Package 'ph2mult'

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Type Package

Title Phase II Clinical Trial Design for Multinomial Endpoints

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Description Provide multinomial design methods under intersection-union test (IUT) and union-intersection test (UIT) scheme for Phase II trial. The design types include : Minimax (minimize the maximum sample size), Optimal (minimize the expected sample size), Admissible (minimize the Bayesian risk) and Maxpower (maximize the exact power level).

License GPL (>= 2)

LazyData TRUE

Imports clinfun,
graphics,
stats

Suggests gsDesign,
survival

R topics documented:

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binom.design   *The design function for Simon (admissible) two-stage design*

Description

Search criterion to find the Optimal, Minimax, Admissible and Maximized power design stopping boundary and corresponding sample size

1

Usage

```
binom.design(type = c("minimax","optimal","maxpower","admissible"), p0, p1,
signif.level=0.05, power.level=0.85, nmax=100, plot.out = FALSE)
```

Arguments

type	the output types of design, choose from "minimax","optimal","admissible" and "maxpower"
p0	undesirable response rate.
p1	desirable response rate for treatment efficacy.
signif.level	threshold for the probability of declaring drug desirable under p0.
power.level	threshold for the probability of declaring drug desirable under p1.
nmax	maximum total sample size
plot.out	logical; if FALSE (default), do not output plot, otherwise, output a plot for design selection.

Value

boundset	the boundaries set: r_1 and n_1 for first stage r and n for second stage

References

Simon, R. (1989). *Optimal two-stage designs for phase II clinical trials. Controlled clinical trials* **10(1)**, 1-10.

Jung, S. H., Lee, T., Kim, K., & George, S. L. (2004). *Admissible two-stage designs for phase II cancer clinical trials. Statistics in medicine* **23(4)**, 561-569.

Examples

```
binom.design(type = "admissible", p0 = 0.15, p1 = 0.3, signif.level = 0.05, power.level = 0.9,
plot.out = TRUE)
```

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binom.power	*The power function for Simon (admissible) two-stage design*

Description

Calculate the type I error or power of a two-stage design

Usage

```
binom.power(r1,n1,r,n,p)
```

Arguments

r1	first stage threshold to stop the trial for futility.
n1	first stage sample size.
r	overall threshold to stop the trial for futility.
n	total sample size.
p	pre-specified response rate, $p = p_0$ for calculating type I error, $p = p_1$ for calculating power.

Value

prob the power function: $\alpha = Pr(R \leq r | p = p_0)$ or $1 - \beta = Pr(R \leq r | p = p_1)$

References

Simon, R. (1989). *Optimal two-stage designs for phase II clinical trials. Controlled clinical trials* **10(1)**, 1-10.

See Also

binom.design

Examples

```
## Calculate type I error
binom.power(5, 31, 16, 76, 0.15)
binom.power(5, 31, 16, 76, 0.3)
```

IUT.design	*The design function for multinomial designs under intersection-union test (IUT)*

Description

Search the type I error or power of a multinomial (response and disease progression) single- or two-stage design under IUT: $H_0 : p_1 \leq p_{01} \ OR \ p_2 \geq p_{02} \ versus \ H_1 : p_1 \geq p_{11} > p_{01} \ AND \ p_2 \leq p_{12} < p_{02}$

Usage

```
IUT.design(method = c("s1", "s2", "s2.f"),
s1.rej, t1.rej, s1.acc, t1.acc, n1, s2.rej, t2.rej, n2,
s1.rej.delta=0, t1.rej.delta=0, s1.acc.delta=0, t1.acc.delta=0,
s2.rej.delta=0, t2.rej.delta=0, n1.delta=0, n2.delta=0,
p0.s, p0.t, p1.s, p1.t, signif.level = 0.05, power.level = 0.85,
show.time = TRUE, output = c("minimax","optimal","maxpower","admissible", "all"),
plot.out=FALSE)
```

Arguments

method design methods according to number of stage and stopping rule, "s1" represents single-stage design stopping for both efficacy and futility, "s2" represents two-stage design stopping for both efficacy and futility, "s2.f" represents two-stage design stopping for futility only.

s1.rej first stage responses threshold to stop the trial for efficacy. Applied for "s1" or "s2".

t1.rej first stage disease progressions threshold to stop the trial for efficacy. Applied for "s1" or "s2".

s1.acc first stage responses threshold to stop the trial for futility. Applied for "s2" or "s2.f".

t1.acc	first stage disease progressions threshold to stop the trial for futility. Applied for "s2" or "s2.f".
n1	first stage sample size. Applied for "s1", "s2" or "s2.f".
s2.rej	second stage responses threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".
t2.rej	second stage disease progressions threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".
n2	second stage sample size. Applied for "s2" or "s2.f".
s1.rej.delta	pre-specified search difference for s1.rej.
t1.rej.delta	pre-specified search difference for t1.rej.
s1.acc.delta	pre-specified search difference for s1.acc.
t1.acc.delta	pre-specified search difference for t1.acc.
s2.rej.delta	pre-specified search difference for s2.rej.
t2.rej.delta	pre-specified search difference for t2.rej.
n1.delta	pre-specified search difference for n1.
n2.delta	pre-specified search difference for n2.
p0.s	pre-specified response rate under null hypothesis.
p0.t	pre-specified disease progression rate under null hypothesis.
p1.s	pre-specified response rate under alternative hypothesis.
p1.t	pre-specified disease progression rate under alternative hypothesis. Note: type I error calculation needs to take maximum of the power function with $(p.s, p.t) = (p_{01}, 0)$ and $(p.s, p.t) = (1 - p_{02}, p_{02})$
signif.level	pre-specified significant level.
power.level	pre-specified power level.
show.time	logical; if TRUE (default), show the calculation time for the search function.
output	the output types of design, choose from "minimax","optimal","admissible" and "maxpower".
plot.out	logical; if TRUE, output a plot for design selection.

Value

boundset	the boundaries set satisfying the design types properties: $s.rej$, $t.rej$ and N for "s1", $s1.rej$, $t1.rej$, $s1.acc$, $t1.acc$ and $N1$ for first stage and $s2.rej$, $t2.rej$ and $N2$ for the second stage of "s2", $s1.acc$, $t1.acc$ and $N1$ for first stage and $s2.rej$, $t2.rej$ and $N2$ for the second stage of "s2.f",

References

Chang, M. N., Devidas, M., & Anderson, J. (2007). *One- and two-stage designs for phase II window studies. Statistics in medicine* **, 26(13)**, 2604-2614.

Simon, R. (1989). *Optimal two-stage designs for phase II clinical trials. Controlled clinical trials* **10(1)**, 1-10.

Jung, S. H., Lee, T., Kim, K., & George, S. L. (2004). *Admissible two-stage designs for phase II cancer clinical trials. Statistics in medicine* **23(4)**, 561-569.

Examples

```
p01=0.1; p02=0.9
## Calculate type I error for single-stage design
IUT.design(method="s1",s1.rej=18, t1.rej = 12, n1=80,
s1.rej.delta = 1, t1.rej.delta = 1, n1.delta=1,
p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1, output = "minimax")

## Designs for two-stage design, output PET and EN under null hypothesis
IUT.design(method="s2",s1.rej = 11, t1.rej = 4, s1.acc=8, t1.acc = 5, n1=40,
s2.rej=18, t2.rej = 11, n2=40, p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1, output = "minimax")
IUT.design(method="s2",s1.rej = 11, t1.rej = 4, s1.acc=8, t1.acc = 5, n1=40,
s2.rej=18, t2.rej = 11, n2=40, p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1, output = "optimal")
```

IUT.power	*The power function for multinomial designs under intersection-union test (IUT)*

Description

Calculate the type I error or power of a multinomial (response and disease progression) single- or two-stage design under IUT: $H_0 : p_1 \leq p_{01} \ OR \ p_2 \geq p_{02} \ versus \ H_1 : p_1 \geq p_{11} > p_{01} \ AND \ p_2 \leq p_{12} < p_{02}$

Usage

```
IUT.power(method, s1.rej, t1.rej, s1.acc, t1.acc, n1, s2.rej, t2.rej, n2, p.s, p.t,
output.all)
```

Arguments

method	design methods according to number of stage and stopping rule, "s1" represents single-stage design stopping for both efficacy and futility, "s2" represents two-stage design stopping for both efficacy and futility, "s2.f" represents two-stage design stopping for futility only.
s1.rej	first stage responses threshold to stop the trial for efficacy. Applied for "s1" or "s2".
t1.rej	first stage disease progressions threshold to stop the trial for efficacy. Applied for "s1" or "s2".
s1.acc	first stage responses threshold to stop the trial for futility. Applied for "s2" or "s2.f".
t1.acc	first stage disease progressions threshold to stop the trial for futility. Applied for "s2" or "s2.f".
n1	first stage sample size. Applied for "s1", "s2" or "s2.f".
s2.rej	second stage responses threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".
t2.rej	second stage disease progressions threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".
n2	second stage sample size. Applied for "s2" or "s2.f".

p.s	pre-specified response rate, $p.s = p_{01}$ for calculating type I error , $p = p_{11}$ for calculating power.
p.t	pre-specified disease progression rate, $p.s = p_{02}$ for calculating type I error, $p = p_{12}$ for calculating power. Note: type I error calculation needs to take maximum of the power function with $(p.s, p.t) = (p_{01}, 0)$ and $(p.s, p.t) = (1 - p_{02}, p_{02})$
output.all	logical, if FALSE (default), only output the value of power or type I error, otherwise, also output the probability of early termination (PET) and expected sample size (EN). Applied for "s2" or "s2.f".

Value

prob	the power function $g(..., p.s, p.t)$: $\alpha = \max[g(..., p_{01}, 0), g(..., 1 - p_{02}, p_{02})]$ or $g(..., p_{11}, p_{12})$

References

Chang, M. N., Devidas, M., & Anderson, J. (2007). *One- and two-stage designs for phase II window studies. Statistics in medicine* , **26(13)**, 2604-2614.

Examples

```
p01=0.1; p02=0.9
## Calculate type I error for single-stage design
max(IUT.power(method="s1", s1.rej=6, t1.rej=19, n1=25, p.s=p01, p.t=0),
IUT.power(method="s1", s1.rej=6, t1.rej=19, n1=25, p.s=1-p02, p.t=p02))
## Calculate power for single-stage design
IUT.power(method="s1", s1.rej=6, t1.rej=19, n1=25, p.s=p01+0.2, p.t=p02-0.2)


## Calculate type I error for two-stage design
max(IUT.power(method="s2", s1.rej=4, t1.rej=9, s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01, p.t=0),
IUT.power(method="s2", s1.rej=4, t1.rej=9, s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=1-p02, p.t=p02))
## Output PET and EN under null hypothesis
IUT.power(method="s2", s1.rej=4, t1.rej=9, s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01, p.t=p02, output.all=TRUE)[-1]
## Calculate power for two-stage design
IUT.power(method="s2", s1.rej=4, t1.rej=9, s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01+0.2, p.t=p02-0.2)


## Calculate type I error for two-stage design stopping for futility only,
## output PET and EN under null hypothesis
max(IUT.power(method="s2.f", s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01, p.t=0),
IUT.power(method="s2.f", s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=1-p02, p.t=p02))
## Output PET and EN under null hypothesis
IUT.power(method="s2.f", s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01, p.t=p02, output.all=TRUE)[-1]
## Calculate power for two-stage design
IUT.power(method="s2.f", s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01+0.2, p.t=p02-0.2)
```

UIT.design

The design function for multinomial designs under union-intersection test (UIT)

Description

Search the type I error or power of a multinomial (response and disease progression) single- or two-stage design under IUT: $H_0 : p_1 \leq p_{01} \ AND \ p_2 \geq p_{02} \ versus \ H_1 : p_1 \geq p_{11} > p_{01} \ OR \ p_2 \leq p_{12} < p_{02}$

Usage

```
UIT.design(method, s1.rej, t1.rej, s1.acc, t1.acc, n1, s2.rej, t2.rej, n2,
s1.rej.delta=0, t1.rej.delta=0, s1.acc.delta=0, t1.acc.delta=0,
s2.rej.delta=0, t2.rej.delta=0, n1.delta=0, n2.delta=0, p0.s, p0.t, p1.s, p1.t,
signif.level = 0.05, power.level = 0.85, output.all = FALSE, show.time = TRUE)
```

Arguments

method	design methods according to number of stage and stopping rule, "s1" represents single-stage design stopping for both efficacy and futility, "s2" represents two-stage design stopping for both efficacy and futility, "s2.f" represents two-stage design stopping for futility only.
s1.rej	first stage responses threshold to stop the trial for efficacy. Applied for "s1" or "s2".
t1.rej	first stage disease progressions threshold to stop the trial for efficacy. Applied for "s1" or "s2".
s1.acc	first stage responses threshold to stop the trial for futility. Applied for "s2" or "s2.f".
t1.acc	first stage disease progressions threshold to stop the trial for futility. Applied for "s2" or "s2.f".
n1	first stage sample size. Applied for "s1", "s2" or "s2.f".
s2.rej	second stage responses threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".
t2.rej	second stage disease progressions threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".
n2	second stage sample size. Applied for "s2" or "s2.f".
s1.rej.delta	pre-specified search difference for s1.rej.
t1.rej.delta	pre-specified search difference for t1.rej.
s1.acc.delta	pre-specified search difference for s1.acc.
t1.acc.delta	pre-specified search difference for t1.acc.
s2.rej.delta	pre-specified search difference for s2.rej.
t2.rej.delta	pre-specified search difference for t2.rej.
n1.delta	pre-specified search difference for n1.
n2.delta	pre-specified search difference for n2.
p0.s	pre-specified response rate under null hypothesis.

p0.t	pre-specified disease progression rate under null hypothesis.
p1.s	pre-specified response rate under alternative hypothesis.
p1.t	pre-specified disease progression rate under alternative hypothesis. Note: type I error calculation needs to take maximum of the power function with $(p.s, p.t) = (p_{01}, 0)$ and $(p.s, p.t) = (1 - p_{02}, p_{02})$
signif.level	pre-specified significant level.
power.level	pre-specified power level.
output.all	logical; if TRUE, output all possible designs satisfying type I error and power restrictions, otherwise, only output the design with maximum power .
show.time	logical; if TRUE (default), show the calculation time for the search function.

Value

boundset	the boundaries set satisfying the design types properties: $s.rej$, $t.rej$ and N for "s1", $s1.rej$, $t1.rej$, $s1.acc$, $t1.acc$ and $N1$ for first stage and $s2.rej$, $t2.rej$ and $N2$ for the second stage of "s2", $s1.acc$, $t1.acc$ and $N1$ for first stage and $s2.rej$, $t2.rej$ and $N2$ for the second stage of "s2.f",

References

Zee, B., Melnychuk, D., Dancey, J., & Eisenhauer, E. (1999). *Multinomial phase II cancer trials incorporating response and early progression. Journal of biopharmaceutical statistics,* **9(2),** 351-363.

Simon, R. (1989). *Optimal two-stage designs for phase II clinical trials. Controlled clinical trials* **10(1)**, 1-10.

Examples

```
## Calculate type I error for single-stage design
UIT.design(method="s1",s1.rej=18, t1.rej = 12, n1=80,
p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1)

## Designs for two-stage design, output PET and EN under null hypothesis
UIT.design(method="s2",s1.rej = 11, t1.rej = 4, s1.acc=8, t1.acc = 5, n1=40,
s2.rej=18, t2.rej = 11, n2=40, p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1, output.all=TRUE)
```

UIT.power	*The power function for multinomial designs under union-intersection test (UIT)*

Description

Calculate the type I error or power of a multinomial (response and disease progression) single- or two-stage design under UIT: $H_0 : p_1 \leq p_{01} \, AND \, p_2 \geq p_{02} \, versus \, H_1 : p_1 \geq p_{11} > p_{01} \, OR \, p_2 \leq p_{12} < p_{02}$ (Note: original Zee et al. (1999) set up the correct hypotheses, but did not make a match decision.)

Usage

```
UIT.power(method, s1.rej, t1.rej, s1.acc, t1.acc, n1, s2.rej, t2.rej, n2, p.s, p.t,
output.all)
```

Arguments

method
design methods according to number of stage and stopping rule, "s1" represents single-stage design stopping for both efficacy and futility, "s2" represents two-stage design stopping for both efficacy and futility, "s2.f" represents two-stage design stopping for futility only.

s1.rej
first stage responses threshold to stop the trial for efficacy. Applied for "s1" or "s2".

t1.rej
first stage disease progressions threshold to stop the trial for efficacy. Applied for "s1" or "s2".

s1.acc
first stage responses threshold to stop the trial for futility. Applied for "s2" or "s2.f".

t1.acc
first stage disease progressions threshold to stop the trial for futility. Applied for "s2" or "s2.f".

n1
first stage sample size. Applied for "s1", "s2" or "s2.f".

s2.rej
second stage responses threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".

t2.rej
second stage disease progressions threshold to stop the trial for efficacy. Applied for "s2" or "s2.f".

n2
second stage sample size. Applied for "s2" or "s2.f".

p.s
pre-specified response rate, $p.s = p_{01}$ for calculating type I error , $p = p_{11}$ for calculating power.

p.t
pre-specified disease progression rate, $p.s = p_{02}$ for calculating type I error, $p = p_{12}$ for calculating power. Note: type I error calculation needs to take maximum of the power function with $(p.s, p.t) = (p_{01}, 0)$ and $(p.s, p.t) = (1 - p_{02}, p_{02})$

output.all
logical, if FALSE (default), only output the value of power or type I error, otherwise, also output the probability of early termination (PET) and expected sample size (EN). Applied for "s2" or "s2.f".

Value

prob
the power function $g(..., p.s, p.t)$: $\alpha = \max[g(..., p_{01}, 0), g(..., 1 - p_{02}, p_{02})]$ or $g(..., p_{11}, p_{12})$

References

Zee, B., Melnychuk, D., Dancey, J., & Eisenhauer, E. (1999). *Multinomial phase II cancer trials incorporating response and early progression. Journal of biopharmaceutical statistics,* **9(2),** 351-363.

Examples

```
p01=0.1; p02=0.9
## Calculate type I error for single-stage design
UIT.power(method="s1", s1.rej=6, t1.rej=19, n1=25, p.s=p01, p.t=p02)
## Calculate power for single-stage design
```

```
UIT.power(method="s1", s1.rej=6, t1.rej=19, n1=25, p.s=p01+0.2, p.t=p02-0.2)

## Calculate type I error for two-stage design, output PET and EN under null hypothesis
UIT.power(method="s2", s1.rej=4, t1.rej=9, s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01, p.t=p02, output.all=TRUE)
## Calculate power for two-stage design
UIT.power(method="s2", s1.rej=4, t1.rej=9, s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01+0.2, p.t=p02-0.2)

## Calculate type I error for two-stage design stopping for futility only,
## output PET and EN under null hypothesis
UIT.power(method="s2.f", s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01, p.t=p02, output.all=TRUE)
## Calculate power for two-stage design
UIT.power(method="s2.f", s1.acc=0, t1.acc=13, n1=13,
s2.rej=6, t2.rej=18, n2=11, p.s=p01+0.2, p.t=p02-0.2)
```

Index