A Bayesian Stopping Rule for a Single Arm Study: with a Case Study of Stem Cell Transplantation

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• A Case Study: MT9928

Transplantation of Umbilical Cord Blood from Related and Unrelated Donors by Wagner et al. (2001)

— Goal: investigate the use of umbilical cord blood as a source of stem cells for transplantation

— Two strata:

▷ one stratum for a higher dose, with maximum sample size of n = 46

▷ one for a lower dose, with maximum sample size of n = 20.

— Statistical Analysis

⊙ A small single arm study

⊙ Maximum sample size for the study is fixed—required by Institutional Review Board (IRB)

⊙ A sequential stopping rule to examine each patient in turn

⊙ The primary concern and the goal:

Pr (Graft Failure of Day 45) $< 10\%$ with an upper limit of 20%

— Stopping rules used are derived from the program *Best* by Goldman and Hannan (2001)

▷ For the higher dose group: { − − 3 4 11 19 20 38 46 }

▷ For the lower dose group: { − − 3 11 20 }

⊙ For Type I error = 0.05 maximize power of

H_0: **p = 0.10** **vs.** H_1: **p = 0.20**

⊙ The stopping rule for stratum with n = 46:

{ − − 3 4 11 19 20 38 46} with power = 0.6202,

e.g. If `FSSSFFF` $\Longrightarrow$ Do **NOT** stop, continuing enroll the 8^{th} patient

⊙ The stopping rule for stratum with n = 20:

{ − − 3 11 20} with power = 0.3858 (too low!)

e.g. If `FSSSFFF` $\Longrightarrow$ **Stop** at the 7^{th} patient

Different sample size $\Longrightarrow$ Different rules

Motivation:

Unless there is prior information that strata are different the stopping rule for a particular outcome (e.g. `FSSSFFF`) should be identical.

Small sample size

$\Downarrow$

Use prior information to improve stopping rule and statistical analysis

$\Downarrow$

A Bayesian stopping rule

The Proposed Method and Program

Prior:

$$p \sim Beta(a, b)$$

Conditional:

$$x_i \,|\, p \sim^{indep.} Bernoulli(p), i = 1, 2, \ldots, n$$

Posterior:

$$p \,|\, X \sim Beta\left(a + \sum x_i, b + n - \sum x_i\right)$$

- Bayesian stopping rule:

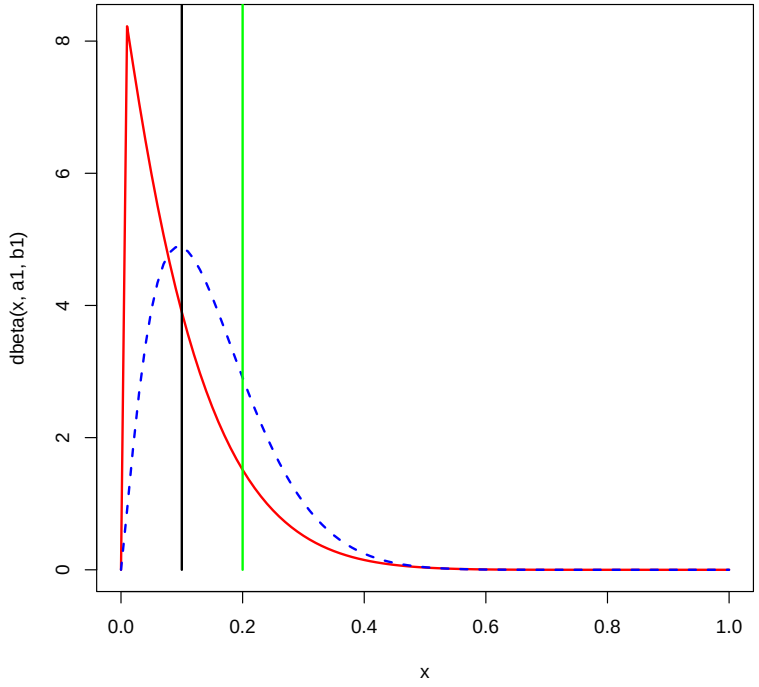
▷ Stop if $Pr(p \leq 0.10|data) \leq p_2$ (e.g. 0.3)

and if $Pr(p \geq 0.20|data) \geq p_3$ (e.g. 0.5)

▷ Stop if, for the new treatment, the posterior probability of graft failure of 10% or less is $\leq 0.30 = p_2$ and posterior probability of graft failure of 20% or more is $\geq 0.50 = p_3$

▷ Otherwise, conclusion is unclear, so continue to use new treatment.

Ex: Suppose for stratum 1 (higher dose) the prior (in red) is with mean $= 0.1$ and s.d. $= 0.09$ ($\simeq Beta(1.01, 9.10)$) and for stratum 2 (lower dose) the prior (in blue) is with mean $= 0.15$ and s.d. $= 0.09$ ($\simeq Beta(2.21, 12.53)$). $p_0 = 0.10$ is marked in black and $p_1 = 0.20$ is in green.



Ex (continued): If $p_2 = 0.30$ and $p_3 = 0.50$ are chosen, Bayesian stopping rules are:

▷ For the higher dose stratum: { – 3 8 13 18 23 28 33 38 43 46 }

size = 0.0896 *(compared to 0.0492)*

power = 0.5649 *(compared to 0.6202)*

e.g. Stop if `FSSSFFF` *(compared to "Continuing enroll the* 8^{th} *")*

▷ For the lower dose stratum: { – 5 10 15 20 }

size = 0.1375 *(compared to 0.0496)*

power = 0.5214 *(compared to 0.3858)*

e.g. Stop if `FSSSFFF` *(compared to "Stop at the* 7^{th} *")*

Different prior information $\Longrightarrow$ Different rules

If for both strata the prior information is the same (i.e. $\simeq Beta(1.01, 9.10)$) the stopping rules are:

▷ For the higher dose stratum: { – 3 8 13 18 23 28 33 38 43 46 }

▷ For the lower dose stratum: { – 3 8 13 18 20 }

Same prior information $\Longrightarrow$ same stopping rules

Outline of Technical Report

- Background and Motivation
- The Proposed Method and Program (in $\mathcal{R}$)
- Case Study—A Bayesian Stopping Rule for MT9928
- Tables Showing rules for different prior distributions, different p_2 and p_3
- Compare rules by
  1. Size
  2. Power
  3. Average Sample Size (ASN)
  4. Expected Relative Loss (ERL)

Conclusion

With some prior knowledge stopping rules can be improved upon.

$\mathcal{R}$ Program is available at:

`http://www.stat.umn.edu/ chaoyin/stopbundle.R`

with functions: ***mbetaplot, sizepower, and stopping***

References

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3. Goldman, A.I. and Hannan, P. Optimal continuous sequential boundaries for monitoring toxicity in clinical trials: a restricted search algorithm. *Statistics in Medicine* 2001; **20**: 1575 - 1589

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