

# Package ‘BE’

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**Version** 0.2.0

**Title** Bioequivalence Study Data Analysis

**Description** Analyze bioequivalence study data with industrial strength. Sample size could be determined for various crossover designs, such as 2x2 design, 2x4 design, 4x4 design, Balaam design, Two-sequence dual design, and William design.

Reference: Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. (2009, ISBN:978-1-58488-668-6).

**Depends** R (>= 3.0.0), rtf

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BE-package	<i>Bioequivalence Study Data Analysis</i>
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**Description**

Analyze bioequivalence study data with industrial strength. Sample size could be determined for various crossover designs, such as 2x2 design, 2x4 design, 4x4 design, Balaam design, Two-sequence dual design, and William design. Basic assumption is that the variable is distributed as a log-normal distribution. This is SAS PROC GLM style. If you want PROC MIXED style, use nlme::lme.

**Details**

It performs bioequivalency tests for several variables of a 2x2 study in a data file.

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**References**

1. Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. (2009, ISBN:978-1-58488-668-6)
2. Hauschke D, Steinijans V, Pigeot I. Bioequivalence Studies in Drug Development. (2007, ISBN:978-0-470-09475-4)
3. Diletti E, Hauschke D, Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. Int J Clinical Pharmacol Ther Tox. 1991;29(1):1-8

**Examples**

```
# write.csv(NCAREsult4BE, "temp.csv", quote=FALSE, row.names=FALSE)
# be2x2("temp.csv", c("AUClast", "Cmax", "Tmax"))
```

---

be2x2	<i>Bioequivalence test of a 2x2 study</i>
-------	---

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**Description**

It performs conventional bioequivalence test for 2x2 study. Input is a file. Basic assumption is that the variable is distributed as a log-normal distribution. This is SAS PROC GLM style. If you want PROC MIXED style, use nlme::lme.

**Usage**

```
be2x2(Data, Columns = c("AUClast", "Cmax", "Tmax"), rtfName="")
```

**Arguments**

Data	A data.frame or a csv file name. This should have at least the following columns and variable column(s) to be tested. AUC and Cmax should be all positive values.  GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T'
Columns	Column names of variables to be tested. This is usually c("AUClast", "Cmax", "Tmax") or c("AUClast", "AUCinf", "Cmax", "Tmax")
rtfName	Output filename of rich text format(rtf)

**Details**

It performs bioequivalency tests for several variables of a 2x2 study in a data file. If you specify output filename in rtfName, the output will be saved in the file.

**Value**

Returns text output of equivalence test result.

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**See Also**

[test2x2](#), [plot2x2](#)

**Examples**

```
be2x2(NCAResult4BE, c("AUClast", "Cmax", "Tmax"))
```

---

ci2cv	<i>Coefficient of variation (CV) from a confidence interval of previous 2x2 study</i>
-------	---

---

**Description**

It calculates coefficient of variation (CV) from a confidence interval of previous 2x2 study.

**Usage**

```
ci2cv(n1, n2, LL, UL, Alpha = 0.1)
```

**Arguments**

n1	Subject count of group 1
n2	Subject count of group 2
LL	Lower limit of the confidence interval of geometric mean ratio (Test/Reference)
UL	Upper limit of the confidence interval of geometric mean ratio (Test/Reference)
Alpha	Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given

**Details**

It calculates coefficient of variation (CV) from a confidence interval of 2x2 bioequivalence study.

**Value**

Returns coefficient of variation (CV) in percent (%).

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
ci2cv(12, 13, 0.85, 1.11)
```

---

ci2mse	<i>Mean squared error (MSE) from a confidence interval of previous 2x2 study</i>
--------	--

---

**Description**

It calculates mean squared error (MSE) from a confidence interval of previous 2x2 study.

**Usage**

```
ci2mse(n1, n2, LL, UL, Alpha = 0.1)
```

**Arguments**

n1	Subject count of group 1
n2	Subject count of group 2
LL	Lower limit of the confidence interval of geometric mean ratio (Test/Reference)
UL	Upper limit of the confidence interval of geometric mean ratio (Test/Reference)
Alpha	Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given

**Details**

It calculates coefficient of variation (CV) from a confidence interval of 2x2 bioequivalence study.

**Value**

Returns mean squared error (MSE).

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
ci2mse(12, 13, 0.85, 1.11)
```

cv2mse

*Mean squared error (MSE) from coefficient of variation (CV)***Description**

It calculates mean squared error (MSE) from coefficient of variation (CV).

**Usage**

```
cv2mse(cv)
```

**Arguments**

cv                      Coefficient of variation (%) in the original scale

**Details**

Coefficient of variation (CV) is percent in original scale and mean squared error (MSE) is log scale.

**Value**

Returns mean squared error (MSE) in log scale).

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
cv2mse(25)
```

hodes

*Hodges-Lehmann estimation for a variable of a 2x2 study***Description**

It performs Hodges-Lehmann estimation for 2x2 study. This is usually for Tmax variable.

**Usage**

```
hodes(bedata, Var)
```

**Arguments**

bedata	Data table name. This should have at least the following columns and a variable column to be tested. GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T'
Var	Variable to be estimated. This should be one of the column names in bedata table. Usually 'Tmax'

**Details**

It nonparametrically tests Var variable equivalency from a 2x2 study. This is done for a variable which we cannot assume log-normal distribution.

**Value**

Wilcoxon Signed-Rank Test

A kind of nonparametric test

Hodges-Lehmann Estimate

90% confidence interval in the original scale and the percent scale

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
hodges(NCAResult4BE, "Tmax")
```

---

mse2cv

*Coefficient of variation (CV) from mean squared error (MSE)*

---

**Description**

It calculates coefficient of variation (CV) from mean squared error (MSE).

**Usage**

```
mse2cv(mse)
```

**Arguments**

mse                      Mean square error (MSE) in log scale

**Details**

Coefficient of variation (CV) is percent in the original scale and mean squared error (MSE) is the log scale.

**Value**

Returns coefficient of variation (CV) in percent (%).

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
mse2cv(0.06062462)
```

---

NCAResult4BE	<i>An Example of Noncompartmental Analysis Result for Bioequivalence Test</i>
--------------	---

---

**Description**

Contains a noncompartmental analysis result table from a concentration simulated bioequivalence study.

**Usage**

```
NCAResult4BE
```

**Format**

A data frame with 48 observations on the following 10 variables.

SUBJ Subject ID  
 GRP Group or Sequence character code: 'RT' or 'TR'  
 PRD Period numeric value: 1 or 2  
 TRT Treatment or Drug code: 'R' or 'T'  
 AUClast AUClast positive numeric value  
 Cmax Cmax positive numeric value  
 Tmax Tmax positive numeric value

**Details**

This contains a simulated data for 2x2 bioequivalence study data analysis. Noncompartmental analysis results are from the NonCompartment package.

---

plot2x2	<i>Plot bioequivalence variable of a 2x2 study</i>
---------	--

---

**Description**

It plots two 2x2 plots for a variable.

**Usage**

```
plot2x2(bedata, Var)
```

**Arguments**

bedata	Data table name. This should have at least the following columns and a variable column to be plotted.  GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T'
Var	Variable to be plotted. This should be one of the column names in bedata table.

**Details**

It plots Var column values according to GRP, PRD, TRT.

**Value**

It just draws two 2x2 plots for equivalence exploration.

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
plot2x2(NCAResult4BE, "AUClast")
plot2x2(NCAResult4BE, "Cmax")
plot2x2(NCAResult4BE, "Tmax")
```

---

pow2x2ci

*Power using a confidence interval of previous 2x2 study*

---

**Description**

It calculates power for the bioequivalence test on ratio using a confidence interval of previous 2x2 study.

**Usage**

```
pow2x2ci(n1, n2, LL, UL, Alpha = 0.1)
```

**Arguments**

n1	Subject count of group 1
n2	Subject count of group 2
LL	Lower limit of the confidence interval of geometric mean ratio (Test/Reference)
UL	Upper limit of the confidence interval of geometric mean ratio (Test/Reference)
Alpha	Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given

**Details**

It calculates power of sample size (n per group) with CV.

**Value**

Returns power [0, 1)

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
pow2x2ci(12, 13, 0.85, 1.11)
```



---

pow2x2mse	<i>Power using mean squared error (MSE) of previous 2x2 study</i>
-----------	---

---

**Description**

It calculates power for the bioequivalence test on ratio using mean squared error (MSE of previous 2x2 study.

**Usage**

```
pow2x2mse(n1, n2, mse, True.R = 1, Alpha = 0.1, ThetaL = 0.8, ThetaU = 1.25)
```

**Arguments**

n1	Subject count of group 1
n2	Subject count of group 2
mse	Mean squared error
True.R	True ratio of test/reference
Alpha	Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given
ThetaL	Lower limit of equivalence criteria
ThetaU	Upper limit of equivalence criteria

**Details**

It calculates power of sample size (n per group) with CV.

**Value**

Returns power [0, 1)

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
pow2x2mse(12, 13, 0.0756530)
```

---

powcv	<i>Power using coefficient of variation (CV)</i>
-------	--

---

**Description**

It calculates power for the bioequivalence test on ratio using coefficient of variation (CV).

**Usage**

```
powcv(n, CV, DesignNo = 1, True.R = 1, Alpha = 0.1, ThetaL = 0.8, ThetaU = 1.25)
```

**Arguments**

n	Sample size, n per group
CV	Coefficient of Variation (%)
DesignNo	Crossover design number.  Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA
True.R	True ratio of test/reference
Alpha	Alpha error level
ThetaL	Lower limit of equivalence criteria
ThetaU	Upper limit of equivalence criteria

**Details**

It calculates power of sample size (n per group) with CV.

**Value**

Returns power [0, 1)

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
powcv(12, 25)
```

---

powmse	<i>Power using mean squared error (MSE)</i>
--------	---

---

**Description**

It calculates power for the bioequivalence test on ratio using mean squared error (MSE).

**Usage**

```
powmse(n, mse, DesignNo = 1, True.R = 1, Alpha = 0.1, ThetaL = 0.8, ThetaU = 1.25)
```

**Arguments**

n	Sample size, n per group
mse	Mean squared error
DesignNo	Crossover design number.  Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA
True.R	True ratio of test/reference
Alpha	Alpha error level
ThetaL	Lower limit of equivalence criteria
ThetaU	Upper limit of equivalence criteria

**Details**

It calculates power of sample size (n per group) with mse.

**Value**

Returns power [0, 1))

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
powmse(12, 0.06)
```

---

scaledBound

*Widened Bound for Scaled Average Bioequivalence*


---

**Description**

It calculates widened bound for scaled average bioequivalence.

**Usage**

```
scaledBound(CV = 40, k=0.76, digits=4)
```

**Arguments**

CV	coefficient of variation in percent
k	0.76. When CV is 30 %, bound becomes (0.8, 1.25). Most regulatory body does not use a more accurate value.
digits	Regulatory bodies usually use four decimal rounded values.

**Details**

CV must be larger than 30 %. If CV is larger than 50

**Value**

widened bound for scaled average bioequivalence

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
scaledBound(30)
scaledBound(35)
scaledBound(40)
scaledBound(45)
scaledBound(50)
```

---

ss2x2ci

*Sample size using a confidence interval of previous 2x2 study*


---

**Description**

It calculates sample size for the bioequivalence test on ratio using a confidence interval of previous 2x2 study.

**Usage**

```
ss2x2ci(n1, n2, LL, UL, Alpha = 0.1)
```

**Arguments**

n1	Subject count of group 1
n2	Subject count of group 2
LL	Lower limit of the confidence interval of geometric mean ratio (Test/Reference)
UL	Upper limit of the confidence interval of geometric mean ratio (Test/Reference)
Alpha	Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given

**Details**

It calculates sample size (n per group) with CV, Alpha, and Beta for bioequivalence test.

**Value**

Returns sample size (n per group) for bioequivalence test with ratio criteria.

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
ss2x2ci(12, 13, 0.85, 1.11)
```

---

SSCV	<i>Sample size using coefficient of variation (CV)</i>
------	--

---

**Description**

It calculates sample size for the bioequivalence test on ratio using coefficient of variation (CV).

**Usage**

```
sscv(CV, DesignNo = 1, True.R = 1, Alpha = 0.1, Beta = 0.2,
      ThetaL = 0.8, ThetaU = 1.25, nMax = 999999)
```

**Arguments**

CV	Coefficient of Variation (%)
DesignNo	Crossover design number.  Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect

```

: RCAB ARBC BACR CBRA
9 4x4x4 (William Design for 4 treatments) - carry-over effect
: RCAB ARBC BACR CBRA

True.R      True ratio of test/reference
Alpha       Alpha error level
Beta        Beta error level
ThetaL      Lower limit of equivalence criteria
ThetaU      Upper limit of equivalence criteria
nMax        Maximum subject number (sample size) per group

```

### Details

It calculates sample size (n per group) with CV, Alpha, and Beta for bioequivalence test.

### Value

Returns sample size (n per group) for bioequivalence test with ratio criteria.

### Author(s)

Kyun-Seop Bae <k@acr.kr>

### Examples

```
sscv(25)
```

---

ssmse

---

*Sample size using mean squared error (MSE)*


---

### Description

It calculates sample size for the bioequivalence test on ratio using mean squared error (MSE).

### Usage

```
ssmse(mse, DesignNo = 1, True.R = 1, Alpha = 0.1, Beta = 0.2,
      ThetaL = 0.8, ThetaU = 1.25, nMax = 999999)
```

### Arguments

```

mse          Mean squared error
DesignNo     Crossover design number.

              Design Number (treatment x sequence x period)
              1 2x2x2 : RT TR
              2 2x4x2 (Balaam Design) : TT RR RT TR
              3 2x2x3 (Two-sequence Dual Design): TRR RTT
              4 2x2x4 : TRRT RTTR
              5 2x4x4 : TTRR RRTT TRRT RTTR
              6 3x6x3 (William Design for 3 treatments) + carry-over effect

```

```

      : RBA ARB BAR ABR BRA RAB
7 3x6x3 (William Design for 3 treatments) - carry-over effect
      : RBA ARB BAR ABR BRA RAB
8 4x4x4 (William Design for 4 treatments) + carry-over effect
      : RCAB ARBC BACR CBRA
9 4x4x4 (William Design for 4 treatments) - carry-over effect
      : RCAB ARBC BACR CBRA

```

True.R	True ratio of test/reference
Alpha	Alpha error level
Beta	Beta error level
ThetaL	Lower limit of equivalence criteria
ThetaU	Upper limit of equivalence criteria
nMax	Maximum subject number (sample size) per group

### Details

It calculates sample size (n per group) with mse, Alpha, and Beta for bioequivalence test.

### Value

Returns sample size (n per group) for bioequivalence test with ratio criteria.

### Author(s)

Kyun-Seop Bae <k@acr.kr>

### Examples

```
ssmse(0.06)
```

---

SSSCV

*Scaled Average BE - Sample size using coefficient of variation (CV)*


---

### Description

It calculates sample size for the scaled average bioequivalence test on ratio using coefficient of variation (CV).

### Usage

```
ssscv(CV, DesignNo = 1, True.R = 1, Alpha = 0.1, Beta = 0.2, nMax = 999999)
```

Arguments

CV	Coefficient of Variation (%)
DesignNo	Crossover design number.  Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA
True.R	True ratio of test/reference
Alpha	Alpha error level
Beta	Beta error level
nMax	Maximum subject number (sample size) per group

Details

It calculates sample size (n per group) with CV, Alpha, and Beta for scaled average bioequivalence test.

Value

Returns sample size (n per group) for scaled average bioequivalence test with ratio criteria.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
ssscv(42.2, DesignNo=4, True.R=0.9) # 14 per group
```

---

test2x2	<i>Bioequivalence test for a variable of a 2x2 study</i>
---------	--

---

Description

It performs conventional bioequivalence test for 2x2 study. Basic assumption is that the variable is distributed as a log-normal distribution. This is SAS PROC GLM style. If you want PROC MIXED style use nlme::lme.



**Usage**

```
test2x2(bedata, Var)
```

**Arguments**

bedata	Data table name. This should have at least the following columns and a variable column to be tested. Var column values should be all positive values.  GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T'
Var	Variable to be tested. This should be one of the column names in bedata table. Usually 'AUClast' or 'Cmax'

**Details**

It tests Var variable equivalency from a 2x2 study. Current regulatory requirement is that the 90% confidence interval of geometric mean ratio (Test/Reference) should be within [0.8, 1.25].

**Value**

Analysis of Variance (log scale)	Analysis of Variance in log scale
Between and Within Subject Variability	Variance in log scale and coefficient of variance in original scale
Least Square Means	Geometric means
90% Confidence Interval	90% confidence interval of geometric mean ratio (T/R)
Sample Size	Sample size for the replication of this study

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

**Examples**

```
test2x2(NCAREsult4BE, "AUClast")
test2x2(NCAREsult4BE, "Cmax")
```

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