Phase 2B Design Considerations Assessing Dose response modeling

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Power: The probability that a statistically significant outcome results for a given effect size

Type I error rate: The power when there is no effect

<u>Factors that impact the power</u>

1. Effect size: Larger effects easier to detect
2. Sample size: More data increases power
3. Variability of data: High variability (noisy data) decreases power

Some Mathematical Facts of Life

Less power

Non-parametric (Rank based tests)

Separate variance t-test

Pooled variance t-test

Common GSK pair-wise Dose Ranging study

Model based mean estimation

Bayesian model based estimates mean estimation

More power

Post-operative nausea and vomiting (PONV) often occurs following local, regional, or general anesthesia and is the most frequently reported patient complaint following anesthesia.

PONV is often of greater concern to patients than is the avoidance of post-operative pain .

In addition to anxiety and discomfort, PONV can lead to complications such as fluid and electrolyte imbalances, surgical wound dehiscence, aspiration of vomitus, and/or severe pulmonary morbidity that can lead to delayed discharge from the recovery area or unscheduled hospital admission.

Emesis rate for Ondansetron is between 45-55%.

It is expected that 140 subjects will be randomized to detect a 20% delta in Complete Response between one or more doses of Investigational Product compared to 4 mg Ondansetron.

Case 1: Comparison of success rate to a constant (0.5)

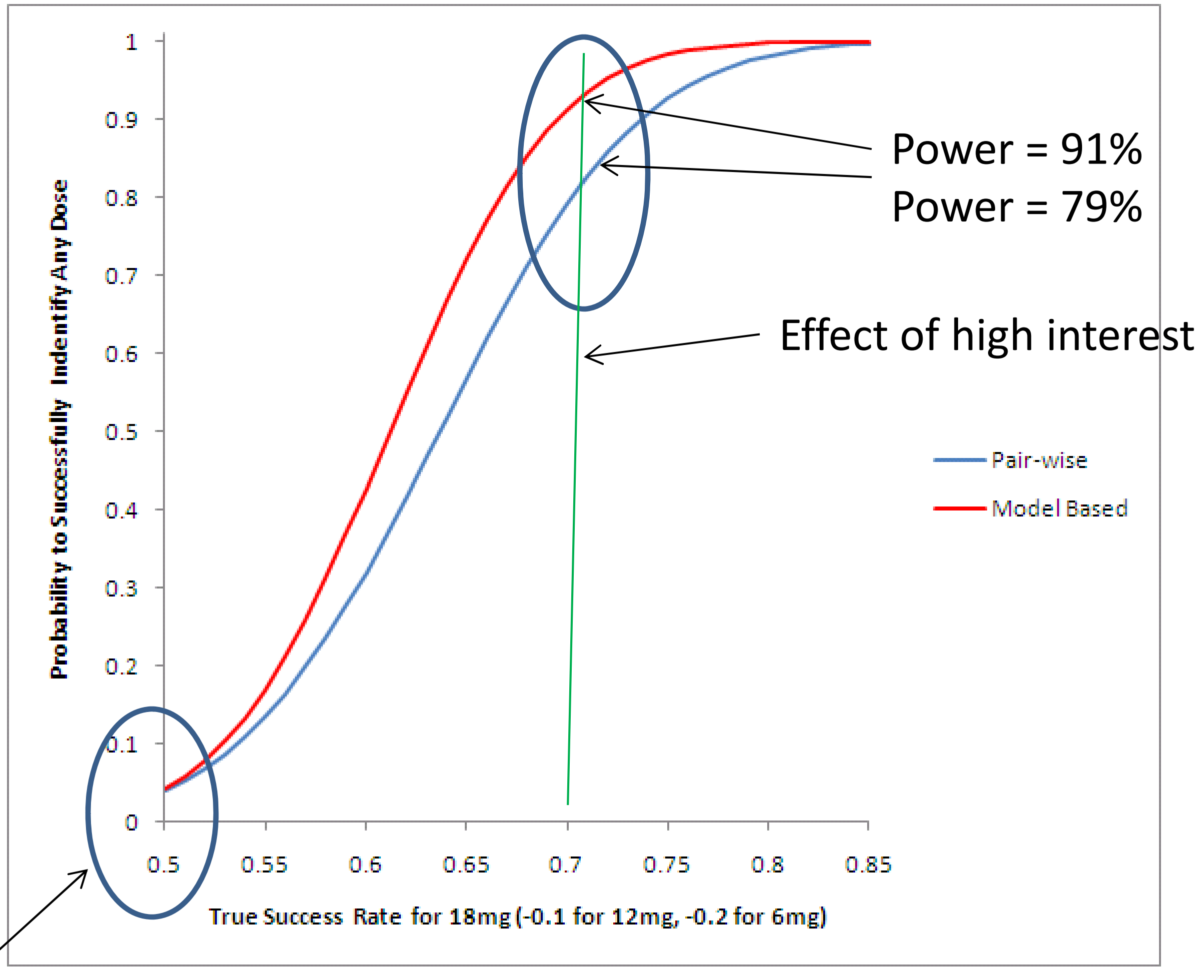
- a. Pair-wise
- b. Model based (logistic regression)

Case 2: Comparison of success rate to Ondansetron arm

- a. Pair-wise
- b. Model based (logistic regression)
- c. Bayesian model based (logistic regression)

H_0: p = 0.5; H_1: p > 0.5

Power (OC) Curve



35:35:35

0.05 type I error rate

Estimated precision of single dose arm

$$\text{var}(\hat{p}_d) \approx \frac{\hat{p}_d(1-\hat{p}_d)}{n_d}$$

Y_d = "d" mg dose result

Estimated model based precision of a dose arm

$$\hat{\pi}_d = \frac{1}{1+\exp(-b_0 - b_1 d)}$$

Y_1 = 6mg dose result

Y_2 = 12mg dose result

Y_3 = 18mg dose result

$$\text{var}(\hat{\pi}_d) \approx \begin{bmatrix} \frac{\partial \hat{\pi}_d}{\partial b_0} & \frac{\partial \hat{\pi}_d}{\partial b_1} \end{bmatrix} \text{var}\left(\begin{bmatrix} b_0 \\ b_1 \end{bmatrix}\right) \begin{bmatrix} \frac{\partial \hat{\pi}_d}{\partial b_0} \\ \frac{\partial \hat{\pi}_d}{\partial b_1} \end{bmatrix}$$

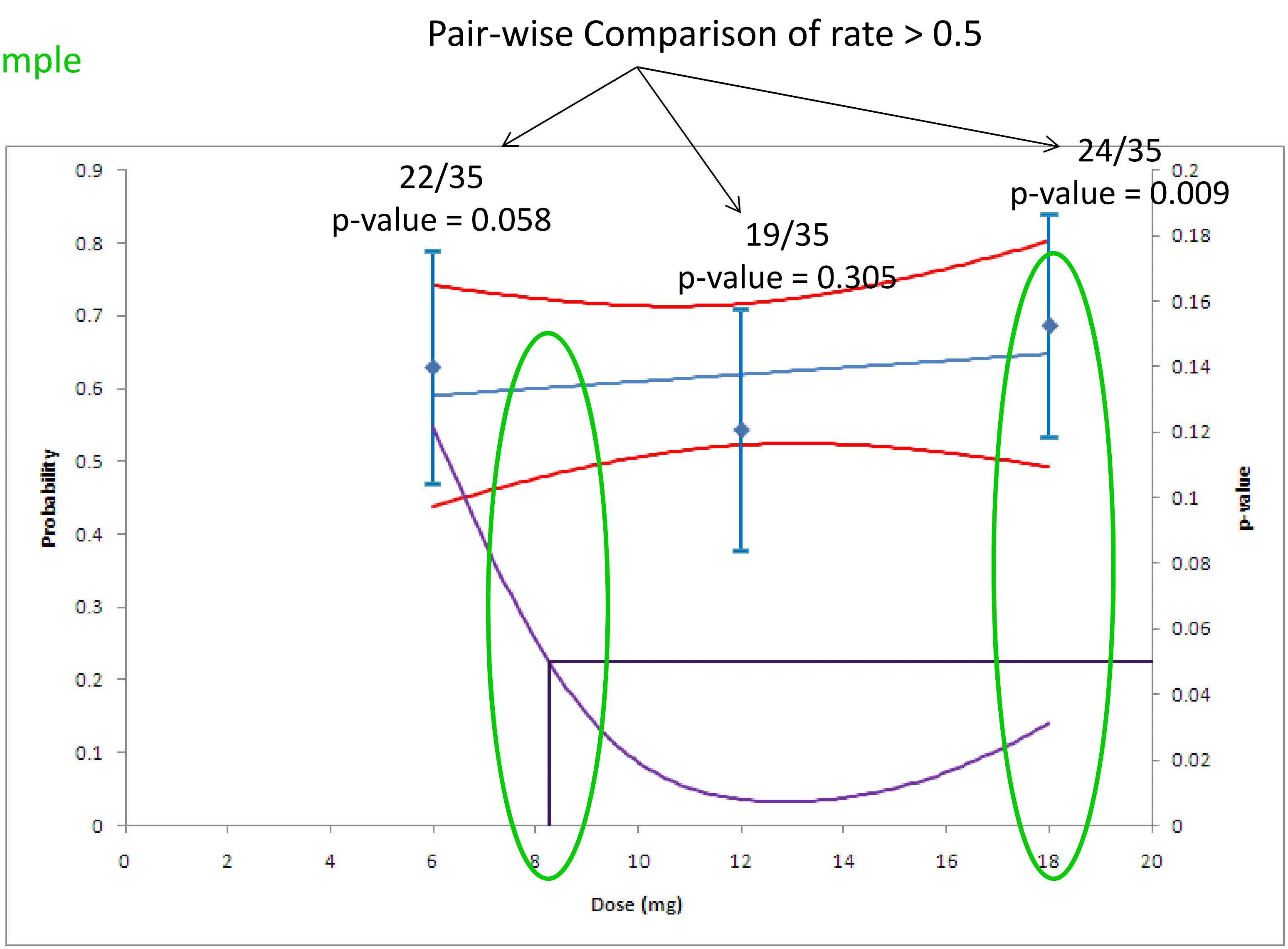
Bottom line

$$\text{var}(\hat{\pi}_d) < \text{var}(\hat{p}_d)$$

Translation

- Estimation from model based results link multiple doses.
- Information is shared between doses.
- Increased information decreases uncertainty (i.e. variability)
- Estimators with less variability result in more powerful comparisons

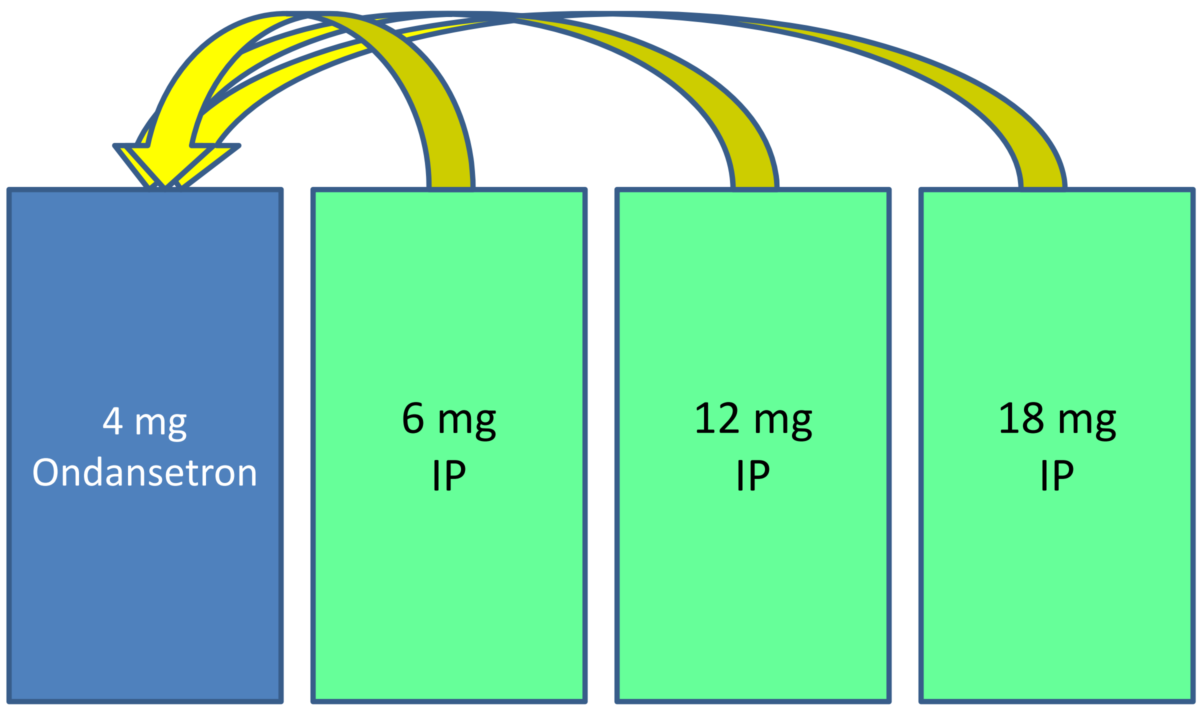
Example



18 mg = minimum efficacious dose by pair-wise comparisons

8.3 mg = minimum efficacious dose by model based comparisons

Pair-wise Comparisons (Step down post hoc comparison to control Type I error rate)



Note: Many approaches to control type I error rate due to multiple comparisons (Bonferonni, Dunnett, Step-down REGWQ)

Pair-wise comparisons

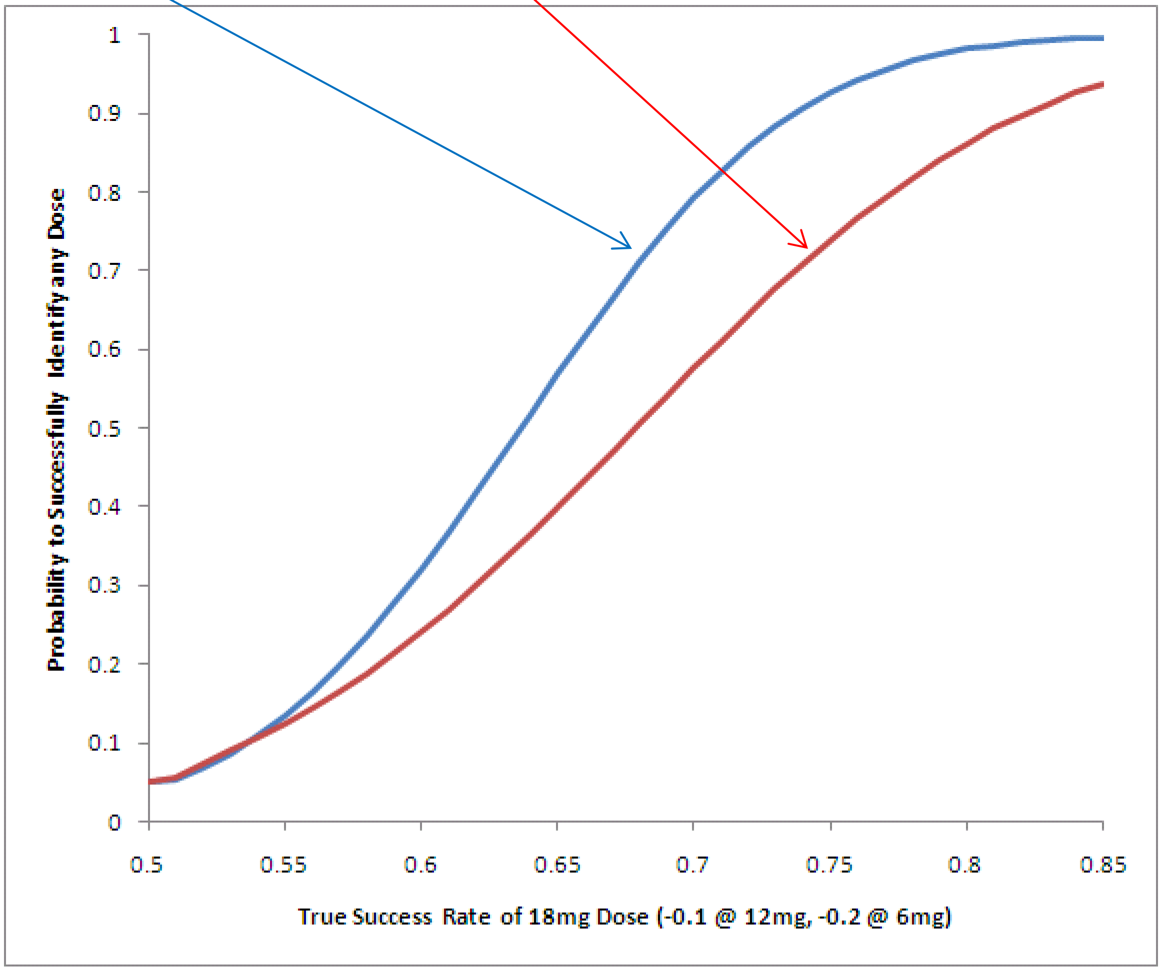
Comparison of IP to Ondansetron

H_0: $p_{Dose} = p_{Control}$; H_1: $p_{Dose} > p_{Control}$

Comparison of Investigational Product to 0.5

H_0: $p_{Dose} = 0.5$; H_1: $p_{Dose} > 0.5$

Big power difference since Ondanestron arm adds noise (variability) that a constant does not have



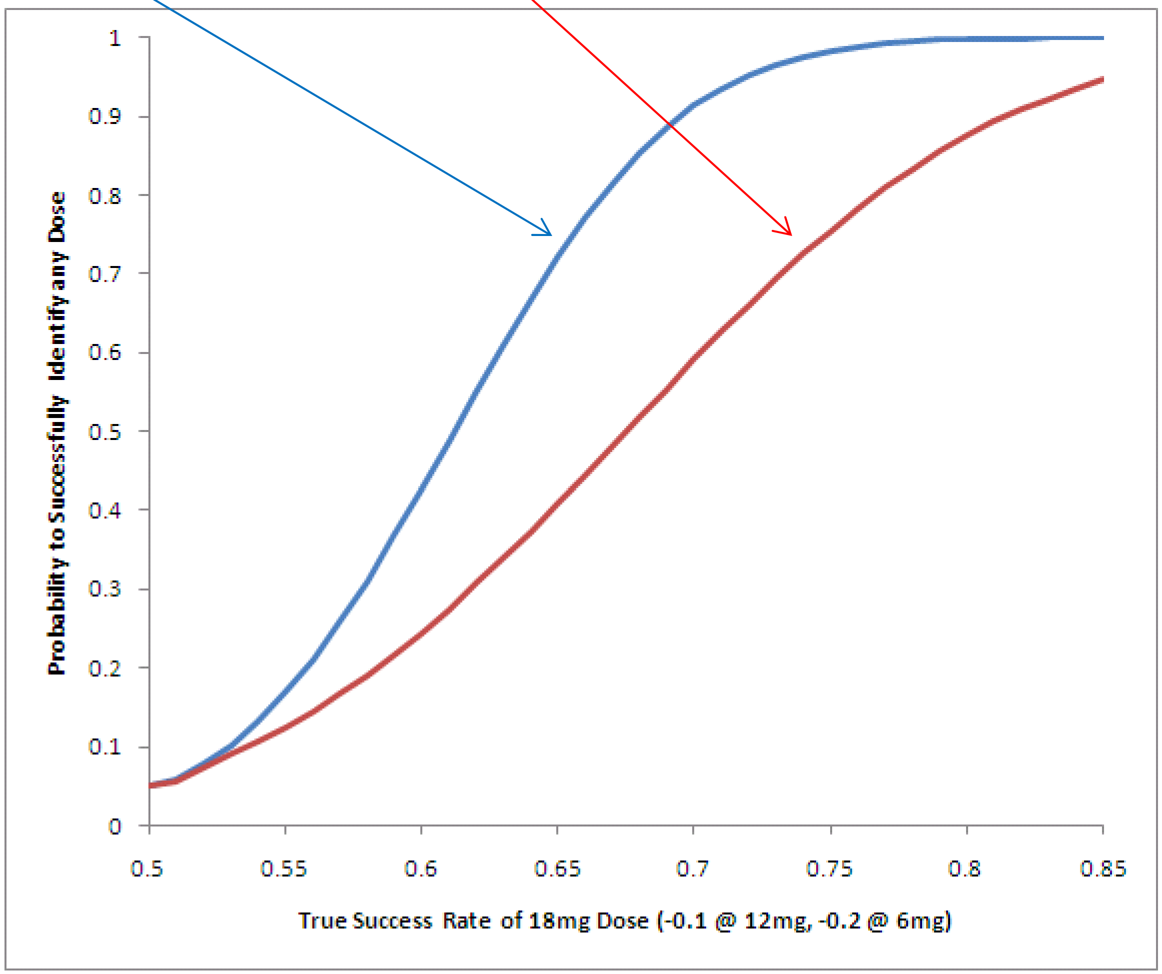
Model based comparisons

Comparison of IP to Ondansetron

H_0: $p_{Dose} = p_{Control}$; H_1: $p_{Dose} > p_{Control}$

Comparison of Investigational Product to 0.5

H_0: $p_{Dose} = 0.5$; H_1: $p_{Dose} > 0.5$



Big power difference since Ondanestron arm adds noise (variability) that a constant does not have

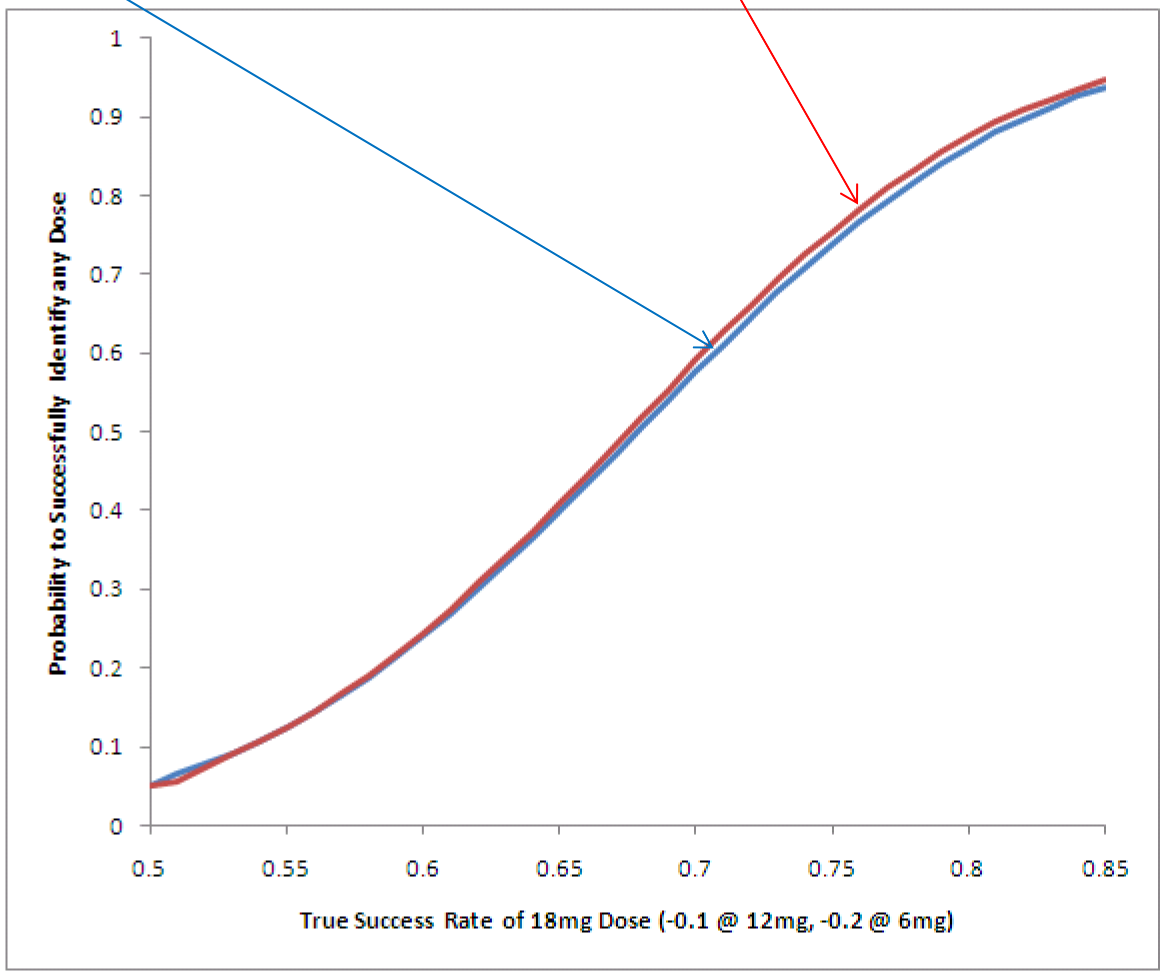
Model based comparison of IP to Ondansetron

H_0: $p_{Dose} = p_{Control}$; H_1: $p_{Dose} > p_{Control}$

Pair-wise comparison of IP to Ondansetron

H_0: $p_{Dose} = p_{Control}$; H_1: $p_{Dose} > p_{Control}$

Small power difference. Model based approach better estimates the IP means but the noise from the Ondanestron arm overwhelms the benefits!



Side Track: Bayesian Methodology

Provides a mathematical approach to incorporate knowledge/beliefs about population parameters to create better estimates

A review of the clinical literature supports "Emesis rate for Ondansetron is between 45-55%."

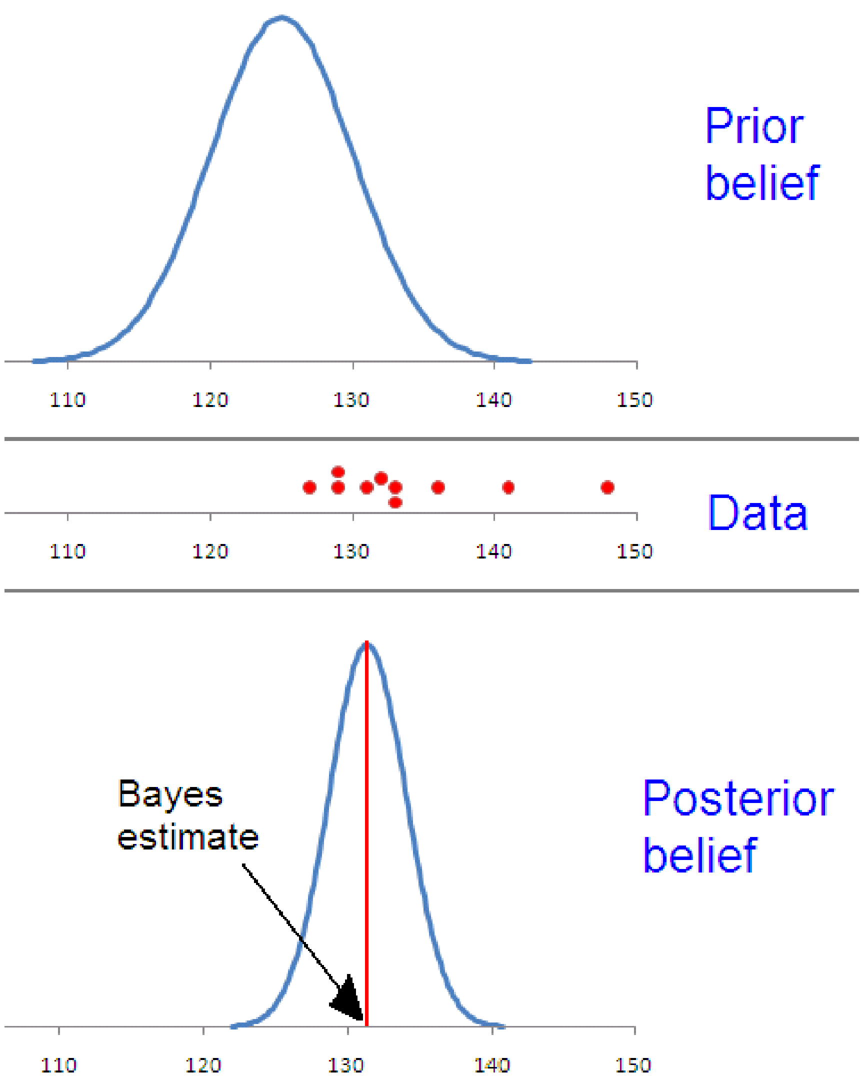
Statistician translates this to mean "$p_{Control}$ ~ Beta(125.6, 101.9)"
Allocation 20:40:40:40 (Ondansetron: 6mg IP : 12mg IP: 18mg IP)

Mathematically, Bayesian methods adds some bias to the estimate greatly reduce its variance

$$MSE(\tilde{p}, p) = \mathrm{var}(\tilde{p}) + bias^2(\tilde{p}, p)$$

How "good" an unbiased estimator (e.g. MLE) can be is limited by the Kramer-Rao lower bound. Biased estimators can do better than this lower bound.

Bayesian Modeling



Prior knowledge/beliefs

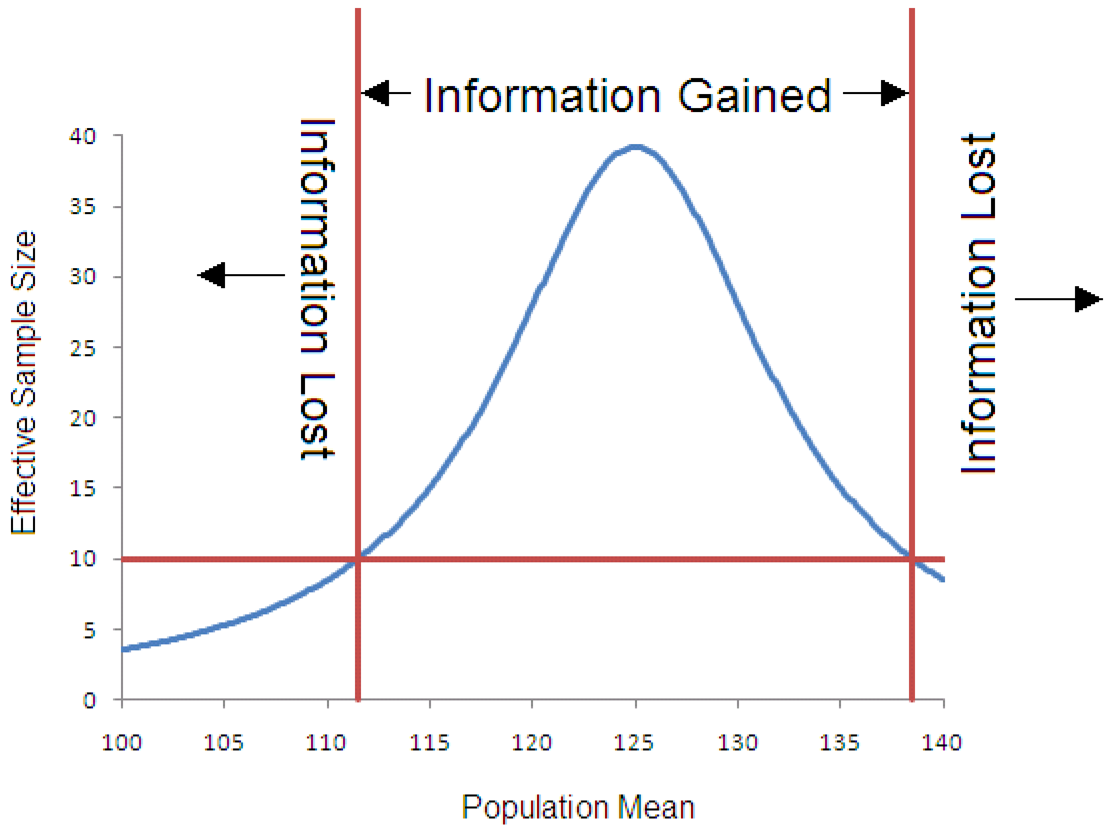
+

Data

↓

Updated knowledge/beliefs

Properties of Bayes Estimates

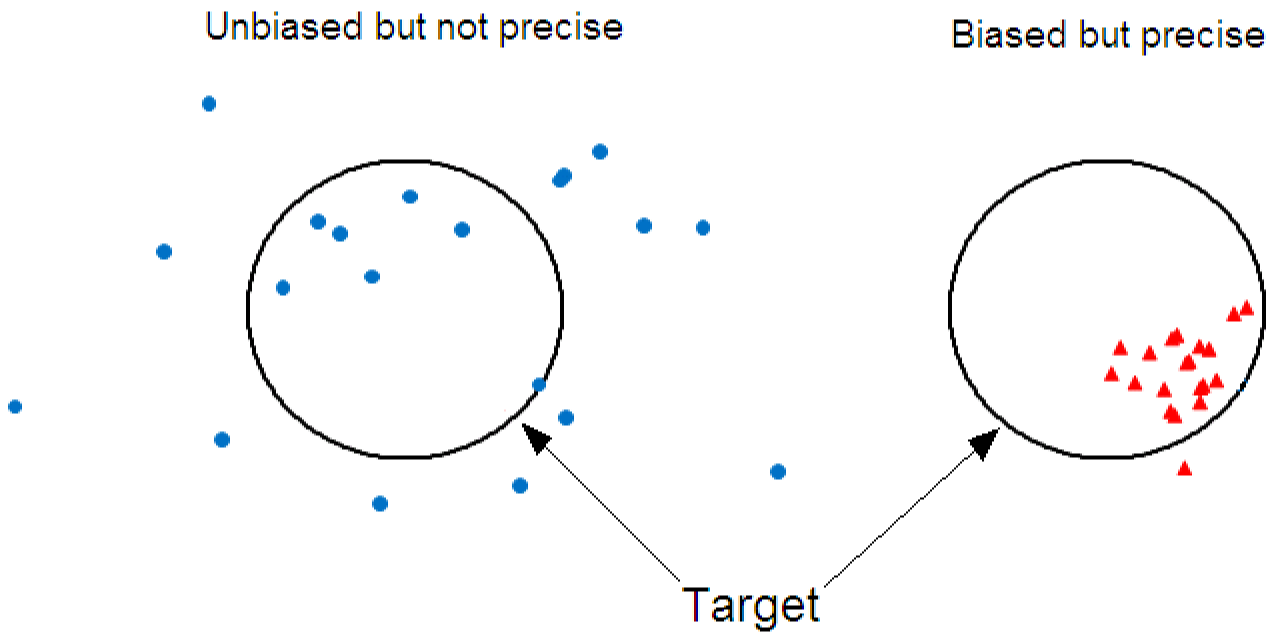


Impact of Info-Gain

- More reliable estimates
- More powerful comparisons
- Potentially smaller studies

"A good Bayesian will always do better than a non-Bayesian, but a bad Bayesian will get clobbered." –Herman Rubin

How is information gained?



Prior information adds Bias but reduces Variance of estimates.

Mean Squared Error = Variance + Bias^2

Goal: To make use of what is known to create better estimates

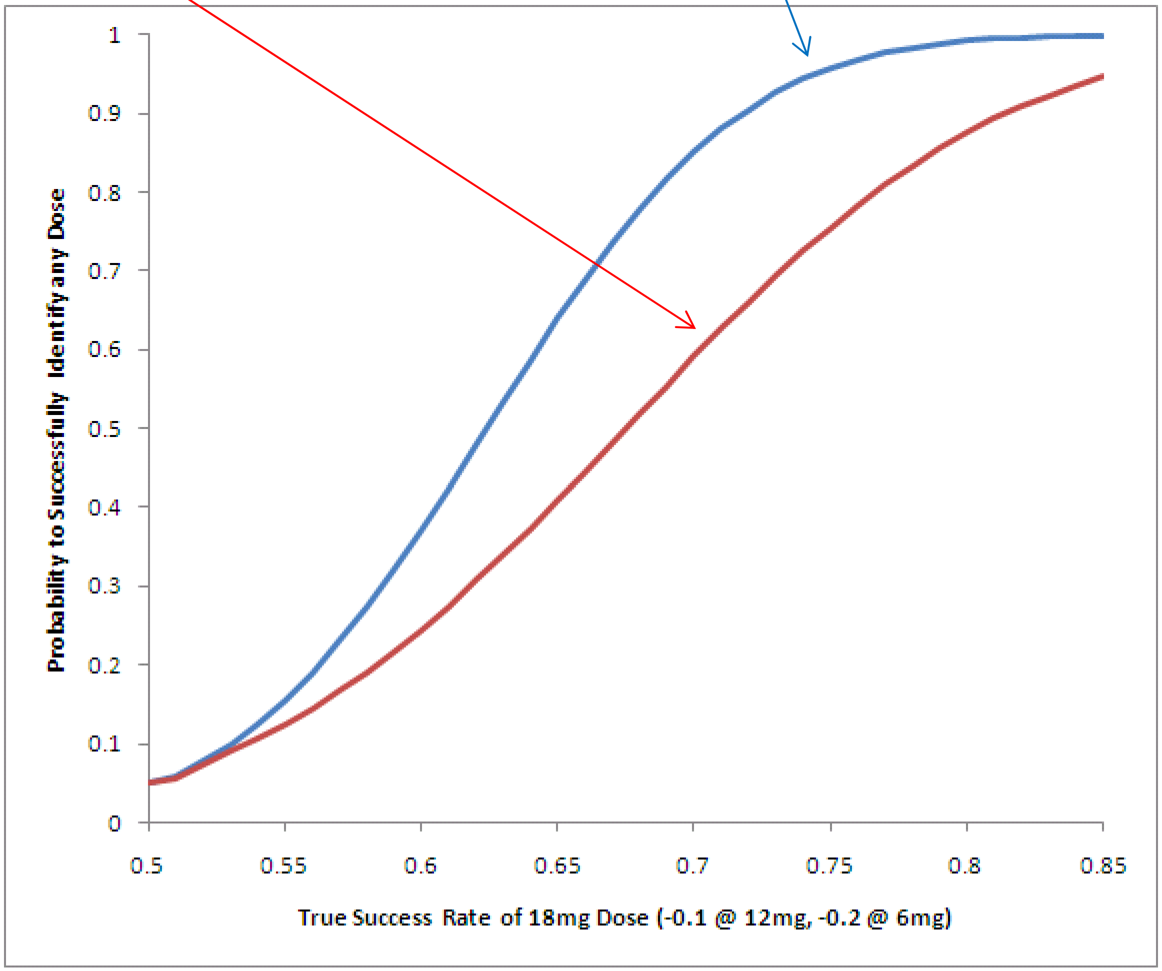
Bayesian model based comparison of IP to Ondansetron

H_0: $p_{Dose} = p_{Control}$; H_1: $p_{Dose} > p_{Control}$

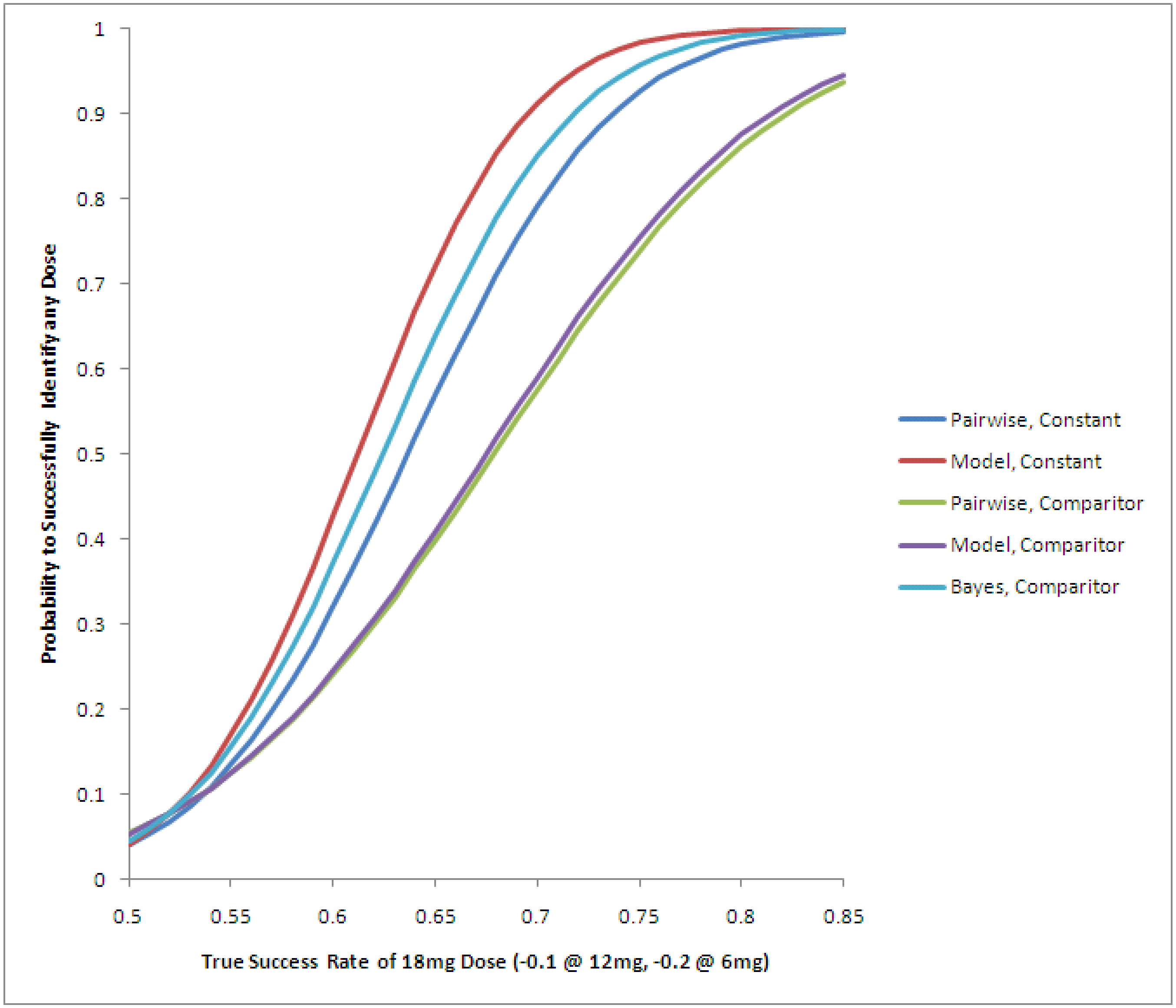
Model based comparison of IP to Ondansetron

H_0: $p_{Dose} = p_{Control}$; H_1: $p_{Dose} > p_{Control}$

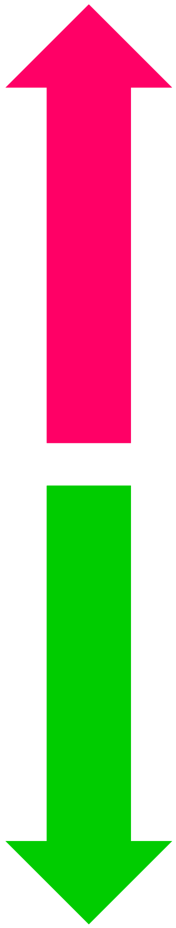
Big power difference. Model based approach better estimates the IP means AND what is known about the performance of Ondanestron is incorporated in the model.



Summary of all Power Curves



Less power



More power

Pair-wise comparison to Ondansetron

Model based comparison to Ondansetron

~~Pair-wise comparison to a constant~~

Bayes model based comparison to Ondansetron

~~Model based comparison to a constant~~

A positive comparator arm is necessary for AE reporting, etc.

140 Patients in Bayesian model based = 340 Pair-wise comparison design

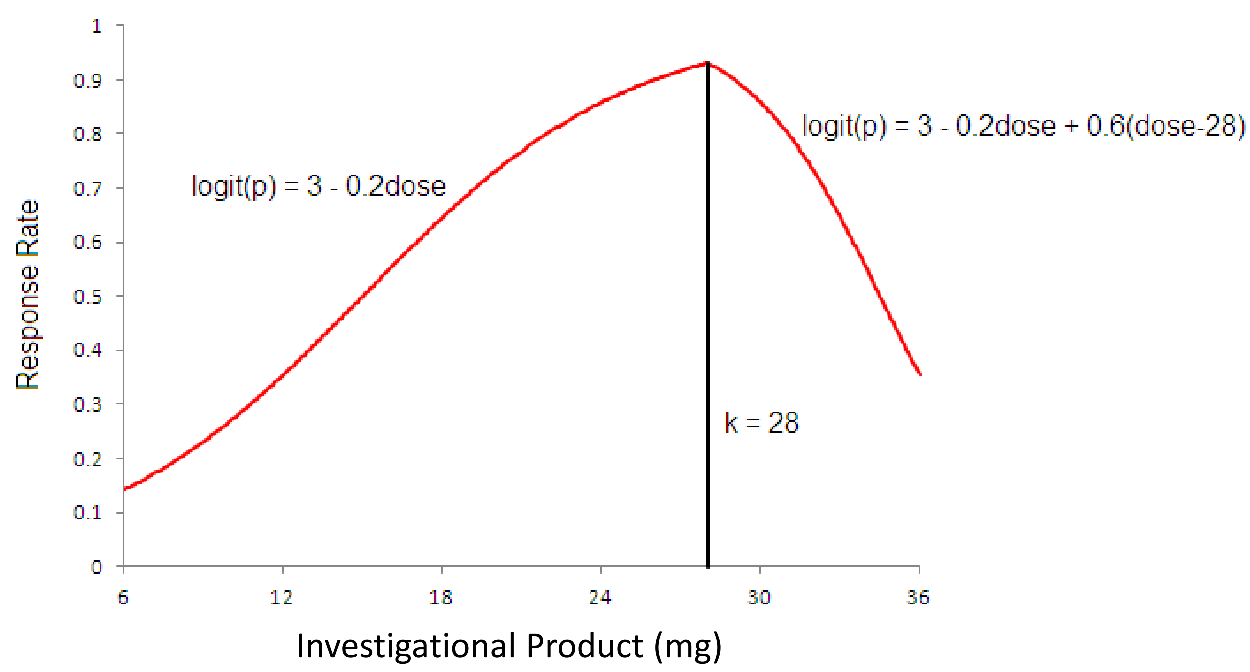
It was believed the dose-response may not be strictly increasing because high doses may actually cause PONV.

Piecewise linear logistic model

$$p_i = \frac{1}{1 + \exp\left(-\beta_0 - \beta_1 dose_i - \beta_2 (dose_i - k) I_{k>dose_i}\right)}$$

$$6 < k < 36$$

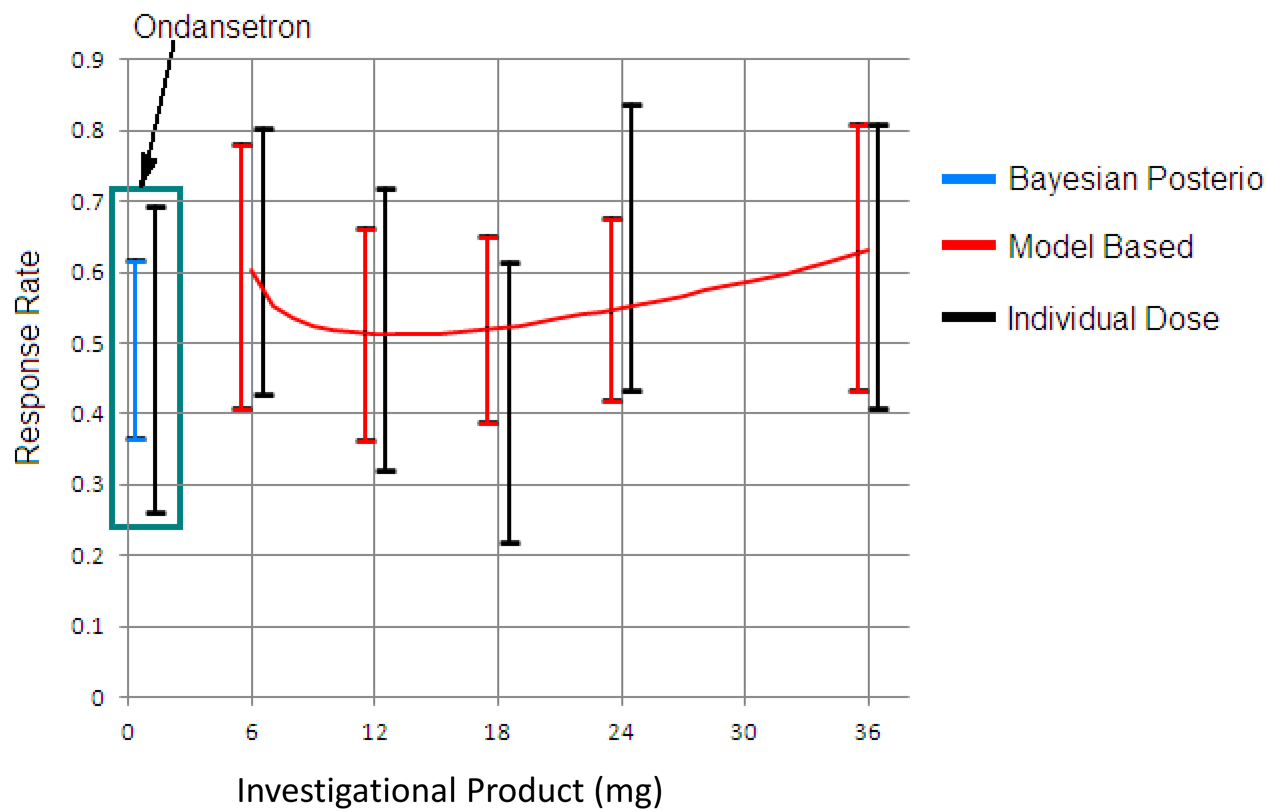
$$I_{k>dose_i} = \begin{cases} 0 & k \leq dose_i \\ 1 & k > dose_i \end{cases}$$



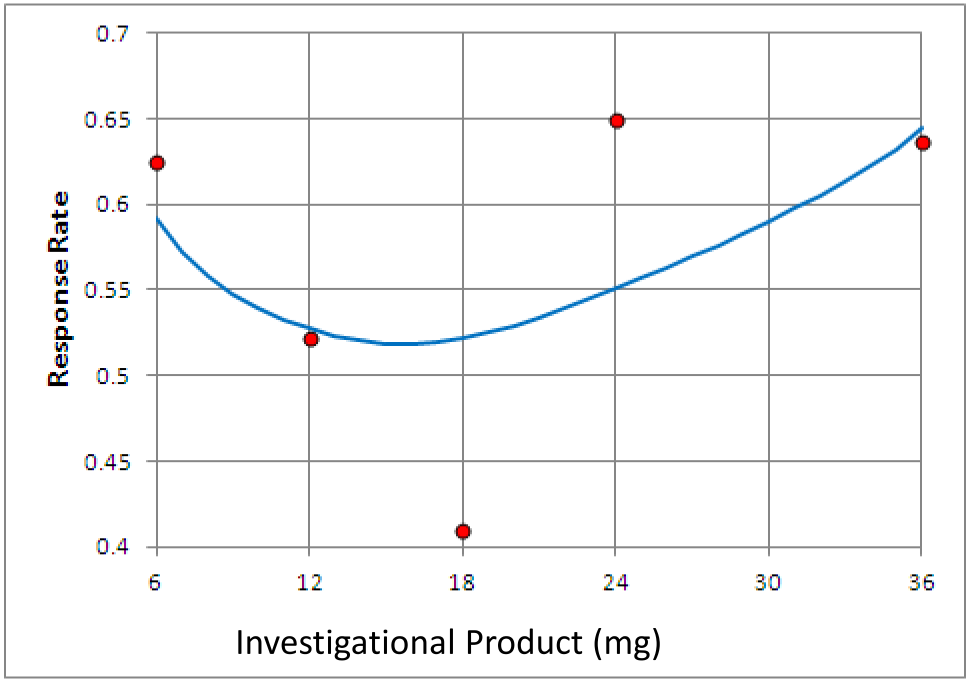
Fully Bayesian approach with non-informative priors

$$p_i = \frac{1}{1 + \exp\left(-\beta_0 - \beta_1 dose_i - \beta_2 (dose_i - k) I_{k > dose_i}\right)}$$

$$\beta_0 \sim N(0, 10^6)$$
$$\beta_1 \sim N(0, 10^6)$$
$$\beta_2 \sim N(0, 10^6)$$
$$k \sim U(6, 36)$$

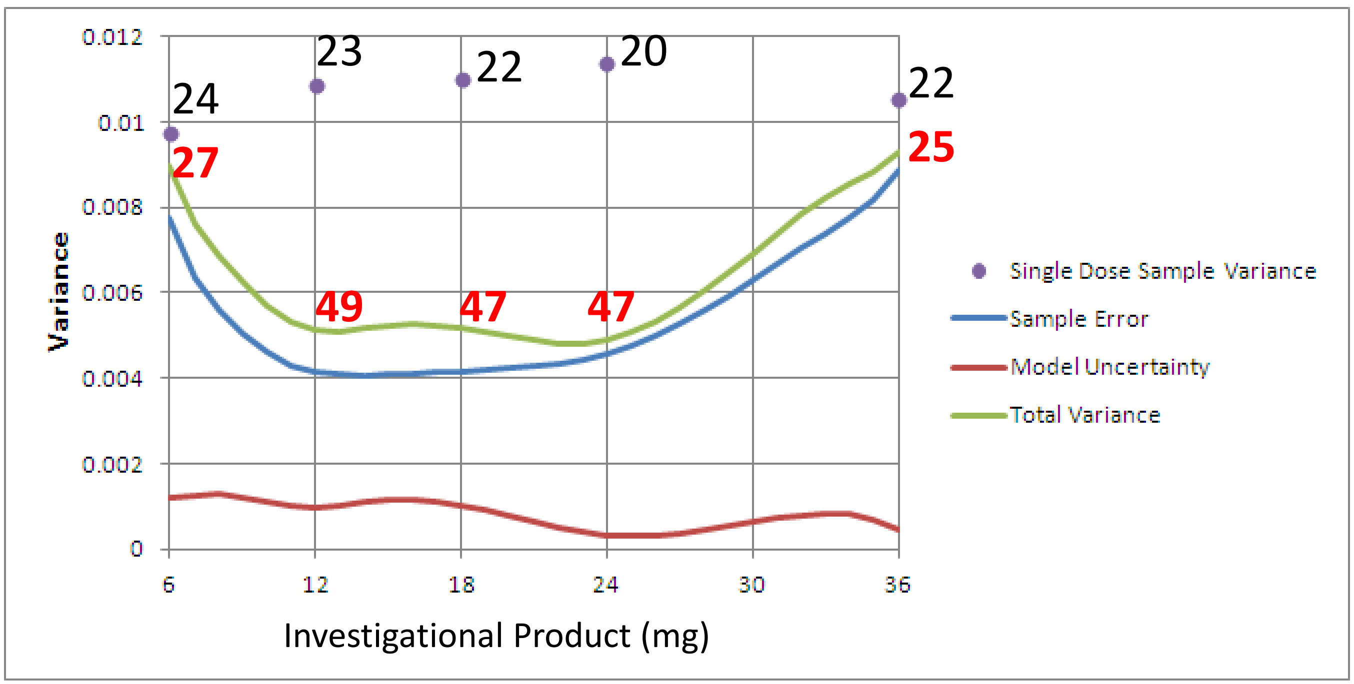


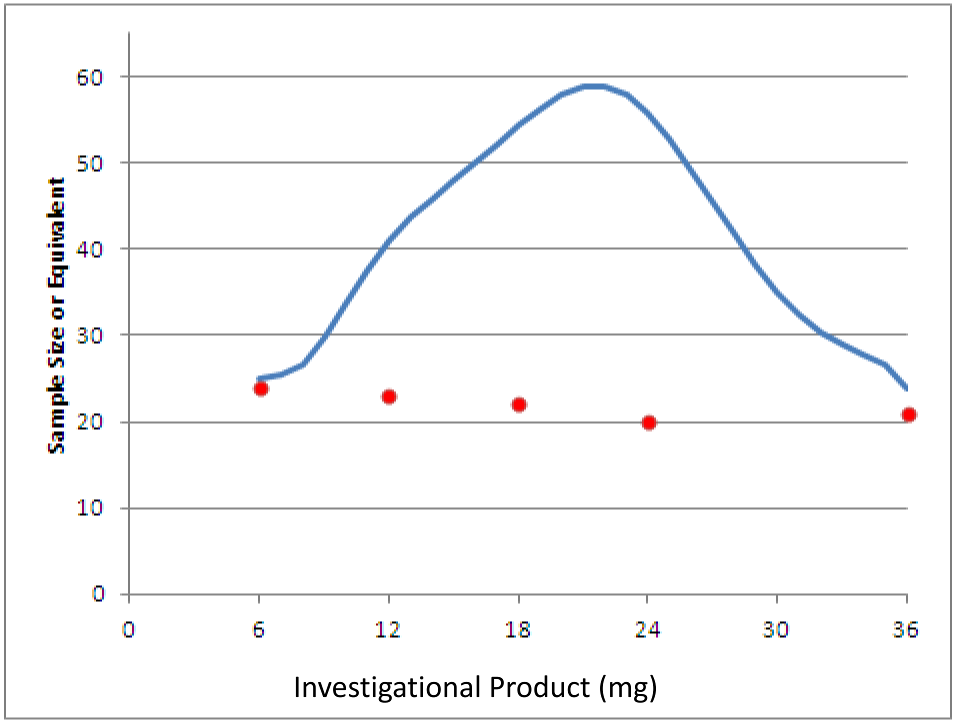
Estimated efficacy rate



Variance components

Actual sample size
Apparent sample size





+40 for Ondansetron (Bayesian)
+90 for model based IP

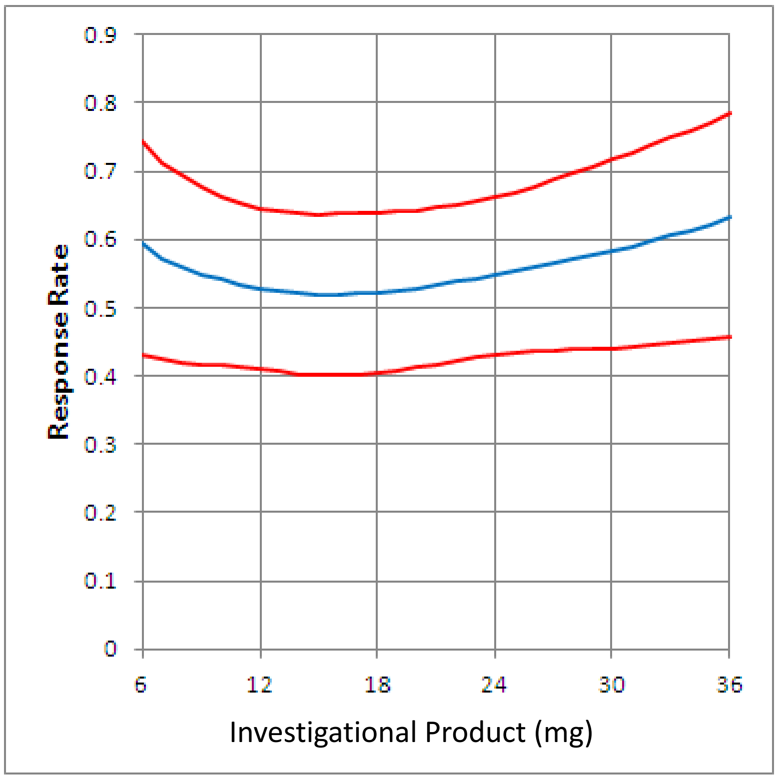
Analysis of **129** patients has statistical information equivalent to study of **240** patients in pair-wise approach

Treatment	Actual Sample Size	Apparent Sample Size
4mg Ondansetron	19	59
6mg IP	24	25
12mg IP	23	41
18mg IP	22	54
24mg IP	20	56
36mg IP	21	24

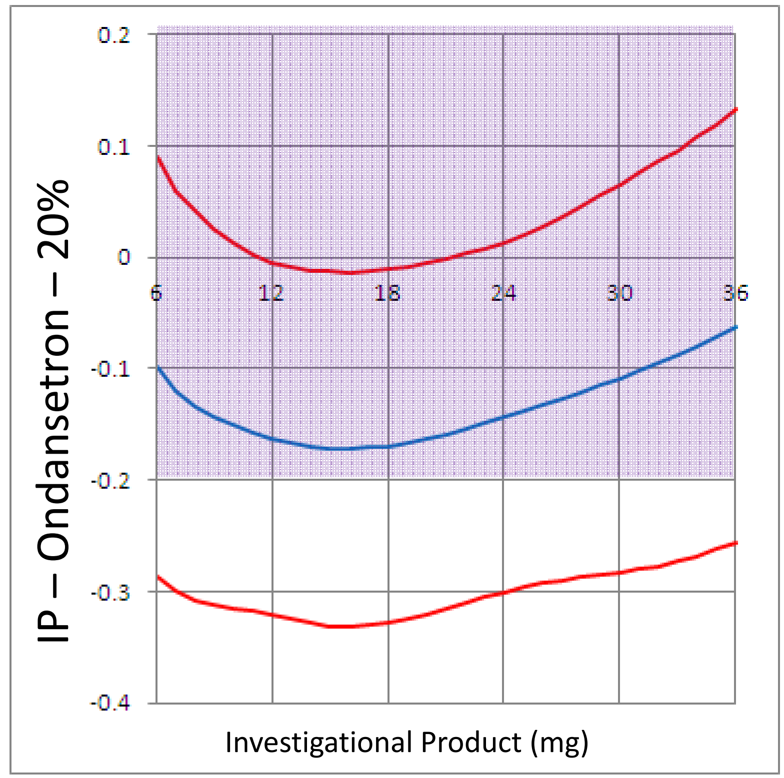
A study objective: Assess the probability that dose "x" of IP is at least 20% better than Ondansetron.

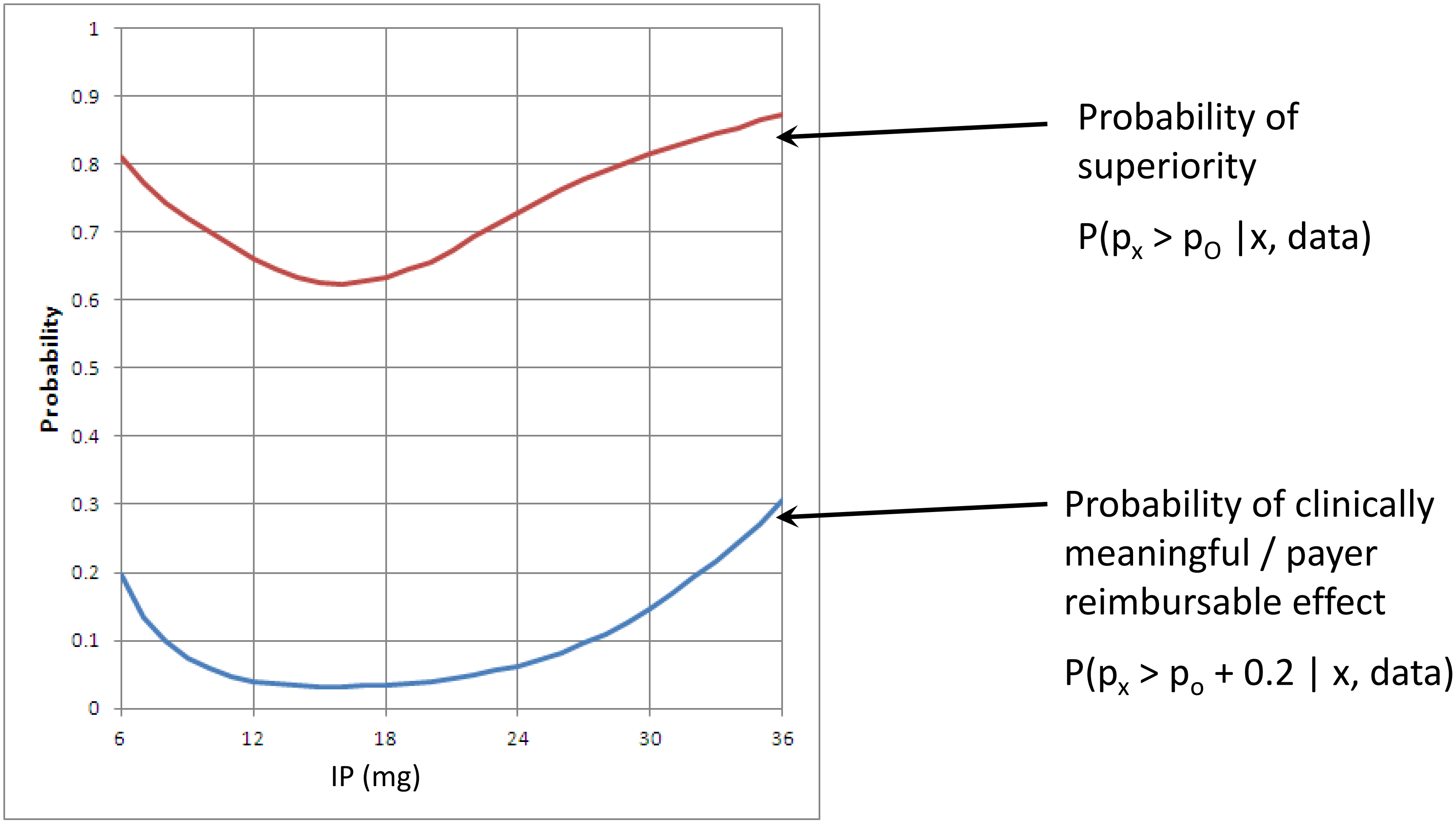
$$P(p_x > p_O + 0.2 \mid x, data)$$

Dose response with 90% CI limits



Clinically relevant effect with 90% CI limits




Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
6
12
18
24
30
36
IP (mg)
Probability of superiority
P(p_x > p_O |x, data)
Probability of clinically meaningful / payer reimbursable effect
P(p_x > p_o + 0.2 | x, data)

Critical Skills for Statisticians

1. Communication
   1. Obtain relevant information from team
   2. Relay options and context back to team

2. Technical theoretical skills
   1. What aspects of an approach are of critical importance?
   2. How can we differentiate between approaches?
   3. Many tools in the toolkit makes options

3. Programming skills
   1. Many innovative approaches are not available as drop down menu options