Clinical Trial Design: Bayesian Approaches With Informative Priors and Adaptive Randomization for Time to Event Data - Methodology and Available Software

Gheorghe Doros[a]

[a]Boston University; Baim Institute; MAVERIC, VA Boston

Pfizer; Groton, CT

April 19, 2018

Bayesian paradigm

- Based on data y, prior π and Likelihood $f(y|\theta)$, the posterior distribution of θ is given by Bayes' Theorem

$$\pi(\theta|y) = \frac{f(y|\theta) \times \pi(\theta)}{f(y)} \propto f(y|\theta) \times \pi(\theta)$$

- Above $f(y) = 1/c(y)$ - prior predictive density

$$f(y) = \int f(y|\tilde{\theta})\pi(\tilde{\theta})d\tilde{\theta}$$

- Predictive denisty based on data y

$$f(\tilde{y}|y) = \int f(\tilde{y}|\tilde{\theta})\pi(\tilde{\theta}|y)d\tilde{\theta}$$

- Bayes' Theorem is the recipe to update the prior distribution using data into the posterior distribution (i.e. a recipe to **LEARN FROM DATA!**)

Software for Bayesian inference

- OpenBUGS - flexible open-source based on Gibbs sampler, Metropolis-Hastings, Slice, and Adaptive Rejection sampling
  - GUI interface for Windows similar to WinBUGS
  - Available under Linux as a command language
  - Syntax similar to S/R language
  - Can be run directly from other software like R
- JAGS (Just Another Gibbs Sampler) - similar syntax to BUGS; works on Macs, too
- Stan - MCMC sampling using Hamiltonian Monte Carlo (HMC) and No-U-Turn Sampler (NUTS)
- NIMBLE - Numerical Inference for Hierarchical Models Using Bayesian and Likelihood Estimation - built in R but compiles your models and algorithms using C++

Potential Benefits of using Bayesian methods

- Sample size reduction via prior information
- Efficiently use Information for Decision Making
- Adaptive Trial Designs - naturally fit in Bayesian paradigm
  - Group Sequential
  - Sample Size Re-estimation
  - Switching hypotheses
  - Dropping arms or doses
  - Adaptive randomization
- Exact (not asymptotic) analysis
- Missing Data
- Multiplicity e.g. multiple endpoints or subgroup analyses

Criteria for Success

- Prior information should be integrated at both prediction and analysis stages
- Prior at the prediction and analysis stages need not be the same
- Criteria of success can based on the relative powterior probability of the Null (H_0) and Alternative (H_A) hypotheses

$$P(H_A|Data)$$

E.g.

  - Superiority Designs $P(\mu_T - \mu_C > 0|Data)$ where μ_T and μ_C are the treatment responses with active and control, resp.
  - Non-Inferiority Designs $P(\mu_T - \mu_C > -\delta|Data)$

- Other approaces based on utilities (loss functions), precision of estimates, Bayes factor, etc.

Time-To-Event outcomes

- **Time-To-Event** (TTE) outcomes (in RCT = Time from randomization to **event**) often used in medical reserach
- In Oncology
  - Overall Survival
  - Progression-free survival (PFS)
  - Time-to-progression (TTP)
  - Relapse-free survival (RFS)
  - Invasive disease-free survival (iDFS)a
  - Distant disease-free survival (D-DFS)
  - Distant relapse-free survival (D-RFS)
  - Distant recurrence-free interval (D-RFi)
  - Locoregional relapse-free survival (L-RFS)
  - Recurrence-free interval (RFi)
  - Breast cancer-specific survival (BCSS)
  - Breast cancer-free interval (BCFi)
- DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) provides recommendations for definitions of TTE outcomes
- When event not observed before end of follow-up, data said to be **censored**

Time-To-Event outcomes

- If n patients are treated, for patient $i \in \{1, \ldots, n\}$, let T_i be the TTE outcome with a survival function

$$S(t) = Pr(T_i \geq t).$$

- Because of censoring, only observe

$$\{(Y_i, \delta_i), i = 1, \ldots, n\}$$

  where $Y_i = \min\{T_i, C_i\}$ where C_i is censoring time, and $\delta_i = \{T_i \leq C_i\}$ indicator $=1$ if an event is observed and 0 otherwise
- Traditionally the survival and censoring times assumed independent

Models for Time-To-Event outcomes

- Hazard or Survival functions, $h(\cdot|x)$ or $S(\cdot|x)$, are often modeled as a function of covariates, x

$$h(t|x) = \frac{f(t|x)}{S(t|x)}, \text{ or } S(t|x) = \exp\left\{-\int_0^t h(s|x)ds\right\}$$

- The popular Cox model assumes, $h(\cdot|x)$ factorizes as

$$h(t|x) = h_0(t)\exp\{x\beta\}$$

- The partial likelihood is independent of $h_0(\cdot)$, therefore can be left unspecified; if d events and $\mathcal{R}_j$ is the j's event risk-set

$$L(\beta|data) = \prod_{j=1}^{d} \frac{\exp\{x_{(j)}\beta\}}{\sum_{k\in\mathcal{R}_j}\exp\{x_{(k)}\beta\}}$$

- Moreover, treatment effect, often defined as ratio of hazards, is

$$HR(t|x) = \frac{h(t|\text{Active,x})}{h(t|\text{Standard,x})} = HR(x)$$

Weibull models

- Weibull distribution is defined by two parameters (α, θ)

$$p(t|\theta) = \alpha t^{\alpha-1} e^{\log\theta - \theta t^{\alpha}}, \; h(t) = \theta > 0$$

- **Likelihood:** If $\{(Y_i, \delta_i), i = 1, \ldots, n\}$ observed, the likelihood is

$$p(\mathbf{y}|\theta) = \alpha^{E_n} \prod_i Y_i^{\delta_i(\alpha-1)} e^{E_n \log\theta - n}$$

  where $E_n = \sum_{i=1}^n \delta_i$ number of events and $F_n = \sum_{i=1}^n Y_i^{\alpha}$ total follow-up
- **Prior:** If α known, $Gamma(\alpha, \beta)$ conjugate for θ
- **Posterior:** $p(\theta|\mathbf{y}) \propto \theta^{\alpha+E_n-1} e^{-\theta(\beta+F_n)}$
- Other priors, $Gamma$ on α and $log - Normal$ on θ

Piecewise Exponential models

- Also called piecewise constant hazard models
- Can accomodate various shape of hazard functions
- Serves as benchmark for more complicated models
- If $I_j = (s_{j-1}, s_j]_{j=1,J}$ disjoint that span follow-up time, with $h(t) = \eta_j$ if $t \in I_j$ then

$$f(y_i|\eta) = \eta_j \exp\left\{\eta_j(y_i - s_{j-1}) + \sum_{l=1}^{j-1} \eta_l(s_l - s_{l-1})\right\} \text{ if } y_i \in I_j$$

- Independent *Gamma* priors on η's are conjugate; alternative priors $\log \eta \sim MVN(\eta_0, \Sigma)$
- Covariates can be incorporated, e.g.

$$h(t|x) = h(t) \exp\{x\beta\}$$

Other models

- Accelarated Failure Time models
- Cure rate models

$$S(t) = \pi + (1 - \pi)S_0(t)$$

- Time varying covariates
- Joint models of Longitudinal and Survival data
- Hierarchical models
- Frailty models
- Semiparametric and Nonparametric models
- etc. ...

Prior Distributions

- Prior elicitation is a complex process - a function of what data are available
- Method of moments: E.g. when restricting to Gamma or Inverse-Gamma family, this process involves the elicitation of 2 parameters
  - Mean & Variance or probability interval
- Power Priors: given external data D_0, introduce a power parameter a to define prior

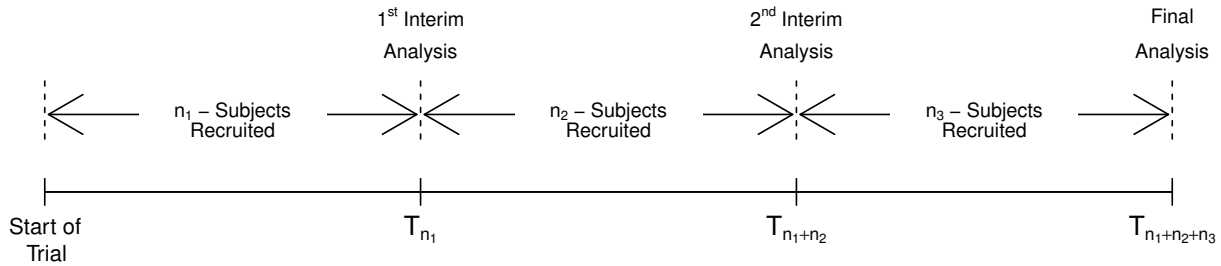
$$\pi(\theta, a|D_0) \propto L(\theta|D_0)^a \pi_0(\theta|\psi)\pi(a|\phi) \text{ or}$$

$$\pi(\theta, a|D_0) = K(a)L(\theta|D_0)^a \pi_0(\theta|\psi)\pi(a|\phi)$$

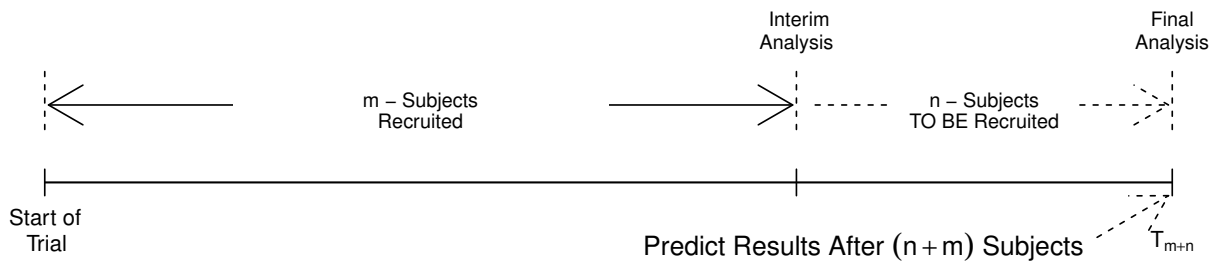
- Prior based on meta-analysis of external data

Monitoring of Clinical Trials

- Monitoring using posterior probabilities, e.g. $P(\theta > B | T_{n_1}) > \pi^*$



- Monitoring using predictive probs., e.g. $P[P(\theta > B | T_{n+m}) > \pi^* | T_m] > \eta$



$T_m = t_m$ – Observed (Past Data) → $T_{m+n} = \frac{T_m \times m + n \times T_n}{m+n}$ ← T_n – NOT Observed (Future Data)

- Other, *e.g.* hypothesis testing.

Group Sequential Designs - role of priors

- A group sequential design with 2 treatments (A and B), interim analyses after m subjects
- With stopping rules, $\pi^* = .95$
  - Stop and declare treatment A better if $p_A = P(\text{TRT}_A \textit{ better than } \text{TRT}_B|\text{Data}) > \pi^*$
  - Stop and declare treatment B better if $p_A = P(\text{TRT}_A \textit{ better than } \text{TRT}_B|\text{Data}) < 1 - \pi^*$
- Exit probabilities a function of prior, π^*, etc.

Non-informative prior

- Exit probabilities higher at the early interim looks

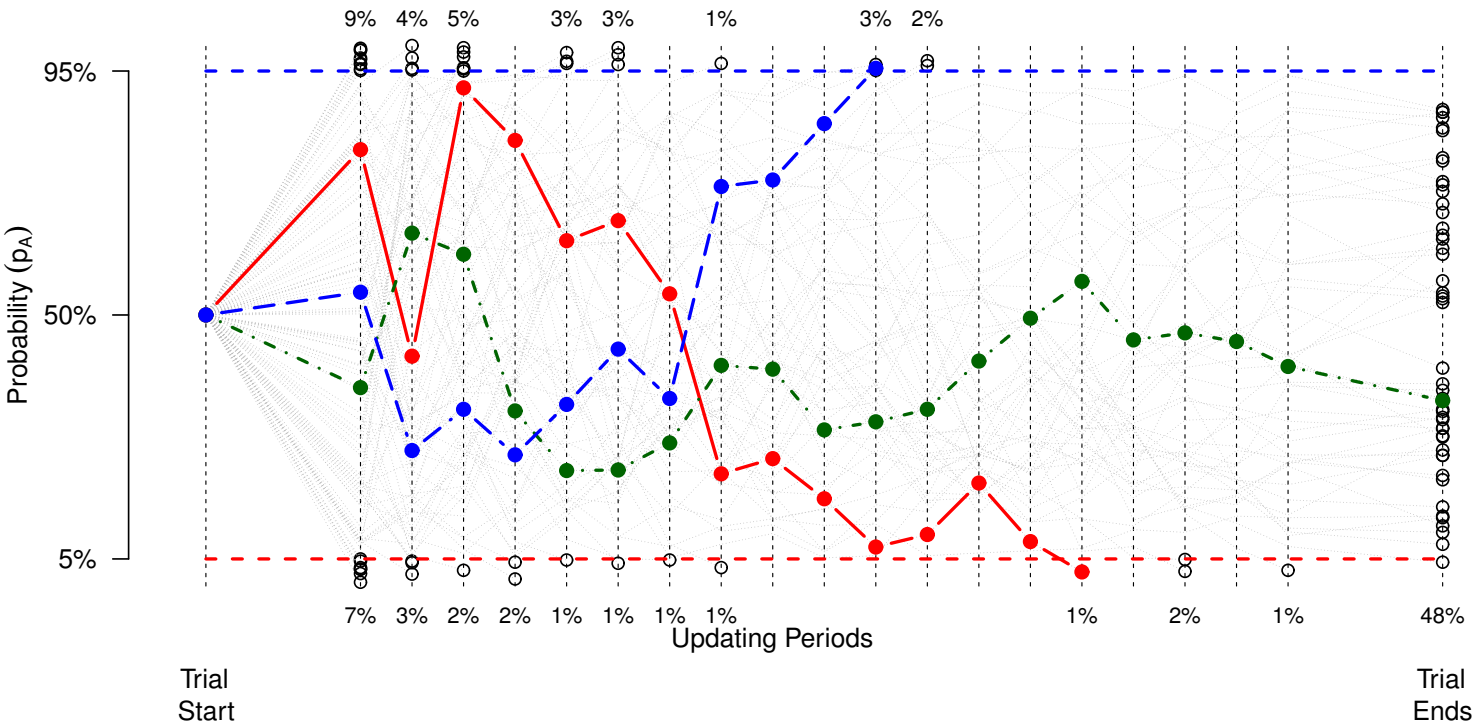


Figure: Trajectories under H_0 along with exit probabilities

Informative prior

- Informative prior centered on the null value
- Lower exit probabilities at early interim looks
- The degree of informativeness acts like a 'handicap'

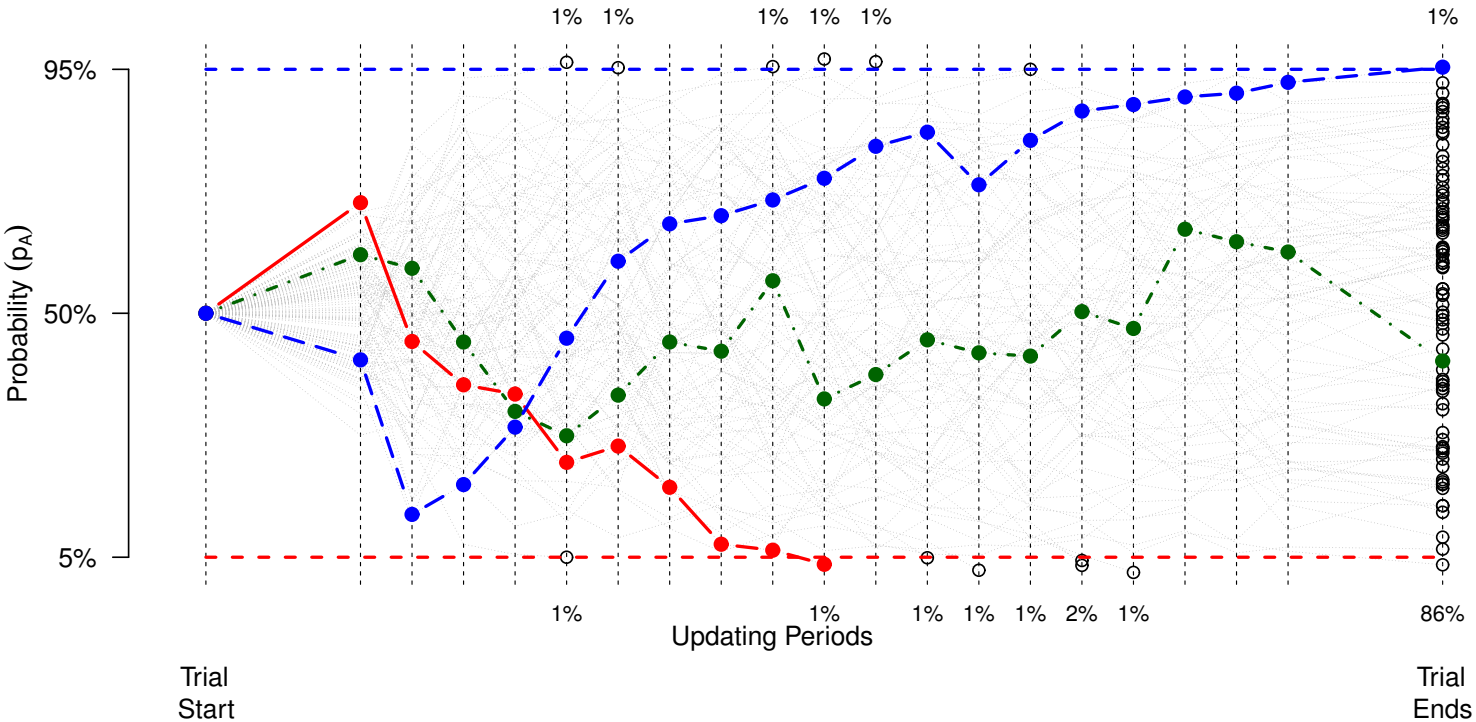


Figure: Trajectories under H_0 along with exit probabilities

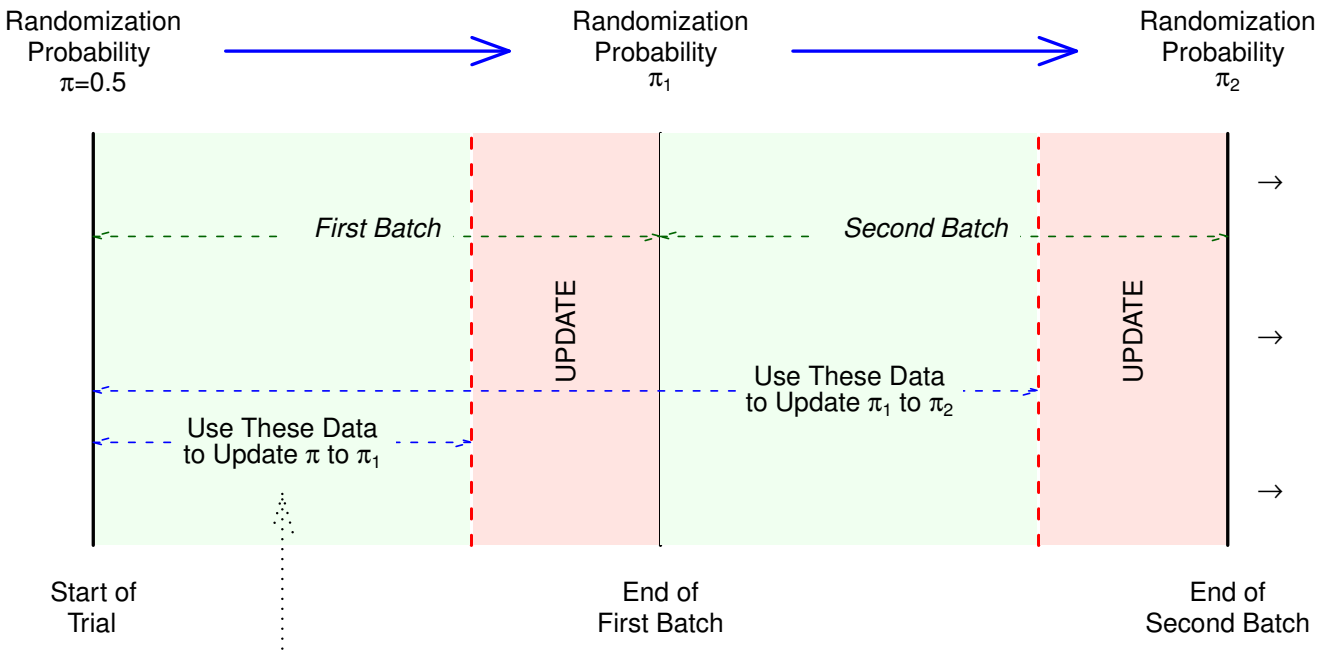
Adaptive Randomization

- Assume interest in choosing best of K treatments (treatment effect θ_i)
- Interim evidence showing $P(\theta_j > \max_{i \neq j} \theta_i | \text{Data})$ large argues against conventional randomization
- Adaptive Randomization changes assignment probability based on the observed results
- It has been used in Phase II trials, dose finding, etc
- Recently (Fiore et al. 2011) it has been proposed for studies of comparative effectiveness under Point-Of-Care Clinical Trials (POC-CT) initiative at VA

Example: Insulin Dosing

- Use Case: Open label randomized trial comparing (A) Sliding scale insulin regimen to (B) Weight based insulin regimen
  - *Participants:* Non-ICU hospitalized diabetic patients who require insulin and able to give informed consent
  - *Primary Endpoint:* Length of hospital stay

Design : Flowchart



Design : Steps

1. Assign subjects to either group with probability $\pi = 1/2$
2. With existing data calculate probability

$$p_A = P(\theta_A < \theta_B | \text{DATA}) \quad (\dagger)$$

3. Choose a *cutpoint* κ and consider stopping if

$$p_A > \kappa \text{ or } p_A < 1 - \kappa \quad (\ddagger)$$

   otherwise *continue*

4. If *continue*, calculate

$$\pi_1 = \frac{p_A^\eta}{1 + p_A^\eta}$$

   and assign the following batch with π_1 to protocol A and $1 - \pi_1$ to protocol B

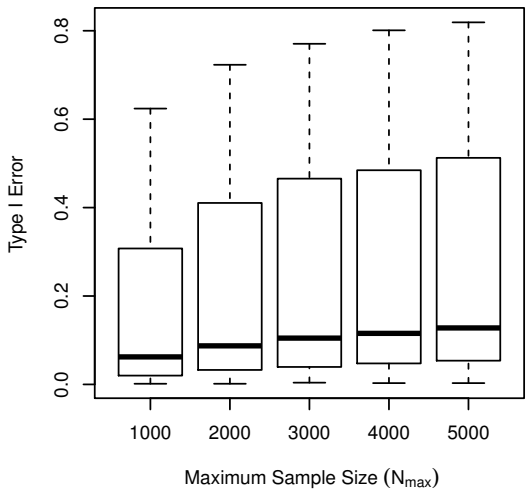
5. After data on following batch become available, calculate the updated *Bayesian* probability p_A (as in $(\dagger)$) and check termination criteria; If criteria not met, update π_1 to π_2 (as in $(\ddagger)$)
6. The process is continued until either the stopping criteria is met or number of subjects enrolled $N = N_{\text{max}}$

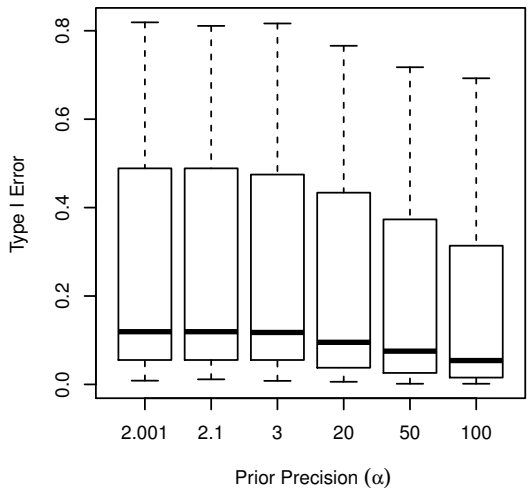
Choice of Design - Criteria

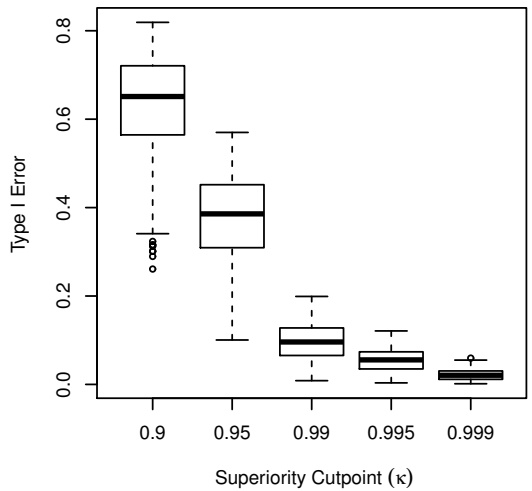
Designs were scored based on the following operating characteristics

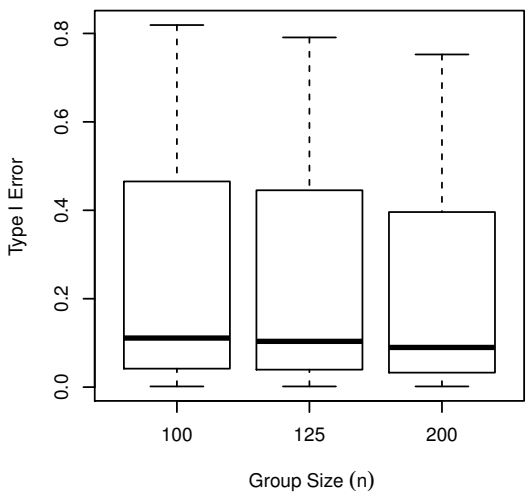
1. *Overall Type I error* - the chance of declaring one of the two protocols better at any time during the trial when if fact there is no difference between the two protocols.
2. *Overall Power* - the chance of declaring a protocol better at any time during the trial when in fact that protocol is better.
3. *Number of patients assigned to best protocol.* The number of patients enrolled will depend on the data collected and hence is a random variable.
4. *Time until a decision is made.* The duration of the study will depend on the data collected and hence is a random variable.

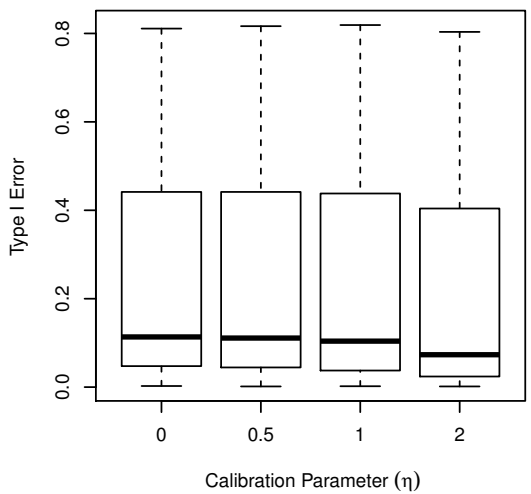
Choice of Design - Results



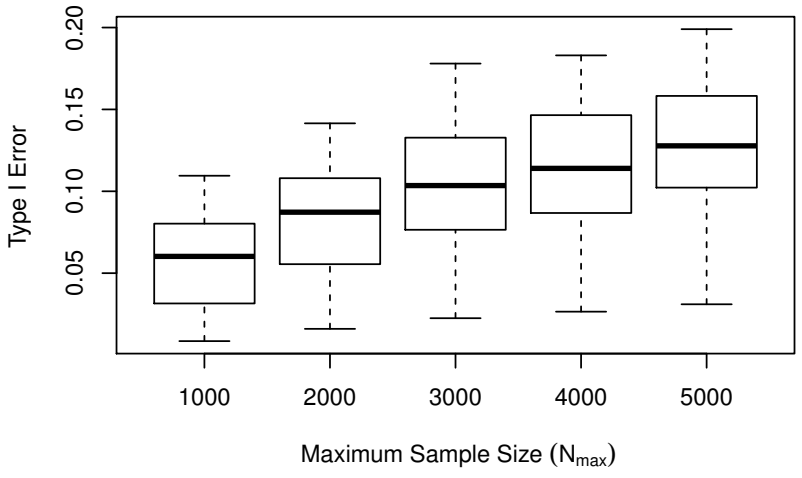


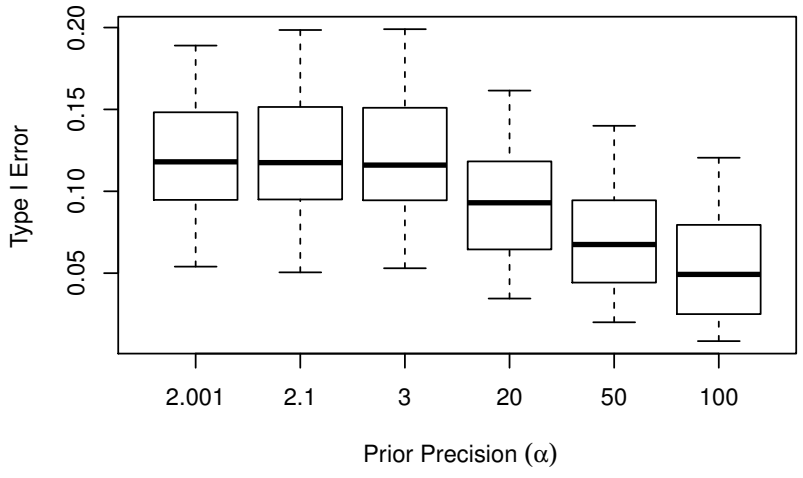


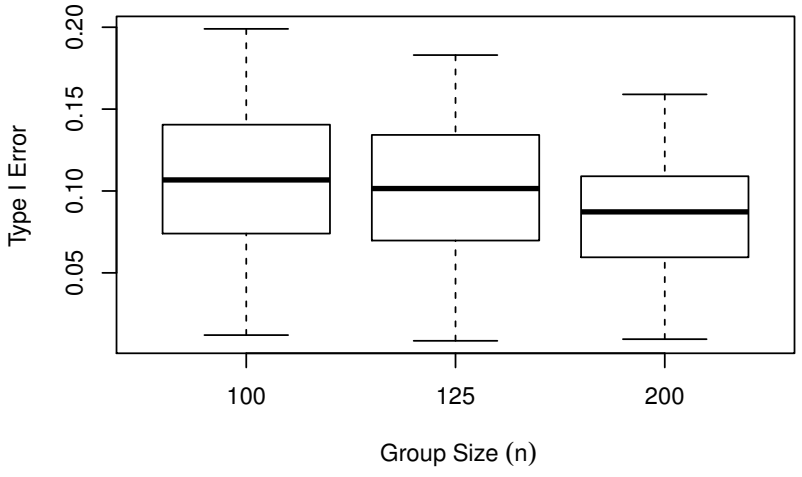


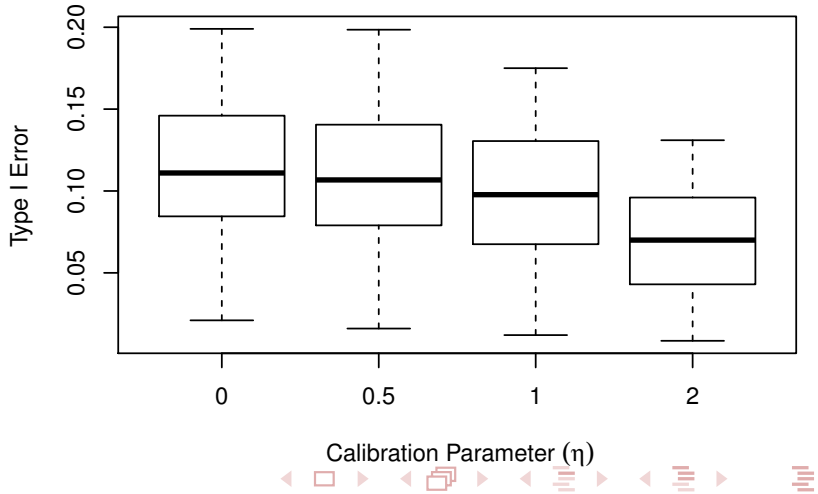


Choice of Design - $\kappa = 0.99$

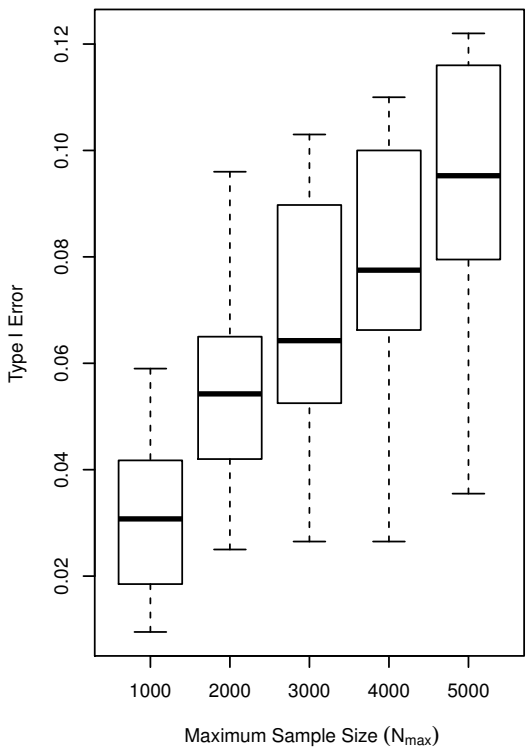


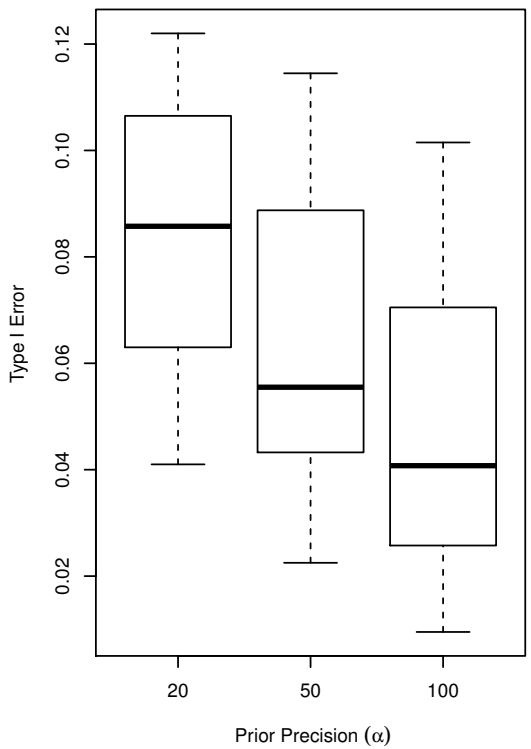


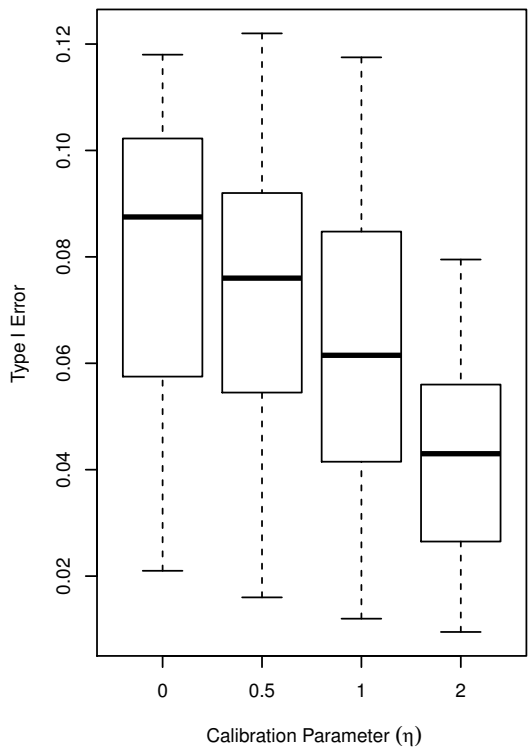




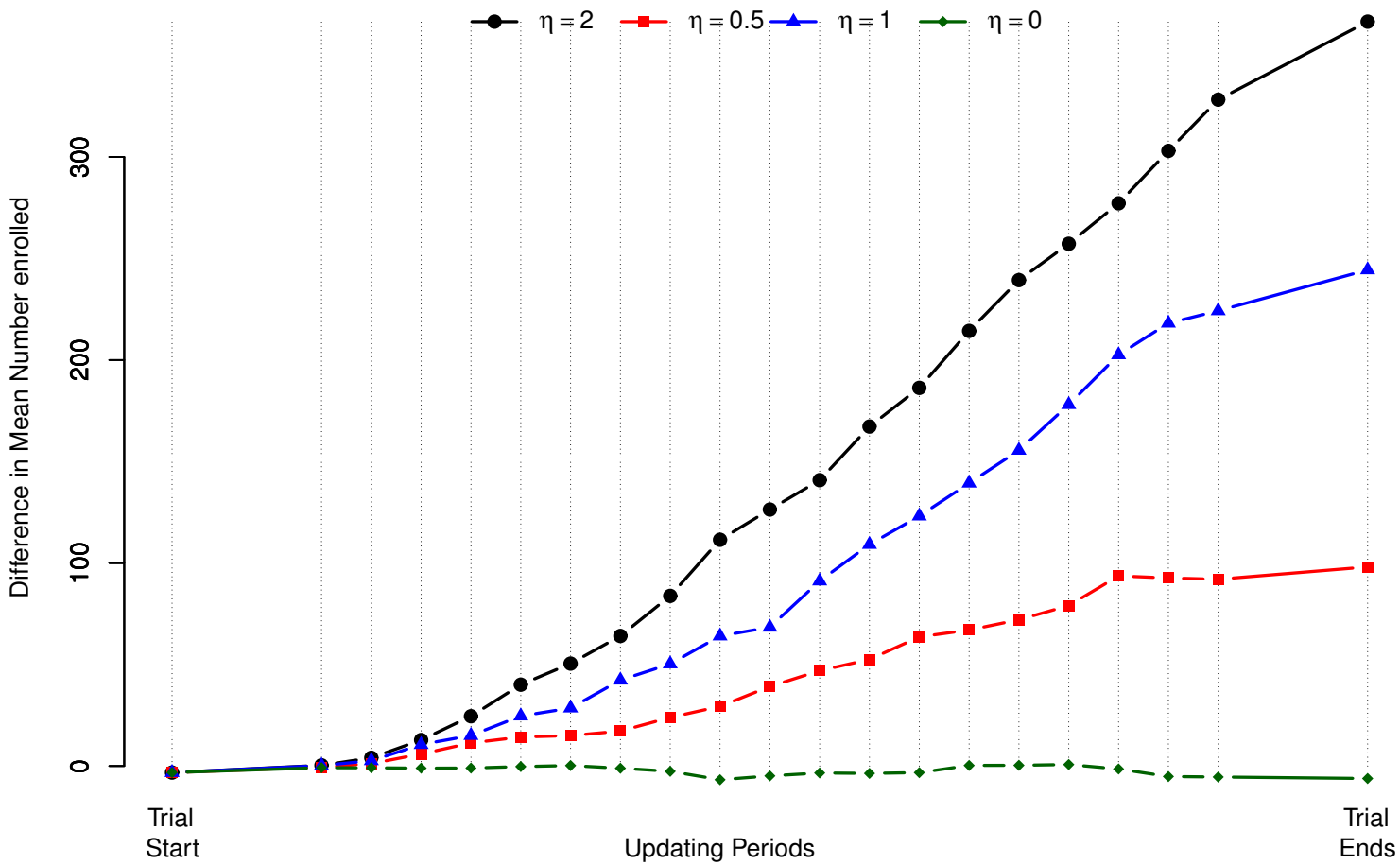
Choice of Design - $\kappa = 0.99, n = 200$







Choice of Design - η



Final Design

On the basis of extensive simulations, we chose a design with the following parameters:

1. Batch size $= 200$,
2. Cutpoint $\kappa = 0.99$,
3. Calibration parameter $\eta = 1/2$,
4. Prior centered on the null median LOS and prior precision parameter $\alpha = 100$, and
5. Maximum number of patients $N_{\max} = 3000$.

(*) In addition, the updating occurs after 150 patients have entered the study, we do not allow stopping after the first batch, and we censor the LOS at 30 days.

Operating Characteristics of the design

Assuming median LOS

- Sliding scale - 5 days
- Weight based - 4.4 days (a reduction of 12% in median LOS)

Operating characteristics of the final design:

Diff. Median LOS (B-A)	Probability A supp.	Probability B supp.	Median n_A	Median n_B	Median Duration (†)
0	3%	3%	1495	1461	599
0.1	8%	1%	1634	1292	598
0.2	17%	0%	1738	1125	597
0.3	30%	0%	1791	969	595
0.4	51%	0%	1719	778	581
0.5	71%	0%	1434	598	408
0.6	86%	0%	1075	465	316
0.7	95%	0%	825	380	240
0.8	99%	0%	673	332	201
0.9	100%	0%	540	289	164
1	100%	0%	506	268	157

(†) In calculating the duration of the study we assumed an accrual rate of 5 patients per day.

Exit probabilities

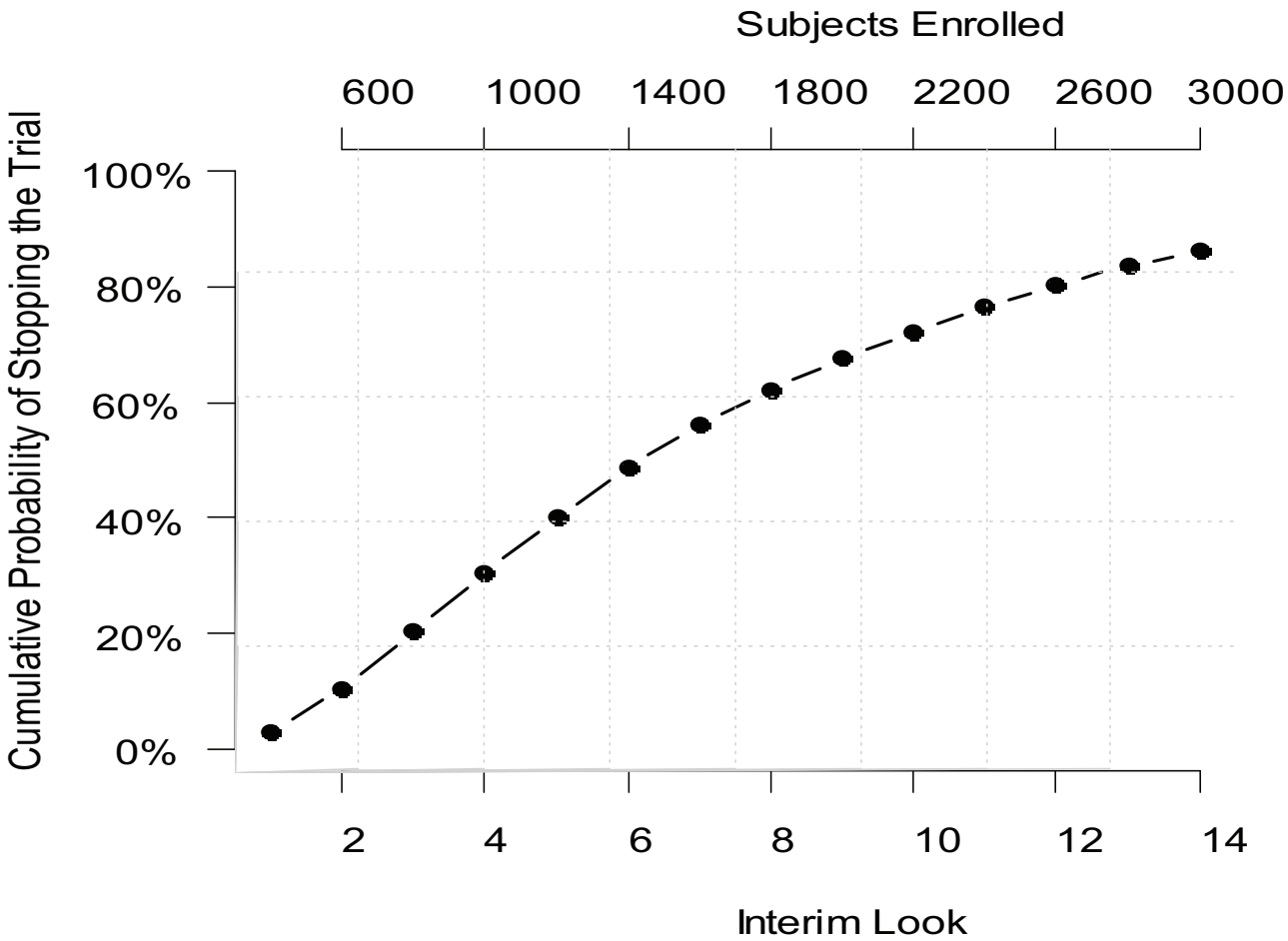


Figure: Exit probabilities by interim analyses

Robustness

Operating characteristics under lognormal data:

Diff. Median LOS (B-A)	Probability A supp.	Probability B supp.	Median n_A	Median n_B	Median Duration (†)
0	4%	3%	1469	1473	599
0.1	8%	2%	1594	1317	599
0.2	16%	1%	1711	1163	597
0.3	28%	0%	1759	998	595
0.4	46%	0%	1724	832	587
0.5	62%	0%	1600	696	485
0.6	78%	0%	1244	535	360
0.7	90%	0%	924	414	275
0.8	96%	0%	715	352	210
0.9	99%	0%	626	309	193
1	100%	0%	522	278	160

(†) In calculating the duration of the study we assumed an accrual rate of 5 patients per day.

Parametrization based on treatment difference

- *Outcome:* T_i: Duration of hospitalization for patient i
- *Treatment:* weight based protocol for administering insulin (Group=0) vs. sliding scale protocol for administering insulin (Group=1)
- *Model:* Time of hospitalizations are assumed exponential while censoring times are assumed normal
  - Event: $T_i \sim Exp(\lambda_i)$, with $\lambda_i = \exp\{-\theta[1] - \theta[2] \times Group_i\}$
  - Censoring: $C_i \sim N^+(\mu_c, \sigma_c^2)$ - truncated (above 0) normal
  - Median duration of hospitalization

$$\mu_i = \log(2) \times \exp\{\theta[1] + \theta[2] \times Group_i\}$$

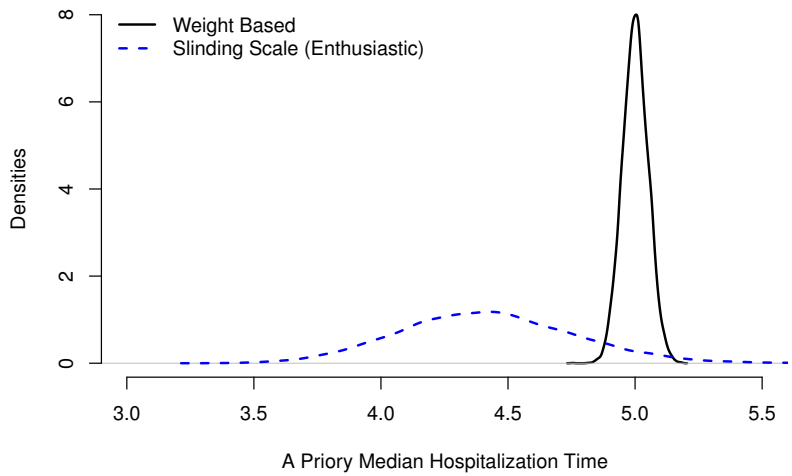
  - Log Median ratio for subject i (sliding scale) vs. subject k (weight based)

$$\log \frac{\mu_i}{\mu_k} = \theta[2]$$

  - Parameter of interest $\theta[2]$!

Parametrization based on treatment difference

- Median hospitalization
  - Weight Based: $\mu^1 = 5$; corresponds to $\theta^0[1] = 1.98$
  - Sliding Scale: $\mu^2 = 4.4$; corresponds to $\theta^0[2] = -0.13$
- Priors
  - $\theta[1]$: Normal with mean $\theta^0[1]$, standard deviation 0.01 - informative prior
  - $\theta[2]$: Normal with mean $\theta^0[2]$, standard deviation 0.08 - enthusiastic prior - gives 5% a priori probability that $\mu^1 < \mu^2$



- Censoring times $C_i \sim N^+(20, 49)$ - results in approx 10% censoring

Natural History data - No concurent control

- Assume multiple sources of patient data on control (standard treatment) are available
- Further, a randomized control trial is not feasible
- A single arm study should compare results to the results of a 'Synthetic Control' while adjusting for relevant predictors
- If for subject i, Y_i^T is the result in the treated group, and Y_{ij}^C is the response in the control group j,

$$Y_i^T \sim N(\mu_i^T, \sigma^2) \text{ and } Y_i^C \sim N(\mu_{ij}^C, \sigma^2)$$

$$\mu_i^T = \mu^T + \beta X_i \text{ and } \mu_{ij}^C = \mu_j^C + \beta X_i$$

$$\mu_j^C \sim N(\mu^C, \tau^2)$$

- Syntetic Control: $\mu_{\text{syn}}^C \sim \int N(\mu^C, \tau^2)\pi(\mu^C, \tau^2|Y)d\mu^C d\tau^2$
- Criteria for success should be based on

$$P(\mu^T - \mu_{\text{syn}}^C > 0|Y^C, Y^T) > \pi^*$$

Natural History data - with concurent control

- Assume multiple sources of patient data on control (standard treatment) are available
- In a randomized control trial enrolment of controls very hard
- A two arm study should compare results to the posterior of concurent control while adjusting for relevant predictors
- If for subject i, Y_i^T is the result in the treated group, and Y_{ij}^C is the response in the control group j,

$$Y_i^T \sim N(\mu_i^T, \sigma^2),\ Y_{0,i}^C \sim N(\mu_{0,i}^C, \sigma^2) \text{ and } Y_i^C \sim N(\mu_{ij}^C, \sigma^2)$$

$$\mu_i^T = \mu^T + \beta X_i \text{ and } \mu_{ij}^C = \mu_j^C + \beta X_i, j = 0, 1, \ldots$$

$$\mu_j^C \sim N(\mu^C, \tau^2)$$

- Criteria for success should be based on

$$P(\mu^T - \mu_0^C > 0 | Y^C, Y^T) > \pi^*$$

Integrating data from single historical study

- Device study is planned to show non-inferiority (NI) of a current stent to an approved stent
- Rate of event with standard stent is 15% with NI margin of 5%
- Criteria of success

$$P(\pi_2 - \pi_1 > -5\% | Data) > 97.5\%$$

where π_1 and π_2 are rates of event with the new and old stents in the new study

- Sponsor has a study ongoing enrolling 1000 patients (500 in each group)
- Direct, full borrowing unlikely be acceptable to regulatory

Integrating data from single historical study

- Model:

$$log\left(\frac{\pi_1}{1-\pi_1}\right) = log\left(\frac{\pi_{10}}{1-\pi_{10}}\right) + \delta_1$$

$$log\left(\frac{\pi_2}{1-\pi_2}\right) = log\left(\frac{\pi_{20}}{1-\pi_{20}}\right) + \delta_2$$

  where π_{10} and π_{20} are rates of event with the new and old stents in the historical study

- Size of bias δ_1 and δ_2 determines amount borrowed from historical study: larger bias lower borrowing
- With a single study, data provide little information to estimate the bias terms, therefore informative priors should be used
- Depending on whether results of the historical study are known, different approaches can be taken

Integrating data from single historical study

- A classical design would need to enroll 2.1K subjects for a power of 90% with one-sided type I error 2.5%
- With full borrowing (bias=0), same sample size for a bayesian design with criteria for success as above
- With a normal bias the sample size is reduced to

	SD=0.10	SD=0.15	SD=0.20	SD=0.25	SD=0.30
Sample Size	1400	1650	1750	1850	1900
Reduced Size	34%	21%	17%	12%	10%

Design With Available Historical Data

- **Task:** Design a Prospective Randomized Multicenter Study to Assess the Effectiveness of Osiro stent
- Proposed Effectiveness hypothesis is non-inferiority relative to Xience stent
- Time to event endpoint: time to TLF during first 12 months
- Data from 2 studies (Bioflow II and Bioflow IV) comparing the two stents available
- Proposed tests should have bounded Type I and Type II errors

Design With Available Historical Data

- **Solution:** Prospective Randomized Trials with a Bayesian Design: Bioflow V study
- Primary analysis based on a Bayesian hierarchical model that
  1. Assumes a bias between the hazard rates of proposed study and historical studies
  2. Allows for discounting of the historical data
- Criterion for success based on the posterior probability of the alternative hypothesis (i.e., of non-inferiority being met).

$$P(H_A|Data) = P(\lambda_X - \lambda_O > -\delta|Data) > \pi^*$$

λ_O and λ_X hazard rates for Orsiro and Xience stents in proposed study; δ non-inferiority margin; π^* the level of evidence required to declare the alternative hypothesis true.

Design With Available Historical Data - **Likelihood**

- Evidence from historical studies is discounted using discount factors a^i
- **Problem:** Linking hazard rates of historical studies and historical studies and proposed studies
  1. Hard to justify equality assumption for the hazard rates of historical studies
  2. Impossible to convince FDA that historical studies have equal hazard rates
- **Solution:** Assume a bias term in linking the hazard rates

$$\log(\lambda_O^i) = \log(\lambda_O) + \delta_O^i \text{ and } \log(\lambda_X^i) = \log(\lambda_X) + \delta_X^i$$

Design With Available Historical Data - **Priors**

- The bias terms assumed to follow a normal distribution with mean 0 and standard deviation τ_O^i and τ_X^i
- Non-informative Prior assumed on event rates in Bioflow V study
- For the above approach several parameters need to be specified:
  - Discount factors a^i are values between 0 and 1. Values close to 0 result in little influence of the results of this study on the final inference, while values close to 1 give larger weight to these data. Alternatively, a prior can be assumed
  - Standard deviation values τ_O^i and τ_X^i of the bias linking the rates in the historical and current study; alternatively, informative priors can be assumed on τ's

Design With Available Historical Data - **SD of Bias**

- The bias standard deviation accomodates possible differences between the historical and current hazard rates
- Every effort should be made to increase similarity between historical and current studies
- In spite of all efforts, unknown factors could lead to differences between the rates of the studies
- To accommodate these differences, bias terms linking the log of the hazard rates in each treatment group of historical and the log hazard of proposed study are integrated.
- Based on the expected differences, reeasonable (values) or priors can be chosen for the bias parameters
  - For example: $\tau_O^i = 0.1$ allows for ratios of 1.48 (thus a difference of 48%) of the 97% to the 2.5% limit for the ratio of hazards of event between historical and current study

Design With Available Historical Data - **Final Analysis**

$$P(\lambda_X - \lambda_O + \delta > 0 | Data) > 0.975$$

- Interim 'blinded' view at data from historical data to adjust the sample size
- Homogenity assessment for treatment effect across sites and across regions
- Reduce heterogeneity across studies by
  1. Purposely buid the protocol to reduce differences among studies
  2. Re-adjudecate endpoints

Design With Available Historical Data - **Sample Size**

Figure: Prior distribution of prior SD

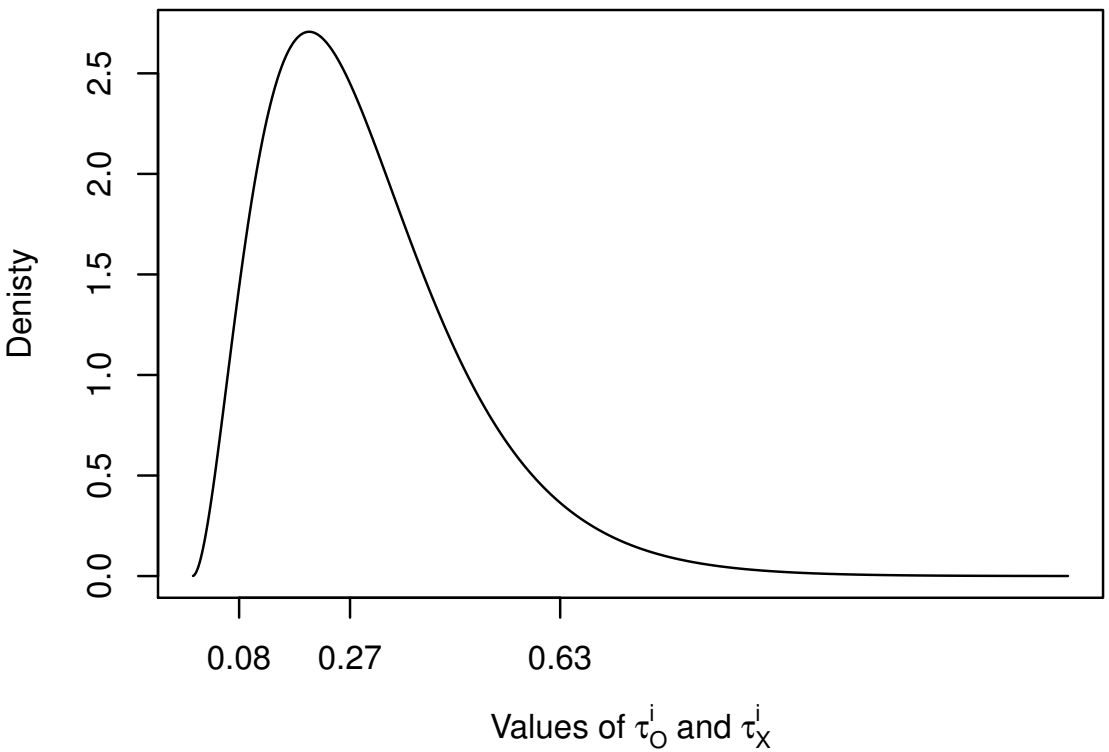


Table: Summaries of Prior

Mean	0.30
Mode	0.20
5% percentile	0.16
50% percentile	0.27
95% percentile	0.63

Design With Available Historical Data - **Sample Size**

Table: Power based on a simulation scenario

%Data used Study 1	%Data used Study 2	Actual Difference (*)	Power Bayes 1(**)	Power Bayes 2(***)
100%	75%	-20%	83.2%	92.6%
100%	75%	-10%	85.8%	94.5%
100%	75%	0%	87.9%	96.0%
100%	75%	10%	89.2%	97.1%
100%	75%	20%	90.4%	97.9%
100%	75%	-20%	2.5%	6.3%
100%	75%	-10%	3.2%	8.7%
100%	75%	0%	3.9%	12.1%
100%	75%	10%	4.7%	15.8%
100%	75%	20%	5.7%	19.9%

(*) Difference Between ODDS of Event Rates in Historical Study 2 and Current study (%)

(**) Assumes a bias with SD of bias following prior on previous slide

(***) Assumes event rates are the same in all studies

Interactive R based Web application using shiny

- Shiny is an open Source web application framework for R, developed by Rstudio
- Tool to convert analytical analysis into interactive web application
- Two main components
  1. User Interface - included into **ui.R** file: Controls the layout, appearance, Widgets that capture user inputs. Also, displays some output - the title, page layout, text input, radio buttons, drop down menus, graphs etc.
  2. Server - included into **server.R** file: Commands that uses the input provided by the user , process them and produces the required output which is further displayed by ui.r script.
- Rshiny provides flexible user interface with a number of popular layouts like sidebar Panel, title Panel, navigation Page
- A number of control widgets are available to make application interactive: data inputs, buttons, checkboxes, radio buttons, select boxes, sliders, file input etc.

Interactive R based Web application using Shiny

ui.R structure

```
shinyUI(fluidPage(
 # Application title
    titlePanel(),
# sidebarLayout(
    # Sidebar panel
    sidebarPanel(),
    # Main Panel
    mainPanel()
 ))
```

sever.R structure

```
shinyServer(
function(input, output) {
  }
)
```

SeqAnalysisApp

The SeqAnalysisApp app consists of 6 components:

1. **ui.R** - a user interface object. It controls the layout and appearance of the application
2. **server.R** - a server function that contains instructions needed to build application and run calculations.
3. **Intro_functions.R** - a set of functions that are called within server.R to convert between pairs of input values in the frist 2 tabs (shape, rate), (mean, variance), (q1, q2)
4. **AdaptiveFunctions.R** - Functions called during Simulation analysis.
5. **AnalysisFunctions.R** - functions called during Interim analysis

Sequential Analysis of Time to Event Endpoint

- Control Design
- Active Design
- Data
- Results

Prior: Control (C)

Prior Distribution Family:

Gamma

Number of bins:

10

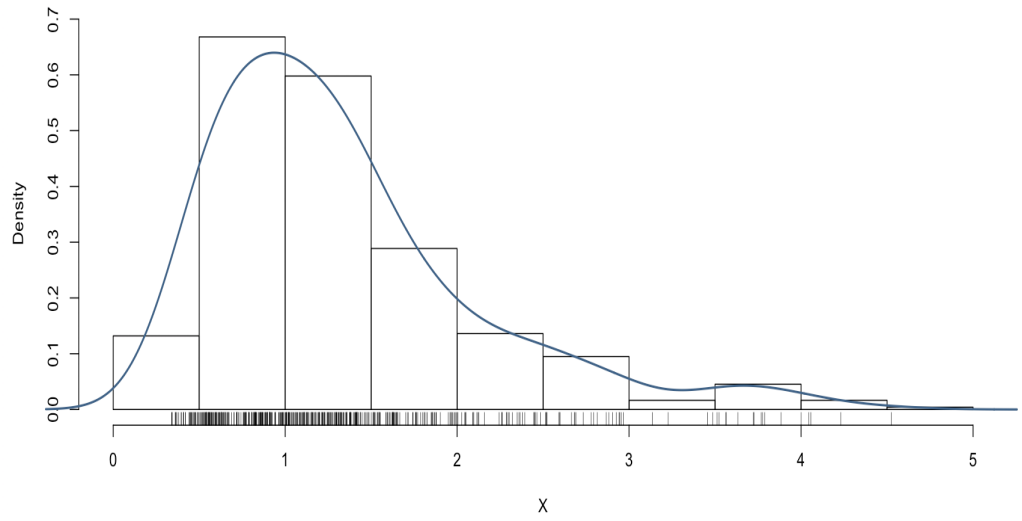
a: 3 **b:** 3

m: 1.5 **v:** 2.25

q1: 0.415 **q2:** 4.849

Update

Histogram



Help Section

Prior: Control (C)

Specifies the prior distribution for the Control group. Can be chosen as Gamma or Inverse Gamma

Prior Distribution Family

Inverse Gamma

$$\frac{\beta^{\alpha}}{\Gamma(\alpha)}x^{-\alpha-1}e\left(-\frac{\beta}{\alpha}\right)$$

Gamma

$$f(x) = \frac{1}{(s^{a}\Gamma(a))}x^{(a-1)}e^{-}\frac{x}{s}$$

Number of Bins

Sequential Analysis of Time to Event Endpoint

- Control Design
- Active Design
- Data
- Results

Prior: Active (A)

Prior Distribution Family:

Gamma

Number of bins:

10

a: 3

b: 3

m: 1.5

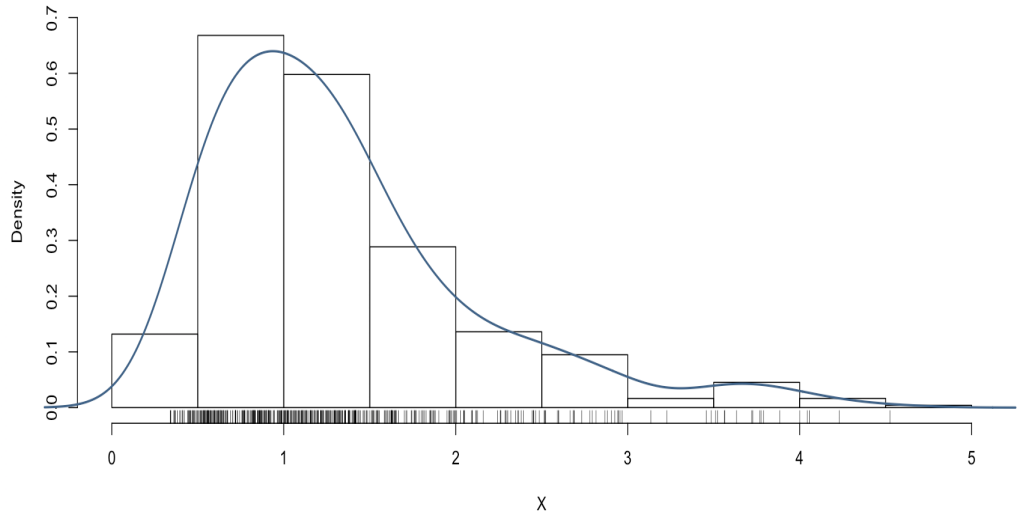
v: 2.25

q1: 0.415

q2: 4.849

Update

Histogram



Help Section

Prior: Control (C)

Specifies the prior distribution for the Active group. Can be chosen as Gamma or Inverse Gamma

Prior Distribution Family

Inverse Gamma

$$\frac{\beta^{\alpha}}{\Gamma(\alpha)} x^{-\alpha-1} e\left(-\frac{\beta}{\alpha}\right)$$

Gamma

$$f(x) = \frac{1}{(s^{a}\Gamma(a))} x^{(a-1)} e^{-\frac{x}{s}}$$

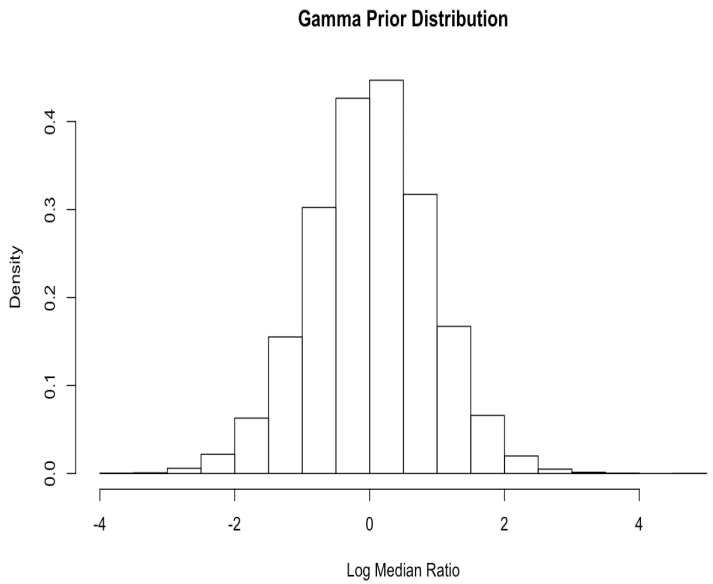
Number of Bins

Sequential Analysis of Time to Event Endpoint

- Control Design
- Active Design
- Data
- Results

Prior Summary

```
         Prior_Control Prior_Active
mean              1.50         1.50
variance          2.25         2.25
```




```
P( Active vs. Control < delta | prior ) =  0.5
```

User Input

Input Type

Interim Analysis

Choose txt File

Browse... DataExample.csv

Upload complete

Select Analysis Type

MCMC using JAGS

Analysis Distribution

Exponential

Clinically Relevant Threshold:

1

V1	V2	V3
1	6.46	1
2	2.11	1
2	3.51	1
2	6.83	1
1	17.49	0
1	1.42	1

Compute

Help Section

Control Design

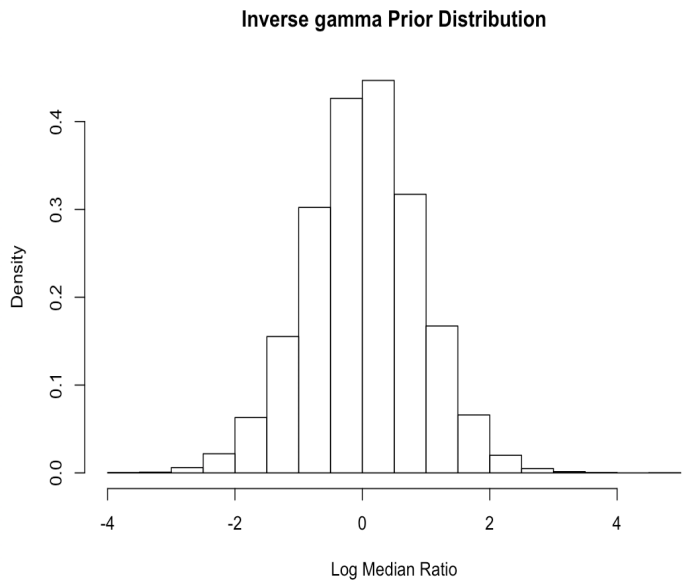
Active Design

Data

Results

Prior Summary

```
          Prior_Control Prior_Active
mean               1.50         1.50
variance           2.25         2.25
```




```
P( Active vs. Control < delta | prior ) =  0.5
```

User Input

Input Type

Simulation with Adaptation

Select Analysis Type

MCMC using JAGS

Choose Distribution for data simulation

Exponential

True median in A: 5

True median in C: 5

Superiority cutpoint: 0.9

Futility cutpoint: 0.9

Max number of subjects: 60

Batch Size Parameter: 20

Randomization Type:

- (•) Adaptive
- ( ) Fixed

Calibration 2

Number of Simulations: 100

Analysis Distribution

Exponential

Clinically Relevant Threshold: 1

Censoring Time: 30

Accrual Rate: 5

Control Design

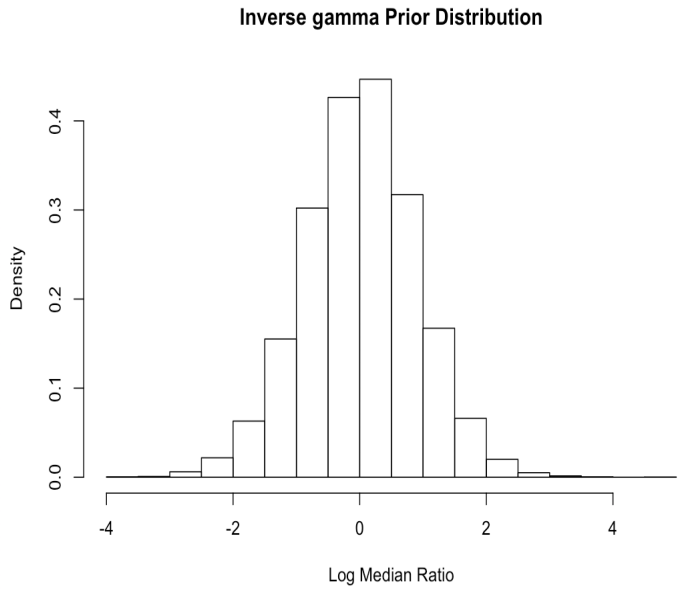
Active Design

Data

Results

Prior Summary

```
          Prior_Control Prior_Active
mean               1.50         1.50
variance           2.25         2.25
```




```
P( Active vs. Control < delta | prior ) =  0.5
```

User Input

Input Type

Simulation without Adaptation

Select Analysis Type

MCMC using JAGS

Choose Distribution for data simulation

Exponential

True median in A: 5

True median in C: 5

Superiority cutpoint: 0.9

Balance: 0.5

Max number of subjects: 60

Number of Simulations: 100

Analysis Distribution

Exponential

Clinically Relevant Threshold: 1

Censoring Time: 30

Accrual Rate: 5

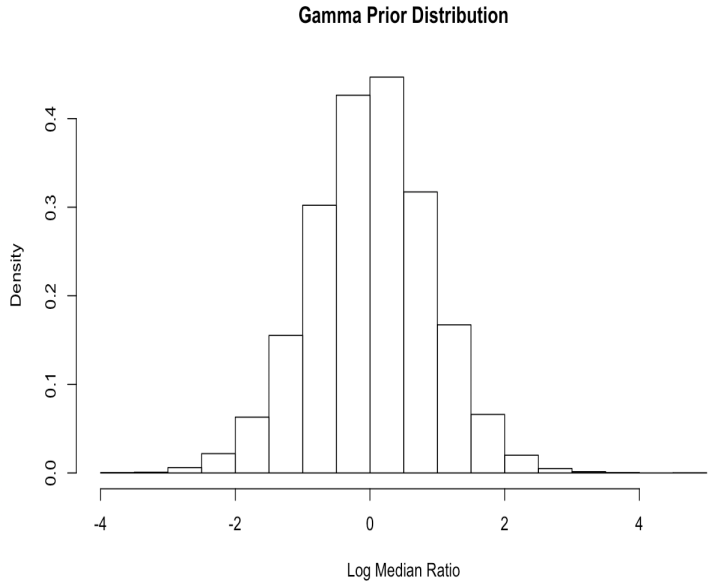
Compute

Sequential Analysis of Time to Event Endpoint

- Control Design
- Active Design
- Data
- Results

Prior Summary

```
         Prior_Control Prior_Active
mean              1.50         1.50
variance          2.25         2.25
```




```
P( Active vs. Control < delta | prior ) =  0.5
```

User Input

Untitled — Edited

Interim Analysis

- Simulation with Adaptation
- Simulation without Adaptation
- Interim Analysis

Upload complete

Untitled 2 — Edited

MCMC using JAGS

- MCMC using OpenBUGS
- MCMC using JAGS

Exponential

- Exponential
- Weibull

V1	V2	V3
1	6.46	1
2	2.11	1
2	3.51	1
2	6.83	1
1	17.49	0
1	1.42	1

Compute

Sequential Analysis of Time to Event Endpoint

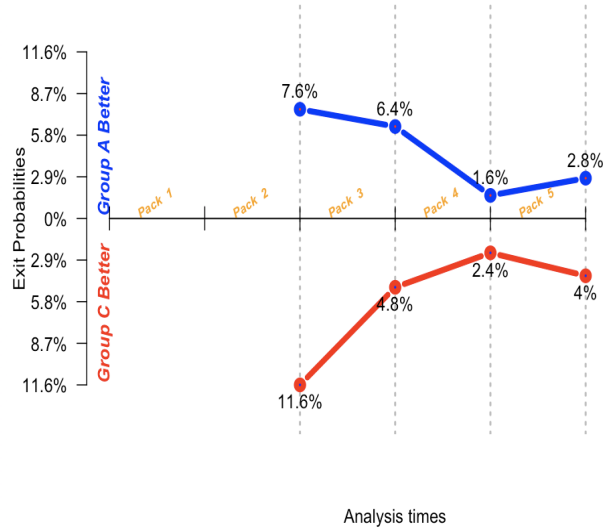
- Control Design
- Active Design
- Data
- Results

Results Output

Parameters	Value
Superiority cutpoint	0.90
Futility threshold	0.90
Clinically Relevant Thresholds	1.00
Calibration Parameter	2.00
True Median (Group A)	5.00
True Median (Group C)	5.00
Maximum Number of Subjects	100.00
Pack (Group) Cohort Size	20.00

Results	Value
Exit Probability (Group A)	0.18
Exit Probability (Group C)	0.23
Final Analysis (Grpoup A)	0.03
Final Analysis (Grpoup C)	0.04
Final Analysis (No Decision)	0.59
Median Study Time	18.42
Mean Sample Size	83.20
Median Group A Size	39.50
Median Group C Size	38.00

Summary Output



Download

Help Section

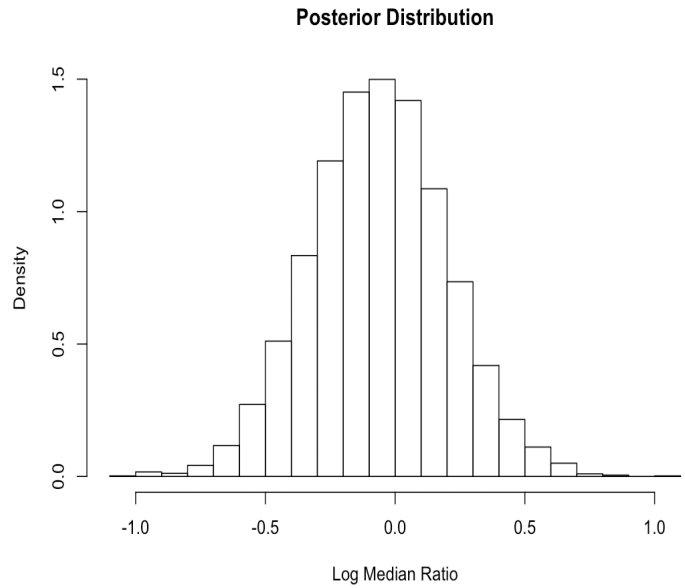
Provides a summary of the analysis performed. A CSV file containing detailed data will be created upon choosing 'compute'.

Control Design
Active Design
Data
Results

Results Output

Group	Events	Mean	SD	2.5%	50%	97.5%
A	31	4.774	0.859	3.378	4.675	6.712
C	25	5.102	1.028	3.463	4.97	7.447
A vs. C		0.972	0.26	0.566	0.939	1.586

Summary Output




```
P( Active vs. Control < delta | data ) =  0.59
```

Download

Help Section

Provides a summary of the analysis performed. A CSV file containing detailed data will be created upon choosing 'compute'.

Simulation Study

The result contains of two parts, the essential statistics and the plot.

This section lists the parameters specified in the previous tab and some output parameters.

Exit Probability (Group A)

Probability of exit due to A being better than C at anytime.

Exit Probability (Group C)

Results Output

Parameters	Value
Superiority cutpoint	0.90
Clinically Relevant Threshold	1.00
Balance	0.50
Probability (Group A > Group C)	0.09
True Median (Group A)	5.00
True Median (Group C)	5.00
Maximum Number of Subjects	60.00

Summary Output

Download

Help Section

Provides a summary of the analysis performed. A CSV file containing detailed data will be created upon choosing 'compute'.

Simulation Study

The result contains of two parts, the essential statistics and the plot.

This section lists the parameters specified in the previous tab and some output parameters.

Exit Probability (Group A)

Probability of exit due to A being better than C at anytime.

Exit Probability (Group C)

Probability of exit due to C being better than A at anytime.

Final Analysis (Group A)

What's next for this app?...

Short Answer: A lot!

1. Parallelization! Use the multicores on personal computers to shorten the duration of simulation
2. Implement piecewise-exponential and cure rate models
3. More tools for prior elicitation
4. Allow for multiple scenario specification
5. Implement designs for other type of endpoints: binary, count or continuous, using the same framework, binary, count or continuous endpoint