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:

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

\[ H_0: p = 0.10 \quad \text{vs.} \quad H_1: p = 0.20 \]

⊙ The stopping rule for stratum with \( n = 46 \):

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

  e.g. If FSSSFFF \(\implies\) 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 \(\implies\) **Stop** at the 7\(^{th}\) patient

**Different sample size \(\implies\) 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.

\[
\begin{align*}
\text{Small sample size} & \quad \Rightarrow \\
\text{Use prior information to improve stopping rule and statistical analysis} & \quad \Rightarrow \\
\text{A Bayesian stopping rule}
\end{align*}
\]
The Proposed Method and Program

Prior:

\[ p \sim \text{Beta}(a, b) \]

Conditional:

\[ x_i \mid p \sim \text{indep. Bernoulli}(p), i = 1, 2, \ldots, n \]

Posterior:

\[ p \mid X \sim \text{Beta} \left( a + \sum x_i, b + n - \sum x_i \right) \]
• 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 (≃ 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 (≃ 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 FSSFF (compared to “Continuing enroll the 8th”)

▷ 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 FSSFF (compared to “Stop at the 7th”)

Different prior information $\Rightarrow$ Different rules
If for both strata the prior information is the same (i.e. 
≈ 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 \implies same stopping rules
Outline of Technical Report

- Background and Motivation
- The Proposed Method and Program (in 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.

R Program is available at:


with functions: mbetaplot, sizepower, and stopping
References


http://home.clara.net/sisa/sprt.htm.