Package 'coprimary'

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Type Package

Title Sample Size Calculation for Two Primary Time-to-Event Endpoints in Clinical Trials

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Description Computes the required number of patients for two time-to-event endpoints as primary endpoint in phase III clinical trial.

License GPL (>= 3.3.2)

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Depends stats, gsDesign, digest, plyr, proto

Collate 'datacheck.R' 'nbevent.R' 'probanofix.R' 'probafix.R' 'ncoprimary.R' 'nsurvival.R'

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coprimary-package *Sample size calculation for two primary time-to-event endpoints in phase III clinical trials*

Description

The coprimary R package computes the required number of patients for two time-to-event endpoints as primary endpoint. This R package contains six functions to check the consistency of the design and computes the sample size with one or two time-to-event endpoints. Both endpoints can be one time to event endpoint, such as Overall Survival (OS), Progression Free Survival (PFS) or the health health-related quality of life (HRQoL), or two time-to-event endpoints, which could be PFS and time to HRQoL score deterioration as example.

Details

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Author(s)

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References

Legault, Claudine. Analyzing multiple endpoints with a two-stage group sequential design in clinical trials. Diss. University of North Carolina at Chapel Hill, 1991.
Chow, Shein-Chung, Hansheng Wang, and Jun Shao. Sample size calculations in clinical research. CRC press, 2007.
Filleron, T., Gal, J., & Kramar, A. (2012). Designing group sequential randomized clinical trials with time to event end points using a R function. Computer methods and programs in biomedicine, 108(1), 113-128.

Examples

```
##############################################################################################
############ Design superiority: two-sided with two co-primary endpoints ############
##############################################################################################
## - For endpoint 1: 2 target variables for the health related quality of life with 3-year
## rate without HRQoL deterioration Se=0.75 and Sc=0.67, alpha1=c(0.01,0.01)
```

```
## - For endpoint 2: 4-year survival rates Se=0.86 and Sc=0.80, alpha2=c(0.015,0.015)
## - with accrual duration of 3 years, study duration of 6 years, power=0.90,
## look=c(2,c(1,1),0.5), and default values i.e  pe=0.5, fup=0, dropout=0

nc1 <- ncoprimary(design=c(1,2),Survhyp1=c(1,5,0.75,0.67),Survhyp2=c(1,5,0.86,0.80),
alpha1=c(0.01,0.01),alpha2=c(0.015,0.015),duraccrual=3,durstudy=6,power=0.90,
look=c(2,c(1,1),0.5),dqol=2)


################################################################################
############ Design superiority: one-sided with two co-primary endpoints ############
################################################################################
## - For endpoint 1: 2-year hazard ratio hype=0.86 and Sc=0.62, alpha1=0.05
## - For endpoint 2: 3-year survival rates hype=0.81 and Sc=0.57, alpha2=0.05
## - with accrual duration of 2 years, study duration of 10 years and default values i.e
## power=0.90, pe=0.5, look=1, fup=0, dropout=0, dqol=0


nc2 <- ncoprimary(design=c(1,1),Survhyp1=c(2,2,0.86,0.62),Survhyp2=c(2,3,0.81,0.57),
alpha1=0.05,alpha2=0.05,duraccrual=2,durstudy=10)

################################################################################
###############   Design non-inferiority with one primary endpoint #################
################################################################################
## 5-year rate without HRQoL deterioration are equal under the alternative hypothesis,
## i.e Se=0.60 and Sc=SeA=0.70, with alpha=0.05, accrual duration of 4 years,study duration
## of 8 years, two interim analysis after the occurence 1/3 and 2/3 of the events, 3 target
## variables for the health related quality of life and default values i.e power=0.80, pe=0.5,
## fup=0, dropout=0

ns <- nsurvival(design=c(2),Survhyp=c(1,5,0.60,0.70, 0.70),alpha=0.05,duraccrual=4,
durstudy=8,look=c(3,c(1,1),c(1/3,2/3)), dqol=3)
```

`datacheck` *check the consistency of the parameters*

Description

this function check the parameters required to calcul the sample size for nsurvival and ncoprimary functions. datacheck is a simple utility for carrying out parameter checks and reporting on problems or errors.

Usage

```
datacheck(design,Survhyp,pe,alfa,beta,duraccrual,durstudy,look,followup,dropout)
```

Arguments

design	Superiority=c(1,sided)[with sided=1 if 1-sided and 2 if 2-sided]; Non inferiority=c(2); Equivalence=c(3)
Survhyp	For Superiority=c(thyp,t,hype,Sc); for Non inferiority=c(thyp,t,hype,Sc,hypeA); for Equivalence=c(t,delta,Sc): parameters at time t if thyp=1 then hype is survival rate in experimental arm under the null hypothesis and hypeA is the survival rate in the experimental arm under the alternative hypothesis; if thyp=2 then hype is the hazard ratio under the null hypothesis and hypeA is the hazard ratio under the alternative hypothesis; Sc is the survival rate in the control arm; delta is the log hazard ratio equivalence margin. When endpoint is HRQoL, the survival rate is replaced by the rate of patients without the HRQoL deterioration.
pe	Proportion (ratio) of patients assigned to the experimental arm (with 0<pe<1)
alfa	Type I error, for Non inferiority, Equivalence and 1-sided superiority, alfa is a vector of length one. For 2-sided superiority, alfa is a vector to length two c(alpha.low, alpha.up).
beta	Probability of a type II error.
duraccrual	Accrual duration, expressed in number of days, months or years
durstudy	Study duration, expressed in number of days, months or years
look	The number interim analyses, c(1) for one final analysis; c(nb, bound, timing) for at least one interim analyses with bound=c(bound.eff,bound.fut):1-sided or bound=c(bound.low,bound.up):2-sided. nb the number of planned looks, bound.eff and bound.fut corresponds to the type of boundaries used for efficacy (i.e. reject H0) and futility (i.e. reject H1). bound.fut=0: No futility monitoring, 1: Lan deMets O.Brien Fleming, 2: Lan deMets Pocock. bound.low and bound.up the type of lower and upper boundaries used (1: Lan deMets O.Brien Fleming, 2: Lan deMets Pocock, 3: O.Brien Fleming, 4: Pocock). Default value = 1.
followup	Follow-up information, No fixed:c(0) (follow-up until the end of study); Fixed:c(1, durfollow) with durfollow is the duration of follow-up
dropout	Drop out information, No drop out:c(0); Drop out:c(1,gammae,gammac) with gammae the hazard drop out rates in experimental arm and control arm respectively.

Details

the datacheck function performs consistency checks on the arguments

---

nbevent *Number of events estimates*

Description

To determine the sample size N in clinical trials with time to event endpoint, it is necessary to proceed in two steps. In the first step, the numbers of events that need to be observed (e) are computed. In the second step, we determine the number of patients necessary to observe the number of events required. This function computes the number of event for one-time-to event.

Usage

```
nbevent(hypsurv,pe,alfa,beta,design)
```

Arguments

hypsurv	For Superiority=c(Sc,Se); for Non inferiority=c(Sc,Se,SeA); for Equivalence=c(Sc, Se), with Sc is survival rate in the control arm; Se is survival rate in experimental arm; SeA is the survival rate in the experimental arm under the alternative hypothesis.
pe	Proportion (ratio) of patients assigned to the experimental arm (with 0<pe<1).
alfa	Type I error, for Non inferiority, Equivalence and 1-sided superiority, alfa is a vector of length one. For 2-sided superiority, alfa is a vector to length two c(alpha.low, alpha.up).
beta	Probability of a type II error.
design	Superiority=c(1,sided)[with sided=1 if 1-sided and 2 if 2-sided]; Non inferiority=c(2); Equivalence=c(1,1)

Details

The nbevent function computes the required number of events to determine the number of patients.

Value

E: Number of events

h: Hazard Ratio under null hypothesis(HR=log(Se)/log(Sc))

h.alt: Hazard Ratio under alternative hypothesis (h.alt=log(SeA)/log(Sc))

References

Chow, S. C., Shao, J., Wang, H. (2003). Sample Size Calculation in Clinical Research. New York: Marcel Dekker.

Schoenfeld. Sample-size formula for the proportional-hazards regression model. Biometrics. 1983 39<499>503.

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ncoprimary *Sample size calculation in clinical trials with two co-primary time-to-event endpoints*

Description

ncoprimary() is used to calculate the sample size for phase III clinical trial with two co-primary endpoints to assess the efficacy of treatment between two groups.

Usage

```
ncoprimary(design,Survhyp1,Survhyp2,alpha1,alpha2,duraccrual,durstudy,power,pe,
look,fup,dropout,dqol)
```

Arguments

design	Superiority=c(1,sided)[with sided=1 if 1-sided and 2 if 2-sided]; Non inferiority=c(2); Equivalence=c(3)
Survhyp1	For Superiority=c(thyp,t,hype,Sc); for Non inferiority=c(thyp,t,hype,Sc,hypeA); for Equivalence=c(t,delta,Sc): parameters at time t for the first endpoint, if thyp=1 then hype is survival rate or the rate of patients without HRQoL deterioration in experimental arm under the null hypothesis and hypeA is the survival rate in the experimental arm under the alternative hypothesis; if thyp=2 then hype is the hazard ratio under the null hypothesis and hypeA is the hazard ratio under the alternative hypothesis; Sc is survival rate in the control arm; delta is the log hazard ratio equivalence margin. When endpoint is HRQoL, the survival rate is replaced by the rate of patients without HRQoL deterioration.
Survhyp2	For Superiority=c(thyp,t,hype,Sc); for Non inferiority=c(thyp,t,hype,Sc,hypeA); for Equivalence=c(t,delta,Sc): parameters at time t for the second endpoint if thyp=1 then hype is survival rate in experimental arm under the null hypothesis and hypeA is the survival rate in the experimental arm under the alternative hypothesis; if thyp=2 then hype is the hazard ratio under the null hypothesis and hypeA is the hazard ratio under the alternative hypothesis; Sc is survival rate in the control arm; delta is the log hazard ratio equivalence margin. When endpoint is HRQoL, the survival rate is replaced by the rate of patients without HRQoL deterioration.
alpha1	Type I error assigned to the first endpoint, for Non inferiority, Equivalence and 1-sided superiority is a vector of length one. For 2-sided superiority is a vector to length two c(alpha.low, alpha.up).
alpha2	Type I error assigned to the second endpoint, for Non inferiority, Equivalence and 1-sided superiority is a vector of length one. For 2-sided superiority is a vector to length two c(alpha.low, alpha.up).
duraccrual	Accrual duration, expressed in number of days, months or years
durstudy	Study duration, expressed in number of days, months or years
power	1-Probability of a type II error. Default value = 0.80.
pe	Proportion (ratio) of patients assigned to the experimental arm (with 0<pe<1). Default value = 0.50.
look	The number of interim analyses, c(1) for one final analysis; c(nb, bound, timing) for at least one interim analyses with bound=c(bound.eff,bound.fut):1-sided or bound=c(bound.low,bound.up):2-sided. nb the number of planned looks, bound.eff and bound.fut corresponds to the type of boundaries used for efficacy (i.e. reject H0) and futility (i.e. reject H1). bound.fut=0: No futility monitoring, 1: Lan deMets O.Brien Fleming, 2: Lan deMets Pocock. bound.low and bound.up the type of lower and upper boundaries used (1: Lan deMets O.Brien Fleming, 2: Lan deMets Pocock, 3: O.Brien Fleming, 4: Pocock). Default value = 1.

fup	Follow-up information, No fixed:c(0) (follow-up until the end of study); Fixed:c(1, durfollow) with durfollow is the duration of follow-up. Default value = 0.
dropout	Drop out information, No drop out=c(0); Drop out=c(1,gammae,gammac) with gammae and gammac are the hazard drop out rates in experimental arm and control arm respectively. Default value = 0.
dqol	number of targeted dimensions for the health related quality of life. Default value = 0.

Details

The ncoprimary function computes the sample size for two primary endpoints. Both endpoints can be one time to event endpoint and health related quality of life (HRQoL) or two times to event endpoints.

Value

Event: number of events estimated

Total: number of patients

Ne: number for experimental arm for each endpoint

Nc: number for control arm for each endpoint

HR: Hazard ratio for each endpoint

Examples

```
#############################################################################################
############ Design superiority:one-sided with two co-primary endpoints ############
#############################################################################################
## - For endpoint 1: 3-year survival rates Se=0.75 and Sc=0.65, alpha1=0.02
## - For endpoint 2: 4-year survival rates Se=0.70 and Sc=0.59, alpha2=0.03
## with accrual duration of 2 years, study duration of 4 years and default values i.e
## power=0.80, pe=0.5, look=1, fup=0, dropout=0, dqol=0

nc1 <- ncoprimary(design=c(1,1),Survhyp1=c(1,3,0.75,0.65),Survhyp2=c(1,4,0.70,0.59),
alpha1=0.02,alpha2=0.03,duraccrual=2,durstudy=4)


#############################################################################################
 ############ Design superiority:two-sided with two co-primary endpoints ############
#############################################################################################
## - For endpoint 1: 2 target variables for the health related quality of life with 3-year
## rate without HRQoL deterioration Se=0.75 and Sc=0.67, alpha1=c(0.01,0.01)
## - For endpoint 2: 4-year survival rates Se=0.86 and Sc=0.80, alpha2=c(0.015,0.015)
## with accrual duration of 3 years, study duration of 6 years, power=0.90, look=c(2,c(1,1),0.5),
## and default values i.e  pe=0.5, fup=0, dropout=0

nc2 <- ncoprimary(design=c(1,2),Survhyp1=c(1,5,0.75,0.67),Survhyp2=c(1,5,0.86,0.80),
alpha1=c(0.01,0.01),alpha2=c(0.015,0.015),duraccrual=3,durstudy=6, power=0.90,
look=c(2,c(1,1),0.5),dqol=2)
```

```
################################################################################
##############  Design non-inferiority with two co-primary endpoints ###############
################################################################################
## - For endpoint 1: 3-year survival rates Se=0.75 and Sc=SeA=0.75, alpha1=0.01
## - For endpoint 2: 4-year survival rates Se=0.67 and Sc=SeA=0.80, alpha2=0.04
## with accrual duration of 2 years, study duration of 6 years, power=0.95, pe=0.60 and
## default values i.e look=1, fup=0, dropout=0, dqol=0

nc3 <- ncoprimary(design=c(2),Survhyp1=c(1,4,0.65,0.75,0.75),Survhyp2=c(1,5,0.67,0.80,0.80),
alpha1=0.01,alpha2=0.04,duraccrual=2,durstudy=6,power=0.95,pe=0.60)

################################################################################
################  Design superiority with two co-primary endpoints #################
################################################################################

## - For endpoint 1: 2-year survival rate Sc=0.65 and log hazard equivalence margin delta=0.15
## and alpha1=0.025
## - For endpoint 2: 1-year survival rate Sc=0.70 and log hazard equivalence margin delta=0.10
## and alpha2=0.025
## with accrual duration of 3 years, study duration of 5 years, drop out hazard rate of 0.025
## per arm and default values i.e power=0.80, pe=0.5, look=1, fup=0, dqol=0

nc4 <- ncoprimary(design=c(3),Survhyp1=c(2,0.15,0.65),Survhyp2=c(1,0.10,0.70),alpha1=0.025,
alpha2=0.025,duraccrual=3,durstudy=5,dropout=c(1,0.025,0.025))
```

`nsurvival` *Sample size calculation in clinical trials with one primary survival endpoint*

Description

nsurvival() is used to determine the sample size for one time to event endpoint, such as Overall Survival (OS), Progression Free Survival or the health related quality of life (HRQoL). If it is HRQoL, several HRQoL dimension can be considered.

Usage

```
nsurvival(design,Survhyp,alpha,duraccrual,durstudy,power,pe,look,fup,dropout,dqol)
```

Arguments

`design`	Superiority=c(1,sided)[with sided=1 if 1-sided and 2 if 2-sided]; Non inferiority=c(2); Equivalence=c(3)

Survhyp	For Superiority=c(thyp,t,hype,Sc); for Non inferiority=c(thyp,t,hype,Sc,hypeA); for Equivalence=c(t,delta,Sc): parameters at time t if thyp=1 then hype is survival rate in experimental arm under the null hypothesis and hypeA is the survival rate in the experimental arm under the alternative hypothesis; if thyp=2 then hype is the hazard ratio under the null hypothesis and hypeA is the hazard ratio under the alternative hypothesis; Sc is survival rate in the control arm; delta is the log hazard ratio equivalence margin. When endpoint is HRQoL, the survival rate is replaced by the rate of patients without HRQoL deterioration.
alpha	Type I error, for Non inferiority, Equivalence and 1-sided superiority is a vector of length one. For 2-sided superiority is a vector to length two c(alpha.low, alpha.up).
duraccrual	Accrual duration, expressed in number of days, months or years
durstudy	Study duration, expressed in number of days, months or years
power	1- Probability of a type II error. Default value=0.80.
pe	Proportion (ratio) of patients assigned to the experimental arm (with 0<pe<1). Default value = 0.5.
look	The number of interim analyses, c(1) for one final analysis; c(nb, bound, timing) for at least one interim analyses with bound=c(bound.eff,bound.fut):1-sided or bound=c(bound.lown,bound.up):2-sided. nb the number of planned looks, bound.eff and bound.fut corresponds to the type of boundaries used for efficacy (i.e. reject H0) and futility (i.e. reject H1). bound.fut=0: No futility monitoring, 1: Lan deMets O.Brien Fleming, 2: Lan deMets Pocock. bound.low and bound.up the type of lower and upper boundaries used (1: Lan deMets O.Brien Fleming, 2: Lan deMets Pocock, 3: O.Brien Fleming, 4: Pocock). Default value = 1.
fup	Follow-up information, No fixed:c(0) (follow-up until the end of study); Fixed:c(1, durfollow) with durfollow is the duration of follow-up. Default value = 0.
dropout	Drop out information, No drop out=c(0); Drop out=c(1,gammae,gammac) with gammae the hazard drop out rates in experimental arm and control arm respectively. Default value = 0.
dqol	number of targeted dimensions for the health related quality of life. Default value = 0.

Details

The nsurvival function computes the sample size for one time to event endpoint, such as OS, PFS or HRQoL. HRQoL has become increasingly important in clinical trials over the past two decades.

Value

Event: number of events estimated

Total: number of patients

Ne: number for experimental arm for each endpoint

Nc: number for control arm for each endpoint

HR: Hazard ratio for each endpoint

Examples

```
############################################################
###############  Design superiority:one-sided ##############
############################################################
## 7-year survival rates Se=0.57 and Sc=0.53, alpha=0.05, accrual duration of 4 years,
## study duration of 8 years and default values i.e power=0.80, pe=0.5, look=1, fup=0,
## dropout=0, dqol=0

ns1 <- nsurvival(design=c(1,1),Survhyp=c(1,7,0.57,0.53),alpha=0.05,duraccrual=4,durstudy=8)

############################################################
############### Design superiority:two-sided ###############
############################################################
## 5-year rate without HRQoL deterioration Se=0.75 and Sc=0.65, alpha=c(0.04,0.01), accrual
## duration of 2 years, study duration of 6 years, power=0.90, pe=0.55, follow-up 5 years,
## 3 target variables for health related quality of life and default values i.e look=1, dropout=0

ns2 <- nsurvival(design=c(1,2),Survhyp=c(1,5,0.75,0.65),alpha=c(0.04,0.01),duraccrual=2,
durstudy=6,power=0.90,pe=0.55,fup=c(1,5),dqol=3)

############################################################
###############   Design non-inferiority ##################
############################################################
## 5-year survival rates are equal under the alternative hypothesis, i.e Se=0.60 and Sc=SeA=0.70,
## with alpha=0.05, accrual duration of 4 years, study duration of 8 years, two interim analysis
## after the occurence 1/3 and 2/3 of the events and default values i.e power=0.80, pe=0.5, fup=0,
## dropout=0, dqol=0

ns3 <- nsurvival(design=c(2),Survhyp=c(1,5,0.60,0.70, 0.70),alpha=0.05,duraccrual=4,
durstudy=8,look=c(3,c(1,1),c(1/3,2/3)))

############################################################
###############    Design superiority   ##################
############################################################
## 3-year rate without HRQoL deterioration Sc=0.80 and log hazard equivalence margin delta=0.1
## with alpha=0.10, accrual duration of 3 years, study duration of 5 years, drop out hazard rate
## of 0.05 per arm, 2 target variables for health related quality of life and default values i.e
## power=0.80, pe=0.5, look=1, fup=0

ns4 <- nsurvival(design=c(3),Survhyp=c(3,0.10,0.80),alpha=0.10,duraccrual=3,durstudy=5,
dropout=c(1,0.05,0.05),dqol=2)
```

`probafix` *Probabitility of event when the follow-up is fixed*

Description

In a fixed follow-up design, each subject can only be followed during a fixed period (Tf < infinite) and then goes off study. Using similar reasoning to K. Kim and A.A. Tsiatis (1990), it is easy to compute the probability.

Usage

```
probafix(surv,time,duraccrual,durfollow,limit,gamma)
```

Arguments

surv	Survival estimates
time	Time estimate
duraccrual	Accrual duration, expressed in t time units
durfollow	Follow-up duration
limit	Time limit to estimate the survival probability
gamma	the probability of observing an event by time t

Details

The probafix function estimates the probability of event when the follow-up is fixed.

Value

probafix: event probability at time limit

References

K. Kim, A.A. Tsiatis, Study duration for clinical trials with survival response and early stopping rule, Biometrics 46 (1990) 81-92

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probanofix *Probabitility of event when the follow-up is no fixed*

Description

In the design with variable follow-up, each subject is followed until the end of the study (Tf = infinite), i.e. subjects who are enrolled at the beginning of the enrolment phase are followed for a longer time than subjects who are enrolled later. When there are no drop outs (i.e. = (0,0), the probability of failure in each arm can be directly estimated using the formulation proposed by K Kim and A.A. Tsiatis (1990).

Usage

```
probanofix(surv,time,duraccrual,limit,gamma)
```

Arguments

surv	Survival estimates
time	Time estimate
duraccrual	Accrual duration, expressed in t time units
limit	Time limit to estimate the survival probability
gamma	the probability of observing an event by time t

Details

The probanofix function estimates the probability of event when the follow-up is no fixed

Value

probanofix: event probability at time limit

References

K. Kim, A.A. Tsiatis, Study duration for clinical trials with survival response and early stopping rule, Biometrics 46 (1990) 81-92

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