

Calculation of Efficacy and Futility Boundaries using GrpSeqBnds (Version 2.2)

Grant Izmirlian

February 9, 2018

1 Introduction

The function **GrpSeqBnds** computes efficacy and futility boundaries given the stipulation of the information fraction, total type I and type II error probabilities and method of boundary construction. The efficacy and futility boundaries can be constructed either simultaneously or one at a time. The function also allows for two information scales.

The following sequence of variance fractions resulted from a trial with 7 or so years of accrual and maximum follow-up of 20 years using the stopped Fleming-Harrington weights, **SFH**(0, 1, 10).

```
> frac <- c(0.006995655, 0.01444565, 0.02682463, 0.04641363, 0.0585665,  
+          0.07614902, 0.1135391, 0.168252, 0.2336901, 0.3186155, 0.4164776,  
+          0.5352199, 0.670739, 0.8246061, 1)
```

The same settings resulted in the following sequence of event ratios:

```
> frac.ii <- c(0.1494354, 0.1972965, 0.2625075, 0.3274323, 0.3519184, 0.40231,  
+            0.4673037, 0.5579035, 0.6080742, 0.6982293, 0.7671917, 0.8195019,  
+            0.9045182, 0.9515884, 1)
```

The **SFH**(0, 1, 10) statistic together with an average effect of 20% reduction in risk, subjected to contamination and dropout, resulted in the following sequence of drift function values. Recall that the drift function is the expected value of the statistic at a given alternative hypothesis. The scale is always the same as the main (first) information scale.

```
> drift <- c(0.06214444, 0.1061856, 0.1731267, 0.2641265, 0.3105231, 0.3836636,  
+          0.5117394, 0.6918584, 0.8657705, 1.091984, 1.311094, 1.538582,  
+          1.818346, 2.081775, 2.345386)
```

1. One Sided Efficacy Boundary

In this example, we calculate a one sided efficacy boundary at each of 15 analyses which will occur at the given (known) variance ratios, and we use the variance ratio for type I error probability spending, with a total type I error probability of 0.05, using the Lan-Demets method with O'Brien-Fleming spending (the default). We plot the resulting boundary.

```
> example.1 <- GrpSeqBnds(frac=frac,  
+                        EfficacyBoundary=LanDemets(alpha=0.05, spending=ObrienFleming))  
  
> plot(example.1)
```

2. One Sided Efficacy and Futility Boundaries

In this call, we calculate a one sided efficacy boundary at each of 15 analyses which will occur at the given (known) variance ratios, and we use the variance ratio for type I and type II error probability spending, with a total type I error probability of 0.05 and a total type II error probability of 0.10, using the Lan-Demets method with O'Brien-Fleming spending (the default) for both efficacy and futility. We plot the resulting boundaries, and verify their accuracy via the **SimGSB** function.

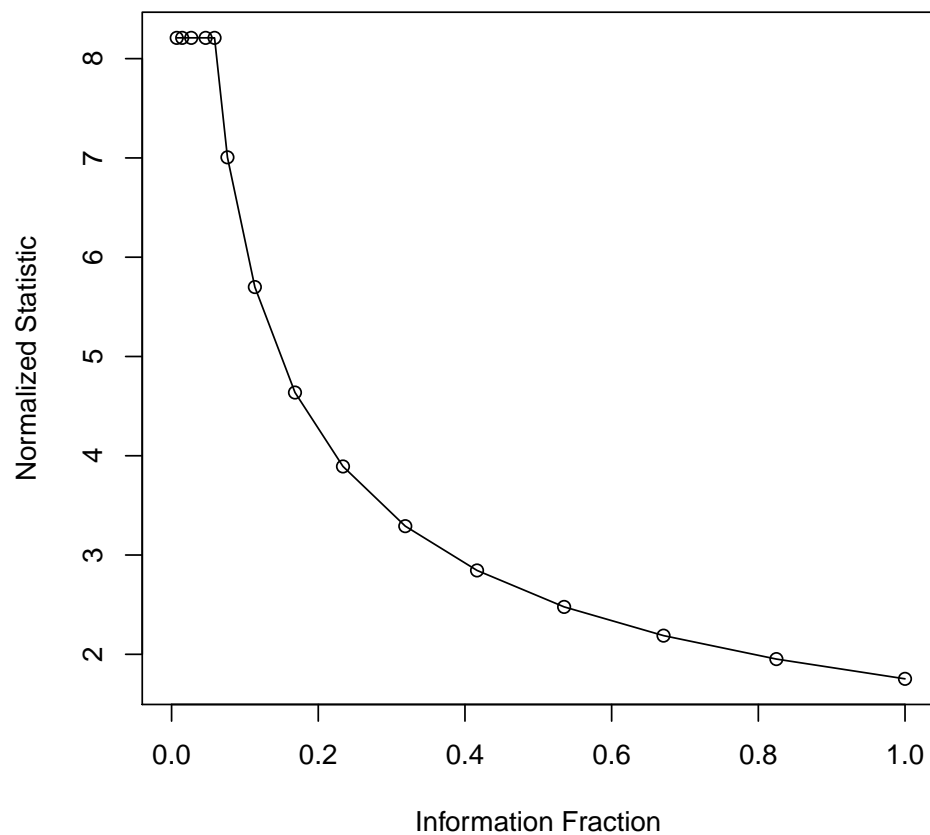


Figure 1: One-sided efficacy boundary constructed via the Lan-Demets method, using the O'Brien-Fleming error probability spending function, with total type I error probability set to 0.05

```

> example.2 <- GrpSeqBnds(frac=frac,
+                          EfficacyBoundary=LanDemets(alpha=0.05, spending=ObrienFleming),
+                          FutilityBoundary=LanDemets(alpha=0.10, spending=ObrienFleming),
+                          drift=drift)
> SimGSB(example.2)

      eI.est      eI.act eII.est      eII.act
0.006996 0.00000 1.000000e-15 0.00000 1.000000e-15
0.01445  0.00000 2.000000e-15 0.00000 2.000000e-15
0.02682  0.00000 3.000000e-15 0.00000 3.000000e-15
0.04641  0.00000 4.000000e-15 0.00000 2.559608e-14
0.05857  0.00000 5.000000e-15 0.00000 1.070201e-11
0.07615  0.00000 1.229520e-12 0.00000 2.512057e-09
0.1135   0.00000 6.002701e-09 0.00000 1.052745e-06
0.1683   0.00001 1.768361e-06 0.00004 6.071218e-05
0.2337   0.00008 5.026046e-05 0.00064 6.675519e-04
0.3186   0.00060 5.160593e-04 0.00324 3.567972e-03
0.4165   0.00235 2.389040e-03 0.01043 1.081021e-02
0.5352   0.00732 7.382981e-03 0.02399 2.455480e-02
0.6707   0.01629 1.670406e-02 0.04328 4.460067e-02
0.8246   0.02971 3.089949e-02 0.06933 7.008565e-02
1         0.04811 5.000000e-02 0.23483 2.362335e-01

> plot(example.2)

```

3. One Sided Efficacy and Futility Boundaries with Two information Scales

The following example illustrates the use of the two information scales. Note that according to the theory, the concept “information fraction” refers to the ratio of variances of the current statistic to the statistic at the end of the trial. In many circumstances, the variance of the test statistic at the end of the trial is known based upon the original design. For example, if the test statistic is the ordinary (unweighted) log-rank statistic, the arms are balanced, and censoring and event rates are relatively rare, then the variance at the end of the trial is roughly one quarter of the total expected events so that the variance ratio equals the ratio of current observed events to the total expected. However, with the introduction of a weighting function, the timing of the events can drastically alter the value of the end of trial variance.

This phenomenon led Lan and Demets to introduce the use of two information scales. In order to understand the nature of this innovation, consider that the information fraction serves two distinct purposes: (i) in the spending of error probability and (ii) in the transformation of the sequence of observed test statistics to a process having normally distributed independent increments with variance linear in information (Brownian paths). The key behind their innovation was the observation that one could use separate information scales for each one of these purposes. First, instead of normalizing the sequence of current and previously recorded statistics to have unit variance at the end of the trial, which required knowledge of the end of trial variance, one could normalize to have unit variance at the current analysis. This still results in Brownian paths. However, the information scale on which error probability is spent must be monotone increasing from 0 to 1 throughout the duration of the trial, but there is no real reason to require this scale of information to grow as the variance ratio. In fact, one may stipulate any scale. The original reason that the two scales were specified on the single variance scale was so that the resulting procedure was equivalent to continuous monitoring of the test statistic (by the reflection principle).

In the following example, suppose that we are performing the 7th interim analysis. We don’t know what the variance will be at the end of the trial, so we normalize variances of the current and previous statistics by the variance of the current statistic. This is equivalent to the following length 7 vector of variance ratios:

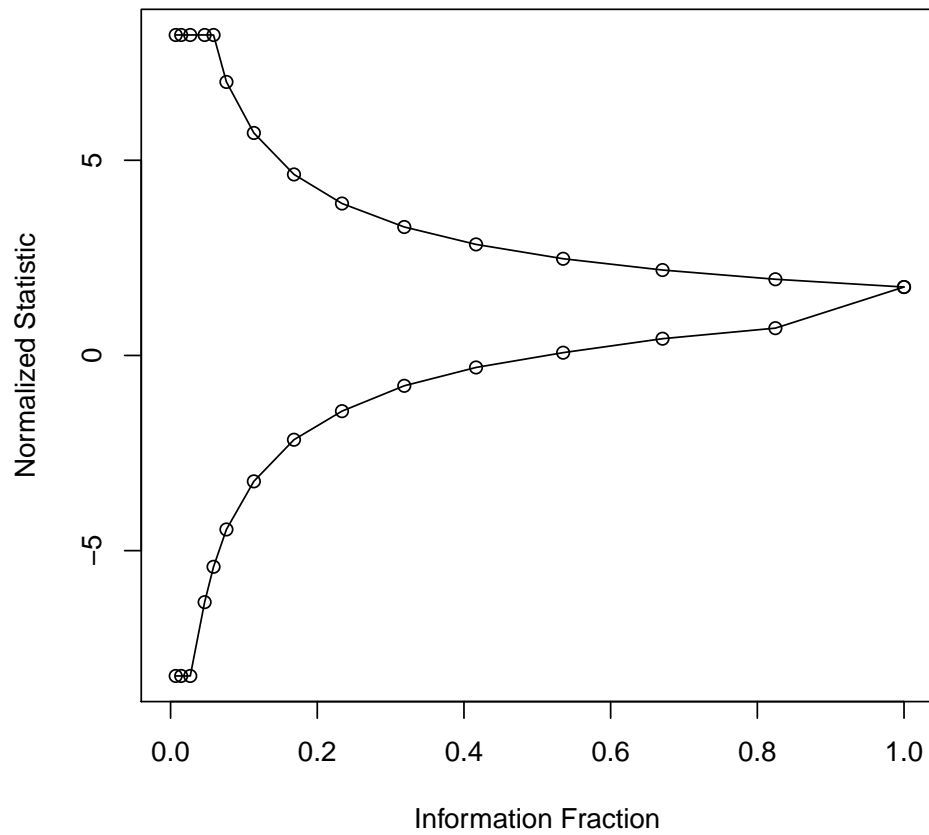


Figure 2: One-sided efficacy and futility boundaries constructed via the Lan-Demets method, using the O'Brien-Fleming error probability spending function, with total type I and type II error probabilities set to 0.05 and 0.10, respectively. The futility boundary is constructed relative to the alternative hypothesis corresponding to the drift sequence above.

```
> frac7 <- frac[1:7]/frac[7]
```

To proceed under the "unknown variance at end of trial" case, we must use a second scale for spending type I and II error probability. Unlike the above scale which is renormalized at each analysis to have value 1 at the current analysis, the alpha spending scale must be monotone increasing and attain the value 1 only at the end of the trial. A natural choice is the event ratio, which is known in advance if the trial is run until a required number of events is obtained, a so called maximum information trial:

```
> frac7.ii <- frac.ii[1:7]
```

the first seven values of the drift function

```
> drift7 <- drift[1:7]/frac[7]^0.5
```

```
> example.3 <- GrpSeqBnds(frac=frac7, frac.ii=frac7.ii,
+                         EfficacyBoundary=LanDemets(alpha=0.05, spending=ObrienFleming),
+                         FutilityBoundary=LanDemets(alpha=0.10, spending=ObrienFleming),
+                         drift=drift7)
> SimGSB(example.3)
```

	eI.est	eI.act	eII.est	eII.act
0.1494	0.00000	3.974892e-07	0.00001	2.090403e-05
0.1973	0.00002	1.021661e-05	0.00018	2.129657e-04
0.2625	0.00017	1.305582e-04	0.00127	1.325597e-03
0.3274	0.00062	6.143221e-04	0.00425	4.046323e-03
0.3519	0.00095	9.534929e-04	0.00562	5.558965e-03
0.4023	0.00172	2.001124e-03	0.00969	9.506958e-03
0.4673	0.00374	4.142034e-03	0.01637	1.612043e-02

```
> plot(example.3)
```

4. Explore different boundary construction methods

The Pow(p) spending function is αf^p . Using $p = 1$ results in linear spending of alpha so that the resulting futility boundary is less conservative.

```
> example.4 <- update(example.3, FutilityBoundary=LanDemets(alpha=0.05, spending=Pow(1)))
> SimGSB(example.4)
```

	eI.est	eI.act	eII.est	eII.act
0.1494	0.00001	3.974892e-07	0.00775	0.007471770
0.1973	0.00003	1.021661e-05	0.01103	0.009864825
0.2625	0.00015	1.305582e-04	0.01434	0.013125375
0.3274	0.00063	6.143221e-04	0.01758	0.016371615
0.3519	0.00092	9.534929e-04	0.01970	0.017595920
0.4023	0.00175	2.001124e-03	0.02230	0.020115500
0.4673	0.00377	4.142034e-03	0.02555	0.023365185

```
> plot(example.4)
```

Of course there are other options not covered in these examples but this should get you started.

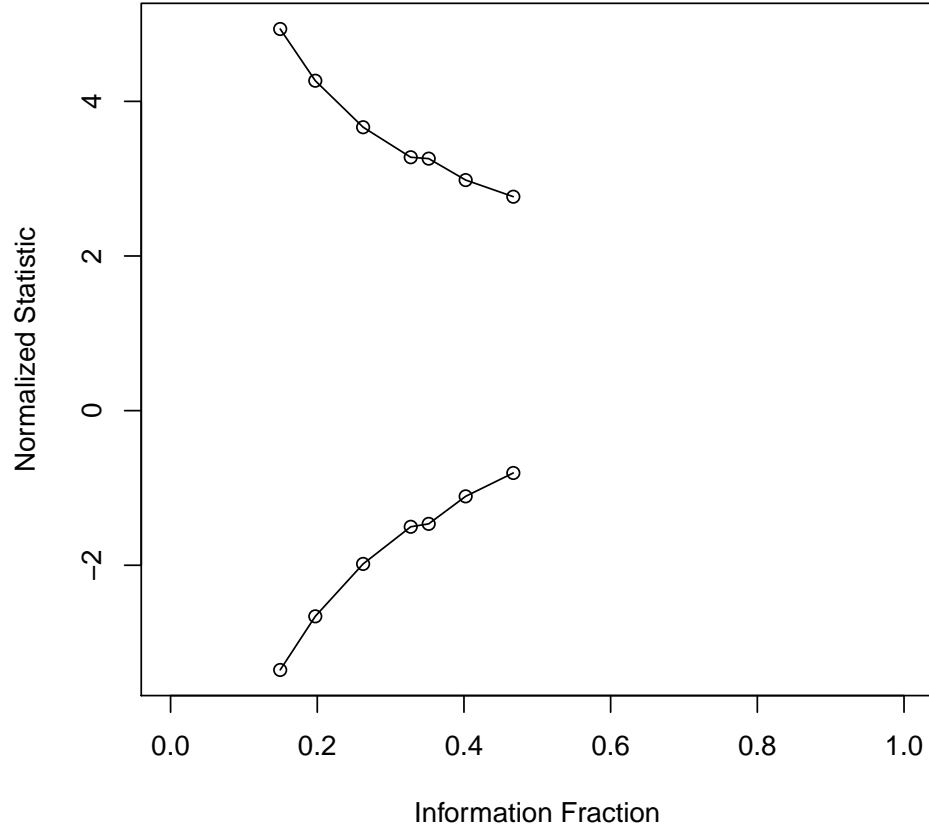


Figure 3: One-sided efficacy and futility boundaries constructed as in example 3, using the two information scales feature. The main information scale in which the sequence of statistics is normalized to the scale of brownian paths, is the variance fraction, normalized to unity at the 7th analysis. The secondary scale upon which error probability is spent is the event ratio.

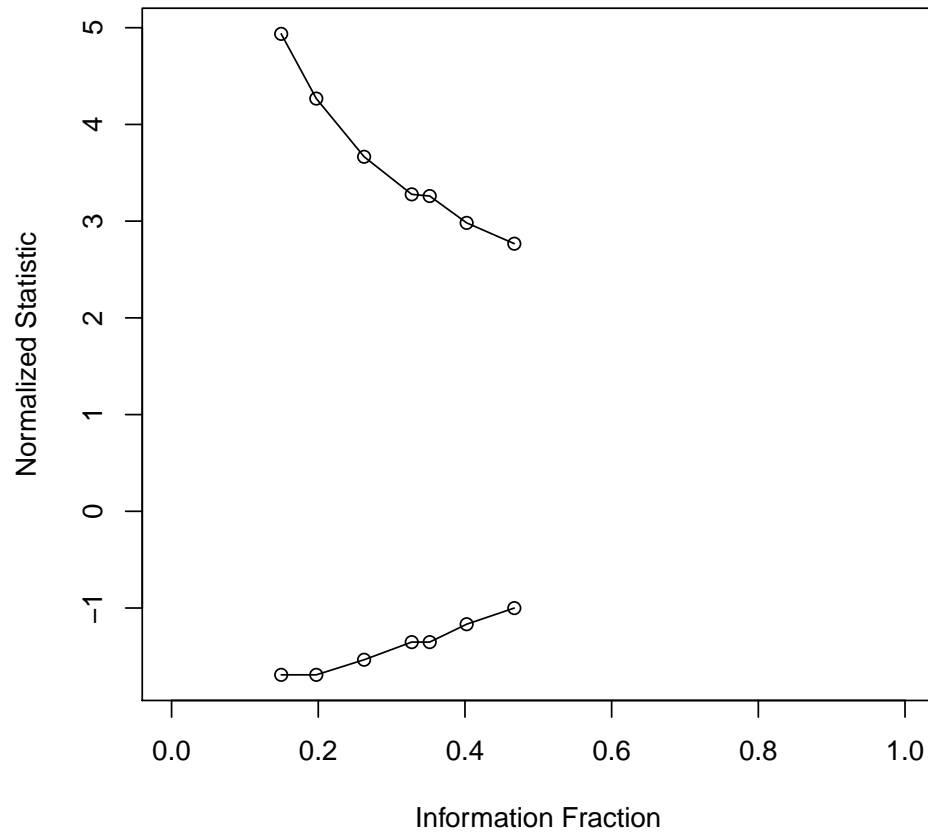


Figure 4: One-sided Lan-Demets efficacy and futility boundaries—efficacy boundary using O'Brien-Fleming spending and futility boundary using linear spending.