Introduction to the Design and Evaluation of Group Sequential Clinical Trials

Session 4 - Bayesian Evaluation of Group Sequential Designs

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Bayesian paradigm

Bayesian Operating Characteristics

- Thus far, we have primarily focused on the evaluation of a clinical trial design with respect to frequentist operating characteristics
  - type I error
  - statistical power
  - sample size requirements
  - estimates of treatment effect that correspond to early termination
  - precision of confidence intervals
- However, there has been much interest in the design and analysis of clinical trials under a Bayesian paradigm

Bayesian paradigm

Bayesian Operating Characteristics

- In the Bayesian paradigm, we consider a joint distribution $p(\theta, X)$ for the treatment effect parameter θ and the clinical trial data X.
- We most often specify the prior distribution $p_\theta(\theta)$ and the likelihood function $p_{X|\theta}(X|\theta)$, rather than specifying the joint distribution $p(\theta, X)$
  - The prior distribution $p_\theta(\theta)$ represents the information about θ prior to (in the absence of) any knowledge of the value of X
- From a clinical trial, we observe data $X = x$ and base inference on the posterior distribution $p_{\theta|X}(\theta|X = x)$, where by Bayes rule

$$p_{\theta|X}(\theta|X = x) = \frac{p_{X|\theta}(X|\theta)\, p_\theta(\theta)}{\int p_{X|\theta}(X|\theta)\, p_\theta(\theta)\, d\theta}$$

Bayesian paradigm

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Bayesian Operating Characteristics

- As with frequentist inference, we are interested in:
  - point and interval estimates of a treatment effect,
  - a measure of strength of evidence for or against particular hypotheses, and perhaps
  - a binary decision for or against some hypothesis.

Bayesian Operating Characteristics

- Bayesian inferential quantities include:

1. *Point estimates of treatment effect* that are summary measures of the posterior distribution such as:

1.1 the posterior mean : $E(\theta|X = x)$,

1.2 the posterior median : $\theta_{0.5}$ such that

$$Pr(\theta \leq \theta_{0.5}|X = x) \geq 0.5 \text{ and } Pr(\theta \geq \theta_{0.5}|X = x) \geq 0.5,$$

1.3 the posterior mode : θ_m such that

$$p_{\theta|X}(\theta_m|X = x) \geq p_{\theta|X}(\theta|X = x) \quad \text{for all } \theta$$

Bayesian Operating Characteristics

2. *Interval estimates of treatment effect* that are computed by finding two values (θ_L, θ_U) such that

$$Pr(\theta_L \leq \theta \leq \theta_U|X = x) = 100(1 - \alpha)\%$$

2.1 the central $100(1 - \alpha)\%$ of the posterior distribution of θ is defined by finding some Δ such that $\theta_L = \hat{\theta} - \Delta$ and $\theta_U = \hat{\theta} + \Delta$ provides the desired coverage probability, where $\hat{\theta}$ is one of the Bayesian point estimates of θ

2.2 the interquantile interval is defined by defining $\theta_L = \theta_{\alpha/2}$ and $\theta_U = \theta_{1-\alpha/2}$, where θ_p is the p-th quantile of the posterior distribution, i.e., $Pr(\theta \leq \theta_p|X = x) = p$

2.3 the highest posterior density (HPD) interval is defined by finding some threshold c_α such that the choices

$$\theta_L = \min\{\theta : p_{\theta|X}(\theta|X = x) > c_\alpha\} \text{ and}$$
$$\theta_U = \max\{\theta : p_{\theta|X}(\theta|X = x) > c_\alpha\}$$

provide the desired coverage probability

Bayesian Operating Characteristics

3. *Posterior probabilities or Bayes factors associated with specific hypotheses* that might be used to make a decision for or against a particular hypothesis.

   3.1 For instance, in the sepsis trial example, we might be interested in computing the posterior probability of the null hypothesis $Pr(\theta \geq 0 | X = x)$ or the posterior probability of the design alternative $Pr(\theta \leq -0.07 | X = x)$.

Bayesian Operating Characteristics

- A note on Bayesian inference under group sequential testing
  - The Bayesian inference presented on the previous slides is unaffected by the choice of stopping rule, so long as there is no need to consider the joint distribution of estimates across the multiple analyses of the accruing data
    - So long as one is content to regard inference at each analysis marginally, then the stopping rule used to collect the data is immaterial
  - However, the expected cost of a clinical trial does depend very much on the stopping rule used, even when Bayesian inference is used as the basis for a decision

Bayesian paradigm

Bayesian posterior probability scale in RCTdesign

- In considering the Bayesian approach, we maintain the stance that the derivation of the stopping rule is relatively unimportant.
- There is a 1:1 correspondence between stopping rules defined for frequentist statistics (on a variety of scales) and Bayesian statistics for a specified prior
- Specifically, in RCTdesign we consider a robust approach to Bayesian inference based on a coarsening of the data by using the asymptotic distribution of a nonparametric estimate of treatment effect
  - For example, in the case of the sepsis trial, we use the approximate normal distribution for the difference in 28 day mortality rates

$$\hat{\theta} \equiv \hat{p}_1 - \hat{p}_0 \dot{\sim} \mathcal{N}\left(\theta, \frac{p_1(1-p_1) + p_0(1-p_0)}{N}\right)$$

Bayesian paradigm

Bayesian posterior probability scale in RCTdesign

- Reasoning behind the “coarsened” Bayesian approach

1. Robustness of inference to misspecification of the likelihood
2. No true conflict between frequentist and Bayesian inference. Instead, they merely answer different questions.
   - 2.1 Role of statistics is to help quantify the strength of evidence used to convince the scientific community
   - 2.2 Reasonable people might demand evidence:

     (1) demonstrating results that would not typically be obtained under any other hypothesis (frequentist), or

     (2) that overpowers his/her prior beliefs
   - 2.3 To address these different standards of proof within the same setting, it would seem most appropriate to use the same probability model in each approach

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Bayesian posterior probability scale in RCTdesign

- Reliance on the asymptotic distribution of the *estimator* implies that a normal prior is conjugate and computationally convenient

$$\theta \sim N(\zeta, \tau^2)$$

- Thus we can define a Bayesian posterior probability statistic by computing the approximate posterior probability that the null hypothesis $H_0 : \theta \geq \theta_0$ is false

$$\begin{aligned} B_j(\zeta, \tau^2, \theta_0) &= Pr(\theta \leq \theta_0 \mid S_j = s_j) \\ &= \Phi\left(\frac{\theta_0[N_j\tau^2 + V] - \tau^2 s_j - V\zeta}{\sqrt{V}\tau\sqrt{N_j\tau^2 + V}}\right), \quad (1) \end{aligned}$$

where $V = p_0(1-p_0) + p_1(1-p_1)$ and $\Phi(z)$ is the cumulative distribution function for a standard normal random variable

Case Study : Sepsis Trial

Boundaries on various design scales

- In the context of the sepsis trial, consider a group sequential design with an O'Brien-Fleming efficacy analysis ($P = 1, R = 0, A = 0$) and a futility bound specified by $P = 0.8, R = 0, A = 0$, specifying 4 equally spaced analyses with max sample size of 1700 patients

```
> Futility.8 <- seqDesign("prop",test="less",,
+         sample.size=c(.25,.5,.75,1)*1700, null=0.30,alt=0.23,
+         power="calculate", nbr.analyses=4, P=c(1,0.8))

> Futility.8

PROBABILITY MODEL and HYPOTHESES:
   Theta is difference in probabilities (Treatment - Comparison)
   One-sided hypothesis test of a lesser alternative:
          Null hypothesis : Theta >=  0.00    (size  = 0.0250)
    Alternative hypothesis : Theta <= -0.07    (power = 0.8888)

STOPPING BOUNDARIES: Sample Mean scale
                     Efficacy Futility
    Time 1 (N=  425)  -0.1697   0.0473
    Time 2 (N=  850)  -0.0848  -0.0097
    Time 3 (N= 1275)  -0.0566  -0.0310
    Time 4 (N= 1700)  -0.0424  -0.0424
```

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Case Study : Sepsis Trial

Boundaries on various design scales

- Bayesian posterior probabilities for observed estimates on the Futility.8 boundary
- Computed using a optimistic ($\zeta = -0.09$) dogmatic prior ($\tau^2 = 0.015^2$) prior

```
> changeSeqScale(Futility.8,
        seqScale("B",priorTheta=-0.09, priorVariation=0.015^2))

STOPPING BOUNDARIES: Bayesian scale
        (Posterior probability of hypotheses based on prior
         distribution having median -0.09
         and variation parameter 0.000225)
                      a      d
    Time 1 (N=  425) 1 0.7954
    Time 2 (N=  850) 1 0.8239
    Time 3 (N= 1275) 1 0.8361
    Time 4 (N= 1700) 1 0.8423
```


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Boundaries on various design scales

- Example interpretation (1st analysis, efficacy bound (a)): Under the optimistic dogmatic prior, after sampling 425 subjects if the observed rate in the treatment arm were 16.97% lower than the control arm, the posterior probability of the event $\theta \leq 0$ is computed to be approx 1
- Example interpretation (1st analysis, futility bound (d)): Under the optimistic dogmatic prior, after sampling 425 subjects if the observed rate in the treatment arm were 4.73% larger than the control arm, the posterior probability of the event $\theta \geq -0.0866$ is computed to be 0.7954

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Boundaries on various design scales

- Bayesian posterior probabilities for observed estimates on the Futility.8 boundary
- Computed using a pessimistic ($\zeta = 0.02$) dogmatic prior ($\tau^2 = 0.015^2$) prior

```
> changeSeqScale(Futility.8,seqScale("B",
        priorTheta= 0.02, priorVariation=0.015^2))

STOPPING BOUNDARIES: Bayesian scale
        (Posterior probability of hypotheses based on prior
         distribution having median 0.02
         and variation parameter 0.000225)
                          a d
    Time 1 (N=  425) 0.5240 1
    Time 2 (N=  850) 0.5228 1
    Time 3 (N= 1275) 0.5218 1
    Time 4 (N= 1700) 0.5208 1
```


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Boundaries on various design scales

- Bayesian posterior probabilities for observed estimates on the Futility.8 boundary
- Computed using a consensus ($\zeta = -0.04$) dogmatic prior ($\tau^2 = 0.015^2$) prior

```
> changeSeqScale(Futility.8,
        seqScale("B",priorTheta=-0.04,priorVariation=0.015^2))

STOPPING BOUNDARIES: Bayesian scale
        (Posterior probability of hypotheses based on prior
         distribution having median -0.04
         and variation parameter 0.000225)
                          a      d
    Time 1 (N=  425) 0.9999 1.0000
    Time 2 (N=  850) 0.9999 1.0000
    Time 3 (N= 1275) 0.9997 0.9999
    Time 4 (N= 1700) 0.9996 0.9999
```

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Boundaries on various design scales

- Note 1: By default, `seqScale()` will compute the posterior probability of the hypothesis being tested for each boundary
  - `seqDesign()` defaults to a symmetric test implying the futility boundary rejects the $(1-\alpha)$ power point for a test with size α
  - For the `Futility.8` design, this is the 97.5% power point corresponding to $\theta = -0.0866$
  - To see this, one can view the `Futility.8$hypothesis`

```
> Futility.8$hypothesis
HYPOTHESES:
   Theta is difference in probabilities (Treatment - Comparison)
   One-sided hypothesis test of a lesser alternative:
           Null hypothesis : Theta >=  0.00    (size  = 0.0250)
    Alternative hypothesis : Theta <= -0.07    (power = 0.8888)

  Boundary hypotheses:
      Boundary a rejects : Theta >=  0.0000    (lower size  = 0.025)
      Boundary b rejects : Theta <= -0.0866    (lower power = 0.975)
      Boundary c rejects : Theta >=  0.0000    (upper power = 0.975)
      Boundary d rejects : Theta <= -0.0866    (upper size  = 0.025)
```


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Boundaries on various design scales

- Note 2: An asymmetric boundary can be obtained by modifying the `alpha` option in `seqDesign()`
  - As this changes the hypotheses being tested at each analysis, it will change the boundaries and operating characteristics of the stopping rule
- Note 3: To simply compute a different posterior probability, you can use the `threshold` option in `seqScale()`

```
changeSeqScale(Futility.8,
        seqScale("B", threshold=-0.06,
                 priorTheta=-0.09,priorVariation=0.015^2))

STOPPING BOUNDARIES: Bayesian scale
        (Posterior probability that treatment effect exceeds -0.06
         based on prior distribution having median -0.09
         and variation parameter 0.000225)
                          a      d
    Time 1 (N=  425) 0.0031 0.1461
    Time 2 (N=  850) 0.0155 0.1471
    Time 3 (N= 1275) 0.0509 0.1365
    Time 4 (N= 1700) 0.1225 0.1225
```

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Boundaries on various design scales

- Bayesian posterior probabilities for observed estimates on the Futility.8 boundary
- Computed using a non-informative prior ($\tau = \infty$)

```
> changeSeqScale(Futility.8,
        seqScale("B",priorTheta= 0.02,priorVariation=Inf))

STOPPING BOUNDARIES: Bayesian scale
        (Posterior probability of hypotheses based on prior
         distribution having median 0.02
         and variation parameter Inf)
                          a      d
    Time 1 (N=  425) 1.0000 0.9991
    Time 2 (N=  850) 0.9975 0.9946
    Time 3 (N= 1275) 0.9891 0.9880
    Time 4 (N= 1700) 0.9766 0.9808
```


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Sensitivity of posterior probabilities to prior

- Bayesian inference can depend heavily on the choice of prior distribution $p_\theta(\theta)$ for the treatment effect parameter
- For that reason, Bayesian inferential procedures have sometimes been criticized because it is not clear how the prior distribution should be selected for any particular problem

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Sensitivity of posterior probabilities to prior

- The Bayesian evaluation of stopping rules proceeds much the same as for the evaluation of stopping rules with respect to frequentist inference
- The major difference relates to the magnitude of the results that need to be presented
  - When evaluating a stopping rule with respect to frequentist inference, we present the estimate, confidence interval, and P value for clinical trial results corresponding to the stopping boundaries
  - For Bayesian inference, we must consider how that inference is affected by the choice of prior

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Sensitivity of posterior probabilities to prior

- In RCTdesign, the approach we take is to use a spectrum of normal prior distributions specified by their mean and standard deviation
  - Normal prior is specified entirely by two parameters, greatly reducing the dimension of the space of prior distributions to be considered
  - Means and standard deviations are commonly used and understood by many researchers
  - Normal distribution is known to maximize entropy over the class of all priors having the same first two moments
    - Potentially deleterious if an individual's well-based prior is more informative than the normal prior with the same mean and standard deviation
    - In this case, an analysis with a normal prior may suggest that the data has overwhelmed an investigator's initial belief, when it in fact has not

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Sensitivity of posterior probabilities to prior

	Efficacy (lower) Boundary				Futility (upper) Boundary			
	Posterior Probability of Beneficial Treatment Effect $\Pr(\theta \leq 0 \mid X)$				Posterior Probability of Insufficient Benefit $\Pr(\theta \geq -0.087 \mid X)$			
Analysis Time	Crude Est of Trt Effect	Optimistic $\zeta = -.09$	Sponsor's Consensus $\zeta = -.04$	Pessimistic $\zeta = .02$	Crude Est of Trt Effect	Optimistic $\zeta = -.09$	Sponsor's Consensus $\zeta = -.04$	Pessimistic $\zeta = .02$
Dogmatic Prior: $\tau = 0.015$								
1:N=425	-0.170	1.000	1.000	0.524	0.047	0.795	1.000	1.000
2:N=850	-0.085	1.000	1.000	0.523	-0.010	0.824	1.000	1.000
3:N=1275	-0.057	1.000	1.000	0.522	-0.031	0.836	1.000	1.000
4:N=1700	-0.042	1.000	1.000	0.521	-0.042	0.842	1.000	1.000
Consensus Prior: $\tau = 0.040$								
1:N= 425	-0.170	1.000	1.000	0.991	0.047	0.981	0.999	1.000
2:N= 850	-0.085	1.000	0.998	0.974	-0.010	0.976	0.997	1.000
3:N=1275	-0.057	0.999	0.993	0.955	-0.031	0.970	0.994	1.000
4:N=1700	-0.042	0.998	0.987	0.936	-0.042	0.963	0.991	0.999
Noninformative Prior: $\tau = \infty$								
1:N= 425	-0.170	1.000	1.000	1.000	0.047	0.999	0.999	0.999
2:N= 850	-0.085	0.998	0.998	0.998	-0.010	0.995	0.995	0.995
3:N=1275	-0.057	0.989	0.989	0.989	-0.031	0.988	0.988	0.988
4:N=1700	-0.042	0.977	0.977	0.977	-0.042	0.981	0.981	0.981

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Sensitivity of posterior probabilities to prior

- As is often the case, the optimistic and pessimistic priors presented were chosen rather arbitrarily, and thus may not be relevant to some of the intended audience for the published results of a clinical trial
- As such, it may be beneficial to present contour plots of Bayesian point estimates (posterior means), lower and upper bounds of 95% credible intervals, and posterior probabilities of the null and alternative hypotheses for a spectrum of prior distributions
- In RCTdesign, such plots can be produced with `seqBayesContour()`

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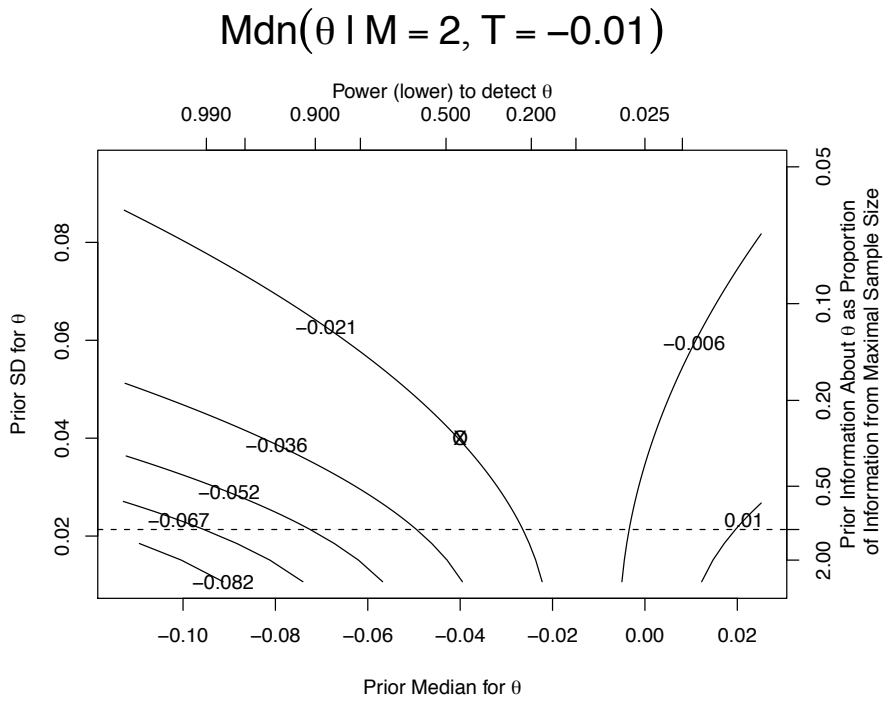
Contour plot of posterior median conditional upon stopping at analysis 2 for futility (observed statistic on boundary)



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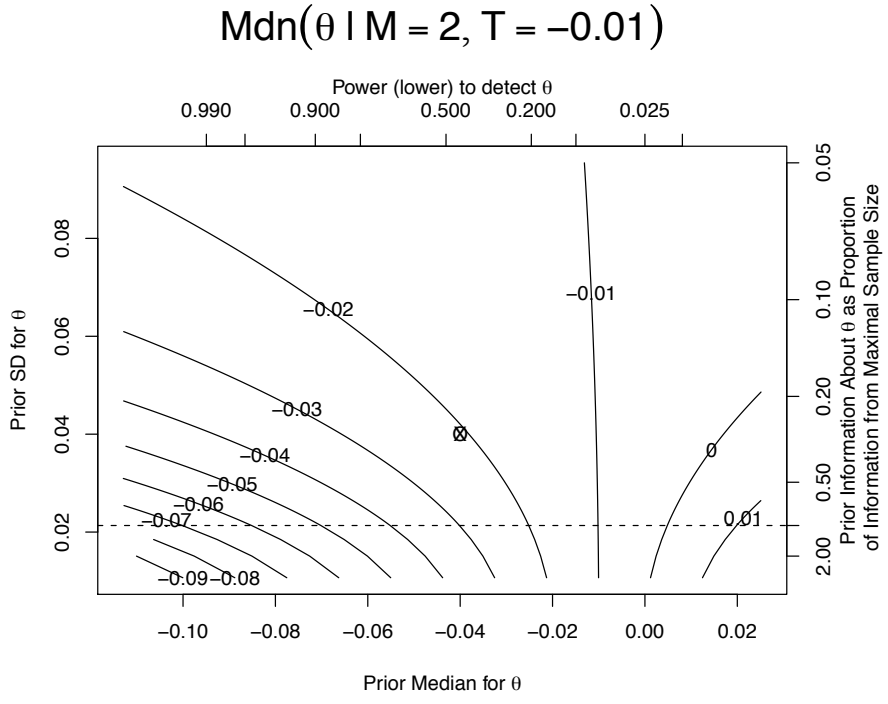
Contour plot of posterior median conditional upon stopping at analysis 2 for futility (user-defined contours)



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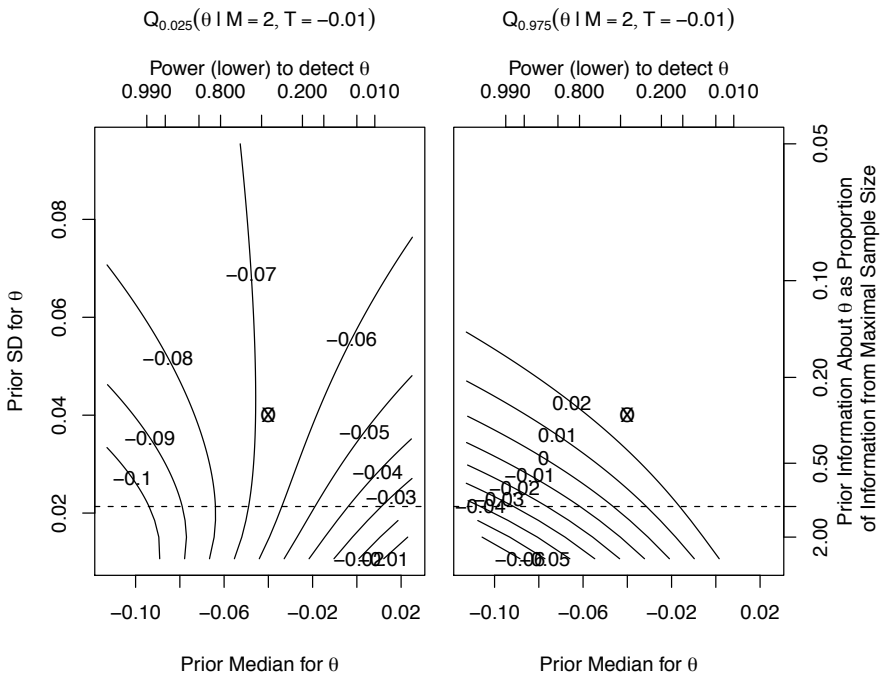
Contour plot of credible interval bounds at analysis 2 futility bound (user-defined contours)



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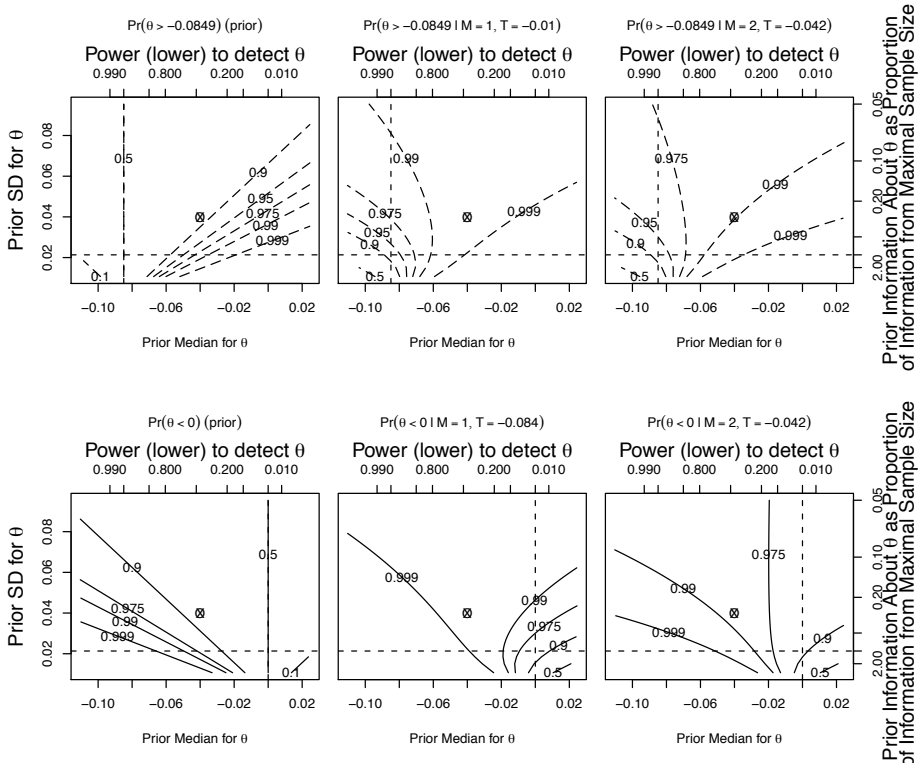
Contour plot of posterior probabilities for a 2 analysis design



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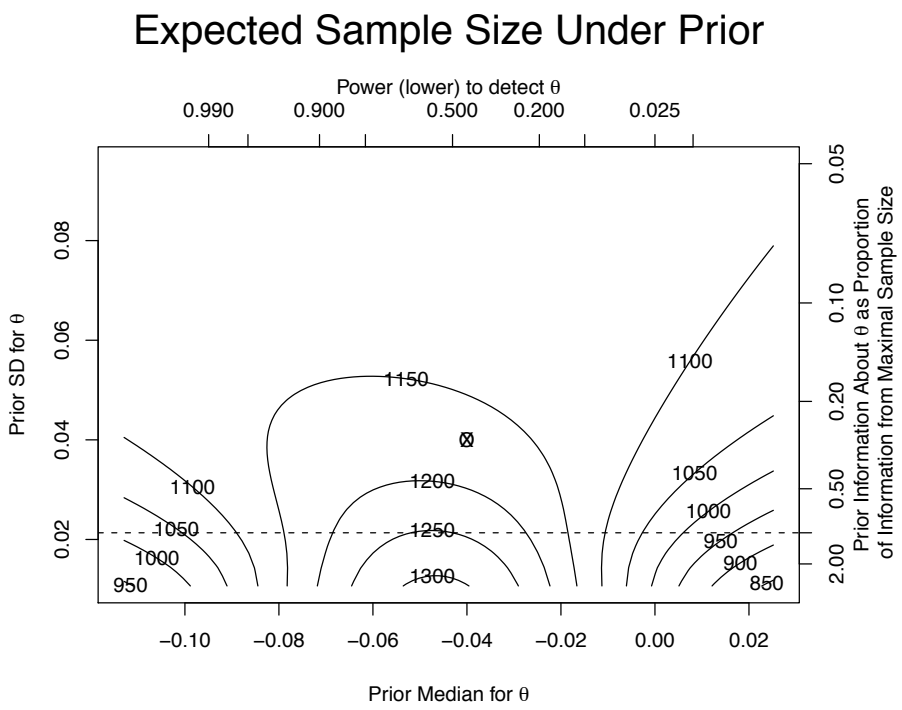
Contour plot of ASN for `Futility.8` design



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The `seqBayesContour()` function

- Important arguments to `seqBayesContour()` are:

`dsn` :	the seqDesign() object used for computing Bayesian operating characteristics
`analysis.index` :	the analysis time to condition on; if missing, operating characteristics will be computed for all analyses
`observed` :	the observed statistic to condition on; if missing, boundary values are used
`priorTheta` :	mean of prior distribution
`priorVariation` :	variance of prior distribution
`thetaThreshold` :	threshold for computing posterior probabilities; if missing, boundary hypotheses are used

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The `seqBayesContour()` function

- Important arguments to `seqBayesContour()` are:

`posteriorProbContours` :	specifies contour lines for which posterior probabilities are to be drawn; defaults to c(0.001, 0.01, 0.025, 0.05, 0.1, 0.5, 0.9, 0.975, 0.99, 0.999)
`posteriorMeanContours` :	if missing, plot with posterior mean contours will be drawn; if NULL, no plot will be drawn
`lowerCredibleBoundContours` :	if missing, plot with contours representing lower limits of specified credible interval will be drawn; if NULL, no plot will be drawn
`upperCredibleBoundContours` :	same as above
`PlotASN` :	ASN contours; defaults to TRUE
`SampSizeQuantiles` :	quantiles of sample size distribution for which contours are to be drawn; defaults to 0.75

Bayesian paradigm

Predictive probability scale in RCTdesign

- A Bayesian approach similar to the stochastic curtailment procedures would consider the Bayesian predictive probability that the test statistic would exceed some specified threshold at the final analysis
- This statistic uses a prior distribution and the observed data to compute a posterior distribution for the treatment effect parameter at the j-th analysis
- Using the sampling distribution for the as yet unobserved data and integrating over the posterior distribution, the predictive distribution of the test statistic at the final analysis can be computed

Predictive probability scale in RCTdesign

- Again relying on the asymptotic distribution of the estimator and utilizing a normal prior, $\theta \sim N(\zeta, \tau^2)$, we can compute a predictive probability statistic analogous to a conditional power statistic as

$$\begin{aligned} H_j(c, \zeta, \tau^2) &= \int Pr(\hat{\theta}_J < c \mid S_j = s_j, \theta)\, p(\theta \mid S_j = s_j)\, d\theta \\ &= \Phi\left(\frac{[\Pi_j \tau^2 + \sigma^2/N_J][c - \hat{\theta}_j] + [1 - \Pi_j][\hat{\theta}_j - \zeta]\sigma^2/N_J}{\sqrt{[1 - \Pi_j][\tau^2 + \sigma^2/N_J][\Pi_j \tau^2 + \sigma^2/N_j]\sigma^2/N_J}} \right). \end{aligned}$$

- Note that taking the limit as $\tau^2 \to 0$ (yielding a point-mass prior at ζ), the predictive probability statistic converges to the conditional power statistic discussed previously

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Probability of observing an economically important estimates of treatment effect

- Science vs. Marketing
  - Just as we separate statistical significance from clinical significance, marketing tends to have it's own threshold for signficance
  - What will sell?
- In this case, Bayesian predictive probabilities may be of use in judging whether it is useful to continue a clinical trial in the hopes of obtaining an economically attractive estimate of treatment effect
- For example, suppose that in the case of the sepsis trial an observed reduction of 6% (difference) in mortality would be deemed highly marketable...

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Boundaries on various design scales

- Bayesian predictive probabilities for observed estimates on the Futility.8 boundary
- Computed using a consensus prior ($\zeta = -0.04$, $\tau^2 = 0.04^2$)

```
> 1-changeSeqScale(Futility.8,seqScale("H",
                priorTheta=-0.04,priorVariation=.04^2,threshold=-.06))

STOPPING BOUNDARIES: Predictive Probability scale
        (Predictive probability that estimated treatment effect
         at the last analysis exceeds -0.06
         based on prior distribution having median -0.04
         and variation parameter 0.0016)
                          a      d
    Time 1 (N=  425) 0.9784 0.0057
    Time 2 (N=  850) 0.8066 0.0101
    Time 3 (N= 1275) 0.3501 0.0085
    Time 4 (N= 1700) 0.0000 0.0000
```


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Boundaries on various design scales

- Bayesian predictive probabilities for observed estimates on the Futility.8 boundary
- Computed using a non-informative prior ($\tau = \infty$)

```
> 1-changeSeqScale(Futility.8,seqScale("H",
                priorTheta=-0.04,priorVariation=Inf,threshold=-.06))

STOPPING BOUNDARIES: Predictive Probability scale
        (Predictive probability that estimated treatment effect
         at the last analysis exceeds -0.06
         based on prior distribution having median -0.04
         and variation parameter Inf)
                          a      d
    Time 1 (N=  425) 0.9985 0.0018
    Time 2 (N=  850) 0.8778 0.0092
    Time 3 (N= 1275) 0.3901 0.0093
    Time 4 (N= 1700) 0.0000 0.0000
```

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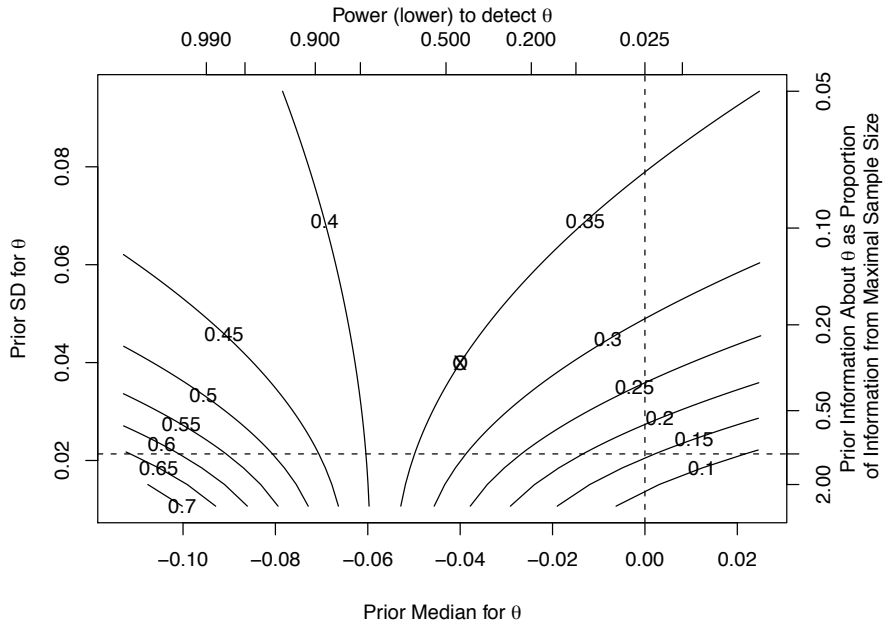
Contour plot of predictive probabilities at 3rd efficacy boundary

$$\Pr(\hat{\theta}_J < -0.06 \mid M = 3, T = -0.057)$$



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Probability of observing an economically important estimates of treatment effect

- For a result corresponding to a crude estimate of treatment effect of -0.0566 at the third analysis, the predictive probability of obtaining a crude estimate of treatment effect less than -0.06 at the final analysis is 35.0% under the sponsor's consensus prior and 39.0% under a noninformative prior
- In either case, such high probabilities of obtaining a more economically viable estimate of treatment effect may be enough to warrant modifying the stopping rule to avoid early termination at the third analysis with a crude estimate between -0.0566 and -0.06.

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Generalization to Bayesian families

Designs can often be re-expressed as a general family:

- Consider the design based on Bayesian posterior tail probabilities (equation (1)):

$$\begin{aligned} B_j(\zeta, \tau^2, \theta_0) &= Pr(\theta \leq \theta_0 \mid S_j = s_j) \\ &= \Phi\left(\frac{\theta_0[N_j\tau^2 + V] - \tau^2 s_j - V\zeta}{\sqrt{V}\tau\sqrt{N_j\tau^2 + V}} \right), \end{aligned}$$

- Reparameterization shows similarity to unified family.
  - Let $\tau^2 = \frac{V}{N_0}$ and $\hat{\theta}_j = \frac{s_j}{N_j}$, then you can show:

$$\begin{aligned} B_j(\zeta, \tau^2, \theta_{ref}) &= Pr(\theta \leq \theta_{ref} \mid \hat{\theta}_j) = \Phi(z) \\ \text{where: } z &= \frac{\theta_{ref}(N_j + N_0) - (N_j\hat{\theta}_j + N_0\zeta)}{\sqrt{V(N_j + N_0)}} \\ &= \frac{\theta_j(\Pi_j + \Pi_0) - (\Pi_j\hat{\theta}_j + \Pi_0\zeta)}{\sqrt{\frac{V}{N_J}(\Pi_j + \Pi_0)}} \end{aligned}$$

where $\Pi_j = \frac{N_j}{N_J}$ and $\Pi_0 = \frac{N_0}{N_J}$.

Generalization to Bayesian families

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Designs can often be re-expressed as a general family:

- Suppose that we want to choose d_j to assure that a superiority decision corresponds to:

$$Pr(\theta \leq \theta_0 \mid \hat{\theta}_j = d_j) = \alpha \quad \text{for all } j \text{ analyses}$$

thereby requiring:

$$z_\alpha = \frac{\theta_j 0(\Pi_j + \Pi_0) - (\Pi_j d_j + \Pi_0\zeta)}{\sqrt{\frac{V}{N_J}(\Pi_j + \Pi_0)}}$$

which implies:

$$d_j = \theta_0 + \left[\Pi_0(\theta_0 - \zeta) - z_\alpha\sqrt{\frac{V}{N_J}(\Pi_j + \Pi_0)} \right] \Pi_j^{-1}$$

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Generalization to Bayesian families

Designs can often be re-expressed as a general family:

- Which implies a generalized family of decision criteria:

$$d_j = \theta_0 + \left[A - G\sqrt{\frac{V}{N_J}(\Pi_j + \Pi_0)} \right] \Pi_j^{-P}$$

  where $A = \Pi_0(\theta_0 - \zeta)$ and $G = z_\alpha$ can be selected to control (frequentist) operating characteristics.
- Notice the similarity to the unified family boundary shape function:

$$d_j = \left[A + \Pi_j^{-P}(1 - \Pi_j)^{-R} \right] \times G$$

- These decision rules can be found using constrained boundaries (as illustrated in *session 7*).

Generalization of design families

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Summary remarks

- The Bayesian example illustrates:
  - Many different statistical frameworks lead to families of group sequential trial designs.
  - These families may differ in their statistical interpretation, but should still be considered as special cases of all group sequential trial designs.
- All sequential stopping rules can (and should):
  - ... be expressed on the scale of the estimated treatment effect.
  - ... be evaluated using the criteria described and illustrated in earlier sessions; including:
    - Power
    - ASN
    - Inference on the boundary
    - Stopping probabilities