The `OptInterim` Package

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Contents

1 Introduction

Phase II oncology trials of cytotoxic compounds measured effect by tumor shrinkage using single-group designs that compared the proportion of responders to well-established historical response rates. With many new drugs targeting molecular pathways or the immune system, such as vaccines and immunotherapies, it may not be appropriate to use tumor shrinkage to evaluate activity. Instead, decision criteria are based on overall survival or imaging endpoints such as progression-free survival (PFS) that require longer follow-up, as treatment differences may be delayed and poorly described by models based on the proportional hazards assumption (Hoose et al., 2010). These endpoints tend to vary more across trials than the consistently low tumor response rates observed in past trials, so two-stage designs with randomized concurrent comparisons may be needed. Ratain and Sargent (2009) argue the most promising endpoints for randomized phase II trials involve a comparison of a primary outcome measure at a single time point between the treatment and control groups. Such endpoints facilitate independent radiologic review, may reduce subtle differences in scanning frequencies, simplify patient scheduling, and can be chosen to represent clinically meaningful time points. Recent EMA draft guidelines on the evaluation of anti-cancer medicinal products (EMA, 2011), state that for some conditions, progression will be observed at a slow rate making frequent assessments a burden to the patients, so event rates at a specified fixed time might be appropriate. Similar design considerations also apply in other therapuetic areas, such as the rate of transplant rejection, which is typically reported after 6 months of treatment following organ transplantation, in studies of immune-suppression drug (French, Thomas and Wang, 2012).

Phase II trials are often designed with an interim analysis so they can be stopped early if a drug is ineffective. However, when the primary endpoint requires a longer observation period, interim analyses are challenging because of incomplete follow-up for some patients at the time of the interim analysis. Standard single-arm designs such as Simon (1989) require suspension of accrual while patient follow-up is completed. Case and Morgan (2003) presented a two-stage design for a phase II oncology trial with a long-term endpoint that does not suspend accrual while the interim analysis is conducted. They proposed to use the Kaplan-Meier or Nelson-Aalen estimators of the event probability, using methods like those in Lin et al (1996). Estimation at the time of the interim analysis includes patients with partial follow-up without necessitating trial suspension, as also proposed by Jennison and Turnbull (2000). The design minimizes either the expected sample size, expected duration of accrual, or the expected total study length under the hypothesis that the drug is ineffective. The null hypothesis for the new design is an (assumed) known event-free rate within a specified time, which has been judged to represent ineffective treatment. This is similar to the hypothesis in the Simon design, but with much longer specified times for events to occur. Schaid, Wieand, and Therneau (1990) proposed a similar design using the log rank statistic, which also incorporates patients with incomplete follow-up; the log rank statistic is not evaluated here, but could be inlcuded as a future software option.

We generalize the Simon design and Case and Morgan's extension and propose an optimal interim design with long-term time specific endpoints, which can do both single-arm and randomized two-arm comparative trials, with one interim (two-stage) or two interim (three-stage) analyses. Because designs with no pause in accrual use partial information from some patients at the interim analysis, they require more patients, so time-savings from the elimination of the accrual pause can be lost due to the need to accrue more

patients. Methods are developed here for compromise designs that specify a brief pause (e.g., 2-3 months) to accumulate more information per patient and permit concentrated data collection and cleaning for the interim analysis.

Both Lin et al (1996) and Case and Morgan (2003) assume a constant accrual rate throughout the trial, which is not typical in practice. We further investigate the design properties by generalizing the accrual distribution to have different accrual rates in user-specified intervals. As noted in Case and Morgan (2003), when only partial follow-up data are available, the level of the testing procedure can depend on the assumed accrual distribution and the assumed time-to-event distribution under the null hypothesis. We evaluate an optimal design and corresponding analysis that ensure the Type I error rate is below the target level. The reduction in power or corresponding increase in sample size necessary to achieve the conservative type I error rates is also evaluated.

The theoretical derivations of the optimal designs specify a fixed time to end the first stage of accrual and to conduct the interim analysis, with corresponding projected sample size. Case and Morgan (2003) also evaluated a modified interim timing rule that ends the first stage when the projected number of patients has been accrued regardless of the planned interim time. They showed this rule has more robust statistical properties when the accrual rate is mis-specified. We also evaluate this interim timing rule and an additional rule based on the projected patient exposure at the optimal interim time. This rule not only accounts for the number of patients actually accrued, but also the length of time patients have been observed. All of the interim timing rules can be easily applied in practice.

This R package *OptInterim* was created to generate the optimal designs and resulting analyses. The package includes code to perform simulations to validate the theoretical calculations, some of which depend on asymptotic approximations. The package also has several options for evaluating a pro-

posed design under conditions that differ from those assumed when the design was created. All these will be elaborated with examples in the subsequent sections.

2 Generate the Optimal Designs

2.1 Optimal Design Functions

```
OptimDes(B.init,m.init,alpha,beta,param,x,target=c("EDA","ETSL","ES"),
        sf=c("futility","OF","Pocock"),num.arm,r=0.5,num.stage=2,
        pause=0,control=OptimDesControl(),...)


np.OptimDes(B.init,m.init,alpha,beta,param,x,n=NULL,pn=NULL,pt=NULL,
        target=c("EDA","ETSL","ES"),sf=c("futility","OF","Pocock"),
        num.arm,r=0.5,num.stage=2,pause=0,control=OptimDesControl(), ...)
```

OptimDes finds an optimal single-arm or two-arm design with either two stages or three stages for a time-specific event-free endpoint (e.g. 1-year OS in oncology) with potential stopping for futility, or it may be stopped for a positive efficacy outcome depending on a pre-specified alpha spending function (argument *SF*) at the interim(s). The design minimizes either the expected duration of accrual (EDA), expected sample size (ES), or the expected total study length (ETSL).

The design calculations assume Weibull distributions for the event-free endpoint in the treated group, and for the (assumed known, "Null") control distribution. The function *weibPmatch* (see Section 5) can be used to select Weibull parameters that yield a target event-free rate at a specified time. Estimation is based on the Kaplan-Meier or Nelson-Aalen estimators evaluated at a target time (e.g., 1 year). The treatment and control distributions and

the accrual distribution affect power (and alpha level in some settings), see Huang, Talukder and Thomas (2010).

Accrual rates are specified by the user. These rates can differ across time intervals specified by the user (this generalizes the results in Case and Morgan). The accrual information is controlled by arguments *B.init* and *m.init*.

The design has the capability of allowing for a brief pause (e.g., 2-3 months) to accumulate more information per patient and permit concentrated data collection and cleaning for the interim analysis.

OptimDes assume no recovery the amount of α potentially saved at the interim analysis (analogous to non-binding in group sequential designs) to ensure control of the type I error rate.

Note: Details of *OptInterim* and all subsequent package functions can be found on the help pages.

2.2 Example 1: Single-Arm Two-Stage Design without Interim Pause

Assume the 1-year survival rate of a standard cancer therapy is 0.40 (H_0). An improvement to 0.60 would be considered clinically significant (H_1). Assume the survival distributions have different shapes and scales under null and the alternative, determined by the weibull parameters $(1, 1.09)$ under H_0 and $(2, 1.40)$ under H_1. Type I error is 0.05. Type II error is 0.1. It is also assumed that the numbers of patients that can be enrolled in the first 5 years are 15, 20, 25, 20 and 15 respectively.

```
> B.init <- c(1, 2, 3, 4, 5)
> m.init <- c(15, 20, 25, 20, 15)
> alpha <- 0.05
> beta <- 0.1
```

```
> param <- c(1, 1.09, 2, 1.40)
> x <- 1
>
> # H0: S0=0.40 H1: S1=0.60
```

The optimal design *object12* minimizing the expected total study length (ETSL) after implementing *OptimDes* can then be obtained.

```
> object12 <- OptimDes(B.init,m.init,alpha,beta,param,x,
+ target="ETSL",sf="futility",num.arm=1,num.stage=2,
+ control=OptimDesControl(n.int=c(1,5)),pause=0)

> print(object12)

           Optimal Design Results

   One-Arm Two-Stage Study

   Interim stopping rule: Futility only

   Pause in accrual before interim analyses: 0

   H0: S0=S1= 0.4 H1: S1= 0.6

   Type I error(1-sided upper): 0.05 type II error: 0.1
   Event-free endpoint time: 1

              target: ETSL
         EDA          ETSL            ES
        2.897         3.222         56.196
```

Sample Size at Each Stage

n1	nmax
48	75

Study time at Each Stage

t1	MDA	MTSL
2.484	3.750	4.750

Projected patient exposure at interim analysis: 35.94

Proportion of the total information at the interim analysis:

Under Null	Under Alternative
0.433	0.402

Hypothesis Test Boundaries

C1L	C1U	C2U
0.452	Inf	1.645

Approximate Rates Corresponding to Test Boundaries*

Event-free rate for C1L: 0.443

Event-free rate for C2U: 0.499

Probability of stopping at an interim analysis
     Under the Null: 0.674

```
      Under the Alternative: 0.059


 Single-stage Design (Exact binomial calculation)
   Single stage N                DA                SL
          56.00               2.84              3.84


 Single-stage Design (Asymptotic normal calculation)
   Single stage N                DA                SL
          64.0                 3.2               4.2
```

```
*Note: Rates corresponding to test boundaries are a function
of the non-parametric SE computed at the time of the analyses.
The approximate rates are based on the asymptotic SE computed
under the null and alternative hypotheses.
```

For single-group trials, normal approximation often produces a larger sample size than the exact test. The *OptimDes* function has the capability to apply the adjustment by Case and Morgan (2003), which is important due to the conservative nature of normal approximation in small single-group studies.

```
> print(object12,CMadj=TRUE)

          Optimal Design Results


  One-Arm Two-Stage Study


  Interim stopping rule: Futility only


  Pause in accrual before interim analyses: 0
```

HO: S0=S1= 0.4 H1: S1= 0.6

Type I error(1-sided upper): 0.05 type II error: 0.1

Event-free endpoint time: 1

target: ETSL

EDA	ETSL	ES
2.535	2.860	49.696

Sample Size at Each Stage

n1	nmax
42	66

Study time at Each Stage

t1	MDA	MTSL
2.174	3.281	4.281

Projected patient exposure at interim analysis: 30.48

Proportion of the total information at the interim analysis:

Under Null	Under Alternative
0.433	0.402

Hypothesis Test Boundaries

C1L	C1U	C2U
0.452	Inf	1.645

Approximate Rates Corresponding to Test Boundaries*

Event-free rate for C1L: 0.446
Event-free rate for C2U: 0.506

Probability of stopping at an interim analysis
Under the Null: 0.674
Under the Alternative: 0.059

Single-stage Design (Exact binomial calculation)

Single stage N	DA	SL
56.00	2.84	3.84

Single-stage Design (Asymptotic normal calculation)

Single stage N	DA	SL
64.0	3.2	4.2

*Note: Rates corresponding to test boundaries are a function
of the non-parametric SE computed at the time of the analyses.
The approximate rates are based on the asymptotic SE computed
under the null and alternative hypotheses.

Note: All sample sizes and times are adjusted by the exact binomial correction
factor: 56/64

A plot function *plot.OptimDes* is used to display the ETSL, ES and EDA for a two-stage design relative to a single-stage design as a function of the combined stage 1 and 2 sample size. It demonstrates the tradeoff between ETSL, EDA and ES as a function of the combined sample size. Robustness of the optimal two-stage design to deviations from the target sample size can be explored. The plot often suggests a compromised design achieving near-optimal results for both EDA and ETSL be a favorable design to the optimal one based on a single criteria. Test boundary values (C_1, C_2), and numerical values of other design parameters, can be obtained for a design selected from the plot using function *np.OptimDes*. Thus, *np.OptimDes* generates the optimal design when the total sample size is fixed.

Using the above case as an example with the optimal plot Figure 1. The optimal design is displayed as the sold circle on the plot. If investigators believe a compromised design with maximum study length ratio $= 1.1$ ($pt = 1.1$ in *np.OptimDes*) will save some patients while still producing near-optimal results, $pt = 1.1$ can be input into *np.OptimDes* and the adjusted "optimal" design can be created

```
> object12_np <- np.OptimDes(B.init,m.init,alpha,beta,param,x,pn=1.1,
+ target="ETSL",sf="futility",num.arm=1,num.stage=2,
+ control=OptimDesControl(n.int=c(1,5)))

> print(object12_np)

          Optimal Design Results


   One-Arm Two-Stage Study


   Interim stopping rule: Futility only
```
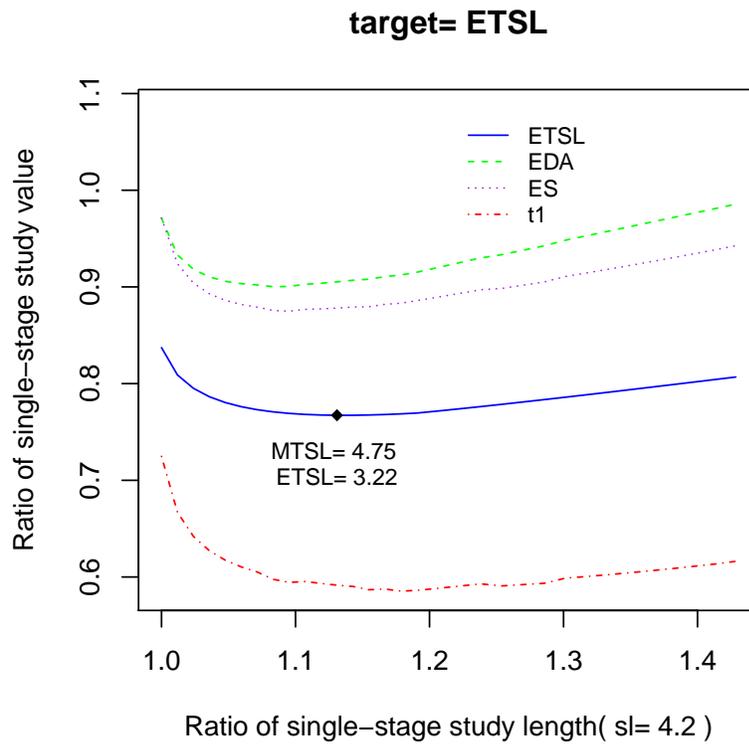
Figure 1: The optimality criteria displayed for a range of maximum sample sizes. The criteria and the maximum sample sizes are expressed as ratios relative to the corresponding value in a single-stage fixed design.

Pause in accrual before interim analyses: 0

H0: S0=S1= 0.4 H1: S1= 0.6

Type I error(1-sided upper): 0.05 type II error: 0.1
Event-free endpoint time: 1

target: ETSL

EDA	ETSL	ES
2.881	3.237	56.038

Sample Size at Each Stage

n1	nmax
48	71

Study time at Each Stage

t1	MDA	MTSL
2.51	3.55	4.55

Projected patient exposure at interim analysis: 36.04

Proportion of the total information at the interim analysis:

Under Null	Under Alternative
0.466	0.432

Hypothesis Test Boundaries

C1L	C1U	C2U
0.368	Inf	1.645

Approximate Rates Corresponding to Test Boundaries*

      Event-free rate for C1L: 0.434
      Event-free rate for C2U: 0.502

Probability of stopping at an interim analysis
     Under the Null: 0.644
     Under the Alternative: 0.048

Single-stage Design (Exact binomial calculation)

Single stage N	DA	SL
56.00	2.84	3.84

Single-stage Design (Asymptotic normal calculation)

Single stage N	DA	SL
64.0	3.2	4.2

*Note: Rates corresponding to test boundaries are a function of the non-parametric SE computed at the time of the analyses. The approximate rates are based on the asymptotic SE computed under the null and alternative hypotheses.

2.3 Example 2: Single-Arm Two-Stage Design with Interim Pause

Assume the 6-month progression-free survival (PFS) rate of a standard cancer therapy is 0.45 (H_0). An improvement to 0.60 would be considered clinically significant (H_1). Assume both the null and alternative PFS distributions follow an exponential distribution. The 1-sided type I error rate is 0.10 and type II error rate is 0.2. Prior assumption includes a fixed enrollment rate of 3 patients per month. We require a pause of 3 months at the end of Stage 1.

```
> B.init <- 1:72
> m.init <- rep(3,72)
> alpha <- 0.10
> beta <- 0.2
> x <- 6
> pnull<-.45
> palt<-.6
> param <- c(1, weibPmatch(x,pnull,shape=1),
+           1, weibPmatch(x,palt,shape=1))
> # p0=.45, p1=.6 at x=1
>
```

The optimal design *object12P3* minimizing the expected total study length (ETSL) after implementing *OptimDes* can then be obtained.

```
> object12P3 <- OptimDes(B.init,m.init,alpha,beta,param,x,
+ target="ETSL",sf="futility",num.arm=1,num.stage=2,
+ control=OptimDesControl(n.int=c(1,5)),pause=3)

> print(object12P3)
```

Optimal Design Results

One-Arm Two-Stage Study

Interim stopping rule: Futility only

Pause in accrual before interim analyses: 3

H0: S0=S1= 0.45 H1: S1= 0.6

Type I error(1-sided upper): 0.1 type II error: 0.2
Event-free endpoint time: 6

target: ETSL

EDA	ETSL	ES
16.762	20.781	47.230

Sample Size at Each Stage

n1	nmax
36	71

Study time at Each Stage

t1	MDA	MTSL
11.668	26.667	32.667

Projected patient exposure at interim analysis: 202.12

Proportion of the total information at the interim analysis:
Under Null   Under Alternative

```
        0.448                    0.451
```

```
    Hypothesis Test Boundaries
        C1L              C1U              C2U
        0.413            Inf              1.282
```

```
Approximate Rates Corresponding to Test Boundaries*

    Event-free rate for C1L:  0.489
    Event-free rate for C2U:  0.529
```

```
Probability of stopping at an interim analysis
    Under the Null: 0.66
    Under the Alternative: 0.121
```

```
Single-stage Design (Exact binomial calculation)
  Single stage N              DA              SL
        53.000              17.667          23.667
```

```
Single-stage Design (Asymptotic normal calculation)
  Single stage N              DA              SL
        58.000              19.333          25.333
```

```
*Note: Rates corresponding to test boundaries are a function
```

of the non-parametric SE computed at the time of the analyses.
The approximate rates are based on the asymptotic SE computed
under the null and alternative hypotheses.

*Note: Interim analysis time(s) are at the beginning of the
accrual pause. Information/exposure are computed at the end
of the pause.

2.4   Example 3: Two-Arm Three-Stage Design with Interim Pause

Because there may not be reliable information about the control rate, and
there is potential for bias due to patient and investigator expectations, a design with a randomized and possibly blinded control group may be necessary.
Under the same clinical background as Example 1, we consider a randomized
two-arm comparative design. This requires much larger sample sizes, so we
assume the enrollment rate at each of the 5 pre-specified time intervals 4
times that in the single-arm design counterpart. The survival distributions
are also different. The null 1-year survival rate is 0.20 versus the alternative
rate of 0.35. Because of the larger sample size, the trial is planned with
two interim analyses for both futility and efficacy stopping (O'Brien-Fleming
type alpha-spending function). We require a pause of 0.3 year at both interim
analyses.

```
> B.init <- c(1, 2, 3, 4, 5)
> m.init <- 4*c(15, 20, 25, 20, 15)
> alpha <- 0.05
> beta <- 0.1
> x<-1
> #p0=.2, p1=.35 at x=1
```

```
> param <- c(1.5, 0.7281438, 1.75, 0.9725991)
>
```

The optimal design *object23P3* minimizing the expected sample size (ES) after implementing *OptimDes* can then be obtained.

```
> object23P3 <- OptimDes(B.init,m.init,alpha,beta,param,x,
+ target="ES",sf="OF",num.arm=2,num.stage=3,
+ control=OptimDesControl(aboveMin=c(1.05,1.10)),pause=0.3)

> print(object23P3)

            Optimal Design Results


   Two-Arm Three-Stage Study: 1 : 1 randomization


   Interim stopping rule: Futility plus Obrien-Fleming boundary


   Pause in accrual before interim analyses: 0.3


   H0: S0=S1= 0.2 H1: S1= 0.35


   Type I error(1-sided upper): 0.05 type II error: 0.1
   Event-free endpoint time: 1


             target: ES
       EDA            ETSL              ES
      3.165          3.638          220.202


      Sample Size at Each Stage
          n1              n2              nmax
```

```
        133              231              373
```

Study time at Each Stage

t1	t2	MDA	MTSL
1.909	3.202	5.483	6.483

Projected patient exposure at interim analysis: 113.36 206.42

Proportion of the total information at the interim analysis:

Under Null Stage 1	Under Null Stage 2
0.258	0.498

Under Alternative Stage 1	Under Alternative Stage 2
0.259	0.499

Hypothesis Test Boundaries

C1L	C1U	C2L	C2U
-0.088	3.686	0.570	2.547

C3U
1.662

Approximate Rates Corresponding to Test Boundaries*

Difference in Event-free rate for C1L: -0.007

Difference in Event-free rate for C1U: 0.334

Difference in Event-free rate for C2L: 0.035

Difference in Event-free rate for C2U: 0.165

Difference in Event-free rate for C3U: 0.074

Probability of stopping at an interim analysis
        Under the Null: 0.753
        Under the Alternative: 0.467

Single-stage Design (Fisher exact calculation)
    Single stage N   DA   SL
            324.000   4.067   5.067

Single-stage Design (Asymptotic normal calculation)
    Single stage N   DA   SL
            303.000   3.788   4.787

*Note: Rates corresponding to test boundaries are a function
of the non-parametric SE computed at the time of the analyses.
The approximate rates are based on the asymptotic SE computed
under the null and alternative hypotheses.

*Note: Interim analysis time(s) are at the beginning of the
accrual pause. Information/exposure are computed at the end
of the pause.

3 Test Statistics and Decision Rules at Each Stage

```
TestStage(tan,tstage,x,num.arm,num.stage,
        Y1,T1,Y0=NULL,T0=NULL,p0=NULL,
        C1L=NULL,C1U=NULL,C2L=NULL,C2U=NULL,C3U=NULL,
        printTest=TRUE,
        cen1=rep(1,length(T1)), cen0=rep(1,length(T0)))
```

The test statistic at the end of each stage is computed and compared to the decision boundaries.

For example, the following decision rules are applied in a two-stage design with early futility stopping only:

- Stage 1: Accrue n_1 patients between time 0 and time t_1. Each patient is followed until they have an event or successfully reach time x, or until study time t_1, whichever is first. Calculate the normalized Z-statistic by *Test2stage*, and denote it by $Z_1(x; t_1)$. If $Z_1(x; t_1) < C_1$, stop the study for futility; otherwise, continue to the next stage. The probability of stopping under the null hypothesis is approximated by $P_s = \Phi(C_1)$, where Φ is the standard normal cummulative distribution function. n_1 is a random variable determined by t_1 and the accrual distribution.

- Stage 2: Accrue n_2 additional patients between times t_1 and maximum duration of accrual (MDA). Follow all patients (both stages) until they have an event or successfully reach time x, then calculate a second Z statistic at the end of maximum total study length ($MTSL$), denoted by $Z_2(x; MTSL)$, and reject H_0 if $Z_2(x; MTSL) > C_2$.

For example, if at the end of Stage 1, the test statistic $Z_1 = 3.391$, $C_1 = 0.085$. Then *Test2stage* will return

`Z1 >= C1, continue to the second stage`

4   Simulation Studies

```
SimDes(
object,B.init,m.init,weib0,weib1,interimRule='e1',
sim.n=1000,e1conv=1/365,CMadj=F,attainI=1,attainT=1,
FixDes="F", Rseed)
```

The *SimDes* function is a powerful function to simulate experiments to compare the true alpha level and power of two-stage or three-stage designs from function *OptimDes* with the targeted nominal values. It can also be used to assess the performance of the optimal design under mis-specification of the design parameters. For example, if the Weibull shape and scale parameters of the time to event distributions are changed, if the accrual rates deviate from the projected ones, or if the interim analysis is conducted differently from the planned one under the more realistic conditions. In addition, the function has the option to determine the timing of the interim analysis by matching the observed information to the expected time, number of patients or patient exposure (interimRule="t1", "n1" or "e1").

4.1   Example 1: Optimal Settings

Recall that in Section 2.2 *object12* is the optimal design minimizing the ETSL. Under the expected parameter settings, 10000 simulations are conducted by matching the expected patient exposure at the interim

```
> (simout12<-SimDes(object12,sim.n=10000))
```

alphaExact	alphaNorm	powerExact	powerNorm	eda	etsl
0.03440000	0.03440000	0.93590000	0.93590000	2.91227019	3.29306377

es	edaAlt	etslAlt	esAlt	n1	n2
57.85340000	3.66122303	4.62994369	74.14560000	48.31550000	NA
t1	t2	aveE	aveE2	pinfoNull	pinfoNull2
2.51272885	NA	35.94124315	NA	0.43756862	NA
pinfoAlt	pinfoAlt2	difIntFutL	difIntSupH	difIntFutH	difIntSupL
0.39513649	NA	0.03624613	0.54862609	0.04402351	Inf
difFinSupL	difFinFutH	pstopNull	pstopAlt	pstopENull	pstopEAlt
0.11040030	0.09715575	0.64320000	0.03240000	0.00000000	0.00000000

Details of the returned values can be found from the help pages. For instance, the estimated alpha level using an exact test for the second stage test is 0.0344.

With the Case and Morgan adjustment, the simulation results are different:

```
> (simout12adj<-SimDes(object12,sim.n=10000,CMadj=TRUE))
```

alphaExact	alphaNorm	powerExact	powerNorm	eda	etsl
0.03620000	0.03620000	0.90810000	0.90810000	2.59910061	2.99035420
es	edaAlt	etslAlt	esAlt	n1	n2
50.86200000	3.20259157	4.15796241	64.89240000	42.09710000	NA
t1	t2	aveE	aveE2	pinfoNull	pinfoNull2
2.25961887	NA	30.47836723	NA	0.41563451	NA
pinfoAlt	pinfoAlt2	difIntFutL	difIntSupH	difIntFutH	difIntSupL
0.36920727	NA	0.03879866	0.54313651	0.04826665	Inf
difFinSupL	difFinFutH	pstopNull	pstopAlt	pstopENull	pstopEAlt
0.11926619	0.10422928	0.63350000	0.04650000	0.00000000	0.00000000

4.2   Example 2: Differed Accrual Rates

Now suppose the actual numbers of patients that can be accrued in the first 5 years are different from the originally planned for the optimal design (*m.init*

below), then the results after 10000 simulated trials become

```
> (simout12_2 <- SimDes(object12,sim.n=10000,m.init = c(5, 5, 25, 25, 25)))
```

alphaExact	alphaNorm	powerExact	powerNorm	eda	etsl
0.03630000	0.03630000	0.93860000	0.93860000	3.88687794	4.27519689
es	edaAlt	etslAlt	esAlt	n1	n2
58.43070000	4.52550112	5.49332978	74.13090000	48.94300000	NA
t1	t2	aveE	aveE2	pinfoNull	pinfoNull2
3.53923421	NA	35.94104744	NA	0.43100668	NA
pinfoAlt	pinfoAlt2	difIntFutL	difIntSupH	difIntFutH	difIntSupL
0.38600320	NA	0.03559947	0.49299710	0.04472567	Inf
difFinSupL	difFinFutH	pstopNull	pstopAlt	pstopENull	pstopEAlt
0.11040030	0.09715575	0.63580000	0.03340000	0.00000000	0.00000000

4.3   Example 3: Differed Interim Timing

If the actual interim time or sample size (depending on *interimRule,interimRule="t1"* below) is different from the originally planned for the optimal design (*attainI*=0.8 below), then the results after 10000 simulated trials become

```
> (simout12_3 <- SimDes(object12,sim.n=10000,interimRule = "t1",attainI = 0.8))
```

alphaExact	alphaNorm	powerExact	powerNorm	eda	etsl
0.02870000	0.02870000	0.89840000	0.89840000	2.59510440	2.99881349
es	edaAlt	etslAlt	esAlt	n1	n2
49.77730000	3.56572854	4.49269163	71.85510000	34.74190000	NA
t1	t2	aveE	aveE2	pinfoNull	pinfoNull2
1.98758296	NA	24.73300162	NA	0.28181398	NA
pinfoAlt	pinfoAlt2	difIntFutL	difIntSupH	difIntFutH	difIntSupL
0.24286220	NA	0.03749681	0.56656092	0.06363181	Inf
difFinSupL	difFinFutH	pstopNull	pstopAlt	pstopENull	pstopEAlt
0.11040030	0.09715575	0.62720000	0.07670000	0.00000000	0.00000000

5 Survival Curves Based on the Weibull Distribution

```
weibPmatch(x, p0, shape, scale)
```

```
weibull.plot(param, x, l.type = 1:3, l.col = c("blue", "red"), ...)
```

weibPmatch and *weibull.plot* are used together to determine the shape and scale parameters of the Weibull distrbution for the survival curves under H_0 and H_1. The Weibull distribution is flexible enough to cover the majority of scenarios likely to encounter in practice.

weibPmatch determines the shape or scale parameter of a Weibull distribution so it has event-free rate P_0 at time x. If the shape is specified, the scale parameter is computed, and if the scale is specified, the shape parameter is computed.

weibull.plot then plots Weibull survival curves with differences at a target time highlighted from the parameters computed from *weibPmatch*. Figure 2 is an example plot implementing the Weibull parameters input to *OptimDes* to create *object12*.
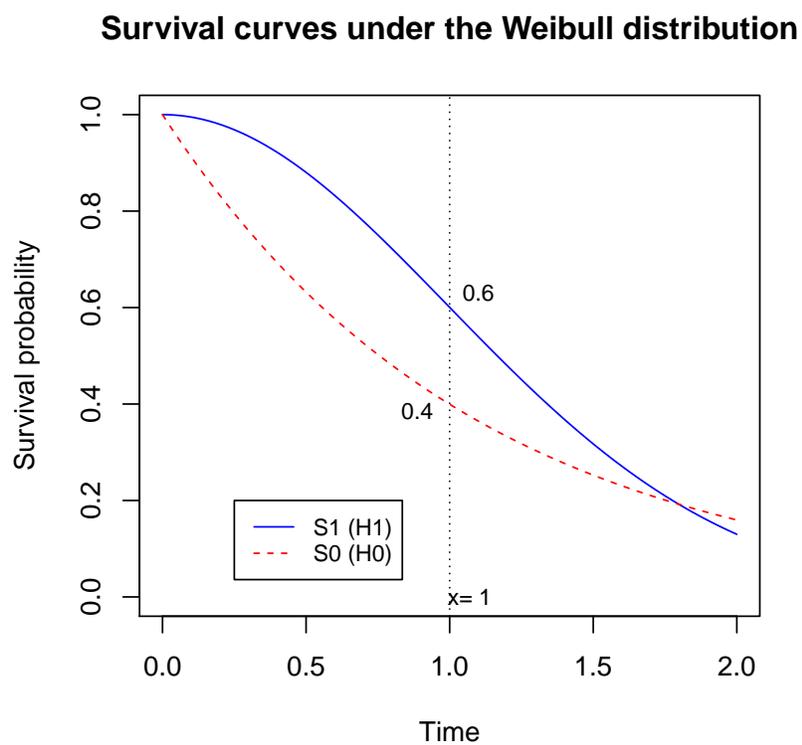
Survival curves under the Weibull distribution

Figure 2: Survival curves under the Weibull distribution

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