Bayesian Clinical Trials

Single Threshold Design

Phase II clinical trials

- **Features:** early trial in patients
- **Purpose:**
  - dose ranging
  - adverse events
  - pathophysiology
  - limited efficacy data
- **Design:**
  - single-stage
  - multi-stage (Simon's optimal and minimax design)

Two-stage design

- A small group of patients are enrolled in the first stage
- The enrollment of another group of patients in stage 2 is *conditional* on the outcome of the first group
  - activating the second stage depends on an adequate number of responses observed from the first stage

Rationale: to not enroll a large group of patients (as in conventional one-stage designs) whether not sure if the new treatment is effective

Two-stage design

- A phase II trial is an uncontrolle trial (tipically one-arm, open-label) to obtain an estimate of the degree of a new treatment (agent) effect
- The aim is to see if the new agent has sufficient activity against a specific target (i.e, type of tumor, etc.) to warrant its further development
  - to combine with other drugs in a phase III trial comparing survival results with a standard treatment

Single Threshold Design (STD)

- R_U: target response
- π_{prior}: anticipated response rate
- λ_1 and λ_2: threshold probabilities (at the interim stage and at the end of the trial) that the true response rate π exceeds R_U

Let the primary endpoint be a dichotomous variable X (e.g $X \sim Bin(n, \pi)$):

-π represents the probability of success, for which a conjugate prior *Beta* distribution is chosen: $\pi \sim Beta(\alpha, \beta)$

Bayesian sample sizing as pre-posterior analysis

- R_U: target response
- λ: minimum desired threshold probability that the true response rate π exceeds R_U

Suppose X is specified from the target response plus some small value (e.g. 0.05):

$$X = (R_U + 0.05) \times n$$

The posterior probability $P[(\pi|X, \alpha, \beta) > R_U]$ is computed:

- if it exceeds $\lambda \Longrightarrow n$ is the chosen sample size
- if it does not exceeds $\lambda \Longrightarrow$ the posterior calculation is repeated for $n + 1$ and continue until λ is exceeded.

Two-stage design

- n patients are recruited to stage 1
- possibily further $N - n$ patients are recruited to stage 2

Practical constraints: There is often practical lower and upper limits to the total study size N:

- designs with stage 1 fewer than 5 patients are unlikely to be adopted
- 2 stage designs with N larger than 100 are unlikely to be adopted
- typically total sample size N lies between 10 and 90

Two-stage design

Suppose X_1 and X_2 represent the hypothetical data that would arise from the trial (they are specified from the target response R_U plus some small value $\epsilon_U \in (0, 0.1)$ (e.g. 0.05)

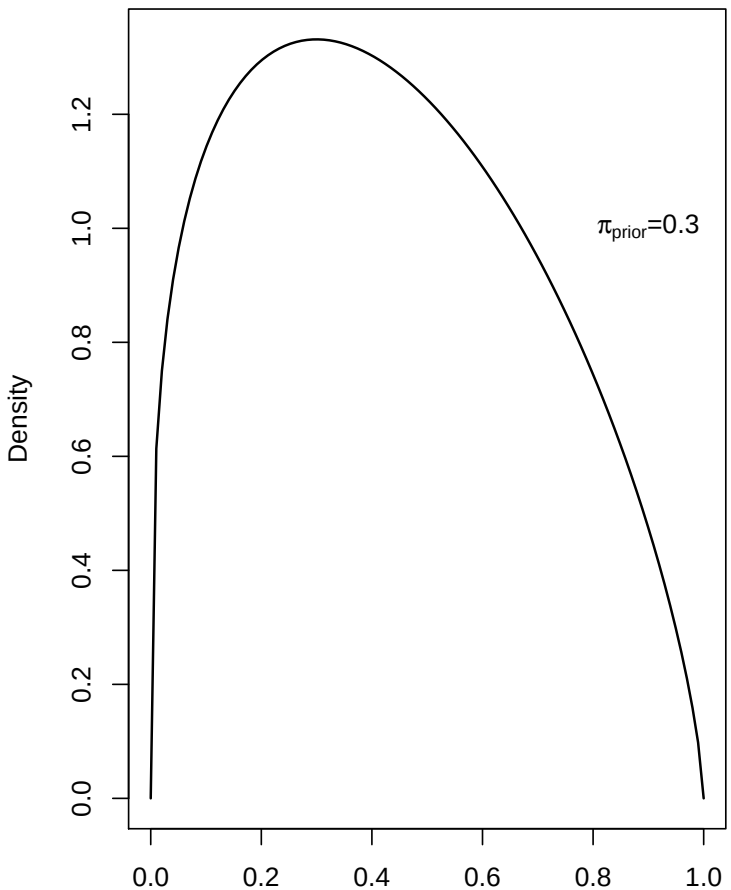
We are searching for:

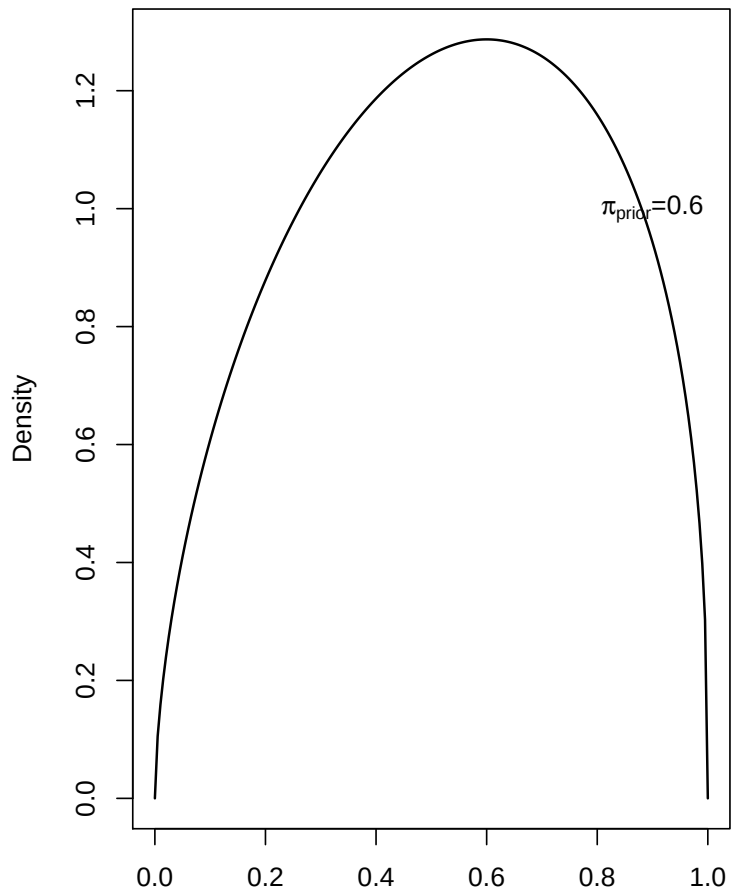
- the smallest N for which $P(\pi > R_U | X_1, X_2) > \lambda_2$
- at the same time, the smallest stage 1 sample size n such that: $P(\pi > R_U | X_1) > \lambda_1$

Computational algorithms

Tan&Machin used a $Beta(\alpha, \beta)$ vague prior distribution for π, where

$$\alpha = \pi_{prior} + 1, \qquad \beta = (1 - \pi_{prior}) + 1$$





Computational algorithms

- Specify $R_U, \pi_{prior}, \lambda_1$ and λ_2; $\epsilon_U = 0.05$
- Set the overall number of successes as $X = (R_U + \epsilon_U) \times N$, starting from $N = 10 \Longrightarrow X \sim Binomial(N, R_U + \epsilon_U)$
- Set the prior $\pi \sim Beta(\pi_{prior} + 1; (1 - \pi_{prior}) + 1)$
- Compute the posterior

$$\pi | X_1, X_2, \alpha, \beta = Beta(\alpha'; \beta')$$

where

- $\alpha' = \pi_{prior} + 1 + (R_U + \epsilon_U) \times N$
- $\beta' = 1 - \pi_{prior} + 1 + N - (R_U + \epsilon_U) \times N$

Priors

Different ways to build prior distribution $Beta(\alpha, \beta)$ for π:

- Building priors solely on the prior parameters and interpreting $\alpha + \beta$ as the total number of subjects (Gelman):
  - α successes and β failures
- Using 90th percent probability interval $W_{90} = (5th, 95th)$-percentiles and elicit information from investigators or past studies through the percentile approach

Informative and non-informative priors

- **Informative priors** are narrow and reflect the knowledge of strong prior information
- **Non-informative priors** are flat and reflect little prior information

Prior elicitation

Two steps for eliciting a-priori distribution

1. eliciting the center value by asking the clinician "what is the most likely response reate you expect to occur?"
   - finding out whether the response is the mean, median or the mode
2. assessing the uncertainty in the "most likely response rate"
   - elicitation of W_{90} is easy for clinicians who think in terms of percentiles
   - W_{90} can be elicited by asking clinicians how uncertain they are regarding their center value
   - for mode answer, the question can be posed as "prior sample size" (increasing or decreasing $\alpha + \beta$)

How to build priors

1. **mode (non-informative):**
   - it has prior parameters $\alpha = \pi_{prior} + 1$ and $\beta = 1 - \pi_{prior} + 1$
   - it has the interpretation of a mode and a prior sample size of $\alpha + \beta = 3$
2. **mode (informative):**
   - it has prior parameters $\alpha = \pi_{prior} + 1 + n_{prior}\pi_{prior}$ and $\beta = 1 - \pi_{prior} + 1 + n_{prior}(1 - \pi_{prior})$
   - it has the interpretation of a mode and a prior sample size of $\alpha + \beta = n_{prior} + 3$

How to build priors

3. **median (informative):**
   - we elicit π_{prior} assuming it is the *median* and we elicit also W_{90}
   - this requires solving the system:

$$F(\pi_{prior}|\alpha\beta) = 0.5$$
$$F^{-1}(0.95|\alpha\beta) - F^{-1}(0.05|\alpha\beta) = W_{90}$$

4. **mean (informative):**
   - we elicit π_{prior} assuming it is the *mean* and we elicit also W_{90}
   - this requires solving the system:

$$E(y) = \pi_{prior}$$
$$F^{-1}(0.95|\alpha\beta) - F^{-1}(0.05|\alpha\beta) = W_{90}$$

Sample size calculation

```
source('R/singleThresholdDesign.R')
source('R/informativePriors.R')
```

- sample size calcultion using the **non-informative mode** prior:
- $R_U = 0.2$, $\pi_{prior} = R_U + 0.05$ and $\lambda = 0.8$

```
stage2(ru = 0.2, pi = 0.2 + 0.05, lambda = 0.8)
```

```
## $N
## [1] 32
##
## $posterior
## [1] 0.8023008
```

Sample size calculation

- Sample size calculation using the **informative mode** prior with $n_{prior} = 10$:
- $R_U = 0.2$, $\pi_{prior} = R_U + 0.05$, $W_{90} = 0.3$ and $\lambda = 0.8$

```
pparameter(pi=0.2+0.05, w90=0.3, prior.method='mode-informa

## $alpha
## [1] 3.75
##
## $beta
## [1] 9.25
```

```
stage2(ru=0.2, pi=0.2+0.05, lambda=0.8, alpha = 3.75, beta

## $N
## [1] 22
##
## $posterior
## [1] 0.8023008
```

Sample size calculation

- Sample size calculation using the **informative median** prior:
- $R_U = 0.2$, $\pi_{prior} = R_U + 0.05$, $W_{90} = 0.3$ and $\lambda = 0.8$

```
pparameter(pi=0.2+0.05, w90=0.3, prior.method='median-infor

## $alpha
## [1] 5.613544
##
## $beta
## [1] 16.1849

stage2(ru=0.2, pi=0.2+0.05, lambda=0.8, alpha = 5.61, beta

## $N
## [1] 27
##
## $posterior
## [1] 0.8005037
```

Sample size calculation

- Sample size calculation using the **informative mean** prior:
- $R_U = 0.2$, $\pi_{prior} = R_U + 0.05$, $W_{90} = 0.3$ and $\lambda = 0.8$

```
pparameter(pi=0.2+0.05, w90=0.3, prior.method='mean-informa

## $alpha
## [1] 5.331685
##
## $beta
## [1] 15.99505

stage2(ru=0.2, pi=0.2+0.05, lambda=0.8, alpha = 5.33, beta

## $N
## [1] 34
##
## $posterior
## [1] 0.80136
```

Pessimistic and optimistic sample size calculations

Using the routines provided, try to find the sample size for different values of R_U according to these definitions of:

- **very optimistic prior**: $\pi_{prior} = R_U + 0.05$
- **optimistic prior**: $\pi_{prior} = R_U$
- **pessimistic prior**: $\pi_{prior} = R_U - 0.2$

Fill in the table

R_U	Prior Type	Very Optimistic	Optimistic	Pessimistic
0.40				
	non informative			
	mode			
	informative mode $n_{prior}=10$			
	informative median			
	informative mean			
0.70				
	non informative			
	mode			
	informative mode $n_{prior}=10$			
	informative			

Sample size versus W_{90}

- $R_U = 0.2$, $\pi_{prior} = R_U$

Sample size versus W_{90}

Plot the relationship between W_{90} and sample size n for $R_U = 0.6$ for

- **very optimistic prior**: $\pi_{prior} = R_U + 0.05$
- **optimistic prior**: $\pi_{prior} = R_U$
- **pessimistic prior**: $\pi_{prior} = R_U - 0.2$

R code

```
w90=seq(from=0.3, to=0.8, length.out = 25)
ru=0.2; pi=ru; lambda=0.8
n.ni=NULL; n.med=NULL; n.mea=NULL

for(i in 1:length(w90)){
  n.ni[i] = stage2(ru=ru, pi=pi, lambda = lambda)
  param = pparameter(pi=pi, w90=w90[i], prior.method='media
  n.med[i] = stage2(ru=ru, pi=pi, lambda = lambda, alpha =
  param = pparameter(pi=pi, w90=w90[i], prior.method='mean-
  n.mea[i] = stage2(ru=ru, pi=pi, lambda = lambda, alpha =
}
plot(w90, unlist(n.ni), lty='solid', xlim=c(0.2,0.9),ylim=c
lines(w90, unlist(n.med), lty='dotted')
lines(w90, unlist(n.mea), lty='longdash')
legend('topright', lty=c('solid','dotted','longdash'),
       legend=c('non-informative','median','mean'))
```

Case Study

- Phase II clinical trial to assess the response to gemcitabile plus docetaxel among patients with leiomyosarcome (LMS)

Problem statistical setup

- **endpoint:** (binary) tumor response: yes/no (Response Criteria)
- **null hypothesis:** $H_0 : \pi = \pi_0$
  - π is the true response (proportion of patients whose tumors shrink by at least 30%)
  - π_0 is a predetermined undesirable level (pu)
- **alternative hypothesis:** $H_A : \pi = \pi_A$
  - π_A is a desirable response rate (pa) _ **Type I and type II errors:** α and β
- **basis for decision:** minimize the number of patients treated in the trial if H_0 is true

The two stage design

- enroll n_1 patients at stage 1:
  - the trial is stopped if r_1 or fewer responses are observed
  - otherwise goes on to the second stage
- enross n_2 patients at stage 2:
  - the trial is not recommended for further development if a total of $r (r > r_1)$ or fewer responses are observed at both stages

Probability of early termination and expected sample size

PET: the probability to observe r_1 or fewer responses at the first stage

$$PET(\pi) = P(R_1 \leq r_1 | n_1, \pi)$$

where P is the cumulative Binomial probability.

EN: expected sample size

$$EN(\pi) = n_1 + (1 - PET(\pi)) \times n_2$$

Probability of not recommending (PNR)

The drug is not remmended if the trial is terminated early (i.e. fewer than r_1 responses are observed at the first stage) or fewer than $r = r_1 + r_2$ are observed at the end of both stages

$$PNR(\pi) = P(R_1 \leq r_1 | n_1, \pi) + \sum_{x=r_1+1}^{\min(n_1, r)} Binom(x | n_1, \pi) \times P(R \leq r - x | n_1, \pi)$$

Two types of errors

- type I error: $\alpha = 1 - PNR(\pi_0)$
- type II error: $\beta = 1 - PNR(\pi_A)$

Simon's approach

- Specify the parameters π_0, π_A, α and β
- Determine the two stage design that satisfies the errors probabilities α and β and minimizes the expected sample size when the response probability is π_0 (optimal design)
- Determine the two stage design that satisfies the errors probabilities α and β and minimizes the maximum sample size when the response probability is π_0 (minimax design)

Sample size according to Simon two-stage design

```
library(clinfun)
```

```
## Warning: package 'clinfun' was built under R version 3.2
```

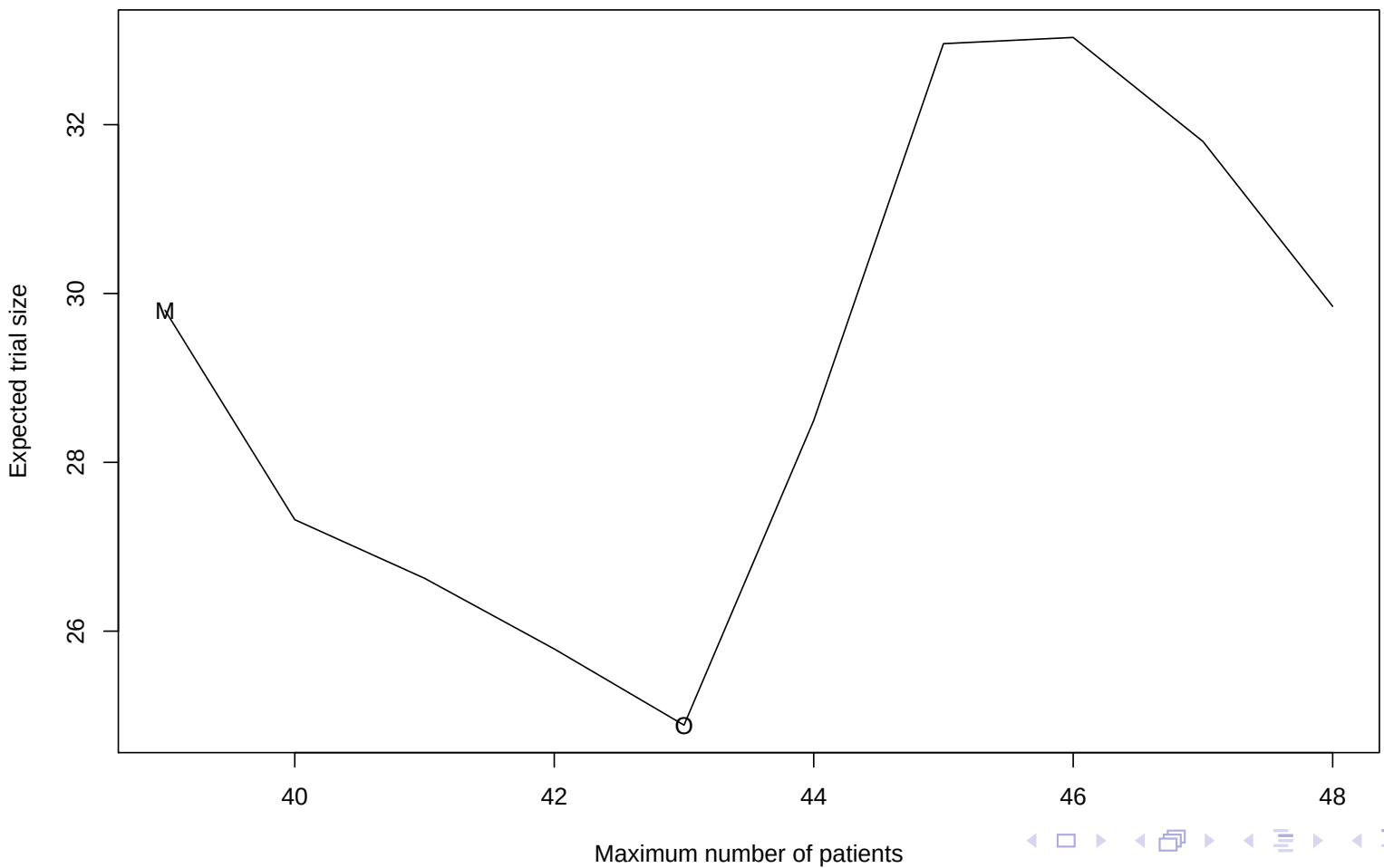
```
ph2simon(pu=0.05, pa=0.15, ep1=0.05, ep2=0.3)
```

```
##
##  Simon 2-stage Phase II design
##
## Unacceptable response rate:  0.05
## Desirable response rate:  0.15
## Error rates: alpha =  0.05 ; beta =  0.3
##
##          r1 n1 r  n EN(p0) PET(p0)
## Optimal   1 19 4 43  24.89  0.7547
## Minimax   0 17 4 39  29.80  0.4181
```

Sample size according to Simon two-stage design

```
library(clinfun)

plot(ph2simon(pu=0.05, pa=0.15, ep1=0.05, ep2=0.3))
```



STD Design

Try to find the number of patients enrolled if a STD was adopted using for comparatibe purposes:

- a non informative very optimistic prior ($\pi_{prior} = R_U + 0.05$)
- an informative mode prior ($n_{prior} = 10$)
- the median and mean ifnormative priors with $W_{90} = 0.3$

R code

```
stage2(ru=0.15, pi=0.2, lambda=0.8)

pparameter(pi=0.2, w90=0.3, prior.method='mode-informative
stage2(ru=0.15, pi=0.2, lambda=0.8, alpha = 3.2, beta = 9.8

pparameter(pi=0.2, w90=0.3, prior.method='median-informati
stage2(ru=0.15, pi=0.2, lambda=0.8, alpha = 3.91, beta = 14

pparameter(pi=0.2, w90=0.3, prior.method='mean-informative
stage2(ru=0.15, pi=0.2, lambda=0.9, alpha = 3.55, beta = 14
```