TTEConduct 2.0 Users Guide

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1 Introduction

`TTEConduct` is a simple Windows program which produces a table containing the information necessary to conduct a single-arm time-to-event safety monitoring trial using the exponential/inverse gamma model described in [1] and summarized below. This software carries out the calculations described in [2].

2 Probability model

Suppose survival time on the standard treatment is exponentially distributed with mean μ_S, where μ_S is distributed as inverse gamma with shape parameter α_S and scale parameter β_S. Similarly, survival time on the experimental treatment is exponentially distributed with mean μ_E, where μ_E is distributed *a priori* as inverse gamma with shape parameter α_E and scale parameter β_E.

(The PDF function for an inverse gamma is given by

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

where α is the shape parameter and β is the scale parameter.)

Let m be the maximum number of patients to be treated in the trial. We stop the trial early if it is unlikely that the experimental treatment is an improvement. Specifically, we stop if m patients have been treated or if

$$P(\mu_E > \mu_S + \delta \,|\, \text{data}) < c \tag{1}$$

where δ is the required improvement and c is a cutoff probability, such as 0.05 or 0.01. The parameter δ is often 0, but may be a positive value as well.

For more information on this clinical trial design, see [1].

Note that time-to-event monitoring rules are useless if the accrual rate is sufficiently high relative to the event rate: one could reach maximum accrual before there have been enough events to demonstrate that an inferior treatment is inferior. One must do a simulation study to determine the operating characteristics of a time-to-event design under the anticipated accrual rate. Keep in mind, however, that accrual rates are often grossly overestimated before a trial begins.

3 Suggestions on choosing parameters

We begin with three observations regarding the inverse gamma distribution. First, one may interpret the α parameter as the number of "prior events" contained in a distribution, meaning that the distribution holds as much information, roughly speaking, as that number of observations. Second, the mean of an inverse gamma random variable is

$$\frac{\beta}{\alpha - 1}$$

provided $\alpha > 1$. Finally, the variance of the inverse gamma distribution is

$$\frac{\beta^2}{(\alpha-1)^2(\alpha-2)}.$$

provided $\alpha > 2$.

Suppose an investigator says that the mean survival time on the standard treatment has been $\hat{\mu}_S$. If this estimate were the result of a study of n patients, one would set $\alpha = n$ and $\beta = (n-1)\hat{\mu}_S$, giving the distribution on μ_S a mean of $\hat{\mu}_S$. If the mean survival time on the standard treatment was not the result of a study, ask the investigator for a hypothetical study size that would correspond to his confidence in the mean estimate.

One often assumes *a priori* that the mean survival time on the experimental treatment has the same mean as the standard but a larger variance. Indeed, if one believed before conducting the study that the mean survival time were *less* on the experimental treatment, the study would be unethical. On the other hand, picking a prior for the mean survival time on the experimental treatment with a mean *greater* than the historical standard would typically be unjustified optimism. And while one often sets the prior means to be equal, the prior variance should be larger for the experimental treatment so that the prior responds quickly to data. One way to pick such prior distribution is to let $\alpha = 3$ and $\beta = 2\hat{\mu}_S$. This maintains the historical mean with a distribution containing three prior events. (One could pick other values of α and set $\beta = (\alpha - 1)\hat{\mu}_S$, but for $\alpha \leq 2$ the prior is so disperse as to not have a variance and so $\alpha = 3$ seems a reasonable choice.)

4 Software usage

`TTEConduct` takes seven numbers as arguments. In the notation of the previous sections, the arguments in order are α_S, β_S, α_E, β_E, δ, c, and m. The mapping of these parameters to fields on the software is straight forward.

Parameter	**Software label**
α_S	Alpha S
β_S	Beta S
α_E	Alpha E
β_E	Beta E
δ	Delta
c	Cutoff
m	Maximum Patients

We assume that μ_S and μ_E correspond to time *measured in months*. However, the stopping times given in the output correspond to time *measured in days*. The reason for this inconsistency is that physicians tend to think of survival times in units of months, whereas for trial conduct it is more convenient to measure survival in units of days.

Note that we model *mean* survival time, not median survival time. With an exponential model, the median is $\log 2 = 0.693$ times the mean. So if you are given median survival time, divide by 0.693 to obtain the mean.

The software echoes its inputs and produces a table of stopping conditions. For a given number of deaths, the table gives the minimum total time on test (in days) for the trial to continue. See [2] for more details regarding the stopping boundaries. The output of the software is in HTML format. It may be copied and pasted into another document, or may be saved to disk using the File → Save menu item. Previously saved output may be reopened by the File → Open menu item.

The software assumes that the average time on test per patient will be less than 10 years; it does not tabulate stopping boundaries that require a total time on test greater than 10 years per patient.

5 Example

Consider a trial in which the primary endpoint is progression-free survival (PFS) time. Suppose the investigator tells us the mean PFS time on standard treatment for this disease is 5 months, based on chart review of 60 patients. This suggests we set $\alpha_S = 60$, though we might set α_S lower if we had doubts

about the applicability of the data to the trial we are planning. We then set $\beta = (60 - 1) \cdot 5 = 295$ so that $E(\mu_S) = 5$.

For the prior on μ_E we pick $\alpha_E = 3$ and $\beta_E = 2 \cdot 5 = 10$, based on the suggestions above for choosing parameters. (The software will compute these values automatically after the α_S and β_S parameters are entered. These become the default values for α_E and β_E, though of course these values may be changed.)

We are looking to extend PFS by at least one month, and so we set $\delta = 1$. Suppose that after considering our expected accrual rate and running a number of simulations, we decide on a cutoff probability of 0.03. Finally, the maximum number of patients is 40.

Clicking on the Compute button brings up the Stopping Boundaries tab with program output.

The first few rows of the stopping boundaries table are given below.

Number of deaths	**Minimum TTT to continue**
1	0
2	0
3	105
4	216
5	330
6	449
⋮	⋮

This means, for example, that two deaths will not stop the trial, even if they occur on the first day. But the trial will stop if total time on test does not exceed 105 days by the time the third death occurs. The trial will also stop after the fourth death if the total time on test at that point is less than 216 days, and so forth.

References

[1] 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).

[2] John D. Cook. Continuous safety monitoring in single-arm time-to-event trials without software. MDACC technical report UTMDABTR-006-05. `http://www.mdanderson.org/pdf/biostats_utmdabtr_001_06.pdf`

This document and the `TTEConduct` software are available at

`http://biostatistics.mdanderson.org/SoftwareDownload`.