# Package 'ph2mult'

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**Type** Package

**Title** Phase II Clinical Trial Design for Multinomial Endpoints

**Version** 0.1.0

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**Description** Provide multinomial design methods under IUT and 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

**Suggests** gsDesign, survival

**RoxygenNote** 5.0.1

## R topics documented:



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

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### Description

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

### Usage

```
binom.design(type, p0 , p1, signif.level, power.level, plot.out)
```

### 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. |
| 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 = T)
```

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

## Value

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

## 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)
```

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

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## 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,
s1.rej, t1.rej, s1.acc, t1.acc, n1, s2.rej, t2.rej, n2,
s1.rej.delta, t1.rej.delta, s1.acc.delta, t1.acc.delta,
s2.rej.delta, t2.rej.delta, n1.delta, n2.delta,
p0.s, p0.t, p1.s, p1.t, signif.level, power.level,
show.time, output, plot.out)
```

## 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,
n1.delta = 1, n2.delta = 1, s1.rej.delta =0, t1.rej.delta =0, s2.rej.delta =0, t2.rej.delta =0,
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,
n1.delta = 1, n2.delta = 1, s1.rej.delta =0, t1.rej.delta =0, s2.rej.delta =0, t2.rej.delta =0,
p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1, output = "optimal")
```

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`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=p
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
## 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
## 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

## Calculate type I error for two-stage design stopping for futility only, output PET and EN under null hypoth
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.al
## 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, t1.rej.delta, s1.acc.delta, t1.acc.delta, n1.delta,
s2.rej.delta, t2.rej.delta, n2.delta,
p0.s, p0.t, p1.s, p1.t, signif.level, power.level,
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,
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)

## 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,
n1.delta = 1, n2.delta = 1, s1.rej.delta =0, t1.rej.delta =0, s2.rej.delta =0, t2.rej.delta =0,
p0.s = 0.15, p0.t = 0.25, p1.s = 0.3, p1.t= 0.1, output.all=TRUE)
```

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# 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". |
| s1.acc | first stage responses threshold to stop the trial for futility. Applied for "s2" or "s2.f". |
| t1.rej | first stage disease progressions threshold to stop the trial for efficacy. Applied for "s1" or "s2". |
| 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
## 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

## Calculate type I error for two-stage design stopping for futility only, output PET and EN under null hypoth
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.al
## 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)
```

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