theta \propto 1$ which yields posterior:

$$\theta | (Z_n = z_n) \sim N(z_n / \sqrt{I_n}, 1/I_n)$$

Results in predictive distribution for Z_{N-n}

$$Z_{N-n} | (Z_n = z_n) \sim N\left(z_n \sqrt{\frac{I_N - I_n}{I_n}}, \frac{I_N}{I_n}\right)$$

Final analysis

Z_N

- N patients enrolled
- I_N Information level
- p_N associated p -value

$$PP(p_n, r, \alpha) = \Phi\left(\frac{\Phi^{-1}(1 - p_n) - \Phi^{-1}(1 - \alpha)\sqrt{r}}{\sqrt{1 - r}}\right)$$

Predictive Probability Approximation

$$PP(p_n, r, \alpha) = \Phi \left(\frac{\Phi^{-1}(1 - p_n) - \Phi^{-1}(1 - \alpha)\sqrt{r}}{\sqrt{1 - r}} \right)$$

Requires only:

- p : interim p-value
- n : information at interim
- N : expected information at trial end

Easy-to-use R functions at
github.com/BerryConsultants/approximatePredictiveProbability

Applying the Approximate Predictive Probability

Endpoint	Example analysis	I_n	I_N
Continuous	T-tests ANOVA/ANCOVA	Interim sample size	Final sample size
Binary	z-tests Chi-squared tests	Interim sample size	Final sample size
Time-to-event	Log-rank test Proportional hazards models	Events at interim	Events at final
Ordinal/ Non-parametric	Ordinal regression Wilcoxon rank-sum	Interim sample size	Final sample size
Count data	Generalized linear regressions (e.g. Poisson regression)	Interim exposure	Final exposure

Key Assumptions:

- primary analysis test statistic \sim Normal
- $r = I_n/I_N$ known

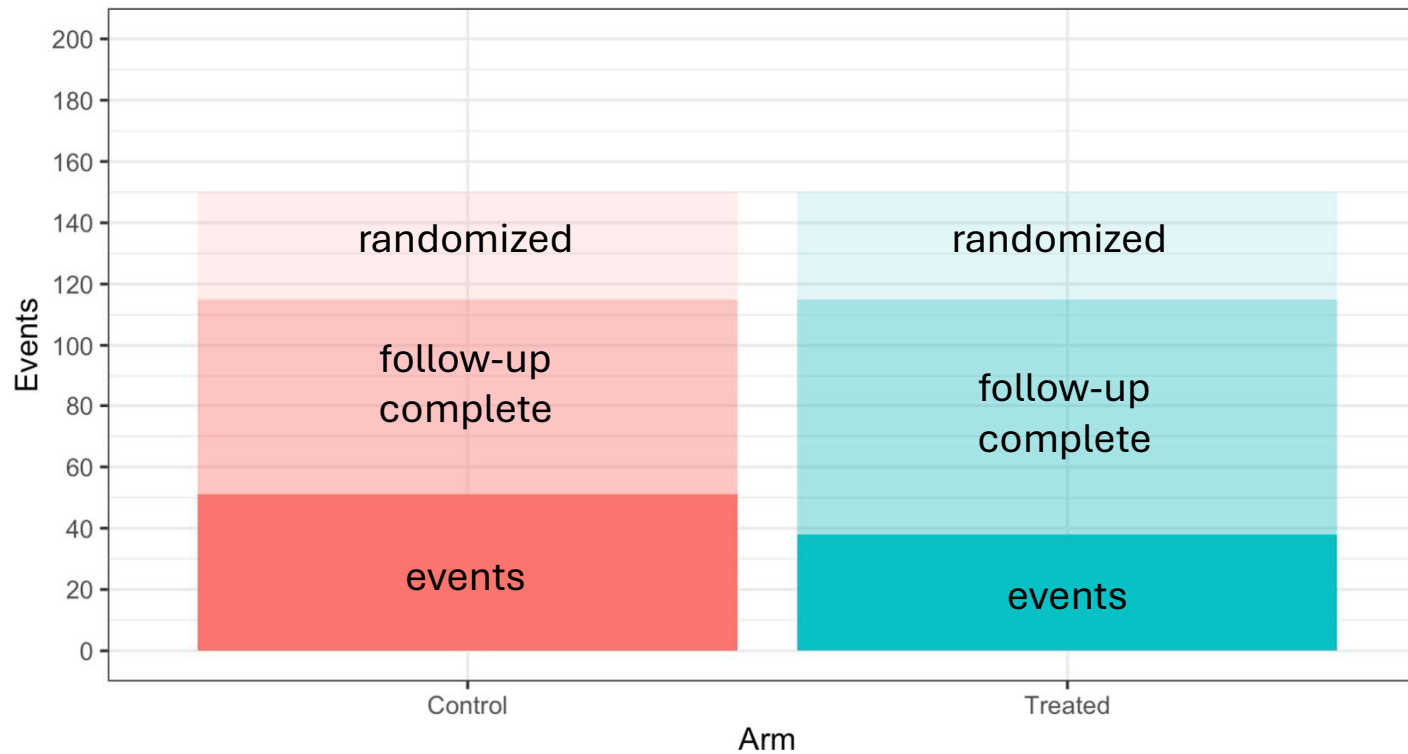
Example: Frequentist Binary Endpoint

- Primary Endpoint: Did a participant die by 90 days?
 - Chi-square analysis
- Maximum Sample Size: 500
 - Interim Goldilocks-style* sample size re-estimations:
 - n = 300 randomized
 - n = 400 randomized
- At each interim, the algorithm can:
 - Stop trial enrollment for expected success at this sample size if $PP_n > 90\%$
 - Stop trial enrollment for futility if $PP_{500} < 5\%$ or
 - Continue trial enrollment

*Broglia et al. 2014 *Not Too Big, Not Too Small: A Goldilocks Approach To Sample Size Selection*

Interim 1: 300 Randomized

Randomized			Follow-up Complete			Events by 90 Days (%)		Predictive Probability of Success at Current N		Predictive Probability of Success at Max N	
Total	Control	Treated	Total	Control	Treated	Control	Treated	PPn	aPPn	PPmaxN	aPPmaxN
300	150	150	230	115	115	0.4435	0.3304	0.5031	0.4940	0.7112	0.7023

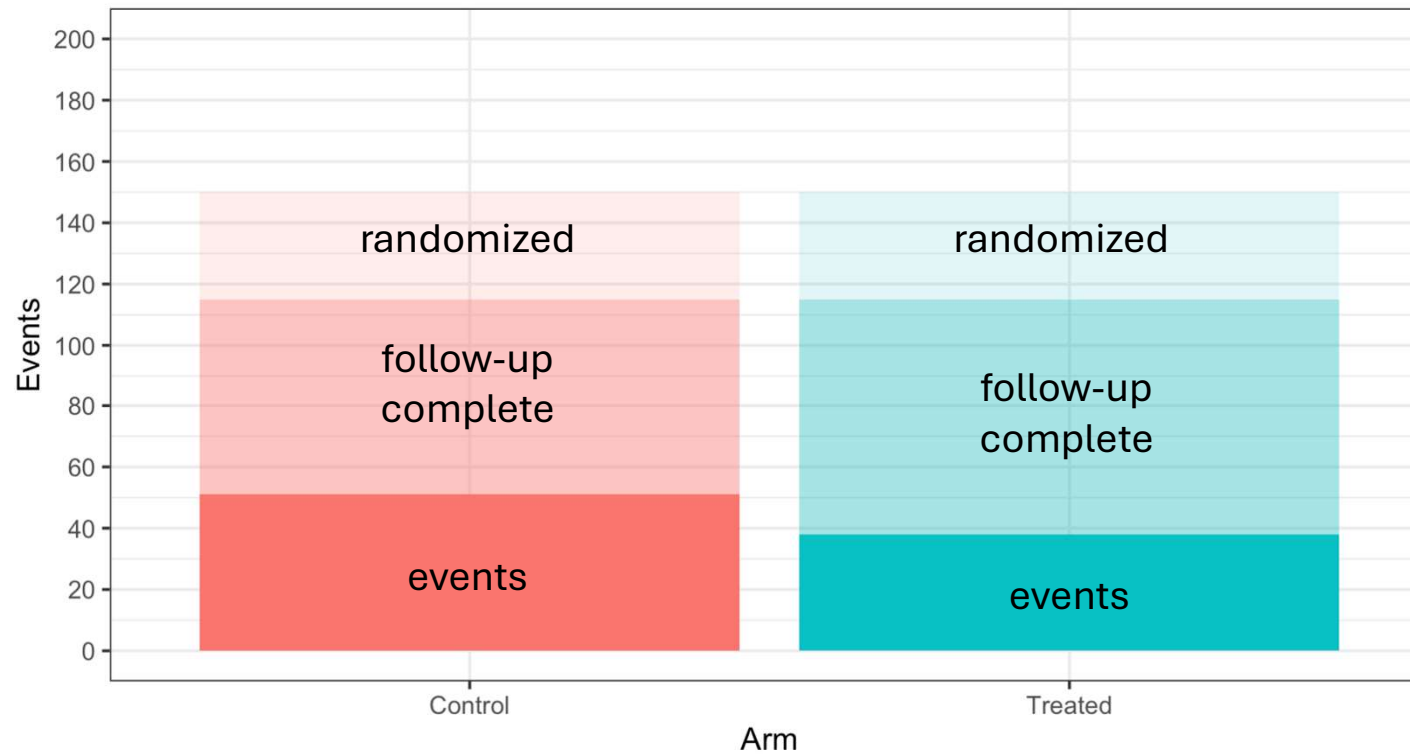


Interim 1: 300 Randomized

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Total	Control	Treated	Total	Control	Treated	Control	Treated	PPn	aPPn	PPmaxN	aPPmaxN
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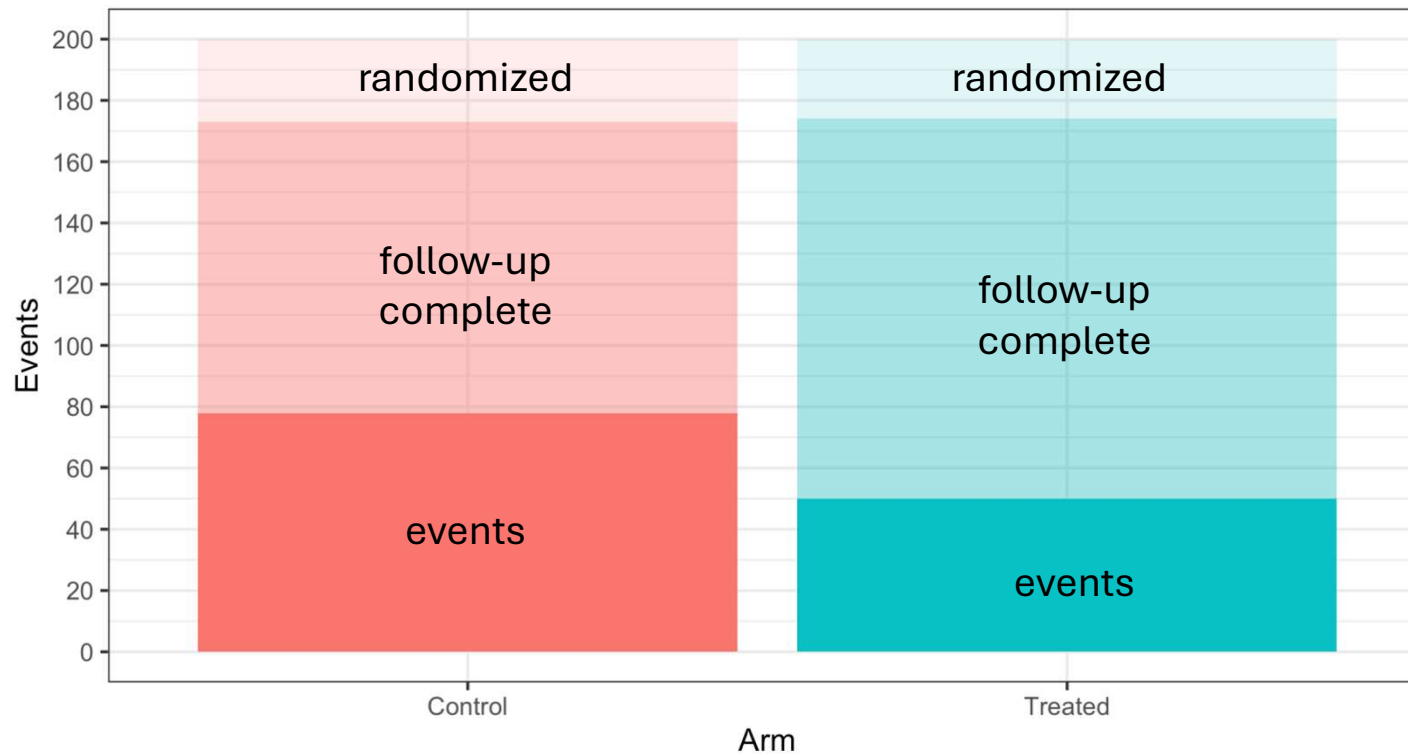
met stopping criteria for expected success? **no**

met stopping criteria for futility? **no**



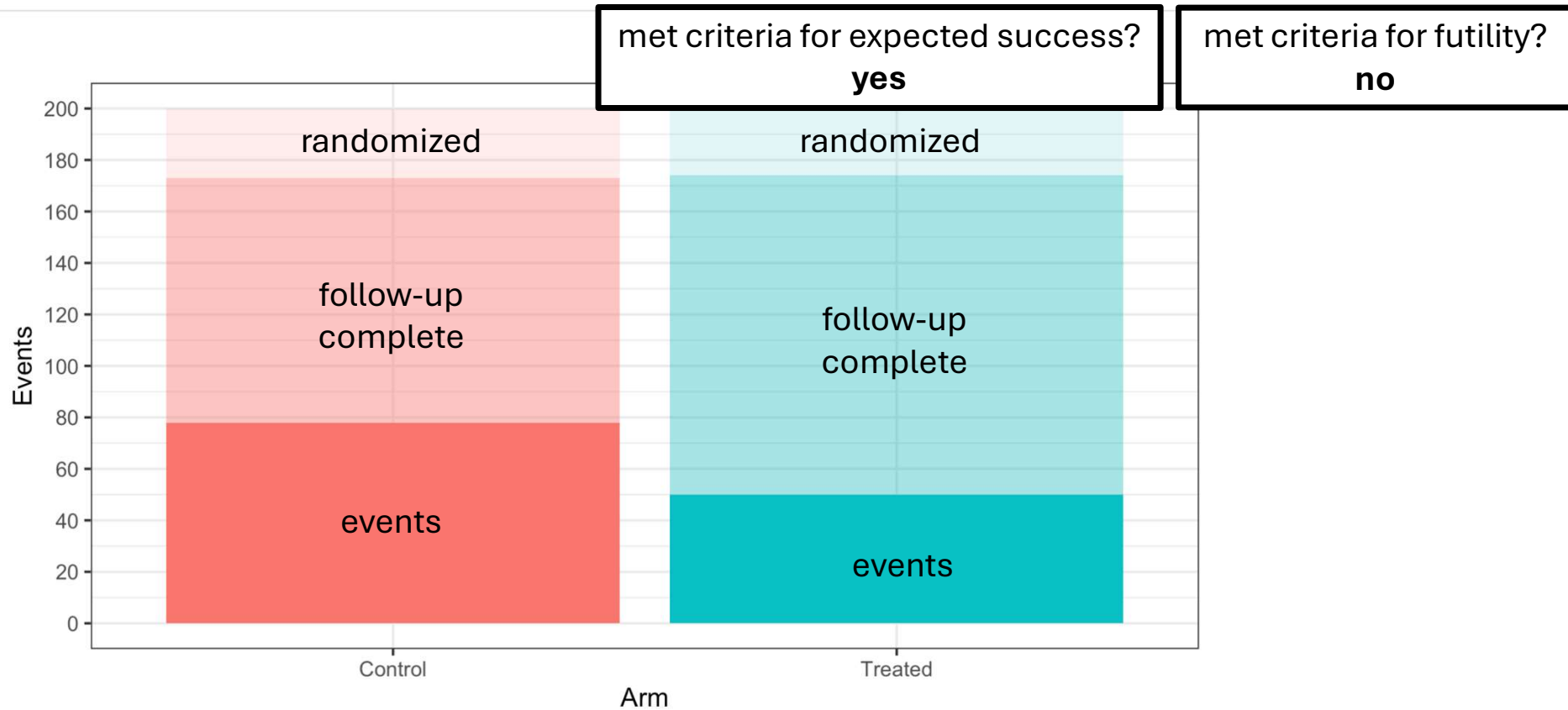
Interim 2: 400 Randomized

Randomized			Follow-up Complete			Events by 90 Days (%)		Predictive Probability of Success at Current N		Predictive Probability of Success at Max N	
Total	Control	Treated	Total	Control	Treated	Control	Treated	PPn	aPPn	PPmaxN	aPPmaxN
300	150	150	230	115	115	0.4435	0.3304	0.5031	0.4940	0.7112	0.7023
400	200	200	347	173	174	0.4509	0.2874	0.9995	0.9998	0.9973	0.9965



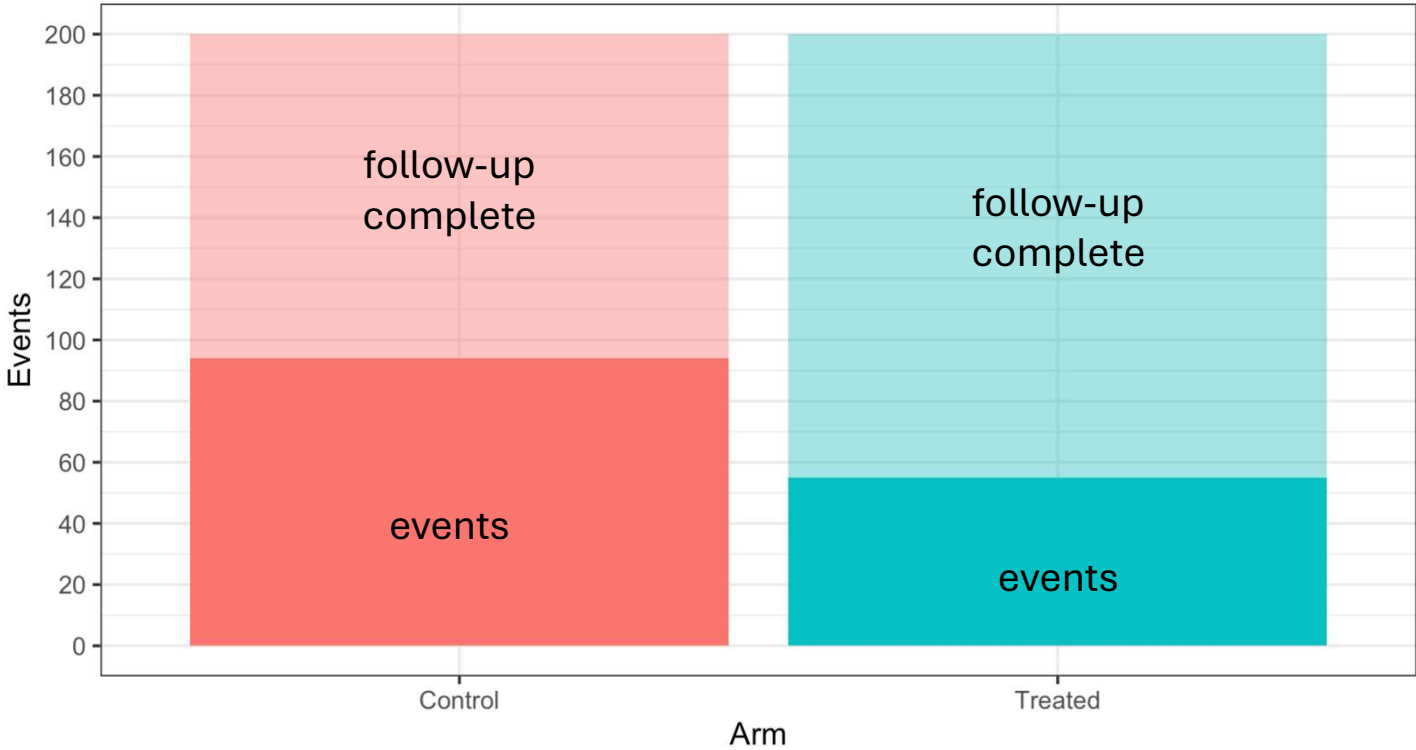
Interim 2: 400 Randomized

Randomized			Follow-up Complete			Events by 90 Days (%)		Predictive Probability of Success at Current N		Predictive Probability of Success at Max N	
Total	Control	Treated	Total	Control	Treated	Control	Treated	PPn	aPPn	PPmaxN	aPPmaxN
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400	200	200	347	173	174	0.4509	0.2874	0.9995	0.9998	0.9973	0.9965



Final Analysis

Randomized			Follow-up Complete			Events by 90 Days (%)		Predictive Probability of Success at Current N		Predictive Probability of Success at Max N		Final Analysis
Total	Control	Treated	Total	Control	Treated	Control	Treated	PPn	aPPn	PPmaxN	aPPmaxN	p
300	150	150	230	115	115	0.4435	0.3304	0.5031	0.4940	0.7112	0.7023	
400	200	200	347	173	174	0.4509	0.2874	0.9995	0.9998	0.9973	0.9965	
400	200	200	400	200	200	0.4700	0.2750					0.0000



success

Simulation Studies

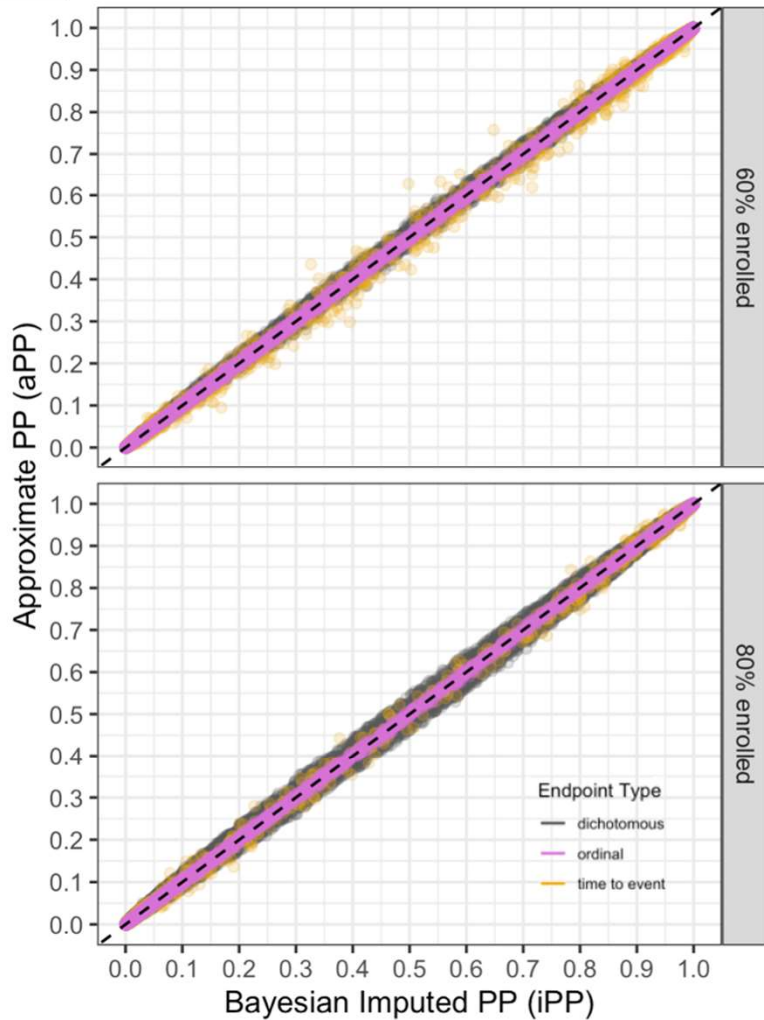
- Interims at 60%, 80% information
- imputed predictive probabilities (iPP) vs approximate predictive probabilities (aPP)
- **Do the iPP and aPP look similar? Make the same decisions?**

Endpoint	Example analysis	I_n	I_N
Continuous	T-tests ANOVA/ANCOVA	Interim sample size	Final sample size
Binary	Z-tests Chi-squared tests	Interim sample size	Final sample size
Time-to-event	Log-rank test Proportional hazards models	Events at interim	Events at final
Ordinal/Non-parametric	Ordinal regression Wilcoxon rank-sum	Interim sample size	Final sample size
Count data	Generalized linear regressions (e.g. Poisson regression)	Interim exposure	Final exposure

iPP vs aPP across endpoint types

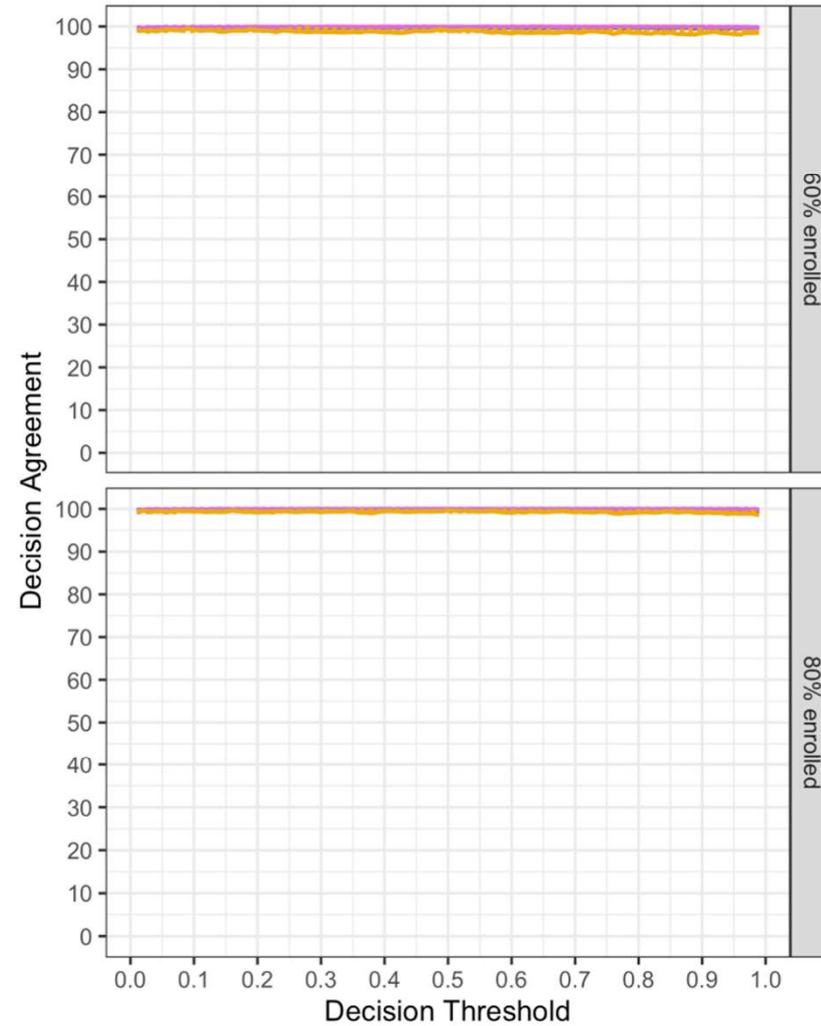
A

aPP vs iPP by Simulated Trial



B

Decisions made by iPP and aPP



Endpoint Type

- dichotomous
- ordinal
- time to event

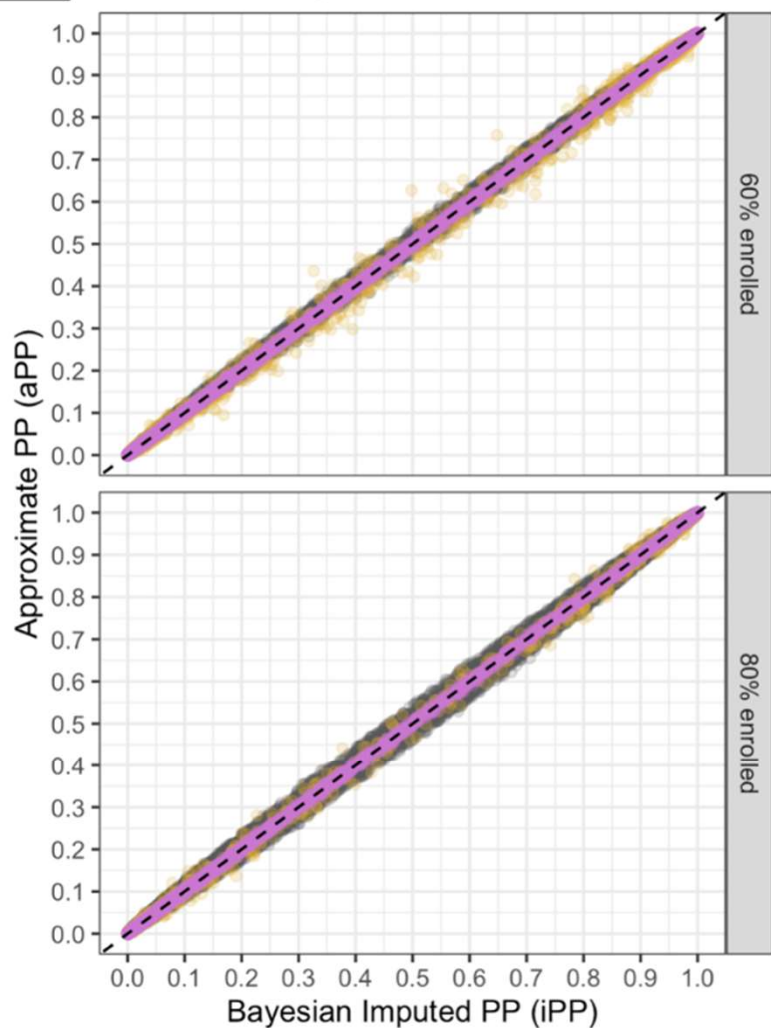
Predictive Probability

- current N at full follow-up
- max N at full follow-up

iPP vs aPP across endpoint types

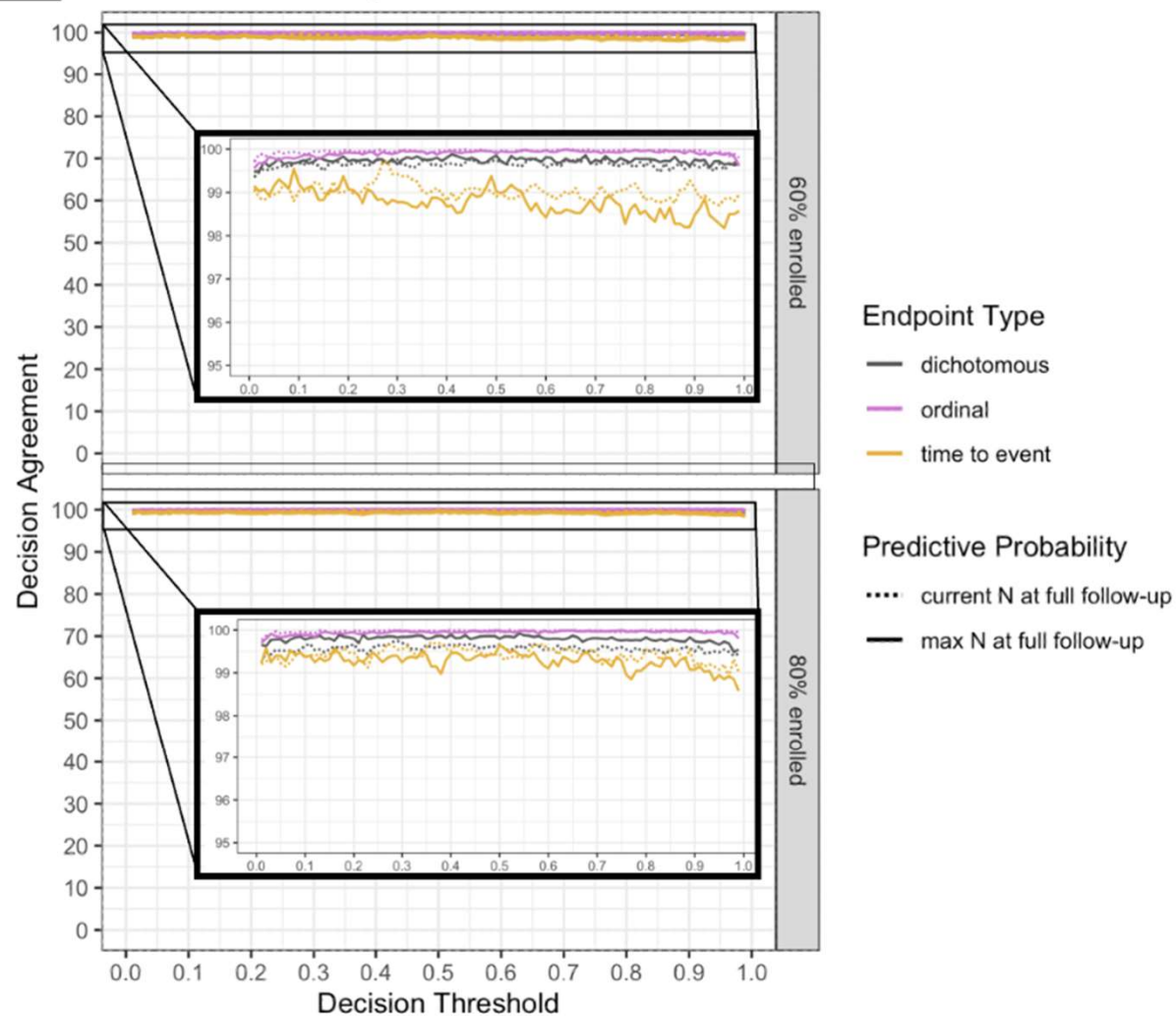
A

aPP vs iPP by Simulated Trial



B

Decisions made by iPP and aPP



Summary

- **Approximate predictive probability from interim z-scores**
- **Fits easily into both frequentist and Bayesian designs**
- High similarity between imputed PP and approximate PP
 - Though there are cases where they disagree (win ratio, analyses with hard-to-compute information)
- **Fast: reduces computational burden**
 - especially during clinical trial simulations

Marion*, Lorenzi*, Allen-Savietta*, Viele, & Berry. **Predictive Probabilities Made Simple: A Fast and Accurate Method for Clinical Trial Decision Making**
under review, available on arXiv

[GitHub.com/BerryConsultants/approximatePredictiveProbability](https://github.com/BerryConsultants/approximatePredictiveProbability)
easy-to-use R functions