Using Bayesian Analysis in Randomised Phase II Trials to Plan Phase III

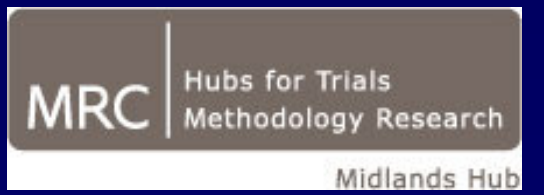
Lucinda Billingham

Professor of Biostatistics

Director, MRC Midland Hub for Trials Methodology Research

Biostatistics Lead, Cancer Research UK Clinical Trials Unit

University of Birmingham



MRC HTMR Network Workshop, London, March 16th 2010

Using Existing Data to Inform Clinical Trial Design

Acknowledgements

- Professor Philip Johnson, University of Birmingham
- Professor Keith Abrams, University of Leicester
- Progen Pharmaceuticals
- Cancer Research UK

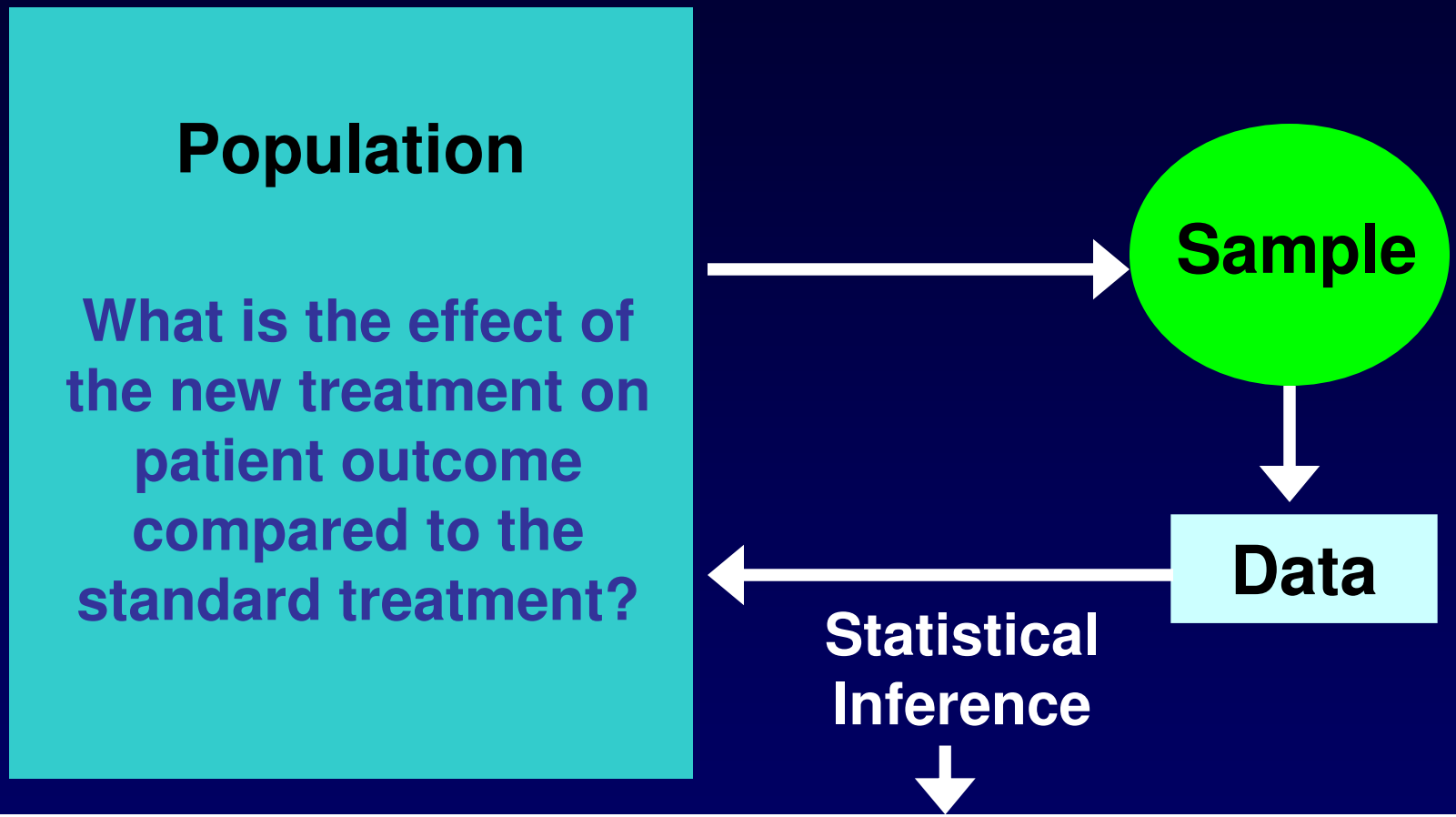
Reference:

David J Spiegelhalter, Keith R Abrams, Jonathan P Myles; Bayesian Approaches to Clinical Trials and Health-Care Evaluation; Wiley 2004

Agenda

- Introduction
  - Bayesian analysis
  - Hazard ratios
  - Randomised phase II trials
- Application of Bayesian analysis to randomised Phase II trials
  - Illustrative example in HCC
  - Why is it a potentially useful approach
  - How to do it
  - Interpretation of results
- Application of Bayesian analysis in seamless Phase II / III setting
- Extensions to methodology
- Objections to Bayesian methods

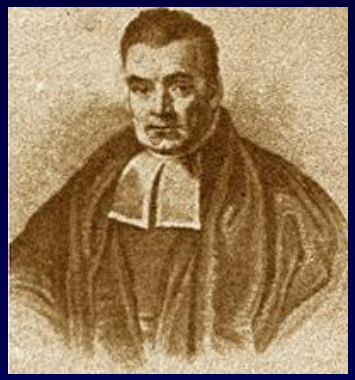
Aim of Statistical Analysis



Classical / frequentist analysis:
Estimate treatment effect with 95% confidence intervals
Statistically test hypothesis → p-value

What is a Bayesian Approach to Analysis?

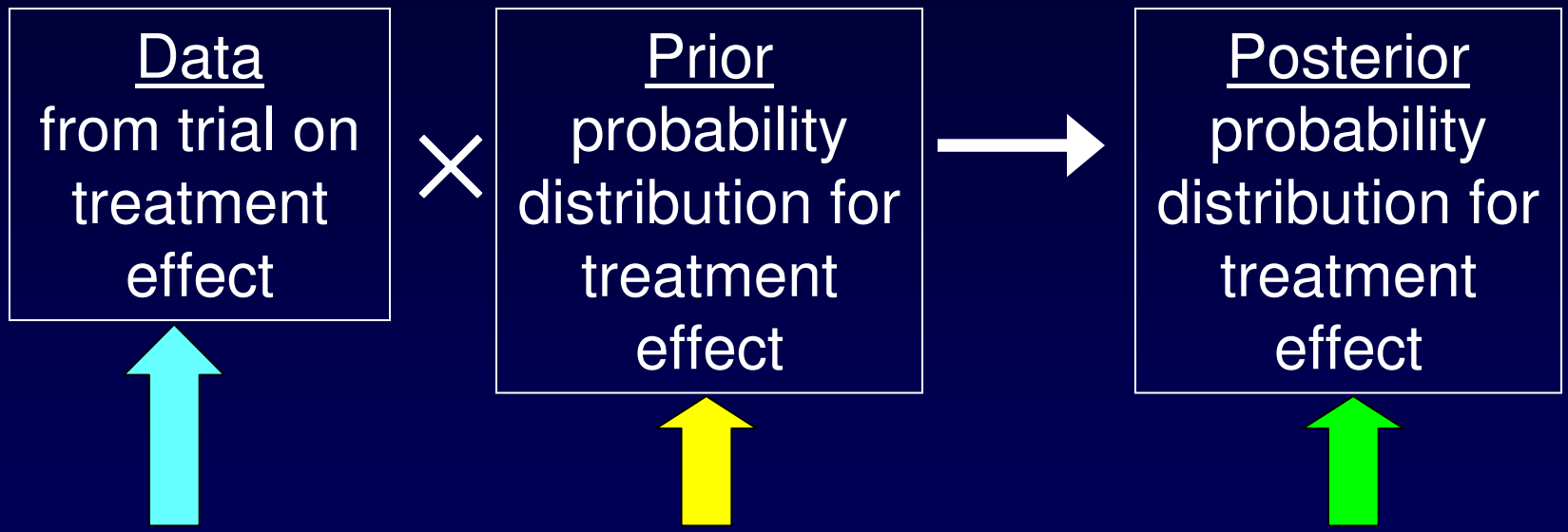
- Method of statistical analysis based on theorem devised by Reverend Thomas Bayes (1702-1761)



$$p(B/A) = \frac{p(A/B) \times p(B)}{p(A)}$$

- Alternative method to the classical / frequentist approach
  - 'Many practising statisticians are fairly ignorant of the methods used by the rival camp and too busy to have time to find out' Bland and Altman BMJ 1998, 317: 1151
- Acknowledges that the unknown quantity of interest is not a fixed value but could be any value with an associated probability

Bayesian Approach to Analysis



Classical / Frequentist analysis just based on this

Enables **prior evidence or beliefs** to be incorporated into the final estimate of the treatment effect

Enables direct probability statements to be made about treatment effects

Advantages of a Bayesian Analysis

Classical

- Results are in the form of a p-value

p-value = p (***data*** | no treatment effect)

Bayesian

- Results are in the form of a probability distribution for the treatment effect
- Allows direct probability statements to be made about treatment effects

posterior $\rightarrow$ p (***treatment effect*** | data, prior)

Measuring Treatment Effect as a Hazard Ratio (HR)

- Specific summary measure for survival data
- Measures the relative survival experience of two groups
- Hazard Ratio = $\frac{\text{Hazard of death on New}}{\text{Hazard of death on Standard}}$

  where the hazard is the instantaneous risk of death at any point in time
- Interpretation for survival

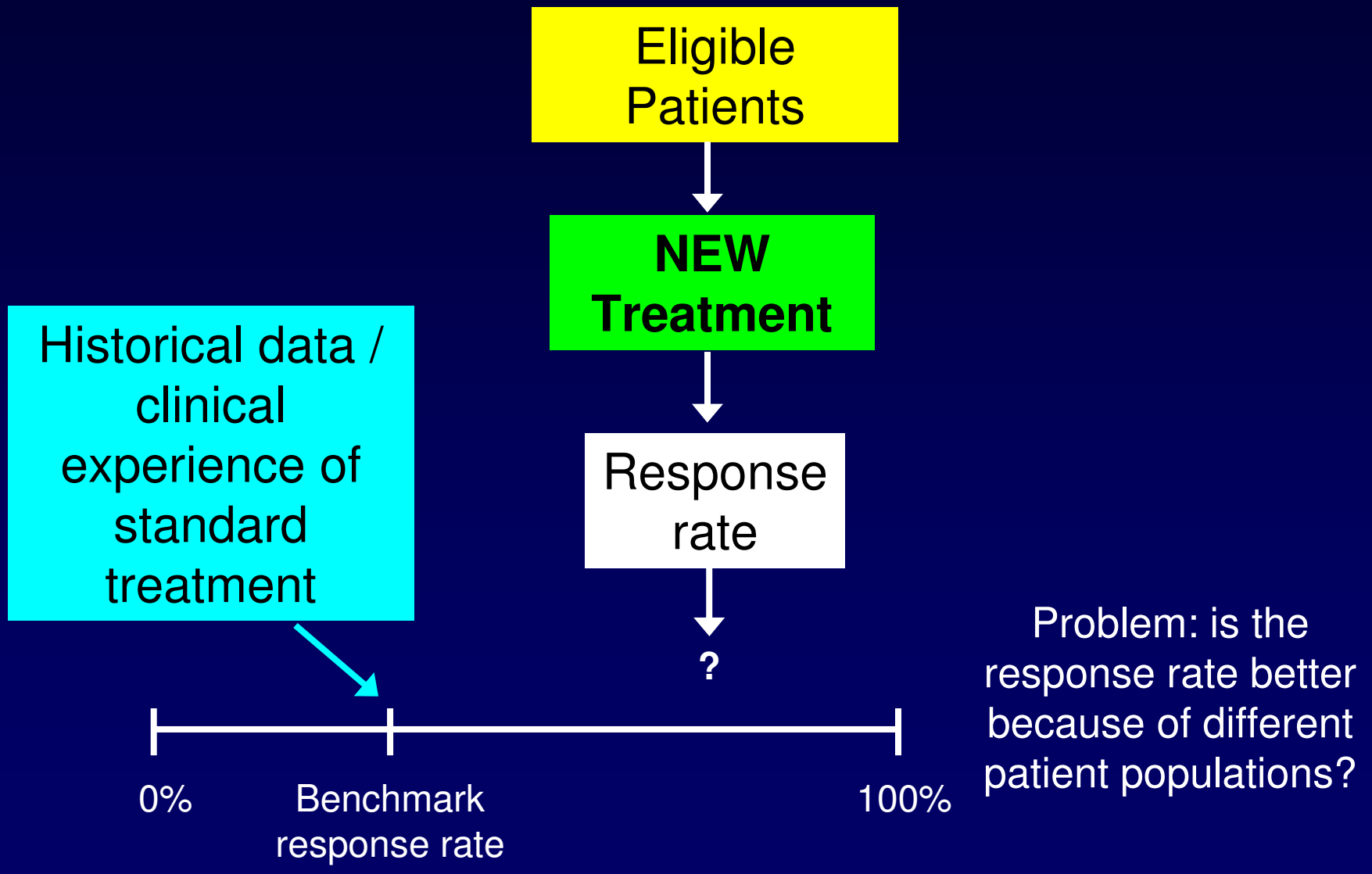
  HR = 1 $\Rightarrow$ no difference between treatments

  HR < 1 $\Rightarrow$ New treatment superior

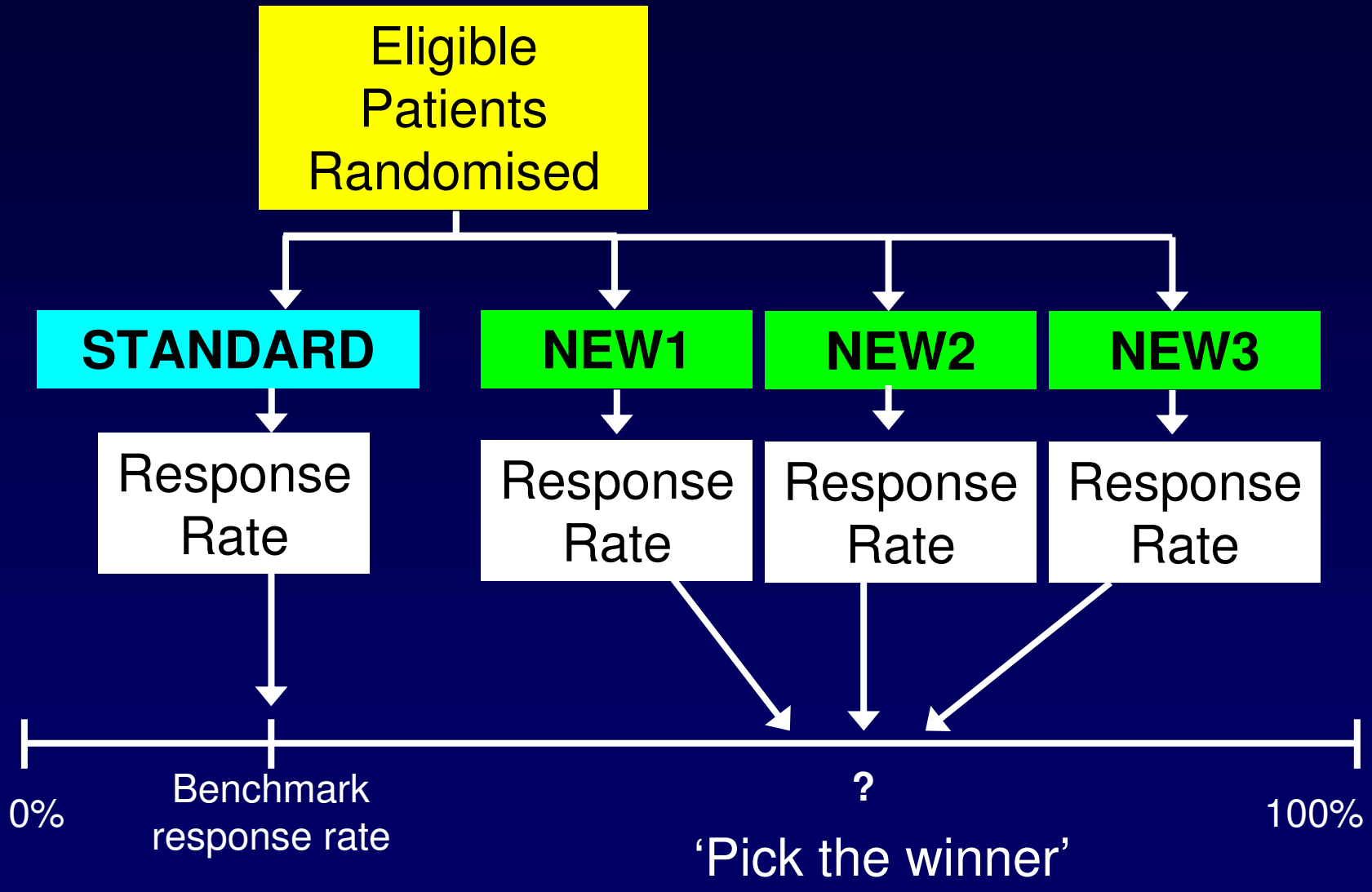
  HR > 1 $\Rightarrow$ New treatment inferior
- Often work with ln HR as tends to have normal distribution

Phase I	What is a safe dose to give for the NEW treatment and with what toxicities?	Toxicities
Phase II	Is the efficacy of the NEW treatment worthy of direct comparison to STANDARD treatment of the day?	Intermediate outcome of efficacy: Response
Phase III	How does the NEW treatment compare to the STANDARD treatment of the day in terms of efficacy?	Overall outcome of efficacy: Survival time

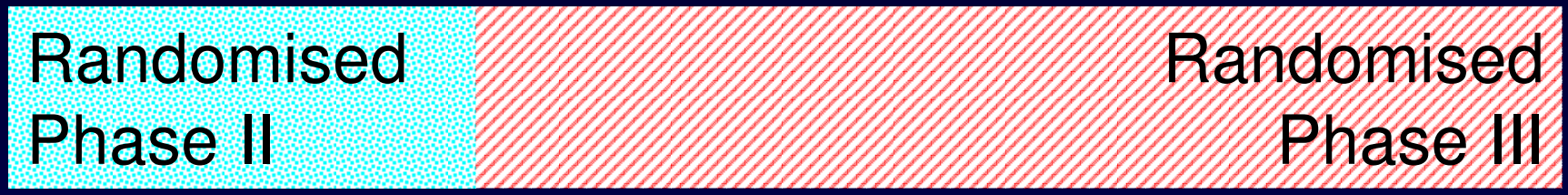
Single Arm Phase II Trial



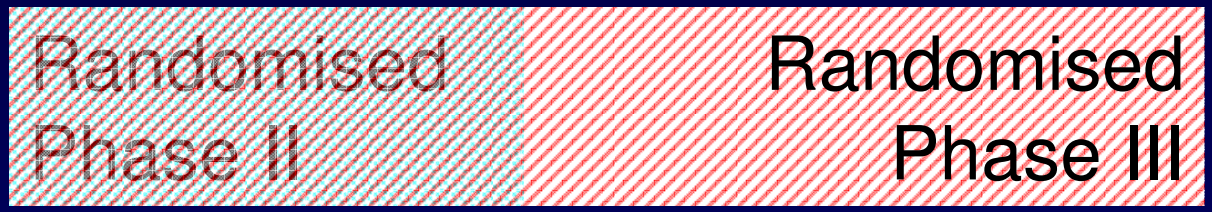
Randomised Phase II Trial



Possible Phase II / Phase III Trial Designs



Seamless phase II/III (e.g. Inoue, Thall, Berry; Biometrics 2002)



Decision Point

Should we proceed to phase III?

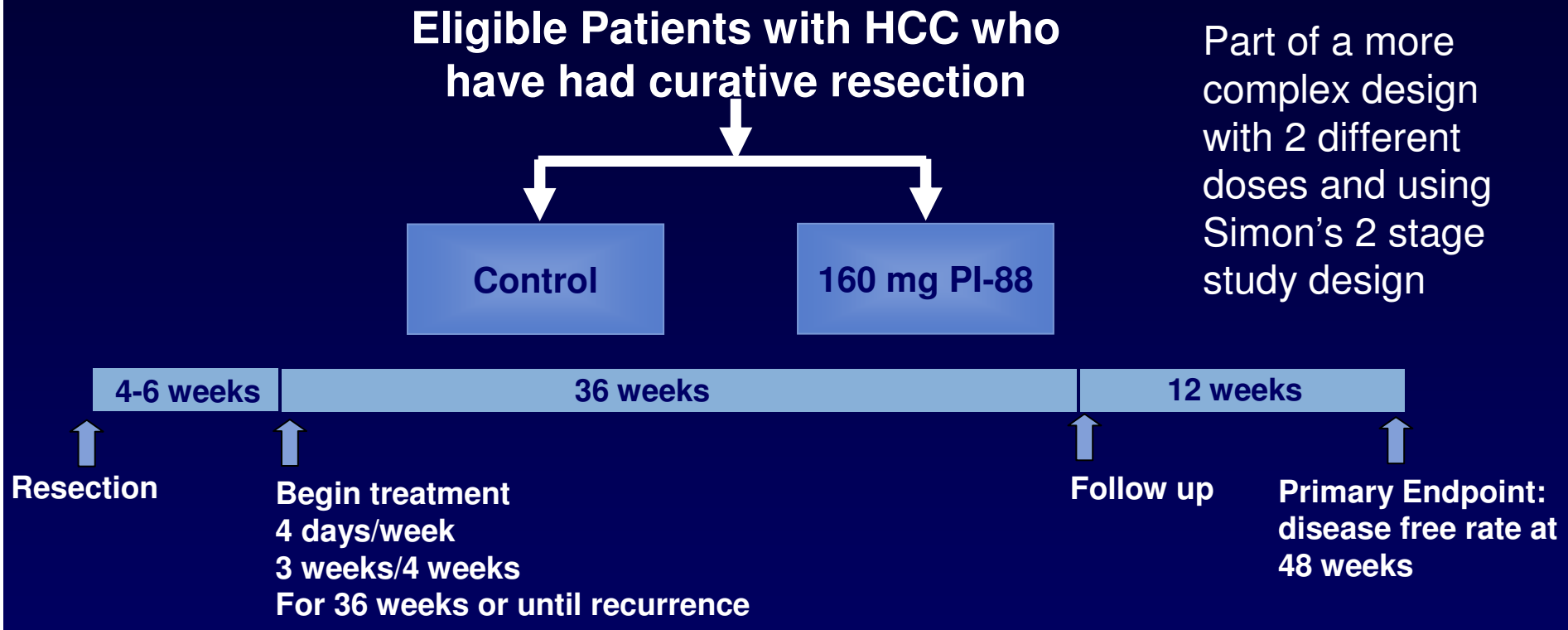
Current Practice for the Analysis of Randomised Phase II Trials

- Estimates and confidence intervals
  - Not clear how decision to proceed is made
- Hypothesis testing
  - Often used inappropriately so RPII just looks like underpowered PIII
  - How do the results help in decision to proceed?

Lack of knowledge on how to appropriately analyse randomised phase II trials

Example: Randomised Phase II Trial of PI-88 in Hepatocellular Carcinoma

P-J Chen EASL 2007; Progen Pharmaceuticals

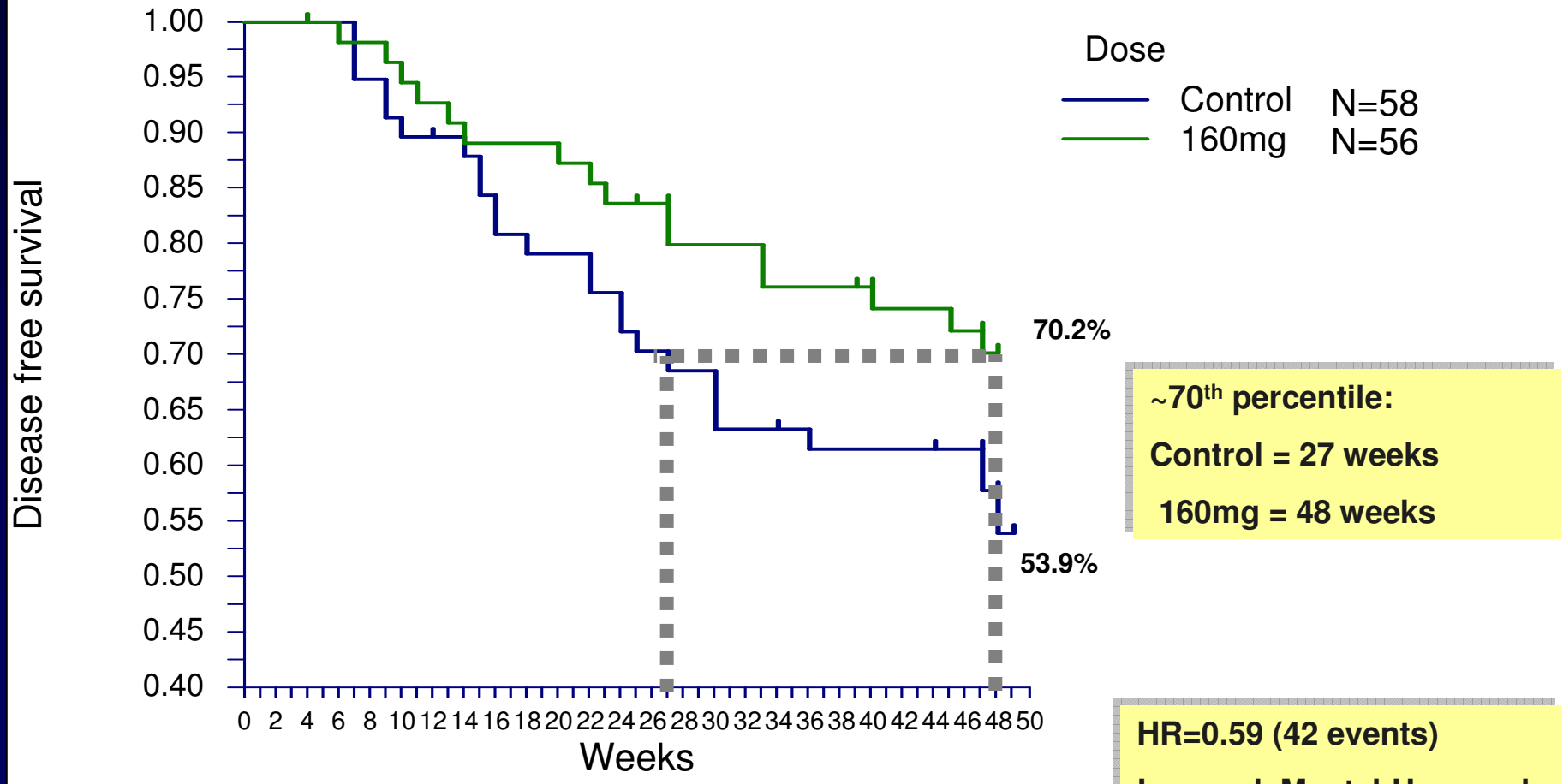


Part of a more complex design with 2 different doses and using Simon's 2 stage study design

Goal of trial: To explore possible efficacy of PI-88 in reducing early tumour recurrence in patients who have had primary liver cancer tumours removed by surgery in order to make a decision to move to Phase 3 clinical development

Disease-free survival analysis

P-J Chen EASL 2007; Progen Pharmaceuticals



~70th percentile:

Control = 27 weeks

160mg = 48 weeks

HR=0.59 (42 events)

Log rank Mantel-Haenszel p= 0.0867

Should they proceed to a Phase III trial?

What Do Researchers Really Want to Know?

- Given the observed treatment effect in the randomised phase II trial (and other prior knowledge)
  - What is the likely value of the true treatment effect?
  - What is the predicted result for the planned phase III trial?
  - What are the chances of getting a statistically significant result if we continue to a phase III?

Bayesian analysis will give these answers

Bayesian Analysis in Clinical Trials

- Recommended approach for monitoring of randomised Phase III clinical trials
  - e.g. Parmar et al Lancet 2001; Berry Nature Reviews 2006
  - Aids decision-making regarding stopping a trial early
- Not explicitly been talked about for randomised phase II, but natural extension from monitoring context

Outcome Measures: Phase II versus Phase III

	Phase II	Phase III
Primary	Response rate	Survival time plus others
Secondary	Survival time	Response rate plus others

Bayesian Analysis

- Unknown parameter of interest is treatment effect measured in terms of log hazard ratio

  θ = ln (HR)

- Bayes theorem for unknown parameter θ

$$p(\theta \mid y) \propto p(y \mid \theta) \times p(\theta)$$

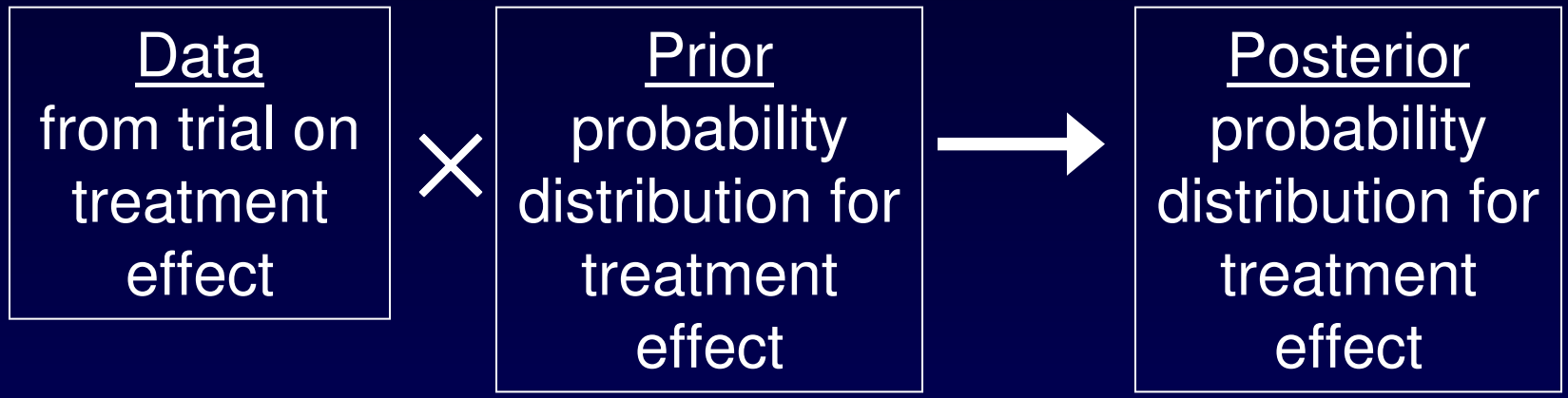
Posterior distribution for θ

Likelihood function for θ

Prior distribution for θ

- Conjugate normal analysis
  - Normal likelihood so use normal prior distributions

Bayesian Analysis of PI-88 HCC Trial



Aim: estimate treatment effect i.e. Hazard Ratio (HR)

Calculations based on ln HR

HR = 1 $\rightarrow$ ln HR = 0

HR < 1 $\rightarrow$ ln HR negative

HR > 1 $\rightarrow$ ln HR positive

Conjugate normal analysis makes calculations straightforward

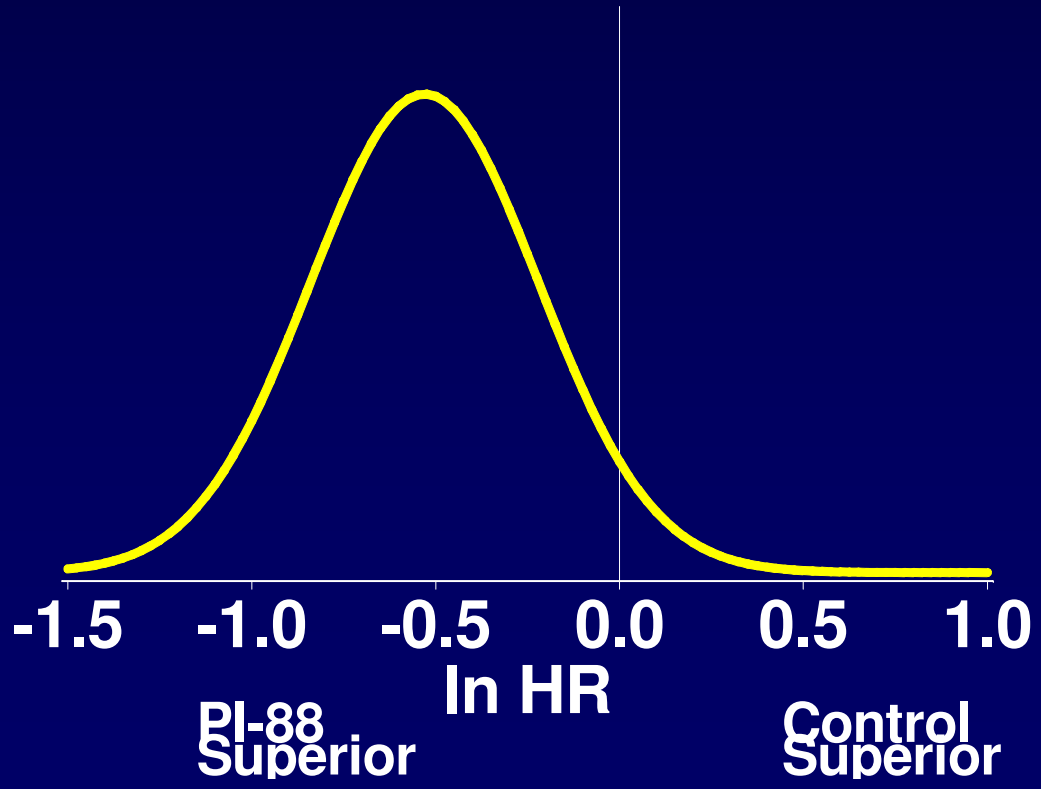
Data from Trial: Likelihood Function

$$y_m \mid \theta \sim N(\theta, 4/m) \quad where\ m = number\ of\ events$$

(Tsiatis 1981)

Trial data gave HR=0.59, m=42

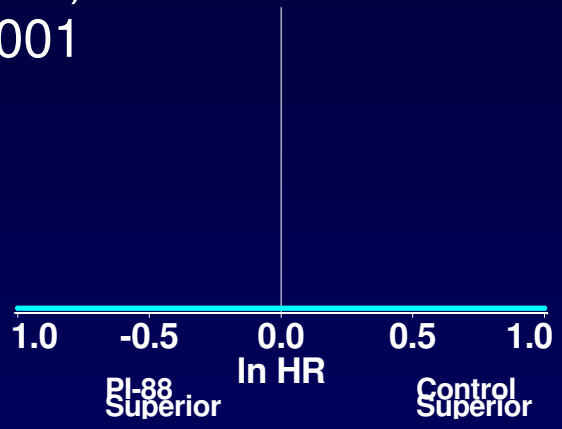
N (-0.53 , 4/42=0.0952)



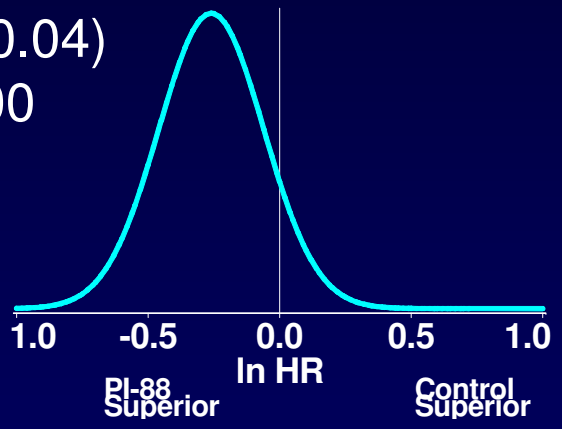
Prior Distributions

$$\theta \sim N(\mu_0, 4/m_0) \quad where\ m_0 = number\ of\ events$$

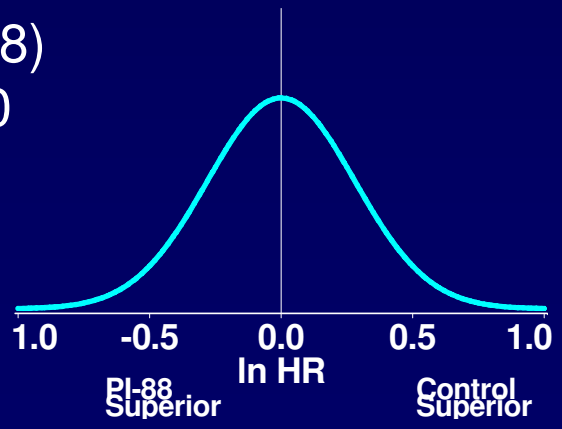
Non-informative
N(0,40000)
m_0=0.0001



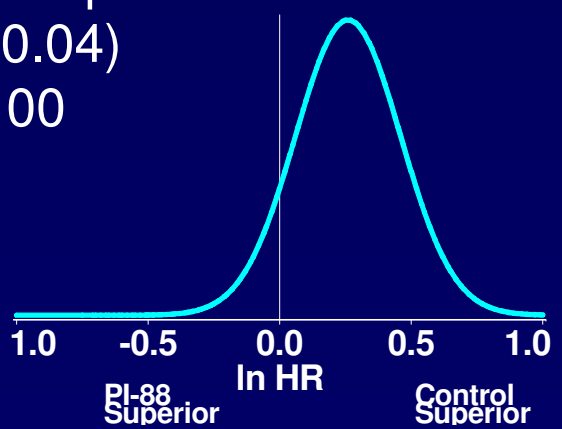
Plausible
Enthusiast
N(-0.26, 0.04)
m_0=100



Sceptic
N(0,0.08)
m_0=50



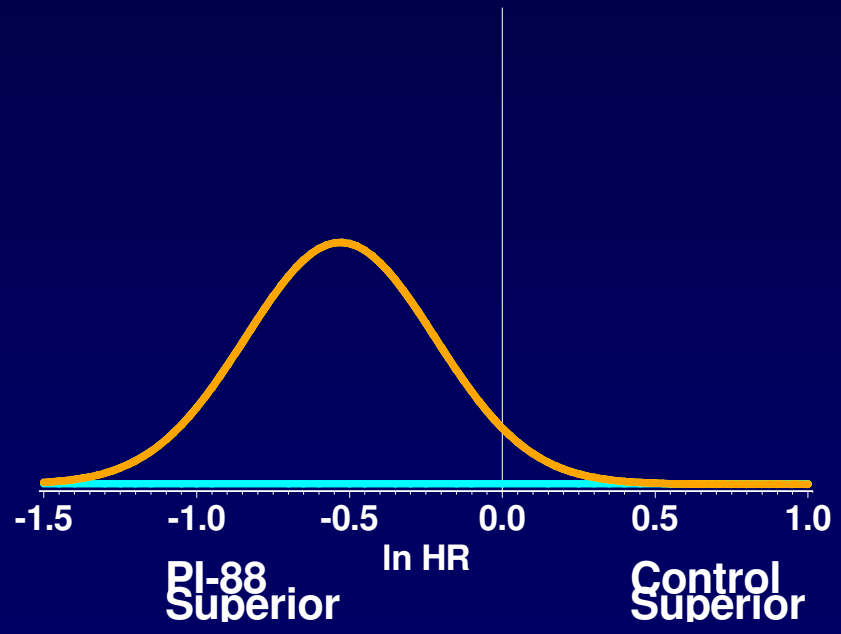
Extreme Sceptic
N(0.26,0.04)
m_0=100



Posterior Distributions (1)

$$\theta \mid y_m \sim N\left(\frac{m_0\mu_0 + my_m}{m_0 + m}, \frac{4}{m_0 + m}\right)$$

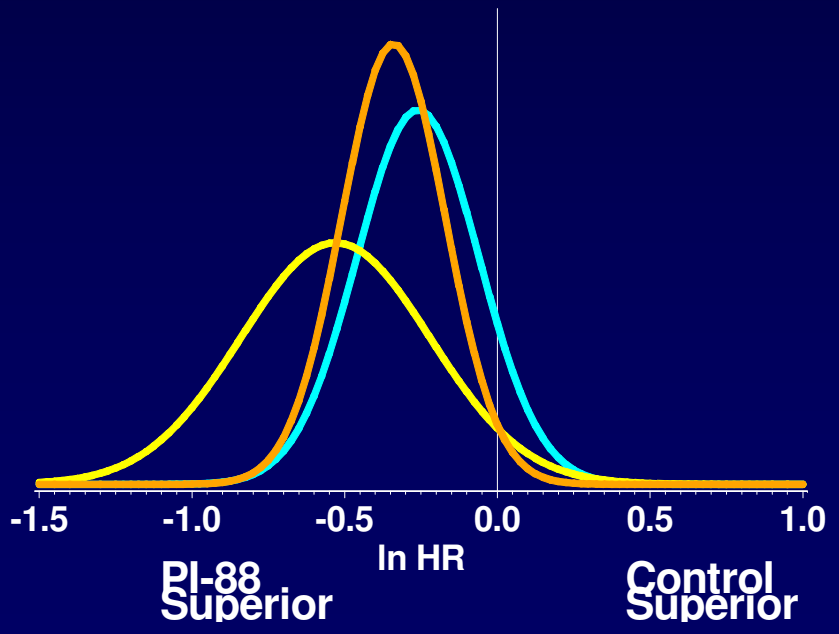
Non-informative



p(HR<1)= p(lnHR<0)=0.96

p(HR<0.75)= p(lnHR<-0.29)=0.78

Plausible Enthusiast

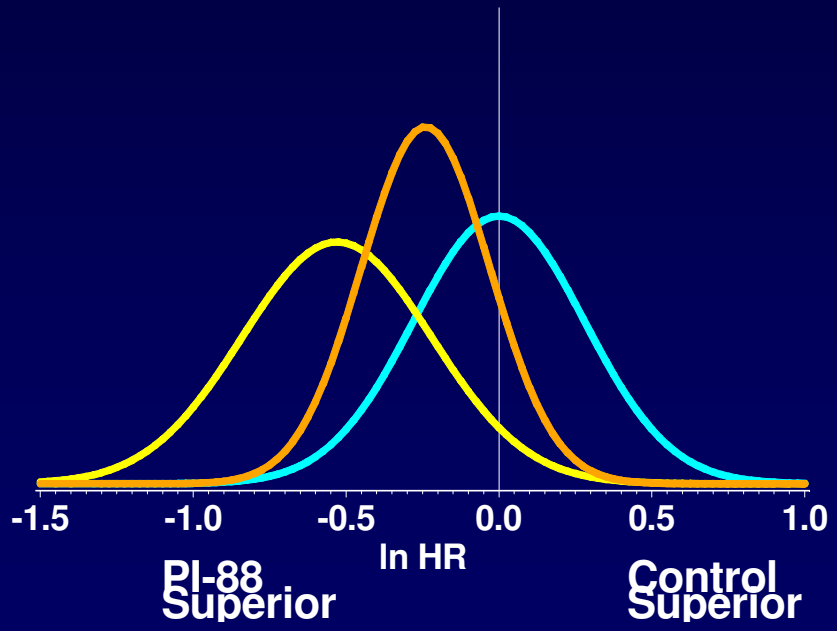


p(HR<1)= p(lnHR<0)=0.98

p(HR<0.75)= p(lnHR<-0.29)=0.62

Posterior Distributions (2)

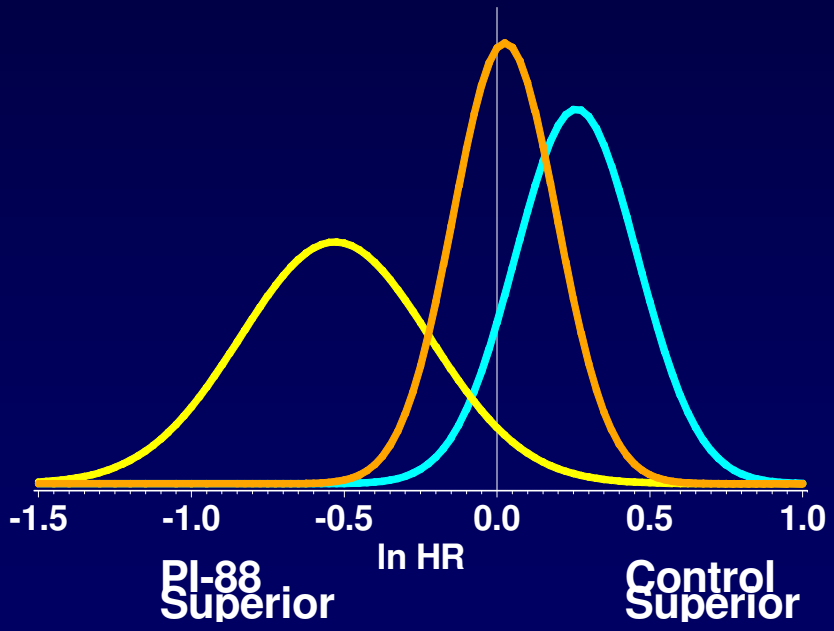
Sceptic



p(HR<1)= p(lnHR<0)=0.88

p(HR<0.75)= p(lnHR<-0.29)=0.41

Extreme Sceptic



p(HR<1)= p(lnHR<0)=0.44

p(HR<0.75)= p(lnHR<-0.29)=0.03

Summary of Posterior Results

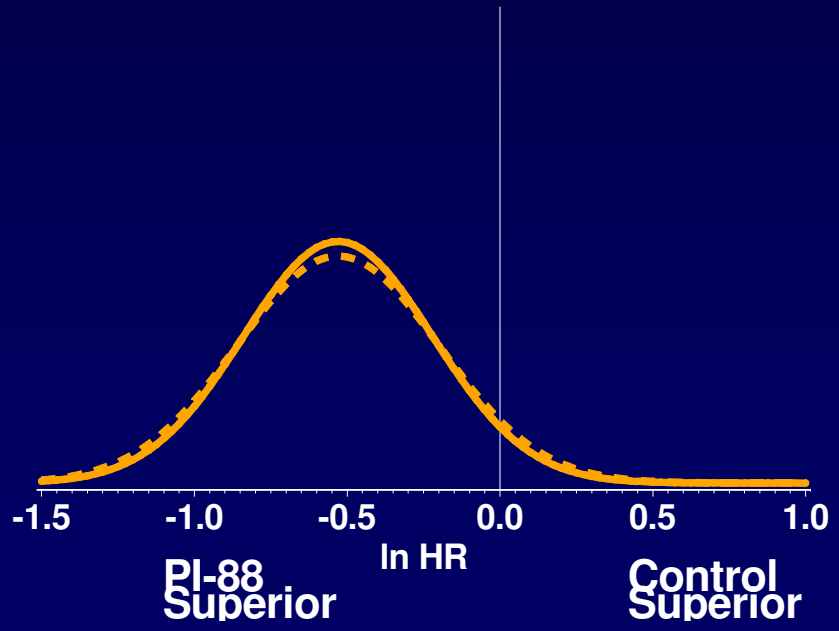
	Posterior	P(HR<1)	P(HR<0.75)
Non-informative	N(-0.53,0.0952)	0.96	0.78
Plausible Enthusiast	N(-0.34, 0.0282)	0.98	0.62
Sceptic	N(-0.24, 0.0435)	0.88	0.41
Extreme Sceptic	N(0.026, 0.0282)	0.44	0.03

Predictive Distributions (1)

$$Y_n \mid y_m \sim N\left(\frac{m_0\mu_0 + my_m}{m_0 + m}, 4\left(\frac{1}{m_0 + m} + \frac{1}{n}\right)\right)$$

Plan new trial with 300 events; increase variance of posterior by 4/300=0.0133

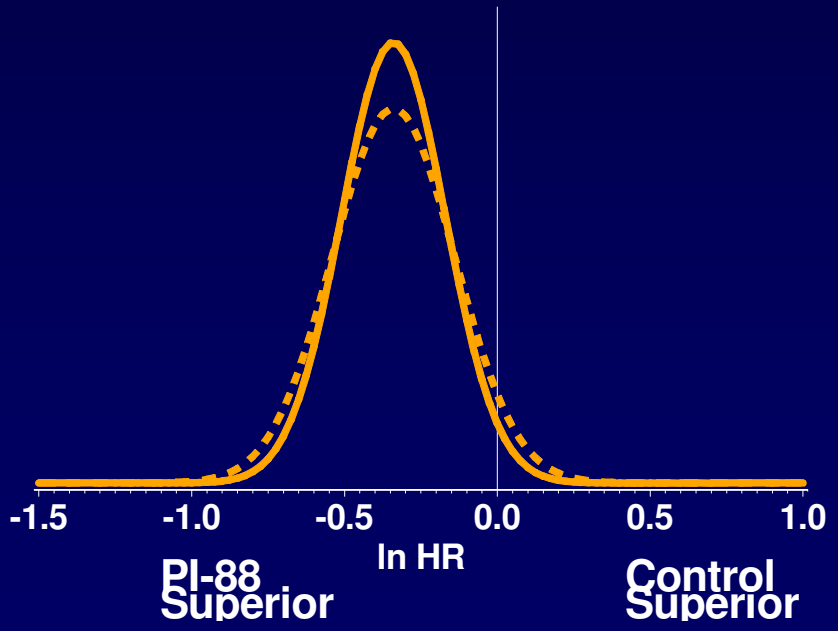
Non-informative



p(HR<1)= p(lnHR<0)=0.95

p(HR<0.75)= p(lnHR<-0.29)=0.77

Plausible Enthusiast

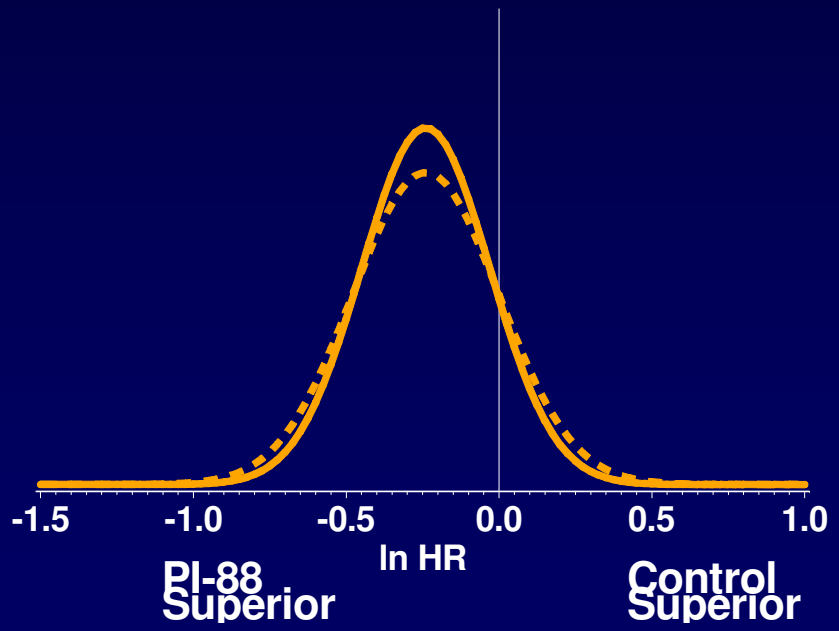


p(HR<1)= p(lnHR<0)=0.95

p(HR<0.75)= p(lnHR<-0.29)=0.60

Predictive Distributions (2)

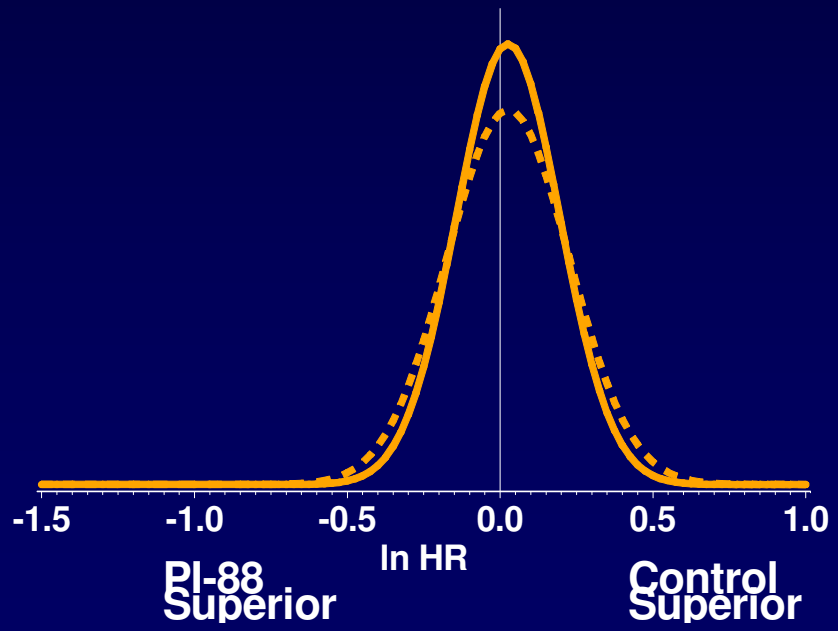
Sceptic



p(HR<1)= p(lnHR<0)=0.84

p(HR<0.75)= p(lnHR<-0.29)=0.42

Extreme Sceptic



p(HR<1)= p(lnHR<0)=0.45

p(HR<0.75)= p(lnHR<-0.29)=0.06

Summary of Predictive Results

	Posterior Predictive	P(HR<1)	P(HR<0.75)
Non-informative	N(-0.53,0.0952) N(-0.53,0.1086)	0.96 0.95	0.78 0.77
Plausible Enthusiast	N(-0.34, 0.0282) N(-0.34, 0.0415)	0.98 0.95	0.62 0.60
Sceptic	N(-0.24, 0.0435) N(-0.24, 0.0568)	0.88 0.84	0.41 0.42
Extreme sceptic	N(0.026, 0.0282) N(0.026, 0.0415)	0.44 0.45	0.03 0.06

Hybrid Classical-Bayesian Approach to Power

- Assume conclusions of trial will be based entirely on classical analysis
- Classical power = p(reject H0 | $\theta=\theta^*$)
- Use predictive distribution to calculate the overall unconditional probability of a 'classically' significant result
  - 'Expected power'
  - 'Assurance' (O'Hagan et al Pharmaceutical Statistics 2005)

Predictive Probability of Obtaining a 'Classically' Significant Result in New Trial

n=300, significance level = 5%

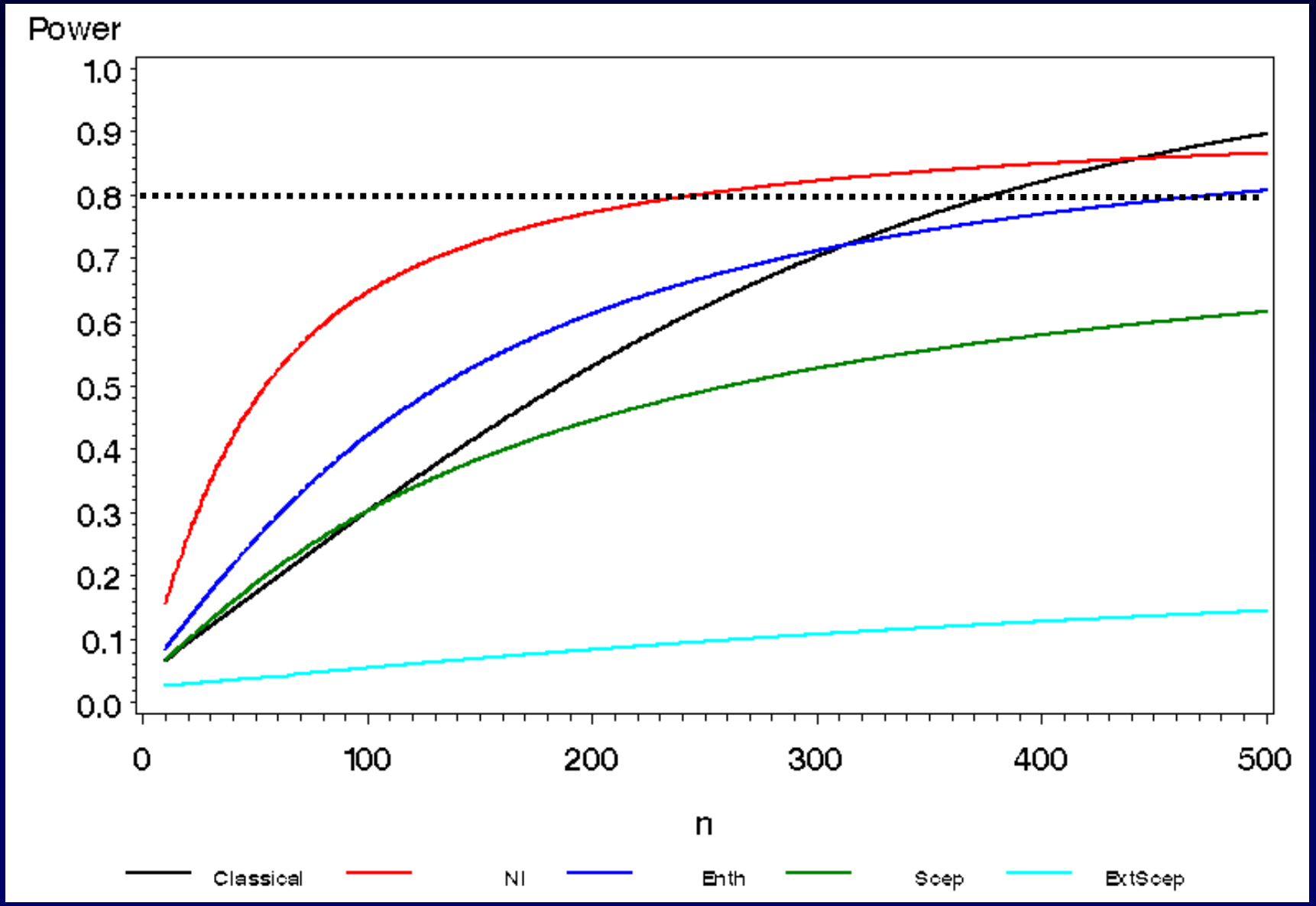
Classical power = p (reject H0 | θ^*=-0.29 ie HR*=0.75) = 0.70

$$Y_n \mid y_m \sim N\left(\frac{m_0\mu_0 + my_m}{m_0 + m}, 4\left(\frac{1}{m_0 + m} + \frac{1}{n}\right)\right)$$

$$Power_C = \Phi\left[\sqrt{\frac{m_0 + m}{m_0 + m + n}}\left(\frac{\mu_n\sqrt{n}}{2} + z_\varepsilon\right)\right]$$

	Power (n=300)
Non-informative	82%
Plausible Enthusiast	71%
Sceptic	53%
Extreme Sceptic	11%

Hybrid Classical-Bayesian Power Curves



‘Bayesian Power’

- Assume conclusions of trial will be based on Bayesian analysis
- Define Bayesian significance

  $p(\theta>0|\text{data}) < \varepsilon$
- Use predictive distribution to calculate the expected ‘Bayesian’ power, averaged with respect to the prior distribution

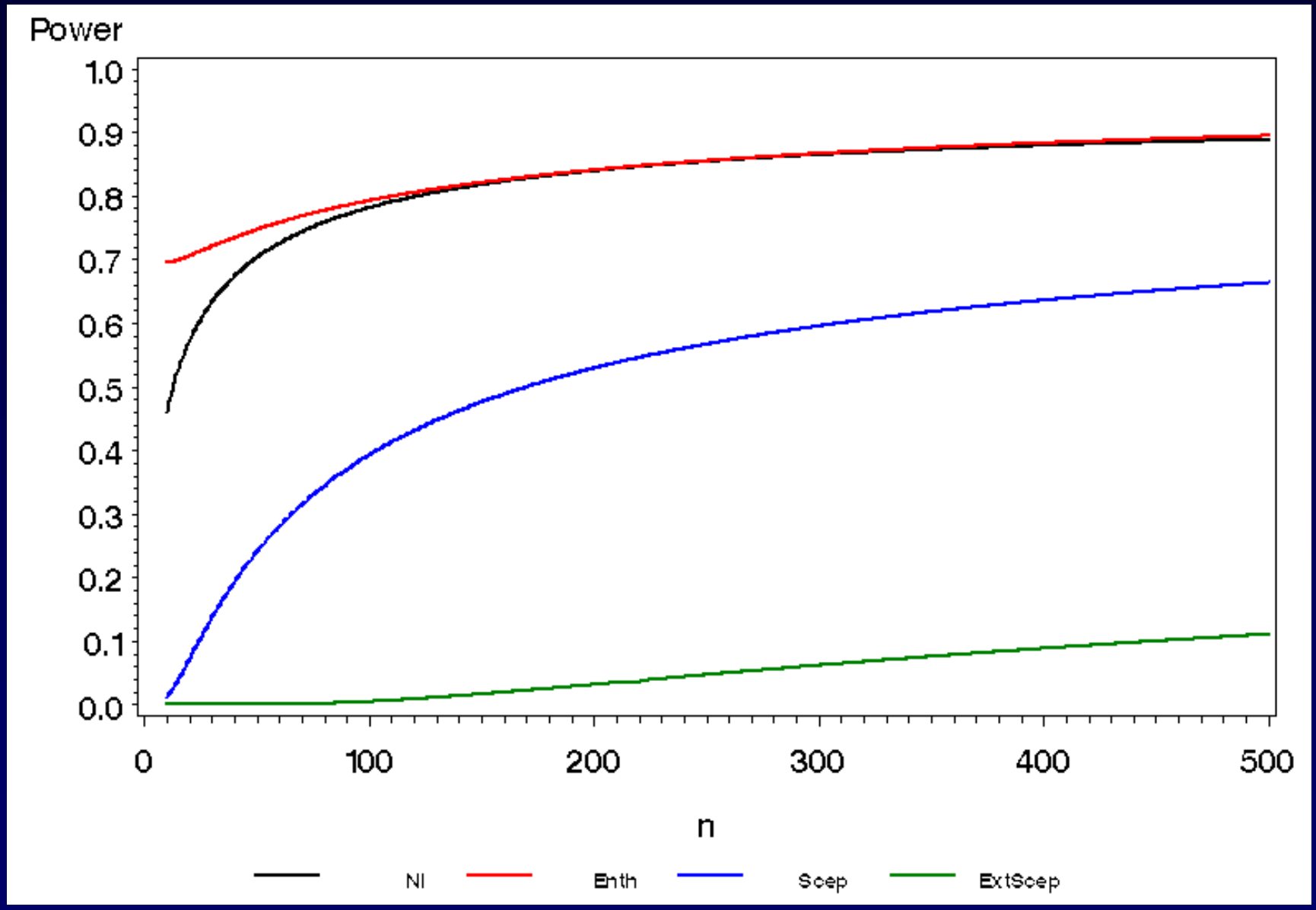
Predictive Probability of Obtaining a 'Bayesian' Significant Result in New Trial

$$Y_n \mid y_m \sim N\left(\frac{m_0\mu_0 + my_m}{m_0 + m}, 4\left(\frac{1}{m_0 + m} + \frac{1}{n}\right)\right)$$

$$Power_B = \Phi\left[\frac{\mu_n\sqrt{m_0 + m + n}\sqrt{m_0 + m}}{2\sqrt{n}} + \sqrt{\frac{m_0 + m}{n}}z_\varepsilon\right]$$

	Power (n=300)
Non-informative	86%
Plausible Enthusiast	87%
Sceptic	60%
Extreme Sceptic	6%

Bayesian Power Curves



Example: Phase II/III
Inoue, Thall & Berry Biometrics 2002

- NSCLC trial, E vs S, n=900, 72 months
- $\phi(t) = p\ (\ \Delta>0 \mid D_{72})$
- Large $\phi(t) \Rightarrow$if maximum allowed future resources were expended then likely that E>S
- Decision based on predictive probabilities involving future data at 72 months
- PII to PIII decision: analysis at t=8, 10, 12 months
  - $0.01 < P\ (\phi(t)>0.98) < 0.80$ then continue PII
  - $P\ (\phi(t)>0.98) \geq 0.80$ then organise PIII
  - $P\ (\phi(12)>0.98) < 0.80$ then conclude E<S

Extensions to Methodology

- Consider other priors: lump and smear, evidence-based
- Response rate as primary outcome measure
  - Binomial likelihood
  - Beta prior
  - Beta-Binomial conjugate analysis
- Non-conjugate analysis
  - Use software to simulate posterior and predictive distribution
- Predicting phase III primary outcome (e.g. survival) from phase II primary outcome (e.g. response)
- Extension to include utilities (Bayesian decision theoretic approach) and costs (value of information) in the decision making
- Trial design appropriate to planned analysis

Why Do People Object to the Use of Bayesian Methods?

- Use of priors introduces an element of subjectivity
- Which priors to use
- No single measure of statistical significance
- Fear of acceptance in terms of publication and regulatory bodies
- Computational aspects
- Lack of experience and understanding

Conclusions

- Use of randomised phase II trials is increasing
- No clear guidance on how to analyse randomised phase II trials
- Bayesian analysis is promoted as method for interim analysis of phase III
- Bayesian analysis seems to be the natural approach for randomised phase II trials that will give researchers the answers they want and should be promoted