

# Bayes Factor Single Arm Binary User's Guide (Version 1.0)

Department of Biostatistics  
P. O. Box 301402, Unit 1409  
The University of Texas, M. D. Anderson Cancer Center  
Houston, Texas 77230-1402, USA

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# 1 Method description

## 1.1 Method overview

The BayesFactorBinary software implements a Bayesian hypothesis test-based method for trials with single arm binary patient outcomes as described in [1].

The software performs simulations to test a single arm binary endpoint based on a null hypothesis ( $H_0$ ) such as: “ $H_0$ : The response rate using the treatment is 20%”, versus an alternative hypothesis ( $H_1$ ) such as: “ $H_1$ : The response rate using the treatment is 30%”. Please note this is testing against a point null hypothesis.

The Bayes Factor method described below is used to determine the odds in favor of the alternative hypothesis as each patient is treated and results observed during trial progression.

## 1.2 Bayesian hypothesis test

In a Bayesian hypothesis test, the posterior odds in favor of the alternative hypothesis 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 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

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

which is a weighted average of the sample density ( $f(x|\theta)$ ) on the parameter of interest  $\theta$  with respect to the prior density ( $\pi_1(\theta)$ ) on  $\theta$ .

### 1.3 Sampling density

In the binary case, the number of  $m$  responses (successes) out of  $n$  treated subjects follows a Binomial distribution. Here  $\theta$  is the probability of responses.

$$f(x|\theta) = \binom{n}{m} \theta^m (1 - \theta)^{(n-m)}$$

### 1.4 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 worthy pointing out that the parameter  $\tau$  is calculated based on the point null hypothesis on  $\theta$ , and the alternative prior mode at  $\theta$ . Specifically, based on the Equation (5) on page 220 in [1], where the mode of the density function was deducted, we could solve for  $\tau$

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

where  $\hat{\theta}$  is the mode of the prior density under  $H_1$  on  $\theta$ , and  $\theta_0$  is the null hypothesis on  $\theta$ .

### 1.5 An example

As an illustration of the method we use an example on page 221 in [1], the null and alternative hypotheses are defined as:

$$\begin{aligned} H_0 &: \theta = 0.2 \\ H_1 &: \pi_1(\theta) \sim \pi_I(\theta; \theta_0 = 0.2, k = 1, \nu = 2, \tau = 0.015) I_{(0.2, 1)}(\theta) \end{aligned}$$

where under the alternative hypothesis, the iMOM density has a mode at 0.2. Based on the point null of 0.2 for response rate and the mode of 0.3

for response rate under the alternative hypothesis, given  $k = 1$  and  $\nu = 2$ , we could calculated that  $\tau = 0.015$  based on formula (1).

## 1.6 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 0.1;  $C_S$  is a number between 0.5 and 1.0, such as 0.9.  $C_I$  and  $C_S$  are tuned to get good operating characteristics.

## 2 Running the software

### 2.1 Executing from the command line

BayesFactorBinary 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_BayesFactorBinary.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:

```
BayesFactorBinary.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_BayesFactorBinary.html`.

## 2.2 Input parameters

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 ##
12345  # random number generator seed for simulation
50     # max number of patients
0.2    # null hypothesis of response rate
0.3    # alternative hypothesis of response rate
0.10   # stop for inferiority if Pr(H1|Data) is less than this value
0.90   # stop for superiority if Pr(H1|Data) is greater than this value
1000   # number of repetitions for the simulation
Yes    # Need stopping boundaries? (Could be "No", or "Yes")
10     # minimum number of patients to enroll before applying the stopping rules
5      # cohort size for monitoring the trial
#####
# Scenario 1
0.2    # true response rate

# Scenario 2
0.25   # true response rate

# Scenario 3
0.3    # true response rate

# Scenario 4
0.35   # true response rate

# Scenario 5
0.4    # true response rate
#####
# END
```

**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 400.

**Null hypothesis of response rate:** Response rate under the null hypothesis, a fraction between 0 and 1.

**Alternative hypothesis of response rate:** Response rate under the alternative hypothesis, must be greater than that under the null hypothesis and less than 1.

**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 0.10. If this boundary value is set to be 0, the trial would never 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 0.90. If this boundary value is set to be 1, the trial would never stop due to superiority.

**Number of repetitions for the simulation:** Number of repetitions for the simulation. It must be positive and up to 100,000. Please note the limit (100,000) is configurable, meaning that you could change this limit in the BayesFactorBinary.exe.config file (included in the package).

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

**Minimum number of patients to enroll before applying the stopping rules:** The trial will run at least this number of patients before applying the stopping rules. If this number is greater than the cohort size, it must be a multiple of the cohort size.

**Cohort size for monitoring the trial:** The trial will enroll patients with a cohort of this many patients at each enrollment, and consequently, the stopping rules will be applied for a complete cohort of patients. The maximum number of patients must be a multiple of the cohort size.

**Scenarios:** A scenario is a true response rate.

## 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, Internet Explorer, etc).

We recommend saving the entire output of the BayesFactorBinary 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

BayesFactorBinary (PID = 702) version 1.0.0  
Bayes Factor One-arm Binary Outcome  
11/14/2012 3:20:36 PM  
Random seed for simulation: 12345  
Input file name: inputFile\_BayesFactorBinary.txt  
Output file name: Output\_BayesFactorBinary.html

### Design input parameters:

Parameter	Value
Maximum number of patients	50
Null hypothesis of response rate	0.2
Alternative hypothesis of response rate	0.3
Cutoff to stop for inferiority (i.e., fail to reject H0) if $\Pr(H1 Data) <$	0.1
Cutoff to stop for superiority (i.e., reject H0) if $\Pr(H1 Data) >$	0.9
Number of repetitions for the simulation	1000
Do you need to print out the stopping boundaries	Yes
Minimum number of patients to enroll before applying the stopping rules	10
Cohort size for monitoring the trial	5

Note: H1 = alternative hypothesis ; H0 = null hypothesis.

### Simulation Results

Scenario	True response rate	Pr(Stopping for superiority)	Pr(Stopping for inferiority)	Average # patients treated (10%, 25%,50%, 75%, 90%)
1	0.20	0.037	0.520	40.00 (20, 25, 45, 50, 50 )
2	0.25	0.168	0.216	42.94 (25, 40, 50, 50, 50 )
3	0.30	0.378	0.085	40.83 (20, 30, 50, 50, 50 )
4	0.35	0.657	0.021	35.40 (15, 20, 35, 50, 50 )
5	0.40	0.858	0.002	29.26 (10, 20, 30, 45, 50 )

## Stopping Boundaries

# Patients (in complete cohorts of 5) (inclusive)	<b>Stop</b> the trial for Inferiority if there are this many Successes (inclusive)	<b>Continue</b> the trial if there are this many Successes (inclusive)	<b>Stop</b> the trial for Superiority if there are this many Successes (inclusive)
10	Never stop for inferiority with this many patients	0-5	6-10
15	0	1-7	8-15
20	0-1	2-8	9-20
25	0-3	4-10	11-25
30	0-4	5-11	12-30
35	0-5	6-12	13-35
40	0-6	7-14	15-40
45	0-8	9-15	16-45
50	0-9	10-16 (The trial always stops at 50 patients, which is the maximum	17-50

For example, when the current number of patients is 25, if we see the number of successes is between 0 and 3, we should stop the trial for inferiority; if the number of successes is between 4 and 10, we continue the trial; if the number of successes is between 11 and 25, we stop the trial for superiority. Please note that when the number of patients is 50, which is the maximum number of patients the trial allows, the trial always stops. However we nonetheless gave the boundaries for stopping for inferiority or superiority, so that the corresponding personnel may make appropriate final conclusion about the trial. That is, whether the final results show that the trial is or is not in favor of the treatment, or inconclusive.