Practical Issues in the Bayesian Design of Early Clinical Studies of Treatment Efficacy

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Summary

- Study Design
- Prior Knowledge
- Decision Criteria
- Study Operating Characteristics
- Interim Analyses
- Issues & Value of Approach

“Proof of Concept” Study

- Novel treatment for Osteoarthritic pain
  - Test compound
  - Positive control (Standard of Care)
  - Negative control (Placebo)
- Response is patient reported pain score
- Design options
  - Parallel groups, 2 weeks duration
  - Cross-over, 2 x 2 weeks + washout

Prior Knowledge

Historical Studies (OA population)

study	treatment	N	CFB.LSmean	se.CFB	residual std (CFB)	baseline mean	scale
1	Placebo	201	-0.7	0.23	3.26	10.8	WOMAC(0-20)
1	Naproxen	198	-2.7	0.23	3.24	11.0	WOMAC(0-20)
2	Placebo	242	-1.2	0.21	3.27	10.5	WOMAC(0-20)
2	Naproxen	226	-2.8	0.21	3.16	11.1	WOMAC(0-20)
4	Placebo	66	-2.6	0.47	3.82		WOMAC(0-20)
4	Naproxen	69	-4.6	0.46	3.82		WOMAC(0-20)
6	Placebo	41	-2.3	0.58	3.70	11.5	WOMAC(0-20)
6	Naproxen	39	-4.4	0.59	3.70	11.5	WOMAC(0-20)
7	Placebo	205	-2.2	0.25	3.57	10.9	WOMAC(0-20)
7	Naproxen	204	-3.3	0.25	3.57	10.7	WOMAC(0-20)
9	Placebo	110	-2.8	0.36	3.82	11.3	WOMAC(0-20)
11	Placebo	42	-1.0	0.50	3.21		WOMAC(0-20)
3	Placebo	217	-0.7	0.21	3.09	10.6	WOMAC(0-20)
3	Naproxen	207	-2.9	0.21	3.02	10.5	WOMAC(0-20)
5	Placebo	73	-3.2	0.47	4.02	13.8	Scaled from VAS (0-100)
8	Placebo	82	-0.4	0.44	4.03	10.5	Scaled from VAS (0-500)
8	Naproxen	75	-3.5	0.47	4.03	10.4	Scaled from VAS (0-500)
10	Placebo	117	-0.9	0.32	3.48		WOMAC(0-20)
10	Naproxen	118	-3.1	0.32	3.48		WOMAC(0-20)
13	Placebo	104	-4.4		4.50	13.2	Scaled from VAS (0-100)
13	Naproxen	117	-7.0		4.50	13.0	Scaled from VAS (0-100)

Prior Distributions from Historical Data

- Normal Linear Mixed Model

$$Y_{ij} = \mu + \alpha_i + s_j + (\alpha s)_{ij} + e_{ij}$$

$$s_j \sim N(0, \omega_s^2)$$

$$(\alpha s)_{ij} \sim N(0, \omega_{\alpha s}^2)$$

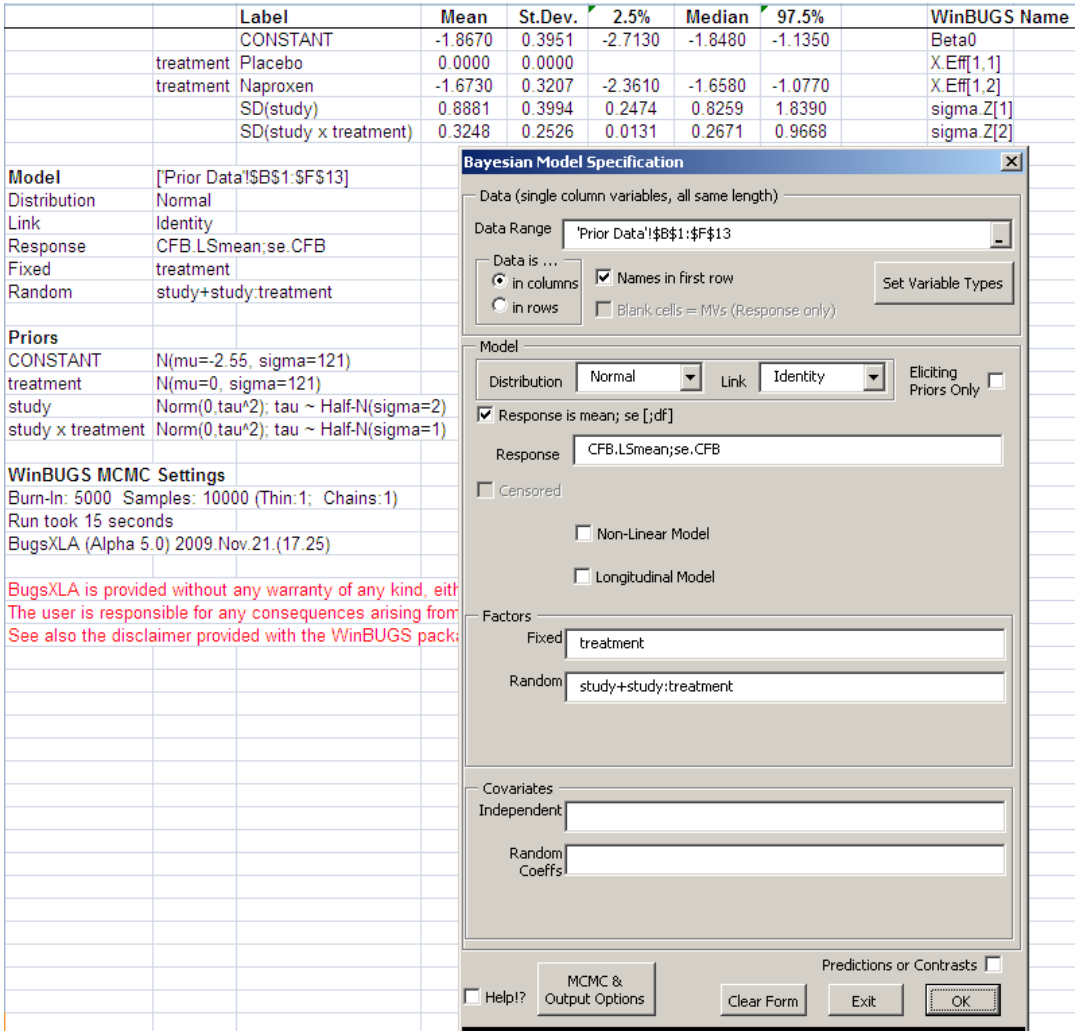
$$e_{ij} \sim N(0, SE_{ij}^2)$$

Y_{ij} are the observed treatment means for the i^{th} treatment in the j^{th} study, and SE_{ij} are their associated standard errors

Prior Distributions from Historical Data

Model fitted using WinBUGS via GUI BugsXLA

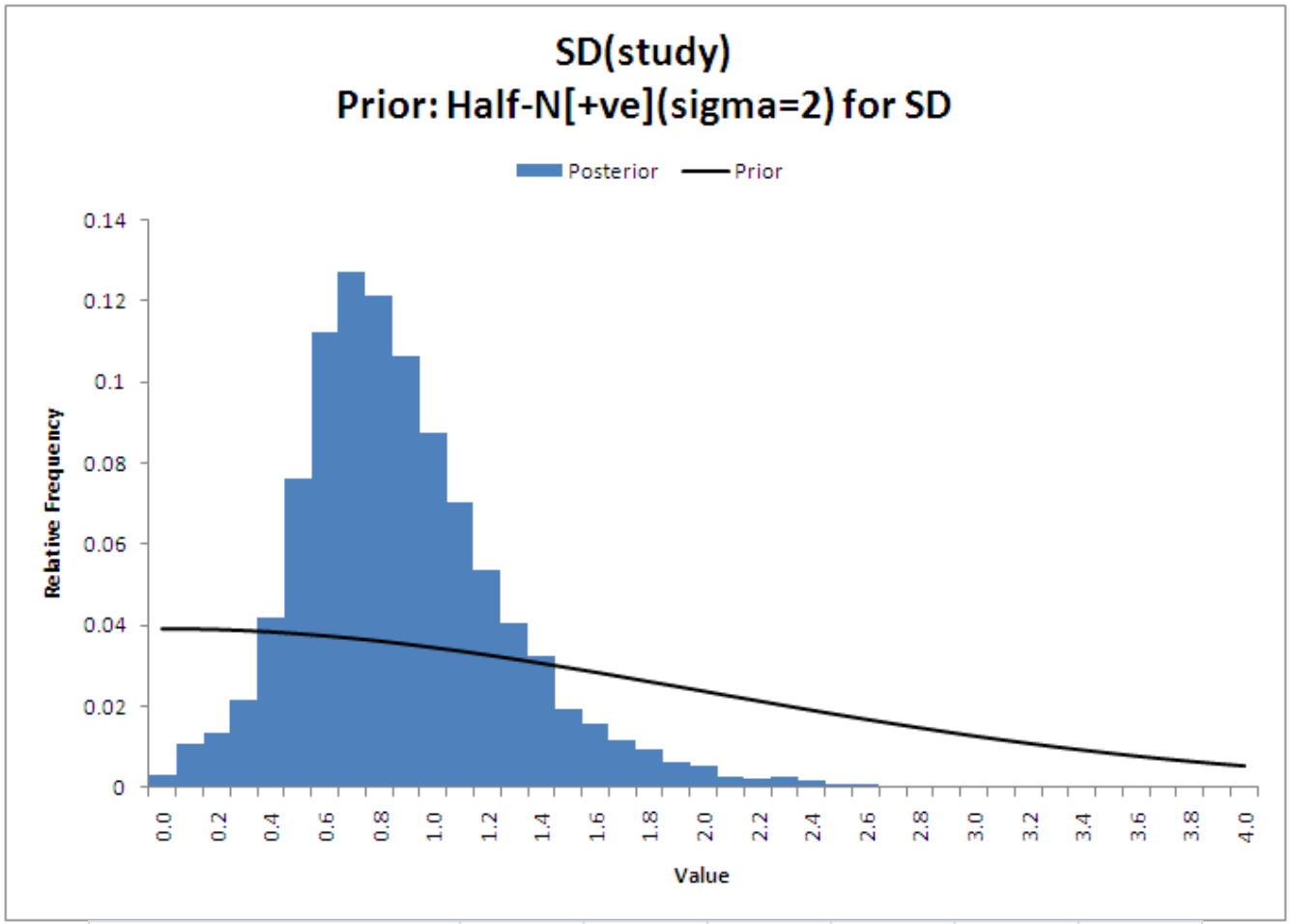
BugsXLA removes need for WinBUGS expertise



		Label	Mean	St.Dev.	2.5%	Median	97.5%	WinBUGS Name
		CONSTANT	-1.8670	0.3951	-2.7130	-1.8480	-1.1350	Beta0
	treatment	Placebo	0.0000	0.0000				X.Eff[1,1]
	treatment	Naproxen	-1.6730	0.3207	-2.3610	-1.6580	-1.0770	X.Eff[1,2]
		SD(study)	0.8881	0.3994	0.2474	0.8259	1.8390	sigma.Z[1]
		SD(study x treatment)	0.3248	0.2526	0.0131	0.2671	0.9668	sigma.Z[2]

Model	['Prior Data'!$B$1:$F$13]
Distribution	Normal
Link	Identity
Response	CFB.LSmean;se.CFB
Fixed	treatment
Random	study+study:treatment
Priors	
CONSTANT	N(mu=-2.55, sigma=121)
treatment	N(mu=0, sigma=121)
study	Norm(0,tau^2); tau ~ Half-N(sigma=2)
study x treatment	Norm(0,tau^2); tau ~ Half-N(sigma=1)
WinBUGS MCMC Settings	
Burn-In: 5000 Samples: 10000 (Thin:1; Chains:1)	
Run took 15 seconds	
BugsXLA (Alpha 5.0) 2009.Nov.21.(17.25)	
BugsXLA is provided without any warranty of any kind, eith	
The user is responsible for any consequences arising from	
See also the disclaimer provided with the WinBUGS packa	

Visual Comparison of Prior & Posterior



Posterior Percentiles								
0.1%	0.5%	1.0%	2.5%	5%	10%	20%	25%	50%
0.0	0.1	0.1	0.2	0.4	0.5	0.6	0.6	0.8
99.9%	99.5%	99.0%	97.5%	95%	90%	80%	75%	
3.1	2.3	2.1	1.8	1.6	1.4	1.2	1.1	

Prior Distributions from Historical Data

- Prior for treatment mean responses in future study is predictive distribution not posterior
- Predictive distribution obtained via WinBUGS
  - (Std of Care, Pbo) has a bivariate prior dist.
    - Due to between study variance
  - Multi-Variate Normal fitted
- Study designs assessed via simulation
  - Use “well known” NLM result to derive posterior
  - Analytical result speeds up simulation

Prior Distributions from Historical Data

Lemma: Lindley and Smith (JRSSB,1972,34,1-18)

If θ_1 a vector of p_1 parameters

$y \sim N(A_1\theta_1, C_1)$,

and θ_2 a vector of p_2 hyperparameters

$\theta_1 \sim N(A_2\theta_2, C_2)$,

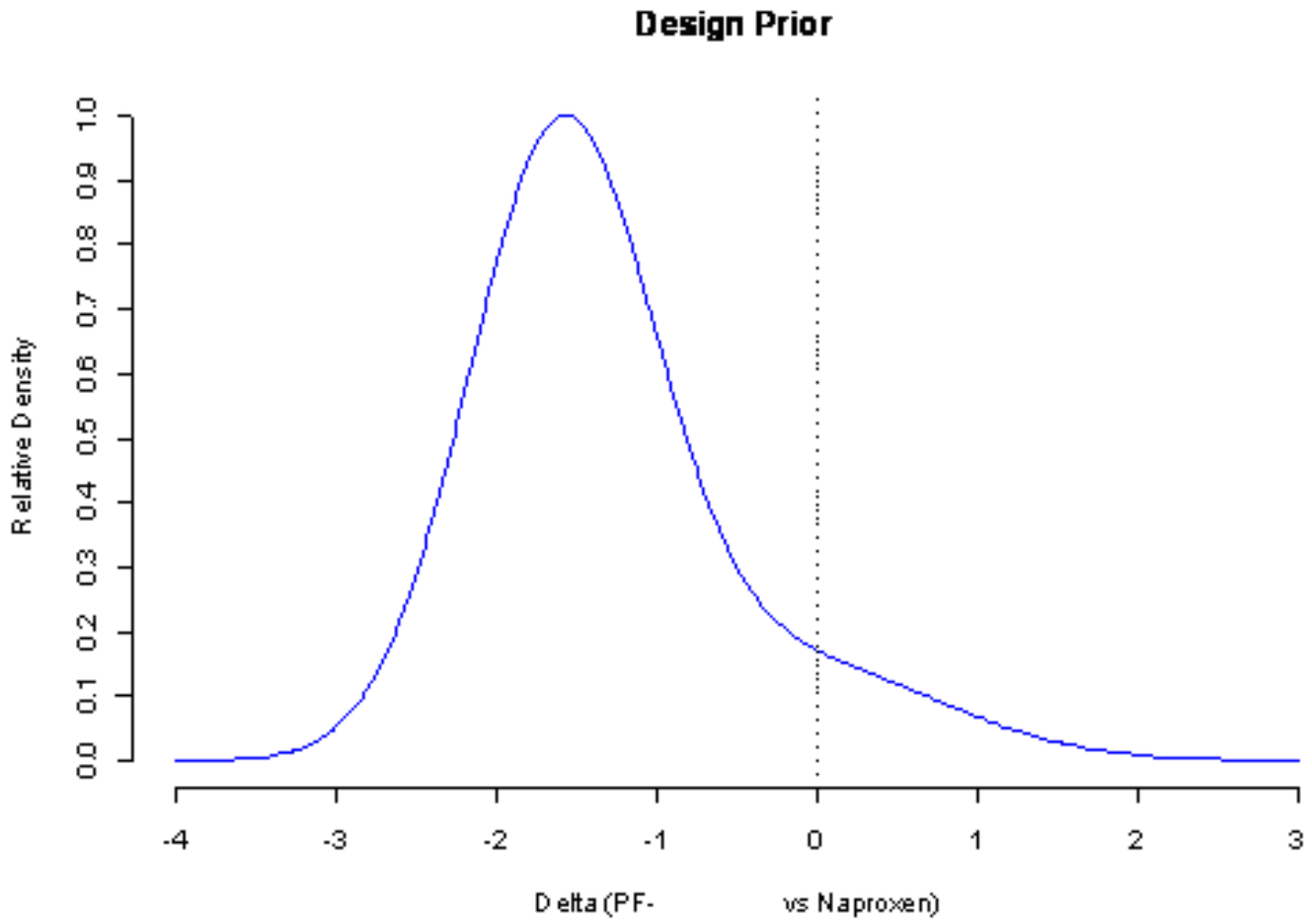
then $p(\theta_1 | y)$ is $N(Bb, B)$ with

$B^{-1} = A'_1C_1^{-1}A_1 + C_2^{-1}$

and

$b = A'_1C_1^{-1}y + C_2^{-1}A_2\theta_2$

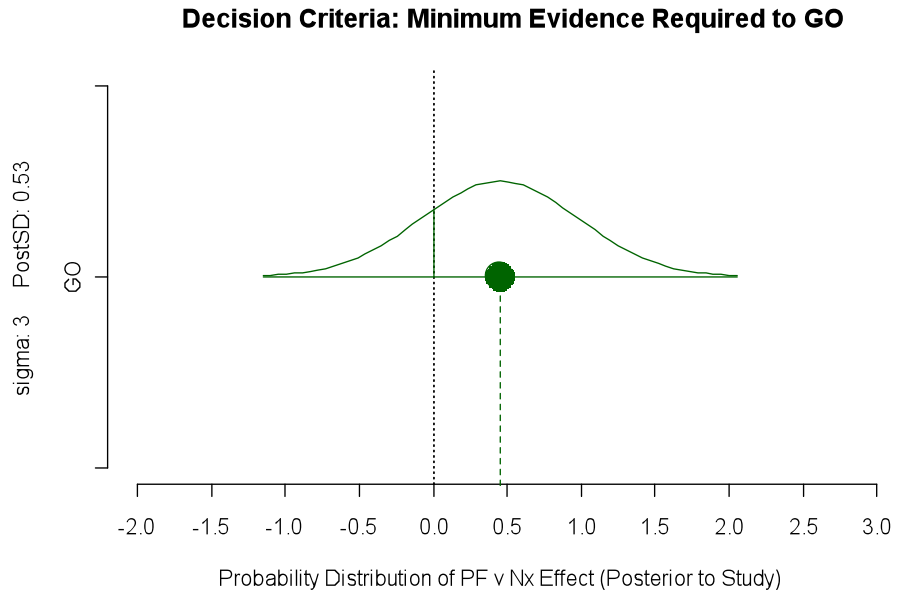
Elicited Prior Distribution (Novel Treatment)



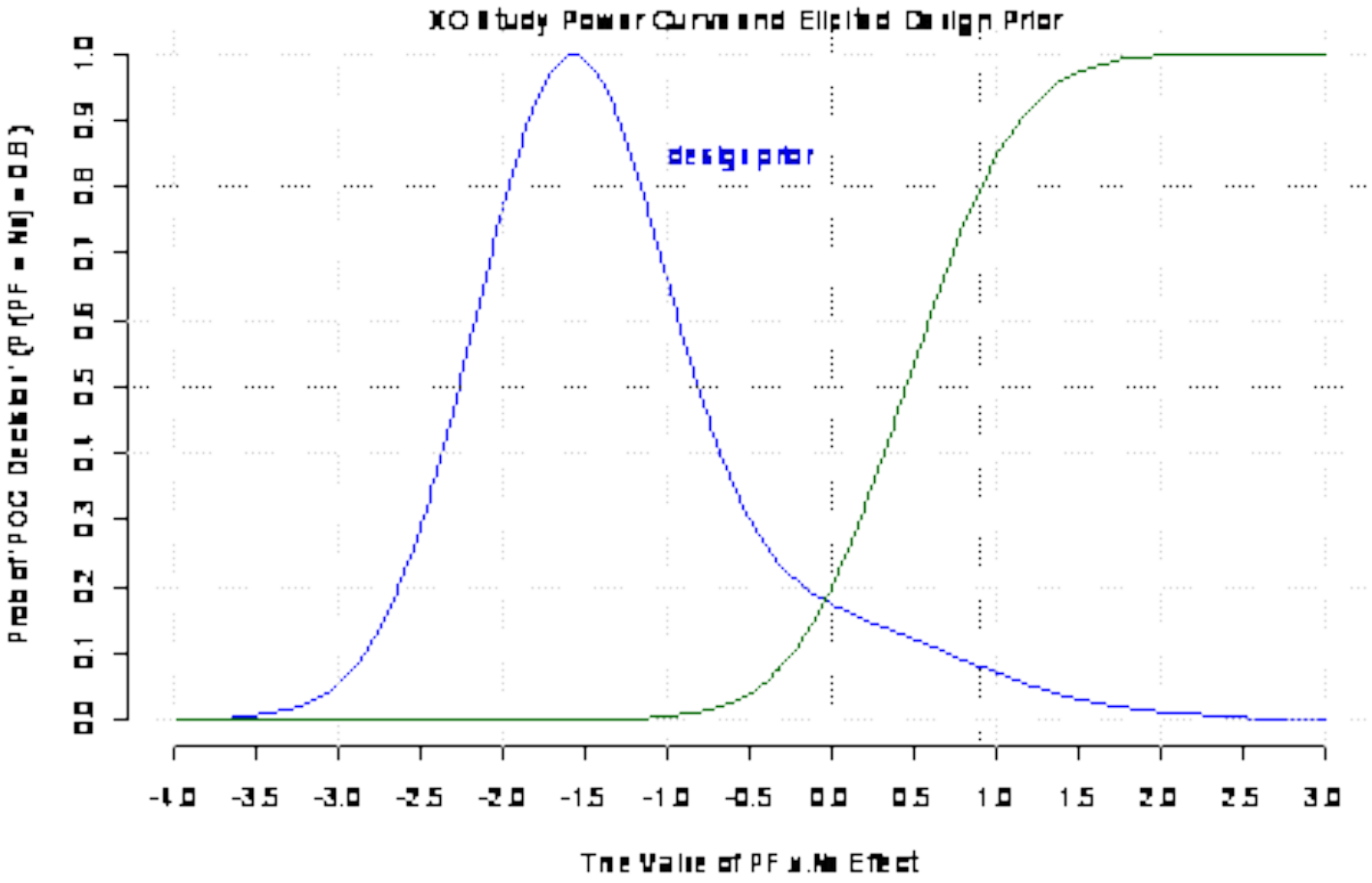
Decision Criteria

C1: At least 90% sure better than placebo.

C2: At least 80% sure better than naproxen.



Study OC (C2) with Prior Overlaid

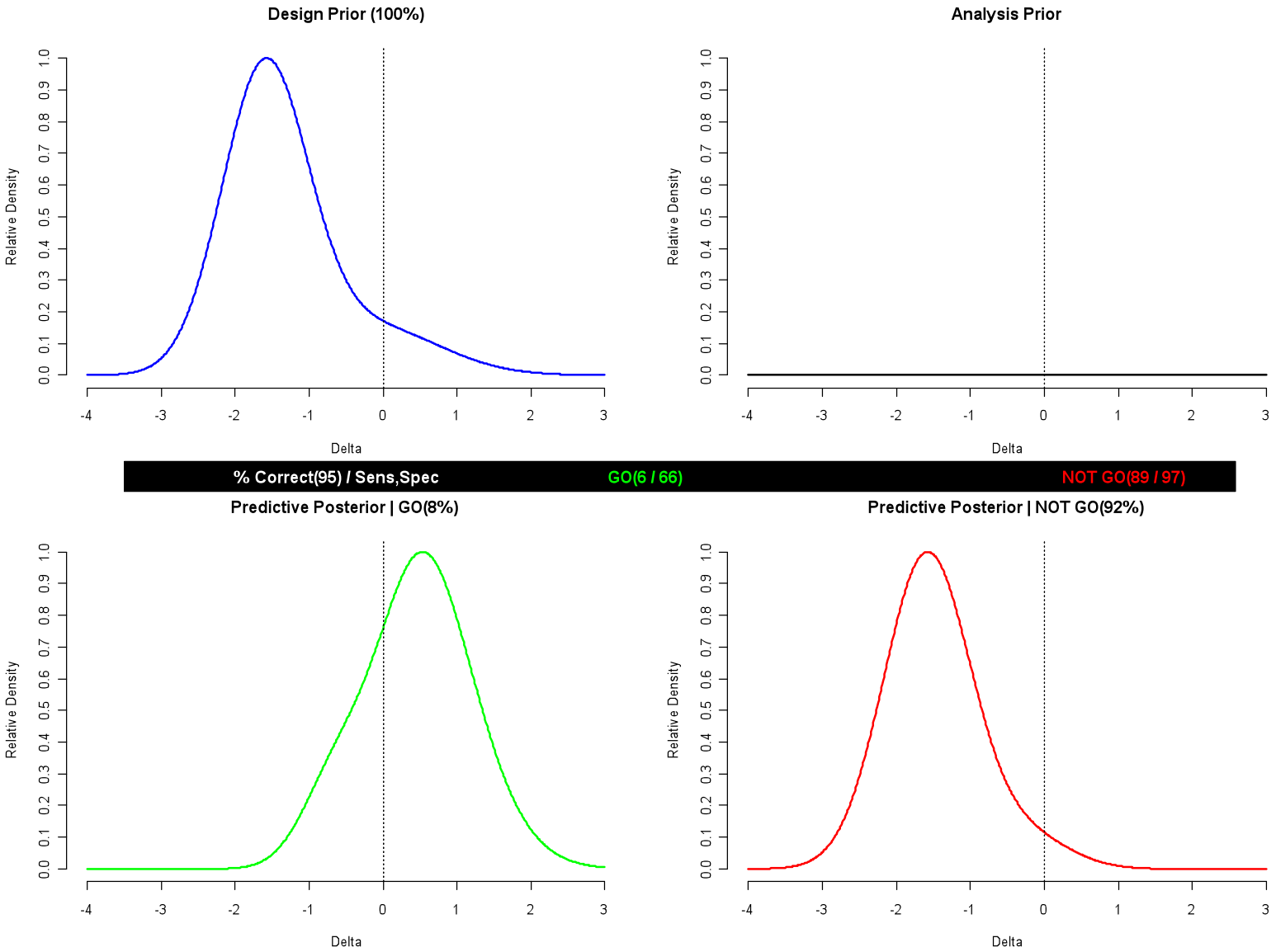


Study OC Summaries

	Effective Cmpd Δ > 0.7	Ineffective Cmpd Δ ≤ 0.7
Stop (Not superior to Pbo)	**0.11** Pr(Stop | Eff)	**0.89** Pr(Stop | Ineff) "Specificity"
Not Stop (Superior to Pbo)	**0.89**	**0.11**
Total	1.0	1.0

	Effective Cmpd Δ > Nx	Ineffective Cmpd Δ ≤ Nx
Not PoC (Not superior to Nx)	**0.42**	**0.99**
PoC (Superior to Nx)	**0.58** Pr(Go | Eff) "Sensitivity"	**0.01** Pr(Go | Ineff)
Total	1.0	1.0

Positive & Negative Predictive Distributions



Interim Analysis

Stop for futility

Probability of C1 at study end < 20%.

Stop for clear efficacy

Probability of C2 at study end > 80%.

Continue otherwise.

Practical Issues & Value of Bayesian Design

Education & training in Bayesian approach

Philosophy as well as methods

Elicitation: purpose & "how to do it"

Software tools for non-experts

e.g. BugsXLA GUI for WinBUGS, R Scripts

Precedented methods not available

What do we do with all the new probabilities?

Classical :	p(Pass test | true value)	: power
Bayesian:	p(Pass test)	: E(power)
	p(true value | Pass test)	: +ve pred. post.
	p(true value)	: prior