

# Package ‘NBDesign’

January 20, 2025

**Type** Package

**Version** 2.0.0

**Date** 2020-09-09

**Title** Design and Monitoring of Clinical Trials with Negative Binomial Endpoint

**Description** Calculate various functions needed for design and monitoring clinical trials with negative binomial endpoint with variable follow-up. This version has a few changes compared to the previous version 1.0.0, including (1) correct a typo in Type 1 censoring, mtbnull=bnull and (2) restructure the code to account for shape parameter equal to zero, i.e. Poisson scenario.

**Depends** R (>= 3.1.2)

**Imports** stats,PWEALL,MASS

**License** GPL (>= 2)

**RoxygenNote** 5.0.1

**LazyData** true

**NeedsCompilation** no

**Author** Xiaodong Luo [aut, cre],  
Sanofi [cph]

**Maintainer** Xiaodong Luo <Xiaodong.Luo@sanofi.com>

**Repository** CRAN

**Date/Publication** 2020-09-10 06:30:22 UTC

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NBDesign-package	<i>Design and Monitoring of Clinical Trials with Negative Binomial Endpoint</i>
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## Description

Calculate various functions needed for design and monitoring clinical trials with negative binomial endpoint with variable follow-up. This version has a few changes compared to the previous version 1.0.0, including (1) correct a typo in Type 1 censoring, mtbnull=bnull and (2) restructure the code to account for shape parameter equal to zero, i.e. Poisson scenario.

## Details

The DESCRIPTION file:

```
Package:      NBDesign
Type:        Package
Version:     2.0.0
Date:        2020-09-09
Title:       Design and Monitoring of Clinical Trials with Negative Binomial Endpoint
Description: Calculate various functions needed for design and monitoring clinical trials with negative binomial endpoint
Authors@R:   c( person(given="Xiaodong", family="Luo", email = "Xiaodong.Luo@sanofi.com", role =c("aut", "cre")), pe
Depends:     R (>= 3.1.2)
Imports:     stats,PWEALL,MASS
License:     GPL (>= 2)
RoxygenNote: 5.0.1
LazyData:   true
Author:      Xiaodong Luo [aut, cre], Sanofi [cph]
Maintainer:  Xiaodong Luo <Xiaodong.Luo@sanofi.com>
```

Index of help topics:

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ynegbinompower	Two-sample sample size calculation for negative binomial distribution with variable follow-up
ynegbinompowersim	Two-sample sample size calculation for negative binomial distribution with variable follow-up
ynegbinomsize	Two-sample sample size calculation for negative binomial distribution with variable follow-up

## Author(s)

NA

Maintainer: NA

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negint2                      *A utility function to calculate the mean exposure under different scenarios*

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### Description

This will calculate the mean exposure under different scenarios: 2: fixed follow-up with drop-out, 3: variable follow-up with a maximum (maxfu), 4: variable follow-up with a maximum and drop-out

### Usage

```
negint2(ux=0.5, fixedfu=1, type=2, u=c(0.5, 0.5, 1), ut=c(0.5, 1.0, 1.5),
        tfix=ut[length(ut)]+0.5, maxfu=10.0, tchange=c(0, 0.5, 1),
        ratec=c(0.15, 0.15, 0.15), eps=1.0e-03)
```

### Arguments

ux	the parameter $a$ in $(a*t)/(1+a*t)$
fixedfu	the minimum follow-up time
type	follow-up type, type=2: fixed fu with fu time fixedfu but subject to censoring; type=3: depending on entry time, minimum fu is fixedfu and maximum fu is maxfu; type=4: same as 3 but subject to censoring
u	recruitment rate
ut	recruitment interval, must have the same length as u
tfix	fixed study duration, often equals to recruitment time plus minimum follow-up
maxfu	maximum follow-up time, should not be greater than tfix
tchange	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero. The above rates and tchange must have the same length.
ratec	piecewise constant drop-out rate
eps	error tolerance for the numerical intergration

### Details

Let  $\tau_{min}$  and  $\tau_{max}$  correspond to the minimum follow-up time  $\tau_{min}$  and the maximum follow-up time  $\tau_{max}$ . Let  $T_f$ ,  $C$ ,  $E$  and  $R$  be the follow-up time, the drop-out time, the study entry time and the total recruitment period ( $R$  is the last element of  $ut$ ). For type 2 follow-up  $T_f = \min(C, \tau_{min})$ . For type 3 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max})$ . For type 4 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max}, C)$ . Let  $f$  be the density of  $T_f$ . We calculate

$$\int_0^{\infty} t f(t) dt$$

and

$$\int_0^{\infty} \frac{at}{1+at} f(t) dt$$

where  $a$  is the ux.

**Value**

mt	mean of $(a^*t)/(1+a^*t)$
tt	mean of t
vt	variance of t

**Author(s)**

Xiaodong Luo

**Examples**

```
##calculating the exposure for type 4 follow-up
exp4=negint2(ux=0.5,fixedfu=1,type=2,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tfix=2.0,maxfu=1.0,tchange=c(0,0.5,1),
  ratec=c(0.15,0.15,0.15),eps=1.0e-03)
#mean exposure
meanexp=exp4$tt
#var exposure
varexp=exp4$vt
c(meanexp,sqrt(varexp))
#mean of (ux*t)/(1+ux*t)
meanuxt=exp4$mt
```

ynegbinompower

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*Two-sample sample size calculation for negative binomial distribution with variable follow-up*

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**Description**

This will calculate the power for the negative binomial distribution for the 2-sample case under different follow-up scenarios: 1: fixed follow-up, 2: fixed follow-up with drop-out, 3: variable follow-up with a minimum fu and a maximum fu, 4: variable follow-up with a minimum fu and a maximum fu and drop-out.

**Usage**

```
ynegbinompower(nsize=200,r0=1.0,r1=0.5,shape0=1,shape1=shape0,pi1=0.5,
  alpha=0.05,twosided=1,fixedfu=1,type=1,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tfix=ut[length(ut)]+0.5,maxfu=10.0,tchange=c(0,0.5,1),
  ratec1=c(0.15,0.15,0.15),ratec0=ratec1,eps=1.0e-03)
```

**Arguments**

nsize	total number of subjects in two groups
r0	event rate for the control
r1	event rate for the treatment

shape0	dispersion parameter for the control
shape1	dispersion parameter for the treatment
pi1	allocation prob for the treatment
alpha	type-1 error
twosided	1: two-side, others: one-sided
fixedfu	fixed follow-up time for each patient
type	follow-up time type, type=1: fixed fu with fu time fixedfu; type=2: same as 1 but subject to censoring; type=3: depending on entry time, minimum fu is fixedfu and maximum fu is maxfu; type=4: same as 3 but subject to censoring
u	recruitment rate
ut	recruitment interval, must have the same length as u
tfix	fixed study duration, often equals to recruitment time plus minimum follow-up
maxfu	maximum follow-up time, should not be greater than tfix
tchange	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero. The above rates and tchange must have the same length.
ratec1	piecewise constant drop-out rate for the treatment
ratec0	piecewise constant drop-out rate for the control
eps	error tolerance for the numerical intergration

### Details

Let  $\tau_{min}$  and  $\tau_{max}$  correspond to the minimum follow-up time `fixedfu` and the maximum follow-up time `maxfu`. Let  $T_f$ ,  $C$ ,  $E$  and  $R$  be the follow-up time, the drop-out time, the study entry time and the total recruitment period ( $R$  is the last element of `ut`). For type 1 follow-up,  $T_f = \tau_{min}$ . For type 2 follow-up  $T_f = \min(C, \tau_{min})$ . For type 3 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max})$ . For type 4 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max}, C)$ . Let  $f$  be the density of  $T_f$ . Suppose that  $Y_i$  is the number of event observed in follow-up time  $t_i$  for patient  $i$  with treatment assignment  $Z_i$ ,  $i = 1, \dots, n$ . Suppose that  $Y_i$  follows a negative binomial distribution such that

$$P(Y_i = y \mid Z_i = j) = \frac{\Gamma(y + 1/k_j)}{\Gamma(y + 1)\Gamma(1/k_j)} \left( \frac{k_j u_i}{1 + k_j u_i} \right)^y \left( \frac{1}{1 + k_j u_i} \right)^{1/k_j},$$

where

$$\log(u_i) = \log(t_i) + \beta_0 + \beta_1 Z_i.$$

Let  $\hat{\beta}_0$  and  $\hat{\beta}_1$  be the MLE of  $\beta_0$  and  $\beta_1$ . The variance of  $\hat{\beta}_1$  is

$$\text{var}(\hat{\beta}_1) = 1/\tilde{a}_0(r_0) + 1/\tilde{a}_1(r_1)$$

where

$$\tilde{a}_j(r) = \sum_{i=1}^n I(Z_i = j) k_j r t_i / (1 + k_j r t_i), \quad j = 0, 1,$$

and  $k_j, j = 0, 1$  are the dispersion parameters for control  $j = 0$  and treatment  $j = 1$ . Note that Zhu and Lakkis (2014) use

$$a_j(r) = \sum_{i=1}^n I(Z_i = j) k_j r E(t_i) / \{1 + k_j r E(t_i)\},$$

to replace  $\tilde{a}_j(r), j = 0, 1$ . Using Jensen's inequality, we can show  $a_j(r) \geq \tilde{a}_j(r)$ , which means Zhu and Lakkis's method will underestimate variance of  $\hat{\beta}_1$ , which leads to either smaller than required sample size or inflated power. For comparison, I provide sample sizes under both  $\tilde{a}_j(r)$  and  $a_j(r)$ .

Zhu and Lakkis (2014) discuss three types of the variance under the null. The first way is to set  $\tilde{r}_0 = \tilde{r}_1 = r_0$ , using event rate from the control group. The second way is to set  $\tilde{r}_0 = r_0, \tilde{r}_1 = r_1$ , using true event rates. The third way is to set  $\tilde{r}_0 = \tilde{r}_1 = \tilde{r}$ , where  $\tilde{r} = \pi_1 r_1 + \pi_0 r_0$ , using maximum likelihood estimation.

Therefore, for each type of follow-up, there are 3 sample sizes calculated (because there are 3 variances under the null) for with and without approximation of Zhu and Lakkis (2014).

Note that PASS14.0 provides 3 ways of null variance with the default being the MLE. PASS does not allow different dispersion parameters between treatment and control. EAST only provides the second way of null variance but allows for different dispersion parameters. Both of these softwares base on the approximation method of Zhu and Lakkis (2014), which underestimate the required sample sizes.

## Value

<code>tildeXPWR</code>	powers (in percentage) not based on current approach, i.e. not based on the Zhu and Lakkis's approximation
<code>XPWR</code>	powers (in percentage) based on on the Zhu and Lakkis's approximation
<code>tildemineffsize</code>	minimum detectable effect sizes not based on approximation
<code>mineffsize</code>	minimum detectable effect sizes based on approximation
<code>Exposure</code>	mean exposure under different follow-up types with element 1 for control, element 2 for treatment and element 3 for overall.
<code>SDExp</code>	Sd of the exposure under different follow-up types with element 1 for control, element 2 for treatment and column 3 for overall.

## Author(s)

Xiaodong Luo

## References

Zhu-H and Lakkis-H. Sample size calculation for comparing two negative binomial rates. *Statistics in Medicine* 2014, 33: 376-387.

**Examples**

```
##calculating the sample sizes
abc=ynegbinompower(nsize=200,r0=1.0,r1=0.5,shape0=1,
  pi1=0.5,alpha=0.05,twosided=1,fixedfu=1,
  type=4,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tchange=c(0,0.5,1),
  ratec1=c(0.15,0.15,0.15),eps=1.0e-03)
###Zhu and Lakkis's powers (i.e. with approximation)
abc$XPWR
###Our powers (i.e. without approximation)
abc$tildeXPWR
```

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ynegbinompowersim	<i>Two-sample sample size calculation for negative binomial distribution with variable follow-up</i>
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**Description**

This will calculate the power for the negative binomial distribution for the 2-sample case under different follow-up scenarios: 1: fixed follow-up, 2: fixed follow-up with drop-out, 3: variable follow-up with a minimum fu and a maximum fu, 4: variable follow-up with a minimum fu and a maximum fu and drop-out.

**Usage**

```
ynegbinompowersim(nsize=200,r0=1.0,r1=0.5,shape0=1,shape1=shape0,pi1=0.5,
  alpha=0.05,twosided=1,fixedfu=1,type=1,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tfix=ut[length(ut)]+0.5,maxfu=10.0,tchange=c(0,0.5,1),
  ratec1=c(0.15,0.15,0.15),ratec0=ratec1,rn=10000)
```

**Arguments**

nsize	total number of subjects in two groups
r0	event rate for the control
r1	event rate for the treatment
shape0	dispersion parameter for the control
shape1	dispersion parameter for the treatment
pi1	allocation prob for the treatment
alpha	type-1 error
twosided	1: two-side, others: one-sided
fixedfu	fixed follow-up time for each patient
type	follow-up time type, type=1: fixed fu with fu time fixedfu; type=2: same as 1 but subject to censoring; type=3: depending on entry time, minimum fu is fixedfu and maximum fu is maxfu; type=4: same as 3 but subject to censoring

u	recruitment rate
ut	recruitment interval, must have the same length as u
tfix	fixed study duration, often equals to recruitment time plus minimum follow-up
maxfu	maximum follow-up time, should not be greater than tfix
tchange	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero. The above rates and tchange must have the same length.
ratec1	piecewise constant drop-out rate for the treatment
ratec0	piecewise constant drop-out rate for the control
rn	Number of repetitions

### Details

Let  $\tau_{min}$  and  $\tau_{max}$  correspond to the minimum follow-up time fixedfu and the maximum follow-up time maxfu. Let  $T_f$ ,  $C$ ,  $E$  and  $R$  be the follow-up time, the drop-out time, the study entry time and the total recruitment period ( $R$  is the last element of  $ut$ ). For type 1 follow-up,  $T_f = \tau_{min}$ . For type 2 follow-up  $T_f = \min(C, \tau_{min})$ . For type 3 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max})$ . For type 4 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max}, C)$ . Let  $f$  be the density of  $T_f$ . Suppose that  $Y_i$  is the number of event observed in follow-up time  $t_i$  for patient  $i$  with treatment assignment  $Z_i$ ,  $i = 1, \dots, n$ . Suppose that  $Y_i$  follows a negative binomial distribution such that

$$P(Y_i = y | Z_i = j) = \frac{\Gamma(y + 1/k_j)}{\Gamma(y + 1)\Gamma(1/k_j)} \left( \frac{k_j u_i}{1 + k_j u_i} \right)^y \left( \frac{1}{1 + k_j u_i} \right)^{1/k_j},$$

where  $k_j, j = 0, 1$  are the dispersion parameters for control  $j = 0$  and treatment  $j = 1$  and

$$\log(u_i) = \log(t_i) + \beta_0 + \beta_1 Z_i.$$

The data will be generated according to the above model. Note that the piecewise exponential distribution and the piecewise uniform distribution are generated using R package PWEALL functions "rpwe" and "rpwu", respectively.

The parameters in the model are estimated by MLE using the R package MASS function "glm.nb".

### Value

power simulation power (in percentage)

### Author(s)

Xiaodong Luo

### Examples

```
##calculating the sample sizes
abc=ynegbinompowersim(nsize=200,r0=1.0,r1=0.5,shape0=1,
  pi1=0.5,alpha=0.05,twosided=1,fixedfu=1,
  type=4,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tchange=c(0,0.5,1),
```



```

      ratec1=c(0.15,0.15,0.15),rn=10)
###Power
abc$power

```

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ynegbinomsize	<i>Two-sample sample size calculation for negative binomial distribution with variable follow-up</i>
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### Description

This will calculate the sample size for the negative binomial distribution for the 2-sample case under different follow-up scenarios: 1: fixed follow-up, 2: fixed follow-up with drop-out, 3: variable follow-up with a minimum fu and a maximum fu, 4: variable follow-up with a minimum fu and a maximum fu and drop-out.

### Usage

```

ynegbinomsize(r0=1.0,r1=0.5,shape0=1,shape1=shape0,pi1=0.5,
  alpha=0.05,twosided=1,beta=0.2,fixdfu=1,
  type=1,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),tfix=ut[length(ut)]+0.5,maxfu=10.0,
  tchange=c(0,0.5,1),ratec1=c(0.15,0.15,0.15),ratec0=ratec1,eps=1.0e-03)

```

### Arguments

r0	event rate for the control
r1	event rate for the treatment
shape0	dispersion parameter for the control
shape1	dispersion parameter for the treatment
pi1	allocation prob for the treatment
alpha	type-1 error
twosided	1: two-side, others: one-sided
beta	tyep-2 error
fixdfu	fixed follow-up time for each patient
type	follow-up time type, type=1: fixed fu with fu time fixdfu; type=2: same as 1 but subject to censoring; type=3: depending on entry time, minimum fu is fixdfu and maximum fu is maxfu; type=4: same as 3 but subject to censoring
u	recruitment rate
ut	recruitment interval, must have the same length as u
tfix	fixed study duration, often equals to recruitment time plus minimum follow-up fixdfu
maxfu	maximum follow-up time, should not be greater than tfix
tchange	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero.

ratec1	piecewise constant drop-out rate for the treatment. The rate and tchange must have the same length.
ratec0	piecewise constant drop-out rate for the control. The rate and tchange must have the same length.
eps	error tolerance for the numerical intergration

### Details

Let  $\tau_{min}$  and  $\tau_{max}$  correspond to the minimum follow-up time `fixedfu` and the maximum follow-up time `maxfu`. Let  $T_f$ ,  $C$ ,  $E$  and  $R$  be the follow-up time, the drop-out time, the study entry time and the total recruitment period ( $R$  is the last element of `ut`). For type 1 follow-up,  $T_f = \tau_{min}$ . For type 2 follow-up  $T_f = \min(C, \tau_{min})$ . For type 3 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max})$ . For type 4 follow-up,  $T_f = \min(R + \tau_{min} - E, \tau_{max}, C)$ . Let  $f$  be the density of  $T_f$ . Suppose that  $Y_i$  is the number of event observed in follow-up time  $t_i$  for patient  $i$  with treatment assignment  $Z_i$ ,  $i = 1, \dots, n$ . Suppose that  $Y_i$  follows a negative binomial distribution such that

$$P(Y_i = y \mid Z_i = j) = \frac{\Gamma(y + 1/k_j)}{\Gamma(y + 1)\Gamma(1/k_j)} \left( \frac{k_j u_i}{1 + k_j u_i} \right)^y \left( \frac{1}{1 + k_j u_i} \right)^{1/k_j},$$

where

$$\log(u_i) = \log(t_i) + \beta_0 + \beta_1 Z_i.$$

Let  $\hat{\beta}_0$  and  $\hat{\beta}_1$  be the MLE of  $\beta_0$  and  $\beta_1$ . The variance of  $\hat{\beta}_1$  is

$$\text{var}(\hat{\beta}_1) = 1/\tilde{a}_0(r_0) + 1/\tilde{a}_1(r_1)$$

where

$$\tilde{a}_j(r) = \sum_{i=1}^n I(Z_i = j) k_j r t_i / (1 + k_j r t_i), \quad j = 0, 1,$$

and  $k_j$ ,  $j = 0, 1$  are the dispersion parameters for control  $j = 0$  and treatment  $j = 1$ . Note that Zhu and Lakkis (2014) use

$$a_j(r) = \sum_{i=1}^n I(Z_i = j) k_j r E(t_i) / \{1 + k_j r E(t_i)\},$$

to replace  $\tilde{a}_j(r)$ ,  $j = 0, 1$ . Using Jensen's inequality, we can show  $a_j(r) \geq \tilde{a}_j(r)$ , which means Zhu and Lakkis's method will underestimate variance of  $\hat{\beta}_1$ , which leads to either smaller than required sample size or inflated power. For comparison, I provide sample sizes under both  $\tilde{a}_j(r)$  and  $a_j(r)$ .

Zhu and Lakkis (2014) discuss three types of the variance under the null. The first way is to set  $\tilde{r}_0 = \tilde{r}_1 = r_0$ , using event rate from the control group. The second way is to set  $\tilde{r}_0 = r_0$ ,  $\tilde{r}_1 = r_1$ , using true event rates. The third way is to set  $\tilde{r}_0 = \tilde{r}_1 = \tilde{r}$ , where  $\tilde{r} = \pi_1 r_1 + \pi_0 r_0$ , using maximum likelihood estimation.

Therefore, for each type of follow-up, there are 3 sample sizes calculated (because there are 3 variances under the null) for with and without approximation of Zhu and Lakkis (2014).

Note that PASS14.0 provides 3 ways of null variance with the default being the MLE. PASS does not allow different dispersion parameters between treatment and control. EAST only provides the second way of null variance but allows for different dispersion parameters. Both of these softwares base on the approximatin method of Zhu and Lakkis (2014), which underestimate the required sample sizes.

**Value**

<code>tildeXN</code>	sample sizes based on current approach, i.e. not based on the Zhu and Lakkis's approximation
<code>XN</code>	sample sizes based on the Zhu and Lakkis's approximation
<code>Exposure</code>	mean exposure under different follow-up types with element 1 for control, element 2 for treatment and element 3 for overall.
<code>SDExp</code>	Sd of the exposure under different follow-up types with element 1 for control, element 2 for treatment and column 3 for overall.

**Author(s)**

Xiaodong Luo

**References**

Zhu~H and Lakkis~H. Sample size calculation for comparing two negative binomial rates. *Statistics in Medicine* 2014, 33: 376-387.

**Examples**

```
##calculating the sample sizes
abc=ynegbinomsize(r0=1.0,r1=0.5,shape0=1,pi1=0.5,alpha=0.05,twosided=1,
  beta=0.2,fixdfu=1,type=4,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tfix=1.5,maxfu=1,tchange=c(0,0.5,1),ratec1=c(0.15,0.15,0.15),
  eps=1.0e-03)
###Zhu and Lakkis's sample sizes (i.e. with approximation)
abc$XN
###Our sample sizes (i.e. without approximation)
abc$tildeXN
```

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