Package 'DelayedEffect.Design'

October 16, 2017

Title Sample Size and Power Calculations using the APPLE, SEPPLE, APPLE+ and SEPPLE+ Methods

Version 1.0.0

Date 2017-10-16

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Description Provides sample size and power calculations when the treatment time-lag effect is present and the lag duration is either homogeneous across the individual subject, or varies heterogeneously from individual to individual within a certain domain and following a specific pattern. The methods used are described in Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017) <doi:10.1002/sim.7157>.

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NeedsCompilation yes

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DelayedEffect.Design *Sample size and power calculations using the APPLE, SEPPLE, APPLE+ and SEPPLE+ methods*

Description

An R package for sample size and power calculation when the treatment time-lag effect is present. The package incorporates two specific lag assumptions:
1. the lag duration is homogeneous across the individual subject;
2. the lag duration varies heterogeneously from individual to individual within a certain domain and following a specific pattern.

Details

The four new methods in this package for performing the sample size and power calculations are:
1. Analytic Power calculation method based on Piecewise weighted Log-rank tEst (APPLE),
2. Simulation-based Empirical Power calculation method based on Piecewise weighted Log-rank tEst (SEPPLE),
3. Analytic Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect (APPLE+),
4. Simulation-based Empirical Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect (SEPPLE+).
See the reference for details of these methods. Specifically, APPLE and SEPPLE assume that the lag duration is homogeneous across the individual subject, whereas APPLE and SEPPLE assume that the lag duration varies heterogeneously from individual to individual or from study to study within a certain domain and following a specific pattern. The functions for computing power corresponding to the above methods are pow.APPLE, pow.SEPPLE, pow.APPLE.plus, pow.SEPPLE.plus and pow.SEPPLE.random.DE. These can be compared to pow.sim.logrk and pow.sim.logrk.rankdom.DE which compute the power from a simulation-based algorithm using the regular log-rank test which ignores the existence of lag effects. The package also includes the function N.APPLE, N.APPLE.plus to back calculate the sample size given the power and hazard ratio, and the functions HR.APPLE and HR.APPLE.plus to back calculate the hazard ratio given the power and sample size, respectively, using the close-from APPLE and APPLE+ methods.

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References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

HR.APPLE *APPLE hazard ratio computation*

Description

Perform the post-delay hazard ratio calculation given power and sample size using the close-form APPLE method based on the piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration is homogeneous across the individual subject

Usage

```
HR.APPLE(lambda1, t1, p, N, tao, A, beta, ap=0.5, alpha=0.05)
```

Arguments

lambda1	Baseline hazard or NULL (see details)
t1	Delayed duration or NULL (see details)
p	Proportion of subjects who survive beyond the delayed period or NULL (see details)
N	Sample size
tao	Total study duration
A	Total enrollment duration
beta	Type II error rate; Power=1-beta
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.

Details

APPLE is an acronym for:
Analytic Power calculation method based on Piecewise weighted Log-rank tEst. See the reference for details of this method.

Out of the three input parameters `lambda1`, `t1` and `p`, only two need to be specified, the remaining one will be computed internally from the formula `lambda1 = -log(p)/t1`. If all three are not NULL, then `lambda1` will be set to `-log(p)/t1` regardless of the user input value.

Value

The hazard ratio

Author(s)

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References

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.APPLE, N.APPLE

Examples

```
lambda1 <- NULL
t1      <- 183
p       <- 0.7
N       <- 200
tao     <- 365*3
A       <- 365
beta    <- 0.2
HR.APPLE(lambda1, t1, p, N, tao, A, beta)
```

HR.APPLE.plus *APPLE+ hazard ratio computation*

Description

Perform the post-delay hazard ratio calculation given power and sample size using the close-form APPLE+ method based on the generalized piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration varies heterogeneously from individual to individual or from study to study, within a certain domain and following a specific pattern.

Usage

```
HR.APPLE.plus(lambda1, tl, tu, N, tao, A, beta, ap=0.5, alpha=0.05)
```

Arguments

lambda1	Baseline hazard
tl	Lower bound of delayed duration domain
tu	Upper bound of delayed duration domain
N	Sample size
tao	Total study duration
A	Total enrollment duration
beta	Type II error rate; Power=1-beta
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.

Details

APPLE+ is an acronym for:
Analytic Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect. See the reference for details of this method.

Value

The hazard ratio

Author(s)

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References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.APPLE.plus, N.APPLE.plus

Examples

```
lambda1 <- 0.001982
tl      <- 30
tu      <- 30*11
N       <- 200
tao     <- 365*3
A       <- 365
beta    <- 0.2
HR.APPLE.plus(lambda1, tl, tu, N, tao, A, beta)
```

N.APPLE *APPLE sample size computation*

Description

Perform the sample size calculation given the power and post-delay hazard ratio using the closeform APPLE method based on the piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration is homogeneous across the individual subject

Usage

```
N.APPLE(lambda1, t1, p, HR, tao, A, beta, ap=0.5, alpha=0.05)
```

Arguments

lambda1	Baseline hazard or NULL (see details)
t1	Delayed duration or NULL (see details)
p	Proportion of subjects who survive beyond the delayed period or NULL (see details)
HR	Post-delay hazard ratio, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
beta	Type II error rate; Power=1-beta
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.

Details

APPLE is an acronym for:
Analytic Power calculation method based on Piecewise weighted Log-rank tEst. See the reference for details of this method.

Out of the three input parameters `lambda1`, `t1` and `p`, only two need to be specified, the remaining one will be computed internally from the formula `lambda1 = -log(p)/t1`. If all three are not NULL, then `lambda1` will be set to `-log(p)/t1` regardless of the user input value.

Value

The sample size

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References

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

`pow.APPLE`, `HR.APPLE`

Examples

```
lambda1 <- NULL
t1      <- 183
p       <- 0.7
HR      <- 0.55
tao     <- 365*3
A       <- 365
beta    <- 0.2
N.APPLE(lambda1, t1, p, HR, tao, A, beta)
```

N.APPLE.plus *APPLE+ sample size computation*

Description

Perform the sample size calculation given the power and post-delay hazard ratio using the closed-form APPLE+ method based on the generalized piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration varies heterogeneously from individual to individual or from study to study, within a certain domain and following a specific pattern.

Usage

```
N.APPLE.plus(lambda1, tl, tu, HR, tao, A, beta, ap=0.5, alpha=0.05)
```

Arguments

lambda1	Baseline hazard
tl	Lower bound of delayed duration domain
tu	Upper bound of delayed duration domain
HR	Post-delay hazard ratio after tu, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
beta	Type II error rate; Power=1-beta
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.

Details

APPLE+ is an acronym for:
Analytic Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect. See the reference for details of this method.

Value

The sample size

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov>, Boguang Zhen<Boguang.Zhen@fda.hhs.gov>, Yongsoek Park <yongpark@pitt.edu> and Bin Zhu <bin.zhu@nih.gov>

References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.APPLE.plus, HR.APPLE.plus

Examples

```
lambda1 <- 0.001982
tl      <- 30
tu      <- 30*11
HR      <- 1.3
tao     <- 365*3
A       <- 365
beta    <- 0.2
N.APPLE.plus(lambda1, tl, tu, HR, tao, A, beta)
```

pow.APPLE *APPLE power computation*

Description

Perform the power calculation using the close-form APPLE method based on the piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration is homogeneous across the individual subject

Usage

```
pow.APPLE(lambda1, t1, p, N, HR, tao, A, ap=0.5, alpha=0.05)
```

Arguments

lambda1	Baseline hazard or NULL (see details)
t1	Delayed duration or NULL (see details)
p	Proportion of subjects who survive beyond the delayed period or NULL (see details)
N	Sample size
HR	Post-delay hazard ratio, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.

Details

APPLE is an acronym for:
Analytic Power calculation method based on Piecewise weighted Log-rank tEst. See the reference for details of this method.

Out of the three input parameters `lambda1`, `t1` and `p`, only two need to be specified, the remaining one will be computed internally from the formula `lambda1 = -log(p)/t1`. If all three are not NULL, then `lambda1` will be set to `-log(p)/t1` regardless of the user input value.

Value

The power

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References

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

N.APPLE, HR.APPLE, pow.SEPPLE, pow.sim.logrk

Examples

```
lambda1 <- NULL
t1      <- 183
p       <- 0.7
N       <- 200
HR      <- 0.55
tao     <- 365*3
A       <- 365
pow.APPLE(lambda1, t1, p, N, HR, tao, A)
```

---

pow.APPLE.plus *APPLE+ power computation*

Description

Perform the power calculation using the close-form APPLE+ method based on the generalized piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration varies heterogeneously from individual to individual or from study to study, within a certain domain and following a specific pattern.

Usage

```
pow.APPLE.plus(lambda1, tl, tu, N, HR, tao, A, ap=0.5, alpha=0.05)
```

Arguments

lambda1	Baseline hazard
tl	Lower bound of delayed duration domain
tu	Upper bound of delayed duration domain
N	Sample size
HR	Post-delay hazard ratio after tu, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.

Details

APPLE+ is an acronym for:
Analytic Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect. See the reference for details of this method.

Value

The power

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov>, Boguang Zhen<Boguang.Zhen@fda.hhs.gov>, Yongsoek Park <yongpark@pitt.edu> and Bin Zhu <bin.zhu@nih.gov>

References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

N.APPLE.plus, HR.APPLE.plus

Examples

```
lambda1 <- 0.001982
tl      <- 30
tu      <- 30*11
N       <- 200
HR      <- 1.3
tao     <- 365*3
A       <- 365
pow.APPLE.plus(lambda1, tl, tu, N, HR, tao, A)
```

---

pow.SEPPLE *SEPPLE power computation*

Description

Perform the power calculation using the numeric SEPPLE method based on the piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration is homogeneous across the individual subject

Usage

```
pow.SEPPLE(lambda1, t1, p, N, HR, tao, A, ap=0.5, alpha=0.05, nsim=10000)
```

Arguments

lambda1	Baseline hazard or NULL (see details)
t1	Delayed duration or NULL (see details)
p	Proportion of subjects who survive beyond the delayed period or NULL (see details)
N	Sample size
HR	Post-delay hazard ratio, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration

ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.
nsim	Number of simulations. The default is 10000.

Details

SEPPLE is an acronym for:
Simulation-based Empirical Power calculation method based on Piecewise weighted Log-rank tEst. See the reference for details of this method.

Out of the three input parameters `lambda1`, `t1` and `p`, only two need to be specified, the remaining one will be computed internally from the formula `lambda1 = -log(p)/t1`. If all three are not NULL, then `lambda1` will be set to `-log(p)/t1` regardless of the user input value.

Value

The power

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References

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.APPLE, pow.sim.logrk

Examples

```
lambda1 <- NULL
t1      <- 183
p       <- 0.7
N       <- 200
HR      <- 0.55
tao     <- 365*3
A       <- 365
pow.SEPPLE(lambda1, t1, p, N, HR, tao, A, nsim=1000)
```

---

pow.SEPPLE.plus *SEPPLE+ power computation*

Description

Perform the power calculation using the numeric SEPPLE+ method based on the generalized piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration varies heterogeneously from individual to individual or from study to study, within a certain domain and following a specific pattern.

Usage

```
pow.SEPPLE.plus(lambda1, tl, tu, N, HR, tao, A, dist="uniform",
              shape1=NULL, shape2=NULL, ap=0.5, alpha=0.05, nsim=10000)
```

Arguments

lambda1	Baseline hazard
tl	Lower bound of delayed duration domain
tu	Upper bound of delayed duration domain
N	Sample size
HR	Post-delay hazard ratio after tu, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
dist	One of "uniform", "beta" or "gamma", for the lag distribution
shape1	NULL or a positive parameter value for the beta or gamma distribution.
shape2	NULL or a positive parameter value for the beta or gamma distribution.
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.
nsim	Number of simulations. The default is 10000.

Details

SEPPLE+ is an acronym for:
Simulation-based Empirical Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect. See the reference for details of this method.

Value

The power

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References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.SEPPLE.random.DE, pow.sim.logrk.random.DE

Examples

```
lambda1 <- 0.001982
tl      <- 30
tu      <- 30*11
N       <- 200
HR      <- 0.55
tao     <- 365*3
A       <- 365
shape1  <- 5
shape2  <- 5
pow.SEPPLE.plus(lambda1, tl, tu, N, HR, tao, A, dist="beta",
                shape1=shape1, shape2=shape2, nsim=1000)
```

---

pow.SEPPLE.random.DE *SEPPLE+ power computation*

Description

Perform the power calculation using the numeric SEPPLE method based on the piecewise weighted log-rank test when the treatment time-lag effect is present and the lag duration varies heterogeneously from individual to individual or from study to study, within a certain domain and following a specific pattern. The purpose of this function is to evaluate the property of SEPPLE which assumes the lag duration is homogeneous across the individual subject, when applied under the random scenario where the lag duration, in fact, varies heterogeneously.

Usage

```
pow.SEPPLE.random.DE(lambda1, tl, tu, N, HR, tao, A, t.fixed, dist="uniform",
              shape1=NULL, shape2=NULL, ap=0.5, alpha=0.05, nsim=10000)
```

Arguments

lambda1	Baseline hazard
tl	Lower bound of delayed duration domain
tu	Upper bound of delayed duration domain
N	Sample size
HR	Post-delay hazard ratio after tu, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
t.fixed	Fixed duration in SEPPLE
dist	One of "uniform", "beta" or "gamma", for the lag distribution
shape1	NULL or a positive parameter value for the beta or gamma distribution.
shape2	NULL or a positive parameter value for the beta or gamma distribution.
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.
nsim	Number of simulations. The default is 10000.

Details

SEPPLE+ is an acronym for:
Simulation-based Empirical Power calculation method based on generalized Piecewise weighted Log-rank tEst with random treatment time-lag effect. See the reference for details of this method.

Value

The power

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov> , Boguang Zhen<Boguang.Zhen@fda.hhs.gov>, Yongsoek Park <yongpark@pitt.edu> and Bin Zhu <bin.zhu@nih.gov>

References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.SEPPLE.plus, pow.sim.logrk.random.DE

Examples

```
lambda1 <- 0.001982
tl      <- 30
tu      <- 30*11
N       <- 200
HR      <- 0.55
tao     <- 365*3
A       <- 365
t.fixed <- (tl+tu)/2
shape1  <- 5
shape2  <- 5
pow.SEPPLE.random.DE(lambda1, tl, tu, N, HR, tao, A, t.fixed, dist="beta",
                     shape1=shape1, shape2=shape2, nsim=1000)
```

---

pow.sim.logrk *Simulated log-rank power computation*

Description

Perform the power calculation using a simulation-based method based on the regular log-rank test when the treatment time-lag effect is present and the lag duration is homogeneous across the individual subject

Usage

```
pow.sim.logrk(lambda1, t1, p, N, HR, tao, A, ap=0.5, alpha=0.05, nsim=10000)
```

Arguments

lambda1	Baseline hazard or NULL (see details)
t1	Delayed duration or NULL (see details)
p	Proportion of subjects who survive beyond the delayed period or NULL (see details)
N	Sample size
HR	Post-delay hazard ratio, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.
nsim	Number of simulations. The default is 10000.

Details

Out of the three input parameters `lambda1`, `t1` and `p`, only two need to be specified, the remaining one will be computed internally from the formula `lambda1 = -log(p)/t1`. If all three are not NULL, then `lambda1` will be set to `-log(p)/t1` regardless of the user input value.

Value

The power

Author(s)

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References

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.APPLE, pow.SEPPLE

Examples

```
lambda1 <- NULL
t1      <- 183
p       <- 0.7
N       <- 200
HR      <- 0.55
tao     <- 365*3
A       <- 365
pow.sim.logrk(lambda1, t1, p, N, HR, tao, A, nsim=1000)
```

pow.sim.logrk.random.DE

Simulated log-rank power computation

Description

Perform the power calculation using a simulation-based method based on the regular log-rank test when the treatment time-lag effect is present and the lag duration varies heterogeneously from individual to individual or from study to study, within a certain domain and following a specific pattern.

Usage

```
pow.sim.logrk.random.DE(lambda1, tl, tu, N, HR, tao, A, dist="uniform",
              shape1=NULL, shape2=NULL, ap=0.5, alpha=0.05, nsim=10000)
```

Arguments

lambda1	Baseline hazard
tl	Lower bound of delayed duration domain
tu	Upper bound of delayed duration domain
N	Sample size
HR	Post-delay hazard ratio after tu, defined as the post-delay hazard rate of the treatment group compared to that of the control group
tao	Total study duration
A	Total enrollment duration
dist	One of "uniform", "beta" or "gamma", for the lag distribution
shape1	NULL or a positive parameter value for the beta or gamma distribution.
shape2	NULL or a positive parameter value for the beta or gamma distribution.
ap	Experimental-control allocation ratio. The default is 0.5.
alpha	Type I error rate (two-sided). The default is 0.05.
nsim	Number of simulations. The default is 10000.

Details

The regular log-rank test is used here

Value

The power

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References

Xu, Z., Park, Y., Zhen, B. & Zhu, B. (2017). Achieving optimal power of logrank test with random treatment time-lag effect. Biometrika. Under review.

Xu, Z., Zhen, B., Park, Y., & Zhu, B. (2017). Designing therapeutic cancer vaccine trials with delayed treatment effect. Statistics in medicine, 36(4), 592-605.

See Also

pow.SEPPLE.plus, pow.SEPPLE.random.DE

Examples

```
lambda1 <- 0.001982
tl      <- 30
tu      <- 30*11
N       <- 200
HR      <- 0.55
tao     <- 365*3
A       <- 365
shape1  <- 5
shape2  <- 5
pow.sim.logrk.random.DE(lambda1, tl, tu, N, HR, tao, A, dist="beta",
                        shape1=shape1, shape2=shape2, nsim=1000)
```

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