

Package ‘interAdapt’

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Title interAdapt

Description A shiny application for designing adaptive clinical trials. For more details, see: <http://arxiv.org/abs/1404.0734>

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compute_design_performance
Compute Design Performance

Description

Generates decision rules for group sequential trial designs with adaptive enrollment criteria. Tables are also generated which compare the performance of these designs to the performance of standard group sequential designs. We use the notation AD to refer to the design with adaptive enrollment, SC to refer to a standard group sequential design enrolling from the combined population, and SS to refer to a standard group sequential design enrolling from only the subpopulation where there is greater prior evidence of a positive treatment effect. Further details are provided in (Fisher et al. 2014).

Usage

```
compute_design_performance(p_1 = 0.33, p_10 = 0.25, p_20 = 0.2,
  p_11 = p_10 + 0.125, per_stage_sample_size_combined_AD = 280,
  per_stage_sample_size_subpop_1_AD = 148, FWER = 0.025,
  FWER_H0C_proportion = 0.09, Delta = -0.5, iter = 10000,
  time_limit = 45, total_number_stages = 5,
  last_stage_subpop_2_enrolled_AD = 3,
  enrollment_rate_combined_population = 420,
  per_stage_sample_size_combined_SC = 106, per_stage_sample_size_SS = 100,
  subpop_2_stop_boundary_constant_AD = 0,
  H01_futility_boundary_constant_AD = 0,
  H0C_futility_boundary_constant_SC = -0.1,
  H01_futility_boundary_constant_SS = -0.1,
  lower_bound_treatment_effect_subpop_2 = -0.2,
  upper_bound_treatment_effect_subpop_2 = 0.2, CSV)
```

Arguments

p_1	The proportion of the population in subpopulation 1, which is the subpopulation having stronger prior evidence of a positive treatment effect.
p_10	The probability of a successful outcome for subpopulation 1 under assignment to the control arm. This is used in estimating power and expected sample size.
p_20	The probability of a successful outcome for subpopulation 2 under assignment to the control arm. This is used in estimating power and expected sample size.
p_11	The probability of a successful outcome for subpopulation 1 under assignment to the treatment arm. Note that the user does not specify the probability of success under treatment for subpopulation 2 (p_{2t}). Instead, compute_design_performance considers a range of possible values of p_{2t} (see the lower_bound_treatment_effect_subpop_2 and upper_bound_treatment_effect_subpop_2 arguments).
per_stage_sample_size_combined_AD	The number of participants enrolled per stage in the adaptive design while both subpopulations are being enrolled.
per_stage_sample_size_subpop_1_AD	The number of participants required for each stage in the adaptive design after enrollment for subpopulation 2 has been stopped.
FWER	The familywise Type I error rate (α) for all designs (see Fisher et al. 2014).

FWER_H0C_proportion	Proportion of α allocated to H_{0C} for the adaptive design. Here, H_{0C} refers to the null hypothesis of no treatment effect in the combined population.
Delta	Used as the exponent in defining the efficacy and futility boundaries, as described (Fisher et al. 2014).
iter	The number of simulated trials used to estimate the power, expected sample size, and expected trial duration.
time_limit	Time limit for simulation in seconds. If the simulation exceeds the time limit, calculations will stop and the user will get an error message ("reached CPU time limit"). See <code>setTimeLimit</code> . To avoid this, the number of iterations (<code>iter</code>) can be reduced or the time limit can be increased.
total_number_stages	Total number of stages used in each design (K). The maximum allowable number of stages is 20.
last_stage_subpop_2_enrolled_AD	The last stage subpopulation 2 is enrolled, under the adaptive design. We refer to this stage number as k^* .
enrollment_rate_combined_population	The assumed enrollment rate per year for the combined population. This impacts the expected duration of each trial design. Active enrollments from the two subpopulations are assumed to be independent. The enrollment rates for subpopulations 1 and 2 are assumed proportional, based on <code>p_1</code> . This implies that each stage of the adaptive design up to and including stage k^* takes the same amount of time to complete, regardless of whether or not enrollment stops for subpopulation 2. Each stage after k^* will also take the same amount of time to complete.
per_stage_sample_size_combined_SC	The number of participants enrolled in each stage of the standard group sequential design enrolling the combined population (SC).
per_stage_sample_size_SS	The number of participants enrolled in each stage for standard group sequential design enrolling only subpopulation 1 (SS).
subpop_2_stop_boundary_constant_AD	Stopping boundary proportionality constant for subpopulation 2 enrollment in the adaptive design.
H01_futility_boundary_constant_AD	Futility boundary proportionality constant for H_{01} in the adaptive design. This is used to calculate the futility boundaries ($l_{1,k}$) for the z-statistics calculated in subpopulation 1 ($Z_{1,k}$) as defined in (Fisher et al. 2014).
H0C_futility_boundary_constant_SC	Futility boundary proportionality constant for H_{0C} in the standard design always enrolling from the combined population.
H01_futility_boundary_constant_SS	Futility boundary proportionality constant for H_{01} in the standard design only enrolling from subpopulation 1.

lower_bound_treatment_effect_subpop_2	Simulations are performed under a range of treatment effect sizes for subpopulation 2 (i.e. $p_{\{2t\}}-p_{\{2c\}}$). This parameter sets the lower bound for this range. This effectively sets the lower bound for the probability of success under treatment for subpopulation 2 (p_{21}), since p_{20} is set by the user.
upper_bound_treatment_effect_subpop_2	Simulations are performed under a range of treatment effect sizes for subpopulation 2 (i.e. $p_{\{2t\}}-p_{\{2c\}}$). This parameter sets the upper bound for this range.
CSV	Rather than manually entering the arguments above, this allows for the arguments to be entered via a tabular csv file. The CSV argument should contain a character vector or list of csv filenames. The table must minimally include the columns "inputId" and "value" (as in the default_parameter_table).

Details

This function is meant to be applied when there is prior evidence that a treatment might work better in a one subpopulation than in another. In this context, a trial with an adaptive enrollment criteria would determine whether or not to continue enrolling patients from each subpopulation based on interim analyses of whether each subpopulation is benefiting. In order for the type I error and the power of the trial to be calculable, the decision rules for changing enrollment must be set before the trial starts. This function generates decision rules for group sequential trial designs with adaptive enrollment criteria, and compares the performance of these designs against standard group sequential designs with fixed enrollment criteria. Performance is compared in terms of power, expected sample size, and expected trial duration.

Value

A list with 5 elements:

performance_comparison	A table comparing the performance of the three trials, in terms of power, expected sample size, and expected duration. See examples.
AD_design	Efficacy and futility boundaries for the group sequential design with adaptive enrollment
SC_design	Efficacy and futility boundaries for the standard group sequential design enrolling from the combined population
SS_design	Efficacy and futility boundaries for the standard group sequential design enrolling subpopulation 1 only
input_parameters	List of input argument values

References

Aaron Fisher, Harris Jaffee, and Michael Rosenblum. interAdapt – An Interactive Tool for Designing and Evaluating Randomized Trials with Adaptive Enrollment Criteria. Working Paper, 2014. <http://arxiv.org/abs/1404.0734>

Examples

```

#Store function output
o<-compute_design_performance()

names(o)

#Decision rules for trial designs
print(o$SS[[1]])
print(o$SC[[1]])
print(o$AD[[1]])

#Plot decision rules
par(mfrow=c(1,3))
matplot(t(o$SS[[1]][2:3,]),type='o',
main='Standard trial - subpop 1',
xlab='stage',ylab='Z-statistic',
col='blue',pch=2:3,lty=3)
legend('topright',c('H01 Efficacy','H01 Futility')
,col='blue',pch=2:3,lty=3)
matplot(t(o$SC[[1]][4:5,]),type='o',
main='Standard trial - combined pop',xlab='stage',
ylab='Z-statistic',col='red',pch=0:1,lty=3)
legend('topright',c('H0C Efficacy','H0C Futility'),
col='red',pch=0:1,lty=3)
matplot(t(o$AD[[1]][4:7,]),type='o',
main='Adaptive Enrollment',xlab='stage',
ylab='Z-statistic',col=c('red','red','blue','blue'),
pch=0:3,lty=3)
legend('topright',c('H0C Efficacy','H0C Futility',
'H01 Efficacy','H01 Futility'),col=c('red',
'red','blue','blue'),pch=0:3,lty=3)

#Check performance
o$performance[[1]]

#Plot performance over a range of treatment effects for subpop2
col1<-c('black','black','black','green','blue')

perform_names<-rownames(o$performance[[1]])

#index for parts of the table corresponding to power
p_ind<- grep('Power',perform_names)
#index for parts of the table corresponding to sample size
s_ind<- grep('Sample Size',perform_names)
#index for parts of the table corresponding to trial duration
d_ind<- grep('DUR',perform_names)

par(mfrow=c(1,3))

```

```

lty1<-c(2,3,1,4,5)
matplot(x=t(o$performance[[1]][1,]),t(o$performance[[1]][p_ind,]),
type='l',lty=lty1,col=col1[1:5],xlab='Subpop.2 Tx. Effect',
ylab='Power',main='Power')
legend('bottomleft',perform_names[p_ind],col=col1[1:length(p_ind)],
lty=lty1)

matplot(x=t(o$performance[[1]][1,]),t(o$performance[[1]][s_ind,]),
type='l',lty=1:3,col=col1[3:5],xlab='Subpop.2 Tx. Effect',
ylab='Expected Sample Size',main='Expected Sample Size')
legend('topright',substr(perform_names[d_ind],1,2),col=col1[3:5],
lty=1:3)

matplot(x=t(o$performance[[1]][1,]),t(o$performance[[1]][d_ind,]),
type='l',lty=1:3,col=col1[3:5],xlab='Subpop.2 Tx. Effect',
ylab="Expected Duration",main='Expected Duration')
legend('topright',substr(perform_names[d_ind],1,2),col=col1[3:5],
lty=1:3)

```

default_parameter_table

Table of default parameters

Description

A table of the default parameters entered to [compute_design_performance](#).

Details

Each row of this table corresponds to one input to [compute_design_performance](#), and contains: (1) the name of the argument passed to [compute_design_performance](#), (2) a label describing the input in more detail, (3) the minimum value the input can take, (4) the maximum value the input can take, and (5) the input's default value.

runInterAdapt

Run the interAdapt shiny application

Description

runInterAdapt Runs the interactive shiny application

Usage

runInterAdapt()

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