(AGSDest)
An R-package for estimation in classical and adaptive group sequential trials

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useR! 2008

Currently available in R:

- seqmon: Computes the Boundary Crossing Probabilities in a Group Sequential Clinical Trial.
- ldbounds: Lan-DeMets Spending Function Method for the Determination of Group Sequential Boundaries.

R-Package AGSDest

Estimation in adaptive group sequential trials

Functions:

plan.GST:	Plans a group sequential trial (GST)
typeIerr:	Computes the type I error rate of a GST
cer:	Computes the conditional type I error rate of a GST at an interim analysis
pvalue:	Computes the repeated or stage-wise adjusted p-value for a classical GST or for a GST with design adaptations
seqconfint:	Computes the lower bound of the repeated confidence interval and the lower confidence bound based on the stage-wise ordering for a GST or for a GST with design adaptations

Classical Group Sequential Trials

With a classical group sequential trial one must fix in advance:

- the number of interim analyses,
- the sample sizes (information) for each interim analysis,
- all rejection and acceptance boundaries.

This requires a priori information on:

- the endpoints
- the minimal relevant effect size

Plan Classical Group Sequential Trials

```
> library(AGSDest)
> GSD<-plan.GST(K=4, Imax=200, SF=1, phi=0, alpha=0.025)
> GSD

4 stage group sequential design
alpha : 0.025 SF: 1 phi: 0 Imax: 200

 Boundaries:   4.333  2.963  2.359  2.014

 Information:   0.25    0.5    0.75     1
```

Group Sequential Trial outcome

- Let us assume that we observe at stage L=2 the z-statistic z=1.09
- We use the function as.GST to build a group sequential trial object containing also the outcome

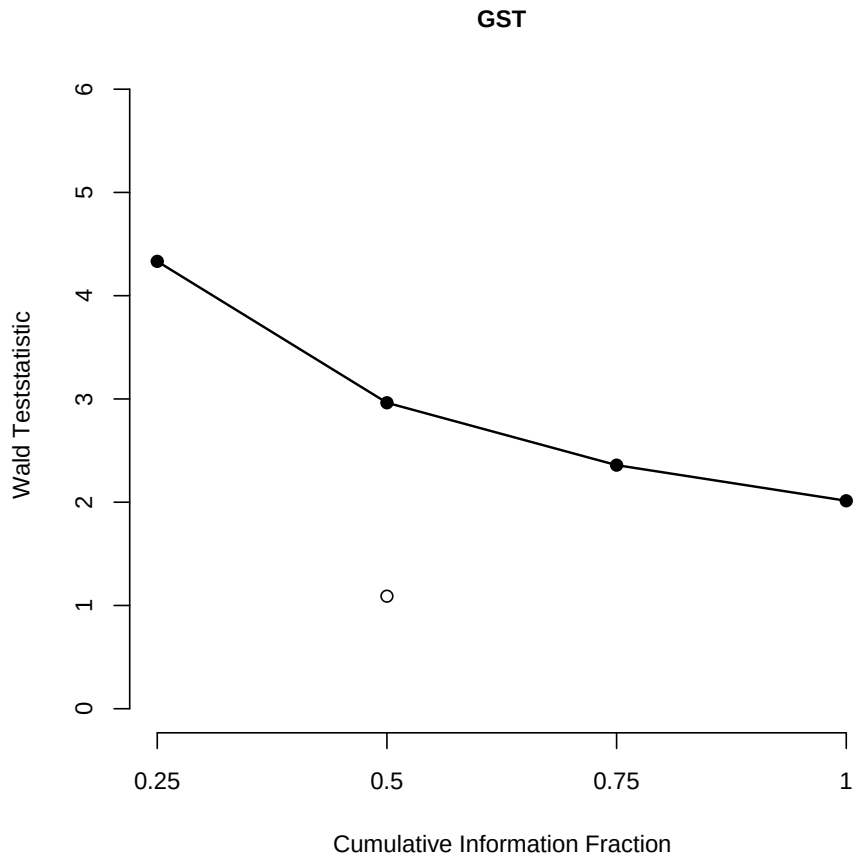
```
> GST<-as.GST(GSD=GSD,GSDo=list(L=2, z=1.09))
```

Print Classical Group Sequential Trial Object

```
> GST

4 stage group sequential design
alpha : 0.025 SF: 1 phi: 0 Imax: 200

 Boundaries:   4.333  2.963  2.359  2.014

 Information:   0.25    0.5    0.75     1
 group sequential design outcome:
                  L:2                    z:1.09
```

Plot Classical Group Sequential Trials

```
> plot(GST)
```



Construction of confidence intervals

- There are two methods for the construction of one-sided confidence intervals and point estimates for a classical group sequential trial.

Construction of repeated confidence intervals (RCI)

- Jennison and Turnbull (1989) introduced the RCIs for classical GSTs
- RCIs can be calculated at every stage of the trial and not just at stage T where the trial stops,
- are also valid if the stopping rule is not met,
- have in general only conservative coverage probability.

Method:

Apply the same group sequential design to all shifted hypotheses and corresponding test-statistics.

Construction of stage-wise adjusted confidence intervals (SWACI)

- Tsiatis, Rosner and Mehta (1984) introduced the SWACIs for classical GSTs
- SWACIs can only be calculated at the stage T where the trial stops,
- are only valid if the stopping rule is met,
- have almost exact coverage probability.

Method:

Based on an ordering of the sample space where early rejections are judged as more extreme than late rejections.

Calculate Lower Confidence bound for Classical Group Sequential Trials

The lower bound for the repeated confidence interval:

```
> seqconfint(object=GST,type="r")
$cb.r
-2.648981
```

The lower bound of the stage − wise adjusted confidence interval :

```
> seqconfint(object=GST,type="so")
$cb.so : z < b[T]; Stopping rule NOT met.
```

Performing Adaptive Changes

- The problem:
  - very ofter the effect size of a group sequential trial is very small and hence the power is low
  - by increasing the sample size or the number of analysis we can gain the power
  - but, this inflates the type I error rate
- How can we perform changes without inflating the type I error rate?
- How can we estimate δ at the end of the trial?

The Problem

Given a K-look group sequential design to test the null hypothesis $H_0 : \delta \leq 0$.

We assume that at some look $L < K$ we want to perform some data dependent changes to the study design.

- Change the sample size
- Change the spending function
- Change the number and spacing of interim looks

Müller and Schäfer principle

- Müller and Schäfer (2001, 2004) presented a general way to make adaptive changes to an on-going group sequential clinical trial while preserving the overall type I error rate.
- The key idea is to preserve the overall type I error rate after a possible design adaptation, by preserving the conditional rejection probability under the null hypothesis.

R-example for adaptive group sequential trial

We use the same example as previously, but this time we perform an adaptation at stage L=2.

```
> iD<-list(L=2, z=1.09)
```

Want to increase sample size and number of interim analysis
We have to calculate the conditional rejection probability

```
> crp<-cer(pT,iD)
0.0413208
```

Design a new, independent secondary trial at level crp

```
> sT<-plan.GST(K=5,SF=1,phi=0,alpha=0.0413208,
+ Imax=400)
```

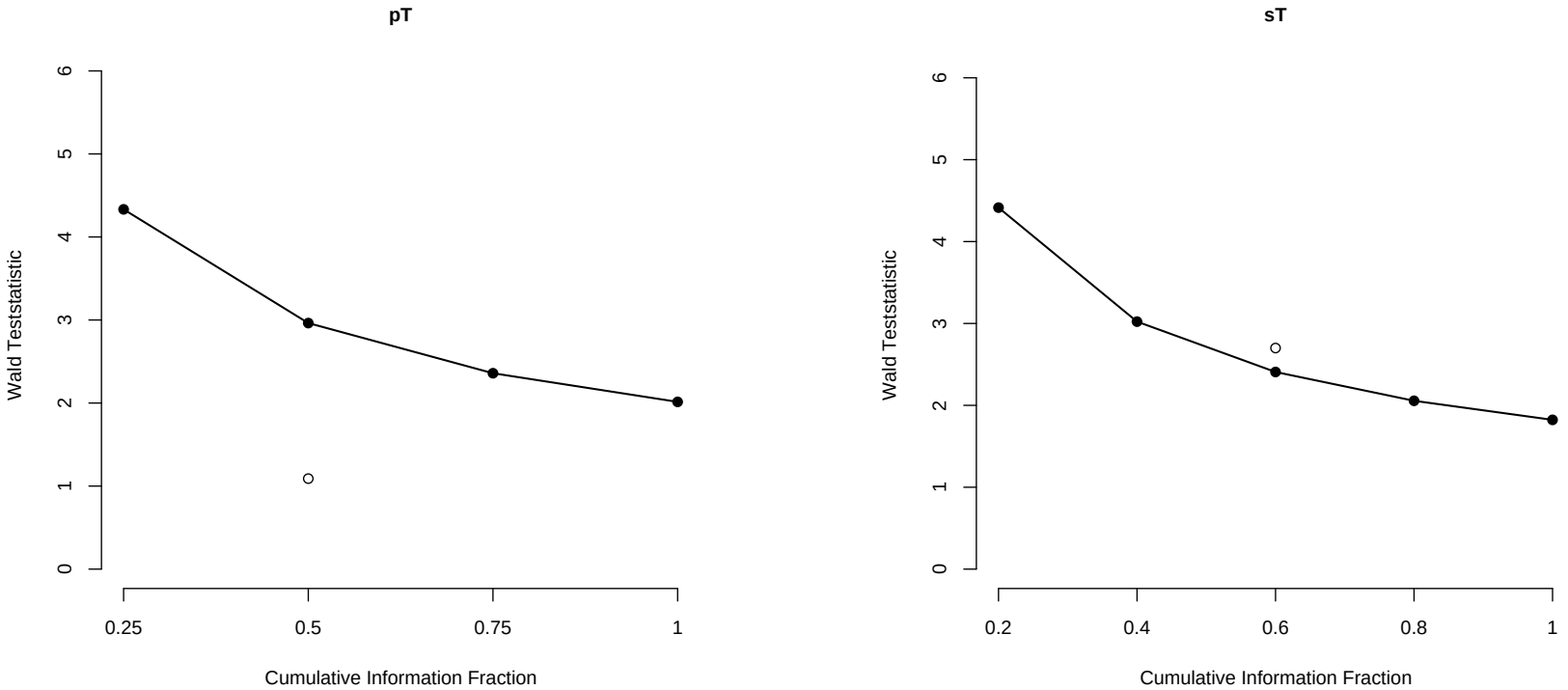
R-example for adaptive group sequential trial

- Let us assume that we observe at stage T=3 of the secondary trial the z-statistic z=2.7
- We use the function as.AGST to build a new adaptive group sequential trial object

```
> AGST<-as.AGST(pT=pT,iD=iD,sT=sT,
+ sTo=list(T=3,z=2.7))
```

Plot adaptive group sequential trial

```
> plot(AGST)
```



Construction of confidence intervals

There are two methods for extending the Müller and Schäfer principle in such a way that we obtain one-sided confidence intervals and point estimates for δ.

- Repeated confidence intervals (RCI):

  Mehta, Bauer, Posch and Brannath (2006) extended the repeated confidence intervals from Jennison and Turnbull (1989) to the adaptive setting

- Stage-wise adjusted confidence intervals (SWACI):

  Brannath, Mehta and Posch (2007) extended the stage-wise adjusted confidence intervals from Tsiatis, Rosner and Mehta (1984) to the adaptive setting

Calculate Lower Confidence Bound for Adaptive Group Sequential Trials

The lower bound of the stage-wise adjusted confidence interval:

```
> seqconfint(object=AGST,type="so")
$cb.so
0.4413923
```

The stage − wise adjusted p − value :

```
> pvalue(object=AGST,type="so")
$pvalue.so
0.00838224
```

Calculate P-Value and Lower Confidence Bound for Adaptive Group Sequential Trials

```
> summary(AGST,ctype="so",ptype="so")
cb.so: 0.441
pvalue.so: 0.008
```

Extentions

- Stopping for futility
- Two-sided confidence intervals

References

- Tsiatis,AA, Rosner,GL, Mehta,CR (1984) Exact confidence intervals following a group sequential test, *Biometrics*, 40, 797-804.
- Jennison,C,Turnbull,BW (1989) Repeated confidence intervals for group sequential clinical trials, *Contr. Clin. Trials*, 5, 33-45.
- Müller,HH,Schäfer,H (2001) Adaptive group sequential design for clinical trials: Combining the advantages of adaptive and of classic group sequential approaches, *Biometrics*, 57, 886-891.
- Müller,HH,Schäfer,H (2004) A general statistical principle for changing a design any time during the course of a trial, *Statistics in Medicine*,23, 2497-2508.
- Mehta,CR,Bauer,P,Posch,M,Brannath,W (2006) Repeated confidence intervals for adaptive group sequential trials, *Statistics in Medicine*.
- Brannath,W,Mehta,CR,Posch,M (2008) Exact confidence bounds following adaptive group sequential tests, accepted.