

Bayes Factor Single Arm Time-to-event User's
Guide
(Version 1.0.0)

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Contents

1 Method description

1.1 Bayesian hypothesis test

The BayesFactorTTE software implements a Bayesian hypothesis test-based method for trials with a single arm time-to-event (TTE) as described in [1].

In a Bayesian hypothesis test, the posterior odds in favor of the alternative hypothesis (H_1) is a multiplication of the prior odds in favor of the alternative hypothesis and the Bayes factor. Usually, the prior odds in favor of the alternative hypothesis is set to be 1.

$$\frac{Pr(H_1|x)}{Pr(H_0|x)} = \frac{m_1(x)}{m_0(x)} = \text{Bayes Factor}$$

where x represents the data, and $m_1(x)$ and $m_0(x)$ denote the marginal densities of the data defined under the alternative and null (H_0) hypotheses, respectively. Bayes factor is the ratio of $m_1(x)$ and $m_0(x)$.

As described in [1], the marginal density under the alternative hypothesis $m_1(x)$ is defined to be

$$m_1(x) = \int_{\Theta} f(x|\theta)\pi_1(\theta)d\theta$$

where $f(x|\theta)$ is the sample density of the data, and is usually assumed to follow an exponential distribution. $\pi_1(\theta)$ is the prior density on the alternative hypothesis, and θ is the mean TTE.

1.2 iMOM prior

For the alternative hypothesis, the proposed class of nonlocal prior densities is used. This class of densities is called inverse moment (iMOM) densities. It takes the form (Equation (10) on page 149 in [2])

$$\pi_I(\theta; \theta_0, k, \nu, \tau) = \frac{k\tau^{\nu/2}}{\Gamma(\nu/2k)} [(\theta - \theta_0)^2]^{-\frac{\nu+1}{2}} \exp\left\{-\left[\frac{(\theta - \theta_0)^2}{\tau}\right]^{-k}\right\}$$

where $k = 1$ and $\nu = 2$ as recommended.

It's worth pointing out that the parameter τ is calculated based on the fact that we know the point null hypothesis on θ , and also the prior mode of

θ under the alternative hypothesis. Specifically, based on the Equation (5) on page 220 in [1], where the mode of the density function was deduced, we could solve for τ

$$\tau = (\hat{\theta} - \theta_0)^2 \left(\frac{2k}{\nu + 1} \right)^{-1/k} \quad (1)$$

where $\hat{\theta}$ is the mode of the prior density under the alternative hypothesis on the mean TTE, and θ_0 is the point null hypothesis on the mean TTE.

1.3 An example

As an illustration of the method we use an example on page 223 in [1]. The null and alternative hypotheses are defined as

$$H_0 : \theta = 6$$

$$H_1 : \pi_1(\theta) \sim \pi_I(\theta; \theta_0 = 6, k = 1, \nu = 2, \tau = 6)I_{(6, \infty)}(\theta)$$

where under the alternative hypothesis, the iMOM density has a mode at 8 (months). Based on the point null of 6 (months) on mean TTE and the mode of 8 (months) under the alternative hypothesis, given $k = 1$ and $\nu = 2$, we could calculated that $\tau = 6$ based on formula (??).

1.4 Stopping rules

The trial stops for inferiority if

$$Pr(H_1|\text{Data}) < C_I$$

The trial stops for superiority if

$$Pr(H_1|\text{Data}) > C_S$$

where C_I is the cutoff for inferiority stopping, and C_S is the cutoff for superiority stopping. Usually it is recommended that C_I is a small number between 0 and 0.5, such as 0.15; C_S is a number between 0.5 and 1.0, such as 0.8. C_I and C_S are tuned to get good operating characteristics.

2 Running the software

2.1 Executing from the command line

BayesFactorTTE is a command line application. It runs on Microsoft Windows 7 using the .NET framework and on Mac OS X and Linux using the Mono [3] framework.

The software reads its input data from a user-prepared input file and writes its output (in HTML format) to an output file. A sample input file called `InputFile_BayesFactorTTE.txt` is supplied along with the program. You may use this file as an example, and edit it to suit your specific trial.

You may run the program from a command line like this:

```
BayesFactorTTE.exe inputfile.txt outputfile.html
```

where “inputfile.txt” and “outputfile.html” are file names supplied by you.

If you do not provide a name for the output file, the default name will be `OutputFile_BayesFactorTTE.html`.

2.2 Input parameters

Random number generator seed: Any non-negative integer up to 4 billion.

Maximum number of patients: Total number of patients enrolled if no early stopping rule applies, a non-negative integer up to 500.

Null hypothesis of median TTE in months: Median time-to-event in months under the null hypothesis, a non-negative number up to 24 months.

Alternative hypothesis of median TTE in months: Median time-to-event in months under the alternative hypothesis, must be greater than that under the null hypothesis but up to 24 months.

Inferiority boundary: The trial will stop for inferiority if the posterior probability of the alternative hypothesis is less than this boundary value. This is typically a small positive value between 0 and 0.5, such as 0.15. If this boundary value is set to be 0, the trial would not stop due to inferiority.

Superiority boundary: The trial will stop for superiority if the posterior

probability of the alternative hypothesis is greater than this boundary value. This is typically a positive value between 0.5 and 1.0, such as 0.80. If this boundary value is set to be 1, the trial would not stop due to superiority.

Accrual rate per month: Number of patients accrued per month. It must be positive and up to 100.

Need stopping boundaries? It could be “No” or “Yes”. This determines whether the program prints a table of stopping boundaries into the output file.

Scenarios: A scenario is a true median time-to-event in months.

Here is a typical input file. Note that the program will ignore blank lines and all characters from the # symbol to the end of a line. (# is the “comment” character).

```
## Design Parameters, TTE = time-to-event ##
12345 # random number generator seed for simulation
50    # max number of patients
4.0   # null hypothesis of median TTE in months
5.5   # alternative hypothesis of median TTE in months
0.15  # stop for inferiority if Pr(H1|Data) is less than this value
0.80  # stop for superiority if Pr(H1|Data) is greater than this value
2.0   # accrual rate per month
1000  # number of repetitions for the simulation
Yes   # Need stopping boundaries? (Could be "No", or "Yes")
#####
# Scenario 1
4.0   # true median TTE in months

# Scenario 2
4.8   # true median TTE in months

# Scenario 3
5.5   # true median TTE in months

# Scenario 4
6.5   # true median TTE in months
#####
# END
```

2.3 Output file

Please see the Appendix for the output html file. This file is in HTML format and may be viewed using your favorite web browser (Safari, InternetExplorer, etc).

We recommend saving the entire output of the BayesFactorTTE program and not just the operating characteristics. This assures that you have all the parameters that went into the design, including the version number of the software.

3 References

- [1] Johnson VE and Cook JD. Bayesian design of single-arm phase II clinical trials with continuous monitoring. *Clinical Trials*. 2009 Jun; 6(3): 217-26.
- [2] Johnson VE and Rossell D. On the use of non-local prior densities in Bayesian hypothesis tests. *Journal of the Royal Statistical Society B*. 72 : 143-170, 2010.
- [3] The Mono project is open source software that allows Microsoft .NET programs to run on Linux. More information is available at <http://Mono-Project.org>

4 Appendix

Output Report

BayesFactorTTE (version 1.0.0)
Bayes Factor One-arm Time-to-event Outcome
5/18/2012 5:09:32 PM
Random seed for simulation: 12345
Input file name: InputFile_BayesFactorTTE.txt
Output file name: Output_BayesFactorTTE.html

Design input parameters:

Parameter	Value
Maximum number of patients	50
Null hypothesis of median (mean) TTE in month	4 (5.77)
Alternative hypothesis of median (mean) TTE in month	5.5 (7.93)
Cutoff to stop for inferiority if $\Pr(H1 Data) <$	0.15
Cutoff to stop for superiority if $\Pr(H1 Data) >$	0.80
Accrual rate per month	2
Number of repetitions for the simulation	1000
Do you need to print out the stopping boundaries	Yes

Note: H1 = alternative hypothesis

Simulation Results

Scenario	True median (mean) TTE	Pr(Stopping for the alternative)	Pr(Stopping for the null)	Average # patients treated (10%, 90%)
1	4.0 (5.77)	0.168	0.730	27.2 (13, 50)
2	4.8 (6.92)	0.392	0.417	30.72 (13, 50)
3	5.5 (7.93)	0.680	0.169	27.98 (12, 50)
4	6.5 (9.38)	0.888	0.057	23.84 (11, 43)

Stopping Boundaries

Number Events	Max total time-on-test in days (months) to claim inferiority	Min total time-on-test in days (months)to claim superiority
0	0 (0)	574 (18.9)
1	0 (0)	834 (27.4)
2	0 (0)	1085 (35.6)
3	0 (0)	1328 (43.6)
4	0 (0)	1568 (51.5)
5	195 (6.4)	1804 (59.3)
6	408 (13.4)	2037 (66.9)
7	621 (20.4)	2268 (74.5)
8	833 (27.4)	2498 (82.1)
9	1044 (34.3)	2726 (89.6)
10	1256 (41.3)	2953 (97)
⋮	⋮	⋮
47	8912 (292.8)	10933 (359.2)
48	9117 (299.5)	11143 (366.1)
49	9321 (306.2)	11353 (373)

For example, if the current number of events is 5, if the total time-on-test is less than 195 days (6.4 months), we stop and claim inferiority; if the total time-on-test is greater than 1804 days (59.3 months), we stop and claim superiority. In comparison, if the total time-on-test is between 195 days (6.4 months) and 1804 days (59.3 months), the trial continues.