# Package 'UnplanSimon'

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**Type** Package

**Title** Methods for Managing Enrollment Deviation in Simon's Two-Stage Design

**Version** 0.1.0

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**Description** Methods for managing under- and over-enrollment in Simon's Two-Stage Design are offered by providing adaptive threshold adjustments and sample size recalibration. It also includes post-inference analysis tools to support clinical trial design and evaluation. The package is designed to enhance flexibility and accuracy in trial design, ensuring better outcomes in oncology and other clinical studies. Yunhe Liu, Haitao Pan (2024). Submitted.

**License** GPL (>= 3)

**Encoding** UTF-8

**RoxygenNote** 7.3.2

**Imports** stats

**Depends** R (>= 3.5.0)

**Suggests** knitr, rmarkdown, clinfun (>= 3.0.0)

**VignetteBuilder** knitr

**NeedsCompilation** no

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**Repository** CRAN

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## Contents

ATSS_Design_Stage1 *Adaptive Threshold and Sample Size Simon Design Interim Analysis*

## Description

ATSS_Design_Stage1( ) provides an Adaptive Threshold and Sample Size Simon Design (ATSS Simon) method for Simon's two stage design in oncology trials when the realized sample sizes in the first stage is different from the planned sample sizes in the first stage. When under-enrollment or over-enrollment occurs at the first stage, we identify the design parameters (r1*, r*, n*) based on the actual sample size n1* ar the first stage to satisfy the type I error rate and power. In addition, the ATSS Simon design also satisfies the other criteria as in the originally planned design, such as minimizing the average sample size under the null hypothesis H0.

## Usage

```
ATSS_Design_Stage1(p0, p1, n1_star, alpha, beta)
```

## Arguments

| | |
|---|---|
| p0 | Unacceptable efficacy rate |
| p1 | Desirable efficacy rate |
| n1_star | The actual number of patients in stage 1 |
| alpha | Original Type-I error rate |
| beta | Original Type-II error rate |

## Value

a data frame includes the Adaptive Threshold and Sample Simon Design interim analysis' adjusted first stage threshold r1*, second stage threshold r*, actual number of patients in the first stage n1*, new design planned two stages' patients n*, attained Type-I error rate and Power, Average sample size under null hypothesis EN(p0) and Probability of early termination under null hypothesis PET(p0).

## References

Yunhe Liu, & Haitao Pan. (2024). *Clinical Trial Design Methods for Managing Under- and Over-Enrollment in Simon's Two-Stage Design, Submitted.*

## Examples

```
# Adaptive Threshold and Sample Size Simon Design interim analysis case 1
ATSS_Design_Stage1(0.05, 0.20, 20, 0.10, 0.10)
#                    r1* r* n1* n* Type I Power EN(p0) PET(p0)
# ATSS_Design_Stage1   1  3  20 35   0.08 0.901 23.962   0.736

# Adaptive Threshold and Sample Size Simon Design interim analysis case 2
ATSS_Design_Stage1(0.10, 0.30, 18, 0.10, 0.10)
```

```
#                     r1* r* n1* n* Type I Power EN(p0) PET(p0)
# ATSS_Design_Stage1   2  4  18 26  0.099 0.904  20.13   0.734
```

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`ATSS_Design_Stage2` *Adaptive Threshold and Sample Size Simon Design Two Stages*

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## Description

ATSS_Design_Stage2( ) provides an Adaptive Threshold and Sample Size Simon Design (ATSS Simon) method for Simon's two stage design in oncology trials when the realized sample sizes in the second stage is different from the planned sample sizes in the second stage from interim analysis new design. Further adjustment of the threshold at the second stage is needed. So, we update again the second stage threshold r* to satisfy the type I error rate given the interim analysis design first stage threshold r1* and actual two stages sample sizes (n1*, n**).

## Usage

```
ATSS_Design_Stage2(p0, p1, r1_star, n1_star, n_double_star, alpha)
```

## Arguments

| | |
|---|---|
| `p0` | Unacceptable efficacy rate |
| `p1` | Desirable efficacy rate |
| `r1_star` | Interim analysis design threshold in stage 1 |
| `n1_star` | The actual number of patients in stage 1 |
| `n_double_star` | The actual total number of patients in stages 1 and 2 |
| `alpha` | Original Type-I error rate |

## Value

a data frame includes the Adaptive Threshold and Sample Size Simon Design interim analysis design adjusted first stage threshold r1*, Adaptive Threshold and Sample Simon Design stage 2 new design adjusted second stage threshold r*, actual number of patients in the first stage n1*, actual total number of patients in stages 1 and 2 n**, attained Type-I error and Power, Average sample size under null hypothesis EN(p0) and Probability of early termination under null hypothesis PET(p0).

## References

Yunhe Liu, & Haitao Pan. (2024). *Clinical Trial Design Methods for Managing Under- and Over-Enrollment in Simon's Two-Stage Design, Submitted.*

## Examples

```
# Adaptive Threshold and Sample Size Simon Design two stages analysis case 1
ATSS_Design_Stage2(0.05, 0.20, 1, 20, 33, 0.10)
#                     r1* r* n1* n** Type I Power EN(p0) PET(p0)
# ATSS_Design_Stage2   1  3  20  33   0.07 0.888 23.434   0.736

# Adaptive Threshold and Sample Size Simon Design two stages analysis case 2
ATSS_Design_Stage2(0.10, 0.30, 2, 18, 24, 0.10)
#                   r1* r* n1* n** Type I Power EN(p0) PET(p0)
#ATSS_Design_Stage2   2  4  18  24   0.08 0.876 19.597   0.734
```

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`ATS_Design` *Adaptive Threshold Simon Design*

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## Description

ATS_Design( ) provides an Adaptive Threshold Simon Design (ATS Simon) method for Simon's two-stage design in oncology trials when the realized sample sizes in the first stage and/or the second stage(s) are different from the planned sample sizes in the first stage and/or the second stage(s). The Proposed ATS Simon design aims to adhere to sample sizes of the original design, to that end, this design updates the original thresholds of (r1, r) in the first and/or the second stages to satisfy the type I error rate as the original planned design (note: power will decrease if the realized sample size is smaller than the original one).

## Usage

```
ATS_Design(n1, n, n1_star, n_star, r1, r, p0, p1, alpha)
```

## Arguments

| | |
|---|---|
| `n1` | The planned number of patients in stage 1 |
| `n` | The planned number of patients in stages 1 and 2 |
| `n1_star` | The actual number of patients in stage 1 |
| `n_star` | The actual total number of patients in stages 1 and 2 |
| `r1` | Original design threshold in stage 1 |
| `r` | Original design threshold in stage 2 |
| `p0` | Unacceptable efficacy rate |
| `p1` | Desirable efficacy rate |
| `alpha` | Original type-I error rate |

## Value

a data frame includes the Adaptive Threshold Simon Design (ATS Simon) first stage threshold r1*, second stage threshold r*, actual first stage patients n1*, actual total sample sizes of the two stages patients n*, updated type I error constraint alpha(n*), attained type-I error and Power, Average sample size under null hypothesis EN(p0) and Probability of early termination under null hypothesis PET(p0).

## References

Yunhe Liu, & Haitao Pan. (2024). *Clinical Trial Design Methods for Managing Under- and Over-Enrollment in Simon's Two-Stage Design, Submitted.*

## Examples

```
# Adaptive Threshold Simon Design Case 1
ATS_Design(19, 36, 17, 34, 3, 10, 0.20, 0.40, 0.1)
#                                r1* r* n1* n* alpha(n*) Type I Power EN(p0) PET(p0)
# Adaptive Threshold Simon Design   3 10  17 34     0.091  0.059 0.847 24.669   0.549

# Adaptive Threshold Simon Design Case 2
ATS_Design(14, 44, 11, 41, 3, 14, 0.25, 0.45, 0.1)
#                                r1* r* n1* n* alpha(n*) Type I Power EN(p0) PET(p0)
# Adaptive Threshold Simon Design   2 14  11 41     0.088   0.06 0.854 27.344   0.455
```

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`SimonAnalysis` *Post-Trial Inference for ATS and ATSS Simon Designs*

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## Description

SimonAnalysis( ) can be used to calculate the Uniformly minimum-variance unbiased estimator (UMVUE), Confidence Intervals (Clopper-Pearson, Jung exact, and Mid-*p*) and *p*-Value given the design parameters obtained from the Adaptive Threshold Simon Design (ATS Simon) design and Adaptive Threshold and Sample Simon Design (ATSS Simon) design using ATS_Design( ), ATSS_Design_Stage1( ) and ATSS_Design_Stage2( ).

## Usage

```
SimonAnalysis(m, s, n1, n2, r1, r, alpha, quantile, CI_option, p0)
```

## Arguments

| | |
|---|---|
| `m` | Stopping stage of the ATS or ATSS Simon Designs |
| `s` | The number of responses observed in total |
| `n1` | The actual number of patients in stage 1 |
| `n2` | The actual total number of patients in stages 1 and 2 |
| `r1` | The design threshold in stage 1 |
| `r` | The design threshold in stage 2 |
| `alpha` | Type-I error rate |
| `quantile` | Two tails probability of the confidence interval |
| `CI_option` | The type of confidence interval, the character can be typed by "CP", "Jung" or "MIDp" corresponding to the Clopper-Pearson, Jung exact, or Midp confidence intervals |
| `p0` | Unacceptable efficacy rate |

## Value

a data frame includes the Uniformly minimum-variance unbiased estimator (UMVUE), chosen Confidence Interval and *p*-Value

## References

Jung, S. H., & Kim, K. M. (2004). *On the estimation of the binomial probability in multistage clinical trials. Statistics in medicine, 23(6), 881-896*, doi:10.1002/sim.1653.
Clopper, C. J., & Pearson, E. S. (1934). *The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26(4),404-413*, doi:10.2307/2331986.
Porcher, R., & Desseaux, K. (2012). *What inference for two-stage phase II trials?. BMC medical research methodology, 12, 1-13*, doi:10.1186/1471228812117.
Jung, S. H., Owzar, K., George, S. L., & Lee, T. (2006). *P-value calculation for multistage phase II cancer clinical trials. Journal of Biopharmaceutical Statistics, 16(6), 765-775*, doi:10.1080/10543400600825645.

## Examples

```
# Post-Trial inference for ATS or ATSS Simon Designs case 1
SimonAnalysis(2,7,13,30,3,12,0.05,c(0.025,0.975),"MIDp",0.40)
# Analysis Plan
#                      UMVUE CI(lower) CI(upper) p_Val
# Post-Trial Inference 0.322     0.108     0.538 0.831

# Post-Trial inference for ATS or ATSS Simon Designs case 2
SimonAnalysis(2,16,11,28,2,13,0.077,c(0.025,0.975),"Jung",0.25)
# Analysis Plan
#                     UMVUE CI(lower) CI(upper) p_Val
# Post-Trial Inference 0.429     0.257     0.568 0.019
```

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