

# Predictive & Pre-Posterior Distributions in Drug Development & Their Properties


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*Pharmaceutical Statistics*

WILEY

## Pre-Posterior Distributions in Drug Development and Their Properties

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### ABSTRACT

The topic of this article is pre-posterior distributions of success or failure. These distributions, determined before a study is run and based on all our assumptions, are what we should believe about the treatment effect if we are told only that the study has been successful, or unsuccessful. I show how the pre-posterior distributions of success and failure can be used during the planning phase of a study to investigate whether the study is able to discriminate between effective and ineffective treatments. I show how these distributions are linked to the probability of success (PoS), or failure, and how they can be determined from simulations if standard asymptotic normality assumptions are inappropriate. I show the link to the concept of the conditional PoS introduced by Temple and Robertson in the context of the planning of multiple studies. Finally, I show that they can also be constructed regardless of whether the analysis of the study is frequentist or fully Bayesian.

## Principal Example: Development of a Drug for Alzheimer's Disease.

Tang Q. Bayesian Probability of Success for Go/No-Go Decision Making  
in M. Lakshminarayanan and F. Natanegara (Eds.) Bayesian Applications in  
Pharmaceutical Development. Baton Rouge: CRC Press, 2020, 247-266

Planning a Phase 2b study concentrating for our purposes on a 3 mg arm.

Primary Endpoint: CFB Week 12 ADAS-Cog Sub-scale Total Score

Targeted effect size:  $-1.38$ ; standard deviation:  $\sigma = 5.12$ .

Phase 2b study was planned to have  $n_1 = 150$  patients per arm, power of  $\sim 75\%$  per arm, success criterion was based on a one-sided  $\alpha = 0.05$ .

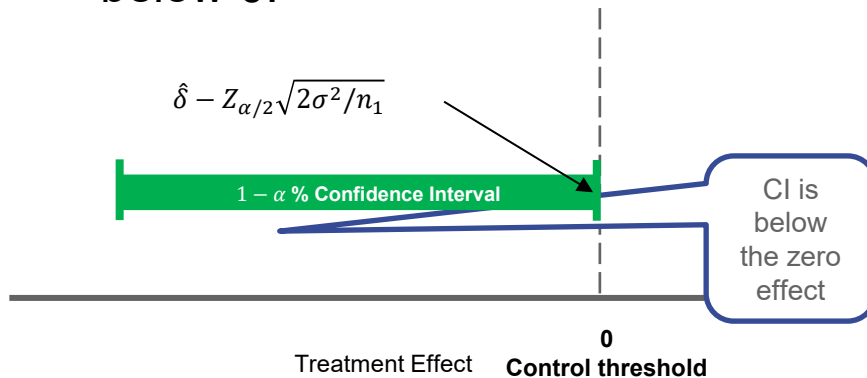
# Decision Criteria: Study with a Single Dose, Single Decision Rule

## Traditional Approach

Success if statistically significant at  $\alpha/2$  % level

Equivalently

If the  $1 - \alpha$  % confidence interval is below 0.



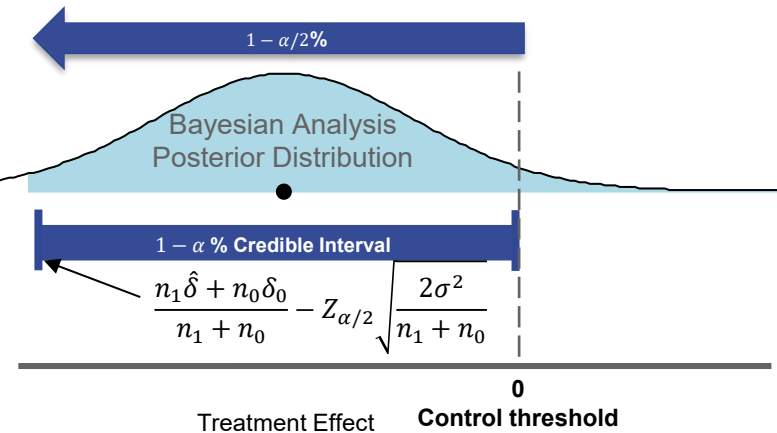
$$DC : \hat{\delta} < Z_{\alpha/2} \sqrt{2\sigma} / \sqrt{n_1}$$

## Bayesian Approach

Success if  $> 1 - \alpha/2$  % posterior probability that true treatment effect  $< 0$

Equivalently

If the  $1 - \alpha$  % credible interval is below 0.

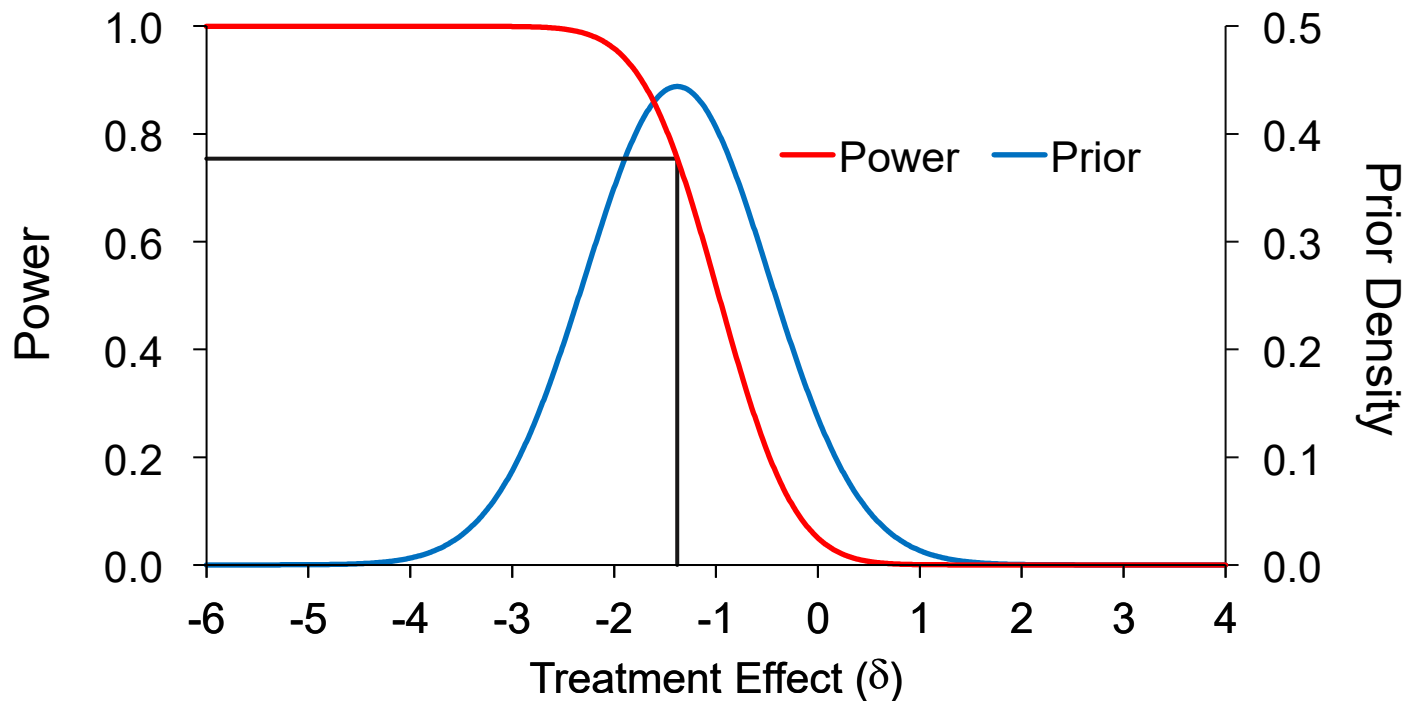


$$DC : \hat{\delta} < \frac{Z_{\alpha/2} \sqrt{2\sigma} \sqrt{n_1 + n_0}}{n_1} - \frac{n_0}{n_1} \delta_0$$

Prior -  $p(\delta) \sim N\left(\delta_0, \frac{\sigma_\delta^2}{n_0}\right), \sigma_\delta^2 = 2\sigma^2$

## Example: Power and Probability of Success (*PoS*)

- From Phase 2a data I constructed a prior distribution for the treatment effect in the 3 mg arm of a future Phase 2b study (Tang, Table 11.3)
- Prior mean =  $-1.38$ , prior variance  $0.807$  based on  $n_0 = 65$  patients/arm



- $PoS$  = expectation of the power function wrt the prior distribution  
$$= \int_{\delta} (1 - \beta(\delta)) p(\delta) d\delta$$

## Alternative Approach to Determine $PoS$

- In the calculation of  $PoS$  change the order of integration

$$\int_{\delta} \left( \int_{DC}^{\infty} p(\hat{\delta}|\delta) d\hat{\delta} \right) p(\delta) d\delta = \int_{DC}^{\infty} \left( \int_{\delta} p(\hat{\delta}|\delta) p(\delta) d\delta \right) d\hat{\delta} = \int_{DC}^{\infty} p(\hat{\delta}) d\hat{\delta}$$

power (conditional  $PoS$ )

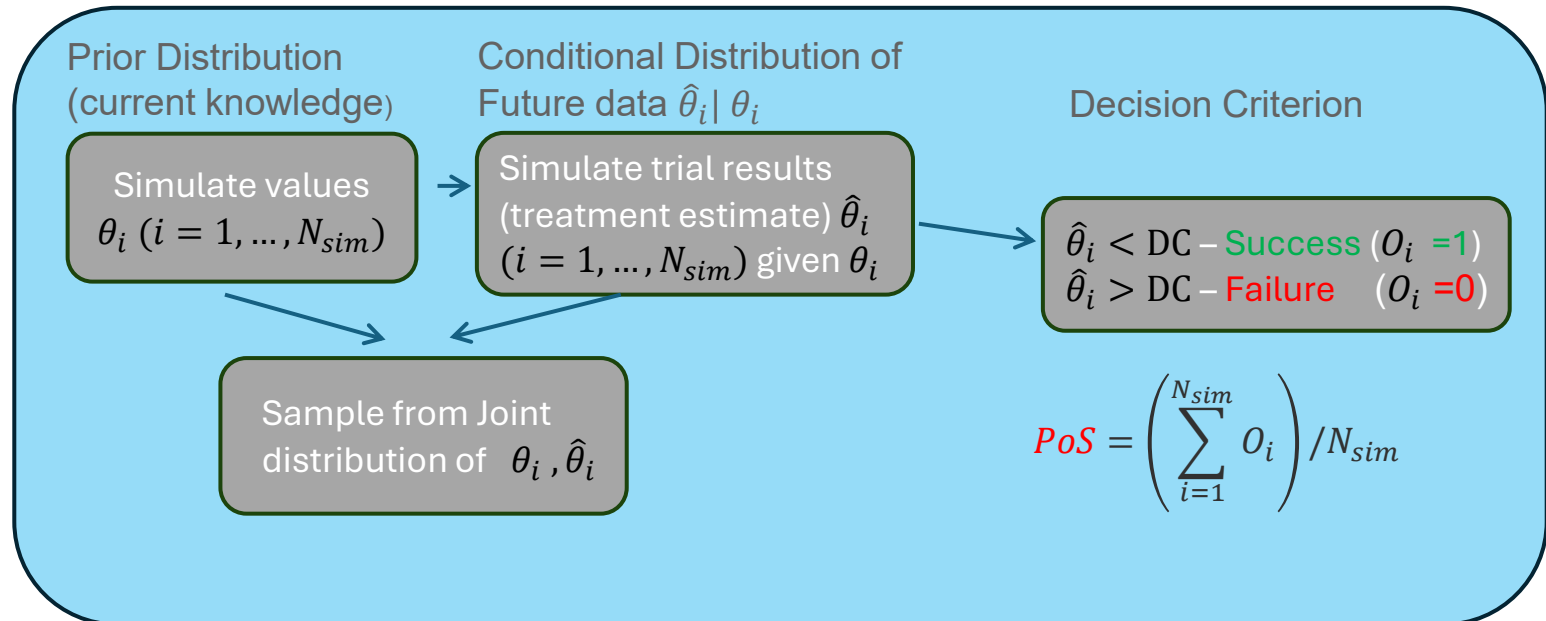
unconditional, or marginal,  
predictive distribution

- For a normal prior and normal likelihood :  $p(\hat{\delta}) = N\left(\delta_0, \sigma_{\delta}^2 \left(\frac{1}{n_0} + \frac{1}{n_1}\right)\right)$

$$DC : \hat{\delta} < Z_{\alpha/2} \sqrt{2}\sigma / \sqrt{n_1} \Rightarrow Pos = \Phi\left(\sqrt{\frac{n_0}{n_1+n_0}} \left(Z_{\alpha} - \frac{\sqrt{n_1}\delta_0}{\sigma_{\delta}}\right)\right) = 0.6477$$

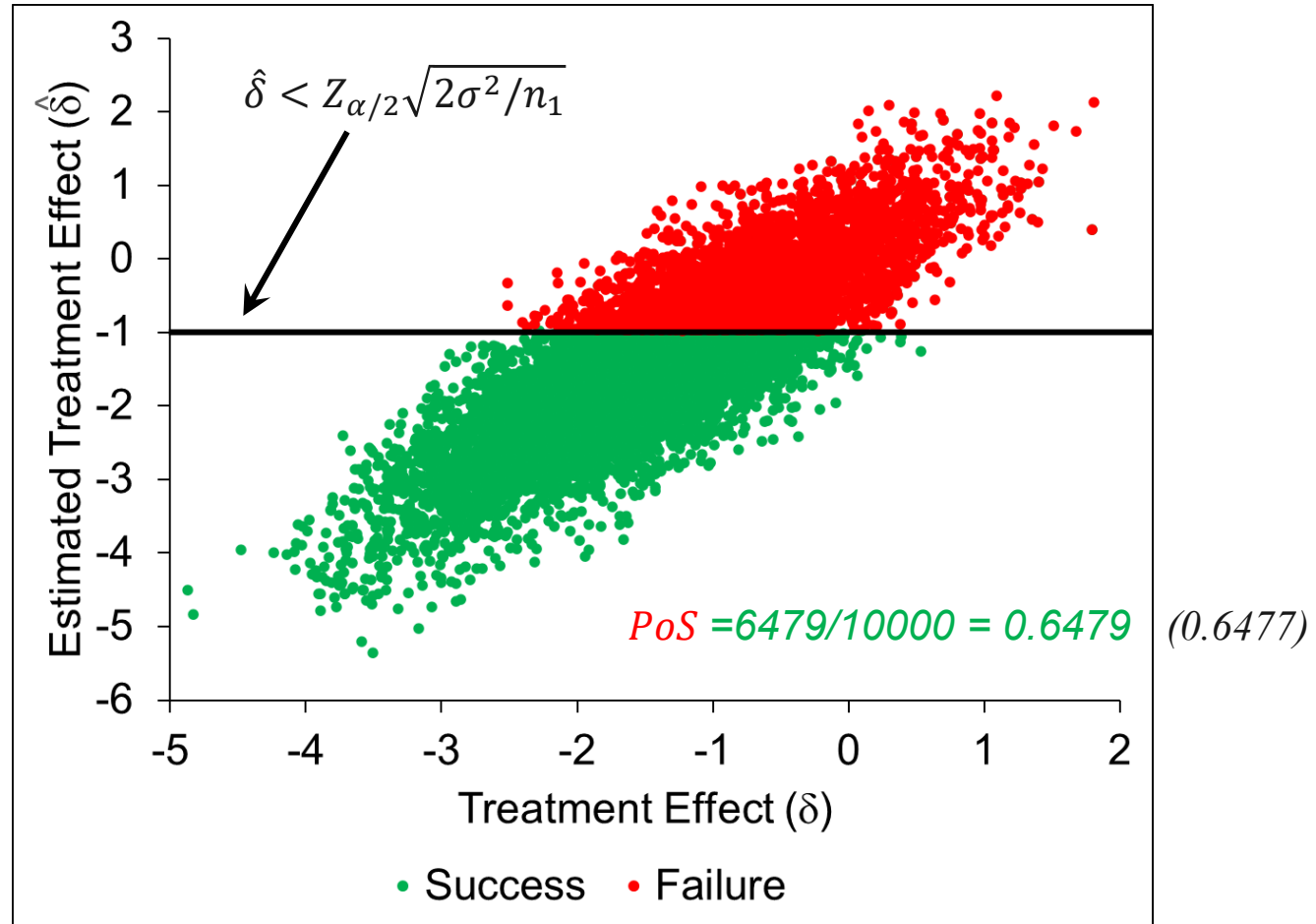
- As  $n_1 \rightarrow \infty, Pos \rightarrow \Phi\left(-\frac{\sqrt{n_0}\delta_0}{\sigma_{\delta}}\right)$  which is the prior probability of success.

# General Structure of Simulation to Determine: a) Probability of Success ( $PoS$ )



Stephen Senn – "Much simulation is just multiple integration"

# Determination of the *PoS* by Simulation (x10000)



## PoS Extension – Pre-Posterior Distributions

- | Walley et al (Pharmaceutical Statistics, 2015) questioned the value of *PoS* in assessing the ability of a design to address its objectives.
- | Their alternative was to propose the “pre-posterior distribution” of  $\delta$  given the study is a **success** (significant)
- | The “pre-posterior distribution can be considered as what one would believe at the end of the study, if only told, the study was successful; any further information on the size of the treatment effect, other than the prior, being withheld.”
- | Correspondingly, if the study is a **failure** (non-significant) we will be interested in the “pre-posterior distribution” of  $\delta$  given the study is a **failure** (non-significant).
- | These can be thought of as a pair of standardised distributions

# Pre-Posterior Success and Failure Distributions (*PPS* & *PPF*)

| The Pre-Posterior Success (*PPS*) Distribution

$$p(\delta|\text{Significant}) = \frac{\text{Power}(\delta) \text{ Prior}(\delta)}{\text{Pr}(\text{Significant})}$$

*PoS (standardisation)*

| Similarly, the Pre-Posterior Failure (*PPF*) distribution

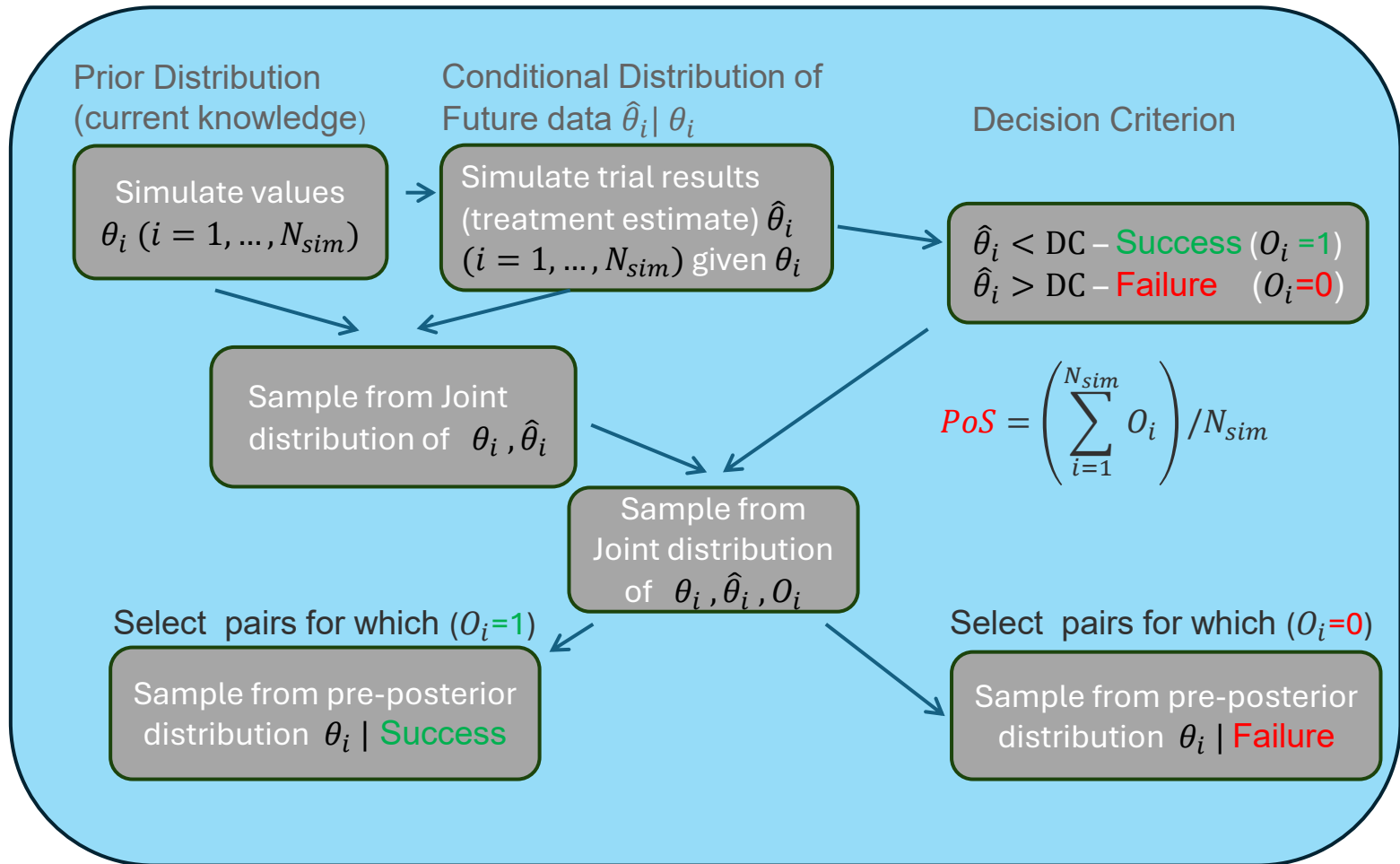
$$p(\delta|\text{Non - significant}) = \frac{1 - \text{Power}(\delta) \text{ Prior}(\delta)}{\text{Pr}(\text{Non - significant})}$$

*1 - PoS (standardisation)*

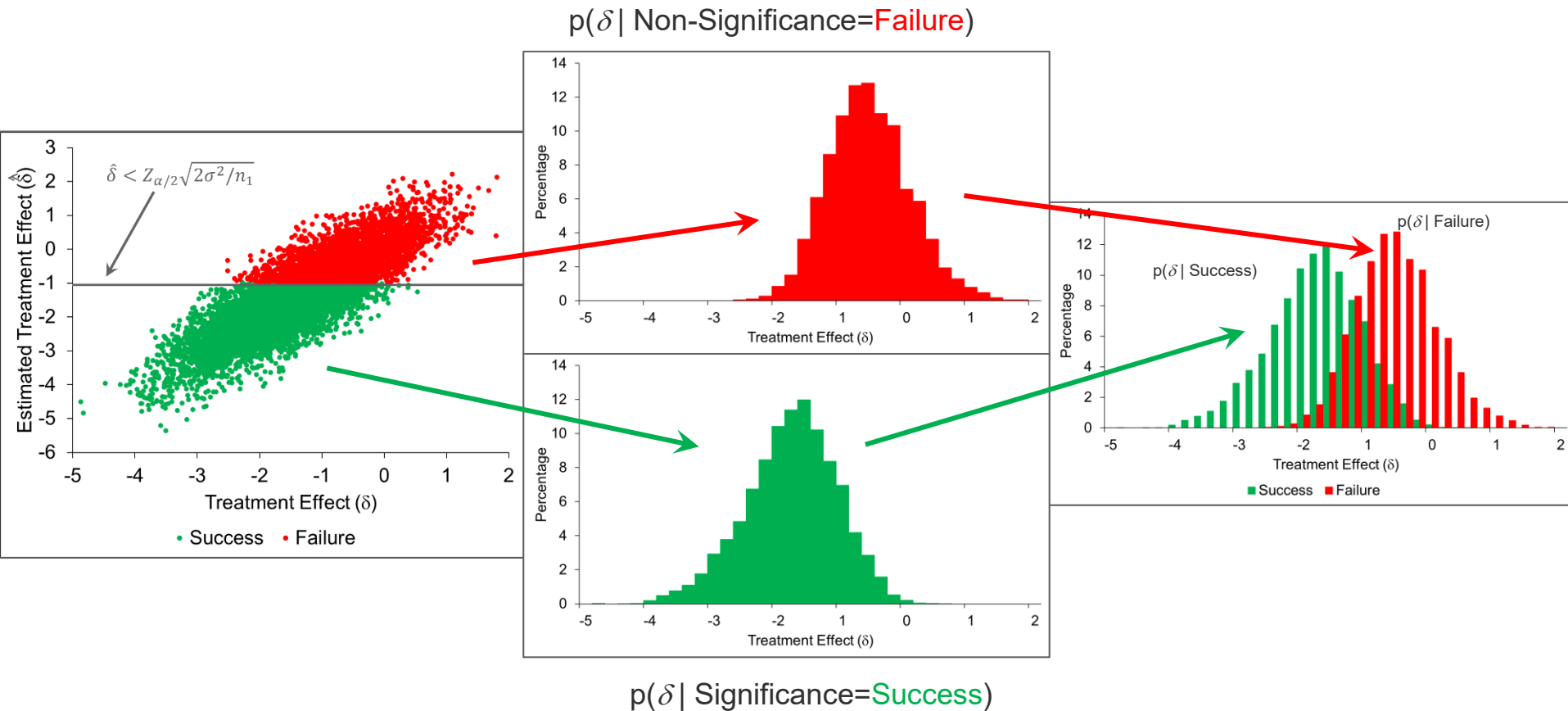
| Wiklund & Burman (Pharm Stats, 2021) call *PPS* “the efficacy density given progression” and they use the unstandardised form -  $\text{Power}(\delta) \times \text{Prior}(\delta)$  - which is a “sub-probability distribution”

# General Structure of Simulation to Determine:

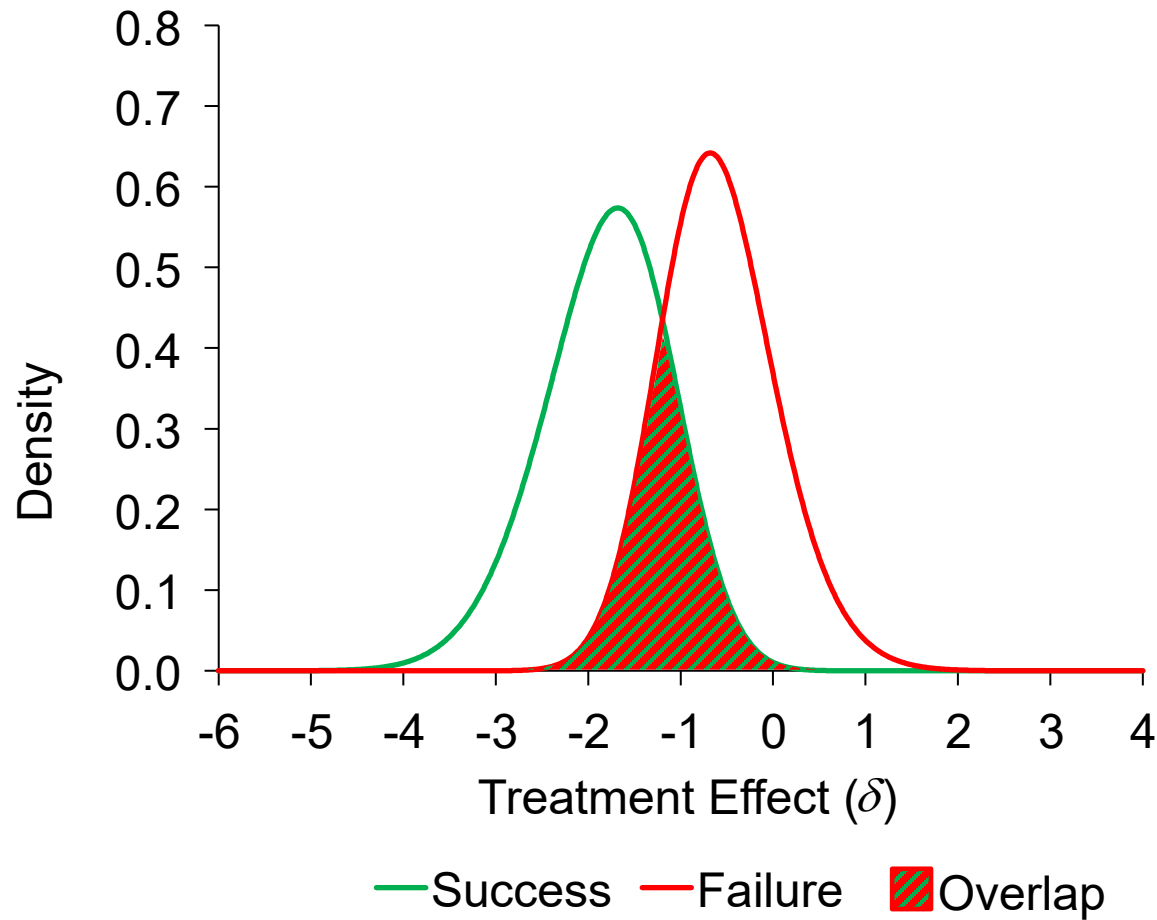
- a) Probability of Success (PoS)
- b) Pre-Posterior Distributions



# Generating Samples (x10000) from the Pre-Posterior Success and Failure Distributions ( $n_1 = 150$ )

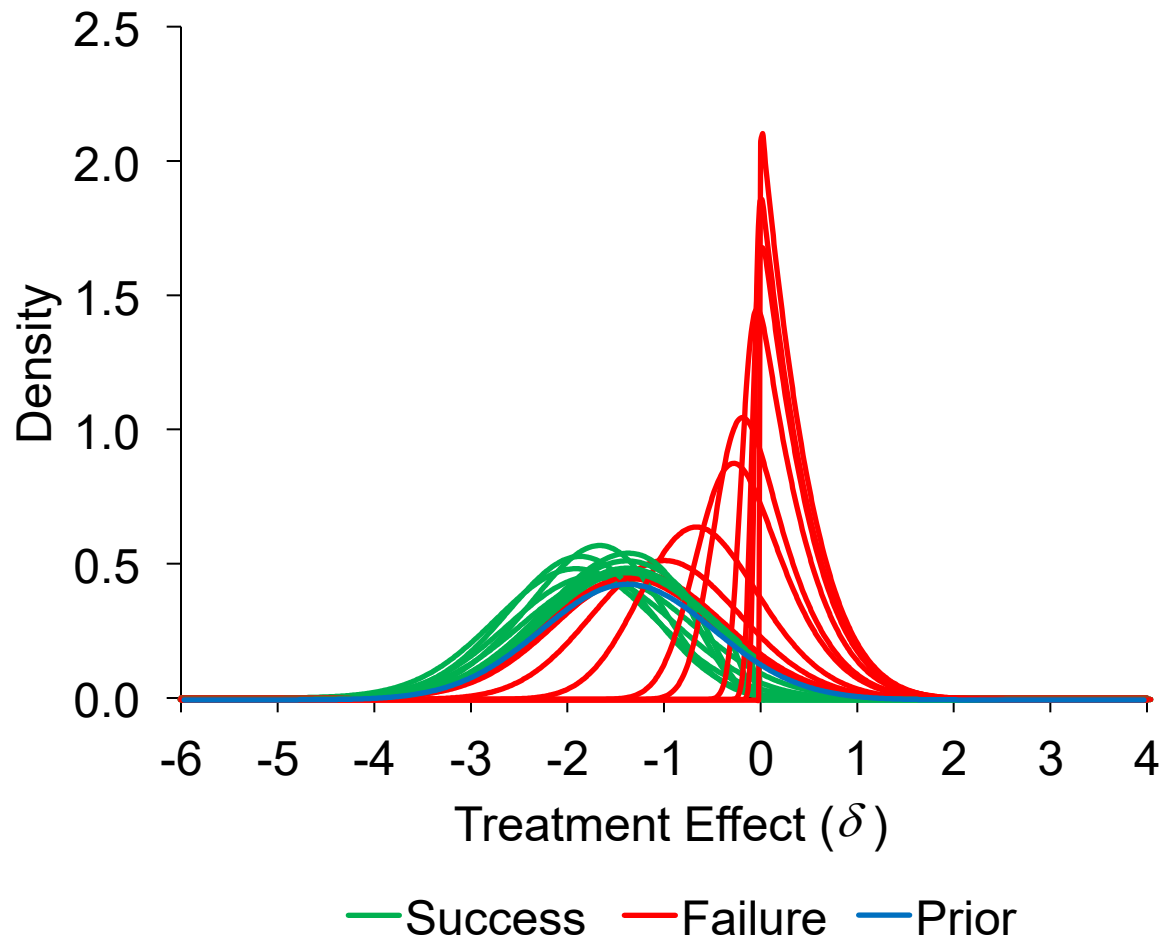


# Principal Example: Pre-Posterior Distributions – Analytical ( $n_1 = 150$ )

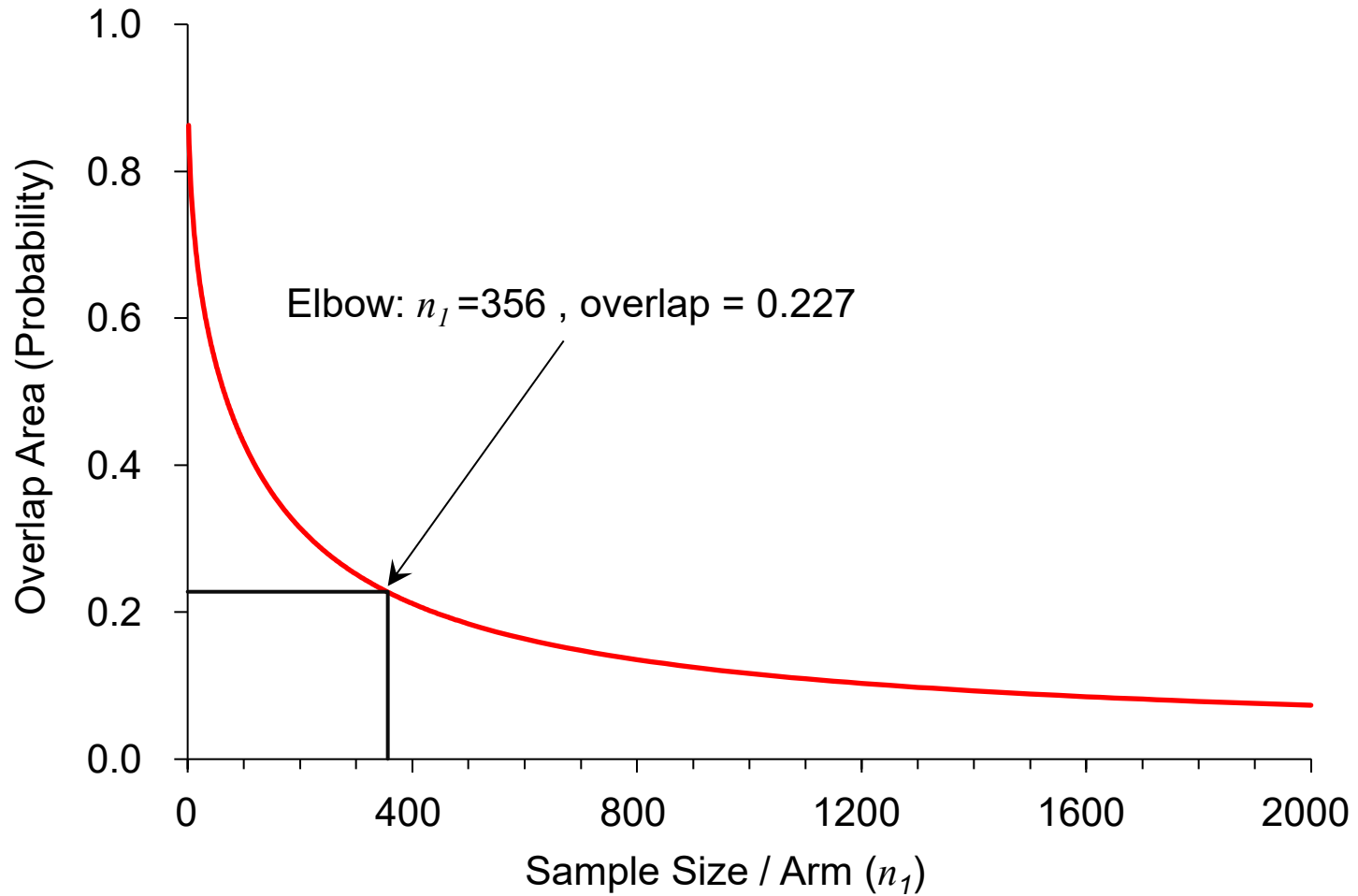


# Principal Example: Pre-Posterior Distributions vs Sample Size / Arm

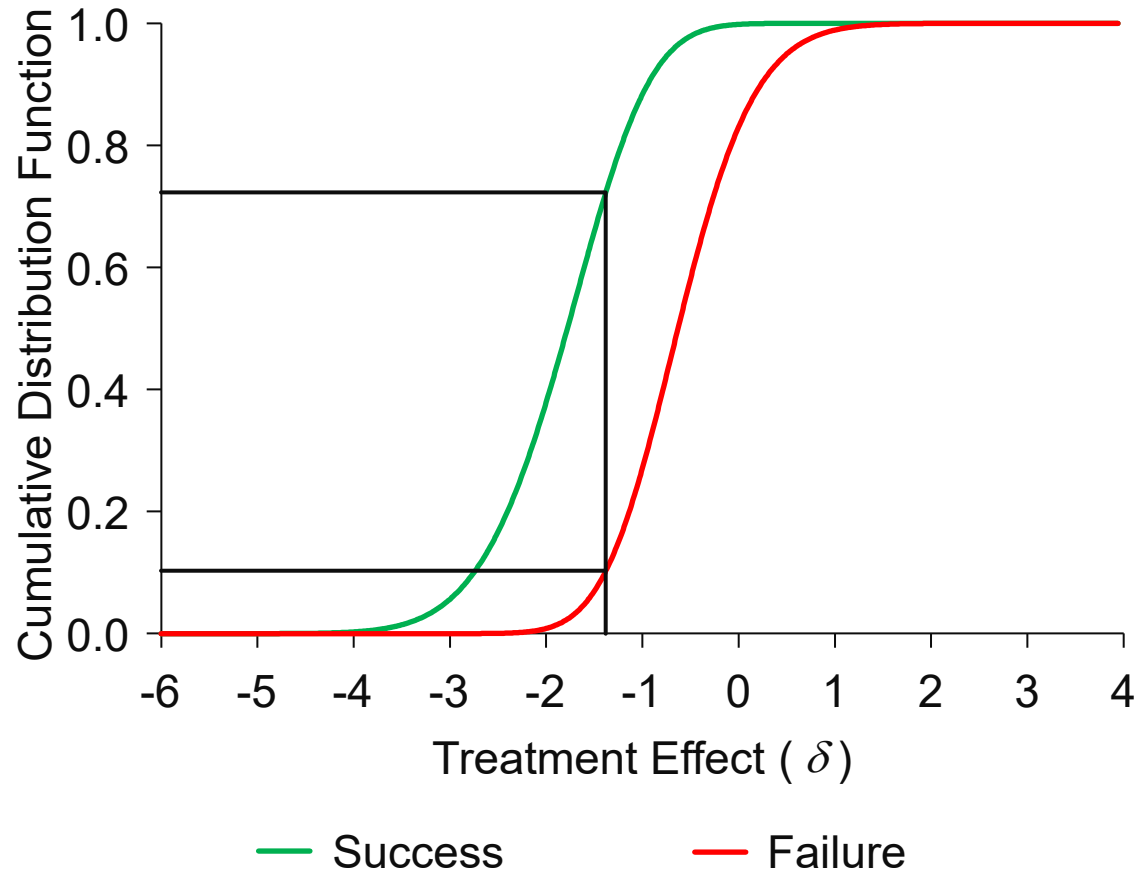
Sample Size/arm: ~~50000~~



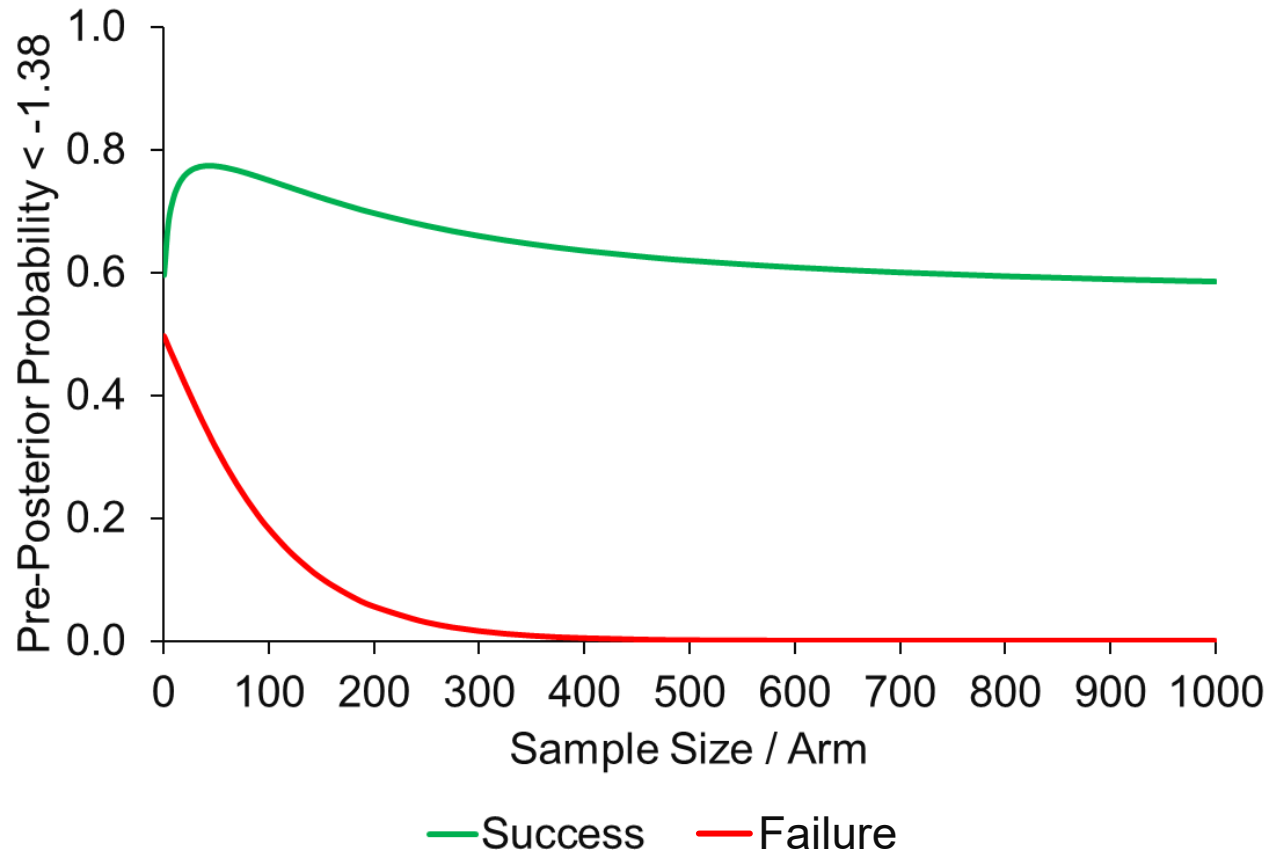
# Principal Example: Overlap vs Sample Size / Arm



# Principal Example: Pre-Posterior CDFs ( $n_1 = 150$ )



# Principal Example: Pre-Posterior Probabilities $\delta < -1.38$ vs Sample Size / Arm



## Pre-Posterior Distributions and Conditional *PoS*

- | Suppose we have two studies (indexed by 1 and 2)
- | Then the *PPS* of study 1 is:  $PPS_1 = \frac{(1 - \beta_1(\delta))p(\delta)}{PoS_1}$
- | If we use  $PPS_1$  as the prior for Study 2, then its  $PoS_2$  is

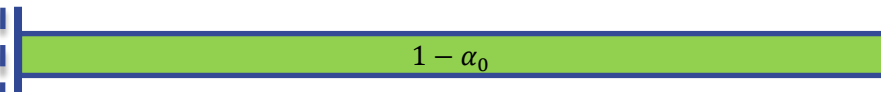
$$\begin{aligned}
 PoS_2 &= \int_{\delta} (1 - \beta_2(\delta)) \frac{(1 - \beta_1(\delta))p(\delta)}{PoS_1} d\delta & (*) \\
 &= \frac{1}{PoS_1} \left[ \int_{DC_1}^{\infty} \int_{DC_2}^{\infty} \left( \int_{\delta} p(\hat{\delta}_2|\delta) p(\hat{\delta}_1|\delta) p(\delta) d\delta \right) d\hat{\delta}_2 d\hat{\delta}_1 \right]
 \end{aligned}$$

(Joint Marginal Predictive Distribution of  $\hat{\delta}_2$  &  $\hat{\delta}_1$ )

- | Consequently, the triple integral [...] is the joint *PoS* of Studies 1 & 2.
- | So (\*) is the conditional *PoS* of Study 2 | Success of Study 1.  
(Temple & Robertson, Pharmaceutical Statistics, 2021; Grieve, 2022).

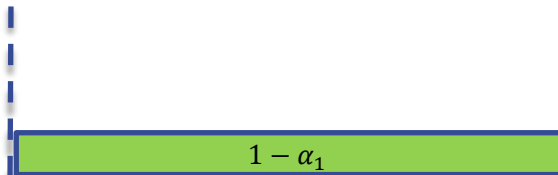
# Dual Decision Criteria

Criterion 1:  $1 - \alpha_0$  % confidence that treatment effect is above  $\delta_{LRV}$



$$\hat{\delta} > \delta_{LRV} - Z_{1-\alpha_0} \sqrt{\frac{2}{n_1}} = CRIT_1$$

Criterion 2:  $1 - \alpha_1$  % certainty that treatment effect is above  $\delta_{TV}$



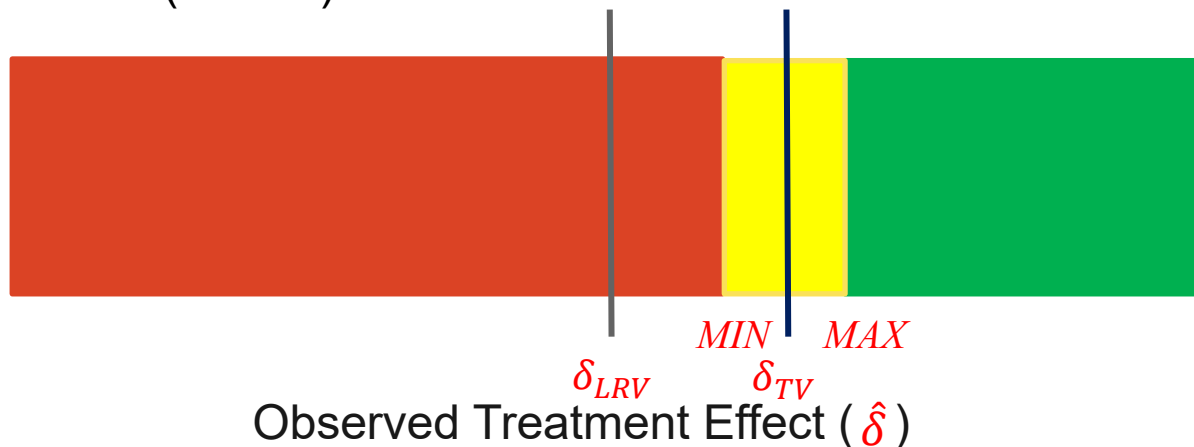
$$\hat{\delta} > \delta_{TV} - Z_{1-\alpha_1} \sqrt{\frac{2}{n_1}} = CRIT_2$$



# Decision Table

		RELEVANCE (Criterion 2)	
		Yes	No
MINIMUM REQUIREMENT (Criterion 1)	Yes	(A): <i>GO</i>	(B): <i>PAUSE</i>
	No	(C): <i>PAUSE</i>	(D): <i>NO GO</i>

- | Both criteria are met (*GO*) if  $\hat{\delta} > \max(CRIT_1, CRIT_2) = MAX$
- | Neither are met (*NO GO*) if  $\hat{\delta} < \min(CRIT_1, CRIT_2) = MIN$
- | Only one criterion (*PAUSE*) is met if  $MIN < \hat{\delta} < MAX$

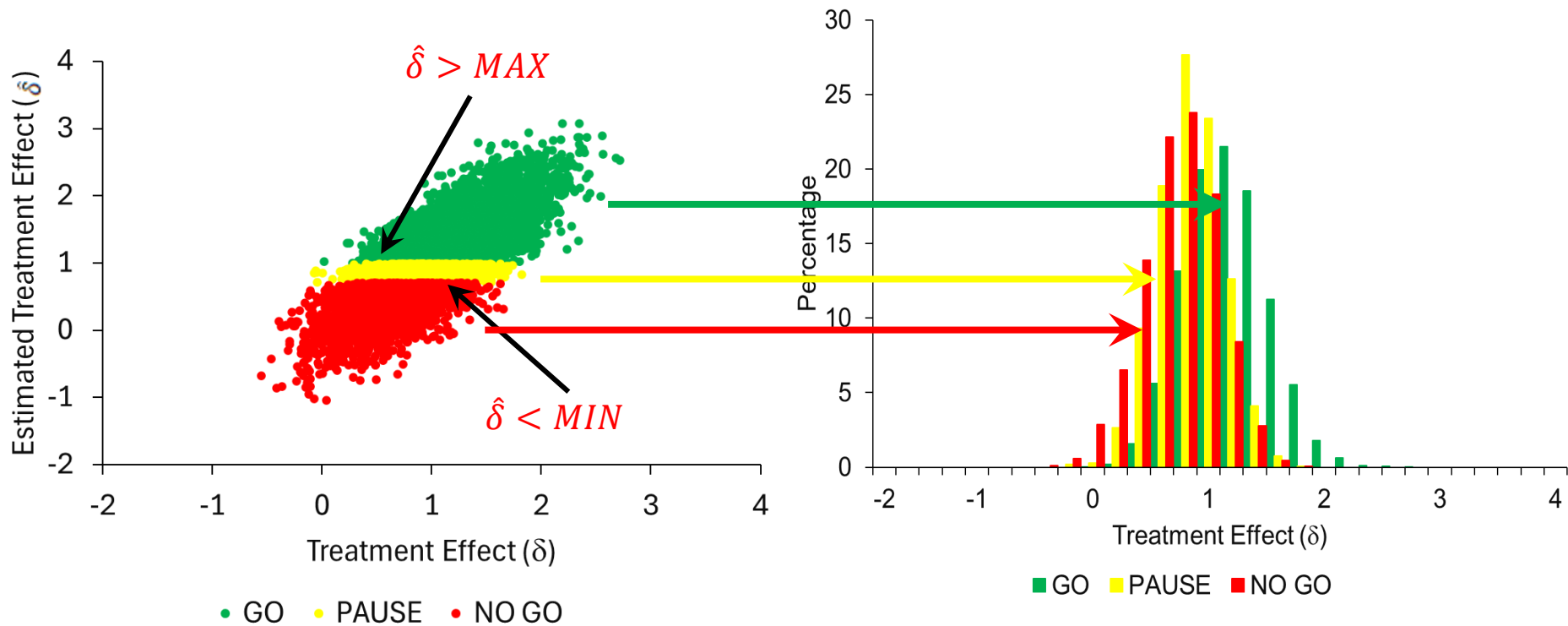


# Dual Criteria Pre-Posterior Distributions – Anonymised Example

|  $\alpha_0 = 0.025, \delta_{LRV} = 0.0, \alpha_1 = 0.3, \delta_{LRV} = 0.8 \alpha_0 = 0.025$

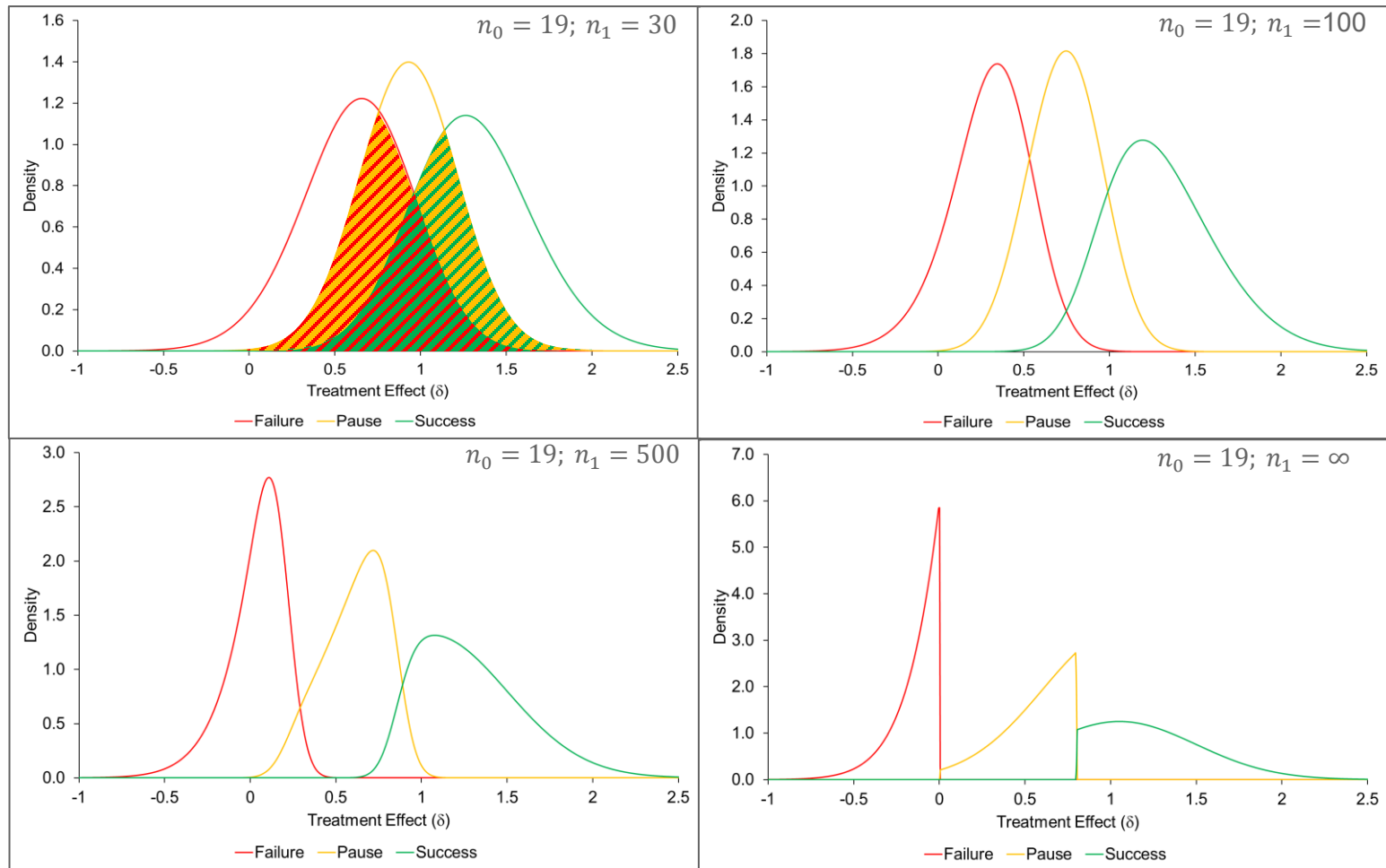
|  $\sigma = 1.37, n_0 = 19, \delta_0 = 1.05, n_1 = 29$

|  $MIN = 0.707, MAX = 0.989$



# Anonymised Example (Continued)

## Pre-Posterior Distributions vs Sample Size / Arm ( $n_1$ ) - Analytical



# Anonymised Example (Continued)

## Overlap Probabilities vs Sample Size / Arm ( $n_1$ )

