OPERATING-CHARACTERISTIC GUIDED DESIGN OF GROUP-SEQUENTIAL TRIALS

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Abstract. Group-sequential designs are commonly used for clinical trials to allow early stopping for efficacy or futility. While the design of a single-stage randomized trial is guided by a target power for an alternative hypothesis of interest, the addition of interim analyses is driven by technical choices that are less understandable for clinicians. For example, the commonly used Lan-DeMets methodology requires specification of the timing of analyses and error spending functions. Since the rationale and effect of these technical choices is often unclear, the operating characteristics of the final design are explored under various values of the parameter of interest, and the design is then adjusted until desired properties are obtained.

In this work we develop methods for constructing designs that achieve the desired operating characteristics without the need to specify error spending functions or the timing of analyses. Specifically, we consider designing a study for the mean difference δ of a normally distributed outcome with known variance. The null hypothesis $H_0 : \delta = \delta_0$ is tested versus $H_a : \delta = \delta_A$, with power π at a significance level α. The interim analyses are designed so that for a pre-specified sequence δ_{Ak} the study stops for efficacy at stage k with probability π if $\delta = \delta_{Ak}$. If stopping for futility is also considered, then the requirement to stop for futility at stage k with probability π_F if $\delta = \delta_{0k}$ for pre-specified sequence δ_{0k} can also be added. We show that under some monotonicity restrictions, such designs exist for any choice of the timing of interim analyses. Specific designs can be selected by imposing additional optimality requirements, such as minimizing the expected sample size under the target alternative δ_A, or the average sample size under a weighted selection of the alternatives.

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1. Main function: calculate design

"../R/gsDesignOC.R" ?≡

```
#'Find optimal group-sequential design
#'
#'The \code{gsDesignOC} function finds the analysis times, boundaries, and sample size
#'for a group-sequential trial
#'
#'@export
#'@param thA numeric; effect size under the alternative hypothesis
#'@param thA.seq numeric vector of decreasing values >thA. For the k-th value the study will stop for eff
#'@param th0 numeric; effect size under the null hypothesis
#'@param th0.seq numeric vector of increasing values <th0. For the k-th value the study will stop for fut
#'@param min.under character string, one of \code{c("alt","null","alt.mixture", "null.mixture")} or their
#'@param sig.level numeric; the one-sided significance level. The default is 0.025.
#'@param sig.level_final numeric; the desired nominal significance level for testing the null hypothesis
#'@param power numeric; the desired study power. The default is 0.9. This value will also be used to set
#'@param power.futility numeric; the probability of stopping for futility at stage k under \code{th0.seq}
#'@param futility.type character string, one of \code{c("non-binding","binding")} or their unique abbrevi
#'@param mix.w numeric vector of length equal to that of \code{thA.seq}. The weights of the elements of \
#'@param control list of parameters controlling the estimation altorithm to replace the default values re
#'@return an object of class \code{gsDesignOC}
#'@author Aniko Szabo
#'@references Szabo, A, Tarima, S (?) Operating-characteristic guided design of group-sequential trials.
#'@keywords nonparametric
#'@examples
#'
#'gsDesignOC(0.3, thA.seq = c(1, 0.5), min.under="alt")
#'
#'@name gsDesignOC

gsDesignOC <- function(thA, thA.seq, th0=0, th0.seq=NULL,
                       min.under=c("alt","null","alt.mixture", "null.mixture"),
                       sig.level = 0.025, sig.level_final=NULL,
                       power=0.9, power.futility = power,
                       futility.type=c("non-binding","binding"),
                       mix.w = rep(1, length(thA.seq)),
                       control=list()){

}
```

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