

# Continuous safety monitoring in single-arm time-to-event trials without software

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## 1 Introduction

This note concerns trial conduct for one-arm trials that monitor safety by comparing time-to-event outcomes of the experimental treatment to an historical treatment. To date, such trials have been conducted using software which evaluates the stopping rule as the trial progresses. We show that is it possible to pre-calculate the stopping conditions, simplifying trial conduct and opening up new possibilities.

## 2 Probability model

Time-to-event trials could involve either time to an undesirable event, such as disease progression, or a desirable event, such as transplant engraftment. To simplify the exposition, we focus on the case of an undesirable event, some kind of treatment failure.

Let  $T_E$  be the time to failure for the experimental treatment and assume that  $T_E | m_E$  follows an exponential distribution with median  $m_E$ . (One could as easily model the mean rather than the median. However, in our experience physicians more often think of median event times.) Also, assume that *a priori*  $m_E$  has an inverse gamma distribution. Then the posterior distribution of  $m_E$  given right-censored time-to-event data is also inverse gamma. Assume that the median time to failure  $m_S$  for an historical standard treatment has a known inverse gamma distribution. We monitor a trial of the the experimental

treatment, stopping if at any point in the trial

$$P(m_E > m_S + \delta | \text{data}) < c \tag{1}$$

for some value  $c$ . Here  $\delta$  is the required improvement over historical ( $\delta$  may be zero) and  $c$  is a cutoff value, say  $c = 0.05$ . This says we stop the trial if the posterior probability that the new treatment improves time to failure relative to the standard is too small. See Thall *et al*<sup>1</sup> for a detailed description of a trial designed according to this probability model.

(Note that if we were monitoring the time to a desirable event, the stopping rule (1) would be

$$P(m_E < m_S - \delta | \text{data}) < c. \tag{2}$$

However, we will not consider the case of a desirable event further.)

A couple simplifications apply immediately. First, it is not necessary to know every patient’s data. For this model, we only need to know two summary statistics: total number of failures and total time on test. The number of failures is added to the shape parameter of the distribution on  $m_E$  and the total time on test is added to the scale parameter. Secondly, we need only evaluate the stopping rule when there has been a failure because the left side of (1) only decreases when a failure occurs. (See Appendix.) In other words, no news is good news.

Since total time on test is real-valued, trials conducted at MDACC have evaluated the stopping criterion repeatedly during the course of the trial using software to calculate the inequality probability (1). However, it is possible to prepare a table before the trial begins which makes such calculations during the trial unnecessary.

### 3 Tabulation

Assume a trial has a maximum accrual of  $N$  patients. At any point during the trial, the number of failures is an integer  $0 \leq n < N$ . Given  $n$  failures, the left side of (1) is an increasing function of total time on test. (See Appendix.) For each  $n$ , we calculate  $\tau(n)$ , the total time on test required to satisfy

$$P(m_E > m_S + \delta | \text{data}) = c.$$

We prepare a table of  $\tau(n)$  values before the trial starts. When an event occurs during the trial, we look up the  $\tau$  value corresponding to that number of events. If the total time on test is less than  $\tau$ , the trial stops. Otherwise, the trial continues.

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<sup>1</sup>Peter F. Thall, Leiko H. Wooten, and Nizar M. Tannir. Monitoring Event Times in Early Phase Clinical Trials: Some Practical Issues, *Clinical Trials*, 2:467-478, 2005.

We could calculate  $\tau(n)$  to many decimal places, but it would often suffice to tabulate the  $\tau$  values only to the nearest integer, assuming time is measured in days. Failure times are seldom known more precisely than on a scale of days. Also, if the decision whether to continue a trial depends on the exact time of day a failure occurred, perhaps accrual should at least be suspended pending further analysis.

A printed table of  $\tau$  values would make it possible to conduct simple time-to-event safety monitoring without using any software. This could serve as a contingency plan for continuing to monitor a trial while software is unavailable, say due to a network outage. One could even use a paper calendar to calculate total time on test, though it would be more convenient to use, for example, Microsoft Excel<sup>2</sup> to calculate the number of days between dates.

There are other advantages to tabulating the  $\tau$  values. Scanning the table could improve understanding of the trial design's operating characteristics. Also, such a table makes it easy to answer questions beyond whether the trial should continue at a given point in time. For example, one could determine whether a particular patient's outcome has the potential to stop the trial. Or more generally, one could determine what combination of events, if any, has the potential to stop the trial.

The software `TTEConduct` will create the table of  $\tau$  values discussed in this section. See <http://biostatistics.mdanderson.org/SoftwareDownload/>. To design a time-to-event trial, see the `TTEDesigner` software available from the same site.

## 4 Appendix

Twice in this note we have assumed a monotonicity result that is proved in the theorem below.

**Lemma 1** *Let*

$$f(x; \alpha, \beta) = \left( \frac{\beta^\alpha}{x^{\alpha+1}\Gamma(\alpha)} \right) e^{-\beta/x}$$

*be the PDF of an inverse gamma random variable. Fix  $\beta_2 > \beta_1 > 0$  and define*

$$k = \frac{\beta_2 - \beta_1}{\alpha(\log \beta_2 - \log \beta_1)}.$$

*Then  $f(x; \alpha, \beta_2) - f(x; \alpha, \beta_1)$  is negative on  $(0, k)$  and positive on  $(k, \infty)$ .*

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<sup>2</sup>To calculate the days between two dates in Excel, simply subtract the dates. For example, if cell A1 contains a start date and cell B1 contains an end date, enter `=B1-A1` in the cell to receive the difference. If the difference appears as a date rather than a number, format the result cell as numeric.

**Proof** Fix  $x > 0$ . Multiplying by  $x^{\alpha+1}\Gamma(\alpha)$  and taking logs shows that  $f(x; \alpha, \beta_2) > f(x; \alpha, \beta_1)$  if and only if

$$\alpha \log \beta_2 - \frac{\beta_2}{x} > \alpha \log \beta_1 - \frac{\beta_1}{x}.$$

Rearranging terms show that this is equivalent to

$$x > \frac{\beta_2 - \beta_1}{\alpha(\log \beta_2 - \log \beta_1)}.$$

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**Theorem 1** Let  $X_1$ ,  $X_2$ , and  $Y$  be independent inverse gamma random variables with  $X_i \sim IG(\alpha, \beta_i)$  and  $Y \sim IG(\alpha_Y, \beta_Y)$ . Let  $\delta \geq 0$  be given. If  $\beta_2 > \beta_1$  then

$$P(X_2 > Y + \delta) > P(X_1 > Y + \delta).$$

**Proof** In the notation of the lemma above,  $P(X_2 > Y + \delta) - P(X_1 > Y + \delta)$  is given by

$$\int_0^\infty f(y; \alpha_Y, \beta_Y) \int_{y+\delta}^\infty f(x; \alpha, \beta_2) - f(x; \alpha, \beta_1) dx dy.$$

Define  $g(x) = f(x; \alpha, \beta_2) - f(x; \alpha, \beta_1)$ . Since  $f(x; \alpha, \beta_1)$  and  $f(x; \alpha, \beta_2)$  are probability density functions,

$$\int_0^\infty g(x) dx = 1 - 1 = 0.$$

Since  $g(x)$  is negative for  $0 < x < k$ , and positive for  $x > k$ , we must have for  $y > 0$ ,

$$\int_{y+\delta}^\infty g(x) dx > \int_0^\infty g(x) dx = 0.$$

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