# Designing group sequential randomized clinical trials with time to event end points using a R function

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Dynamic predictions for repeated markers and repeated events: models and validation in cancer

# Time to event endpoint: Sample Size and Power

- **Sample size is contingent on design, analysis plan, and outcome**

  The power depends on the number of events observed during the trial and not on the number of patients as is the case for binary or continuous endpoints.

  Sample Size
  1. Required number of events
  2. Number of patients needed

- **With an incorrect sample size, you will either**
  - Not be able to make conclusions because the study is "<u>underpowered</u>"

    Too few patients included
    => Too few events => Study Underpowered
  - Waste time and money because your study is <u>larger than is needed</u> to answer the question of interest

# Time To event endpoint: Sample Size and Power

- **Number of events:** superiority trials

$$H0 : \lambda_E = \lambda_C \quad \text{VS} \quad H1 : \lambda_E \neq \lambda_C$$

$$H0 : h = \lambda_E / \lambda_C = 1 \quad \text{VS} \quad H1 : h \neq 1$$

$$e = \frac{\left[z_{1-\alpha/k} + z_{1-\beta}\right]^2}{p_E(1-p_E)\left[\ln(h_a)\right]^2}$$ (Schoenfeld, 1983)

- **Probability of observing** the primary event of interest

$$\Psi(t,\lambda,\gamma) = p_E \times \Psi_E(t,\lambda_E,\gamma_E) + (1-p_E)\Psi_C(t,\lambda_C,\gamma_C)$$

Depend on
- Survival hypothesis
- Lost to follow-up
- Follow-up duration
- Accrual duration

- **Sample Size:** $N = e / \Psi$

- **"The number of subjects in a clinical study should always be large enough to provide a reliable answer to the question(s) addressed."**

- **"The sample size is usually determined by the primary objective of the trial."**

- **"Sample size calculation should be explicitly mentioned in the protocol ."**

  *(from ICH-E9)*

- **"For scientific and ethical reasons, the sample size for a trial needs to be planned carefully, with a balance between medical and statistical considerations."**

  *(from CONSORT statement on reporting clinical trials)*

# Group Sequential Design

- K Analyses:
  - K-1 Interim Analysis
  - 1 Final analysis

- Procedure

  1. After look k = 1, ..., K-1
     - If $p_k \leq \alpha_k$ then stop and reject H0
     - Otherwise continue to k = k + 1

  2. After look k = K,
     - If $p_K \leq \alpha_K$ then reject H0
     - Otherwise do not reject H0

# Overall Probability of Achieving a Result with Given Nominal Significance of 0.05 After N Repeated Tests Under Ho

(McPherson, 1974)

| N° of test (N) | Overall Probability |
|---|---|
| 1 | .05 |
| 2 | .083 |
| 3 | .107 |
| 4 | .126 |
| 5 | .142 |
| 10 | .193 |
| 25 | .266 |

If one carries out ***10*** interim analyses the chance of at least one analysis showing a treatment difference significant at the *5%* level increases to ***0.19*** even if the treatments are truly equally effective

# Value of Nominal Significance Level Necessary to Achieve a True Level of 0.05 After N Repeated Tests

(McPherson, 1974)

| N° of test (N) | Significance Level Which Should be Used |
|---|---|
| 1 | .05 |
| 2 | .0296 |
| 3 | .0221 |
| 4 | . 0183 |
| 5 | . 0159 |
| 10 | . 0107 |

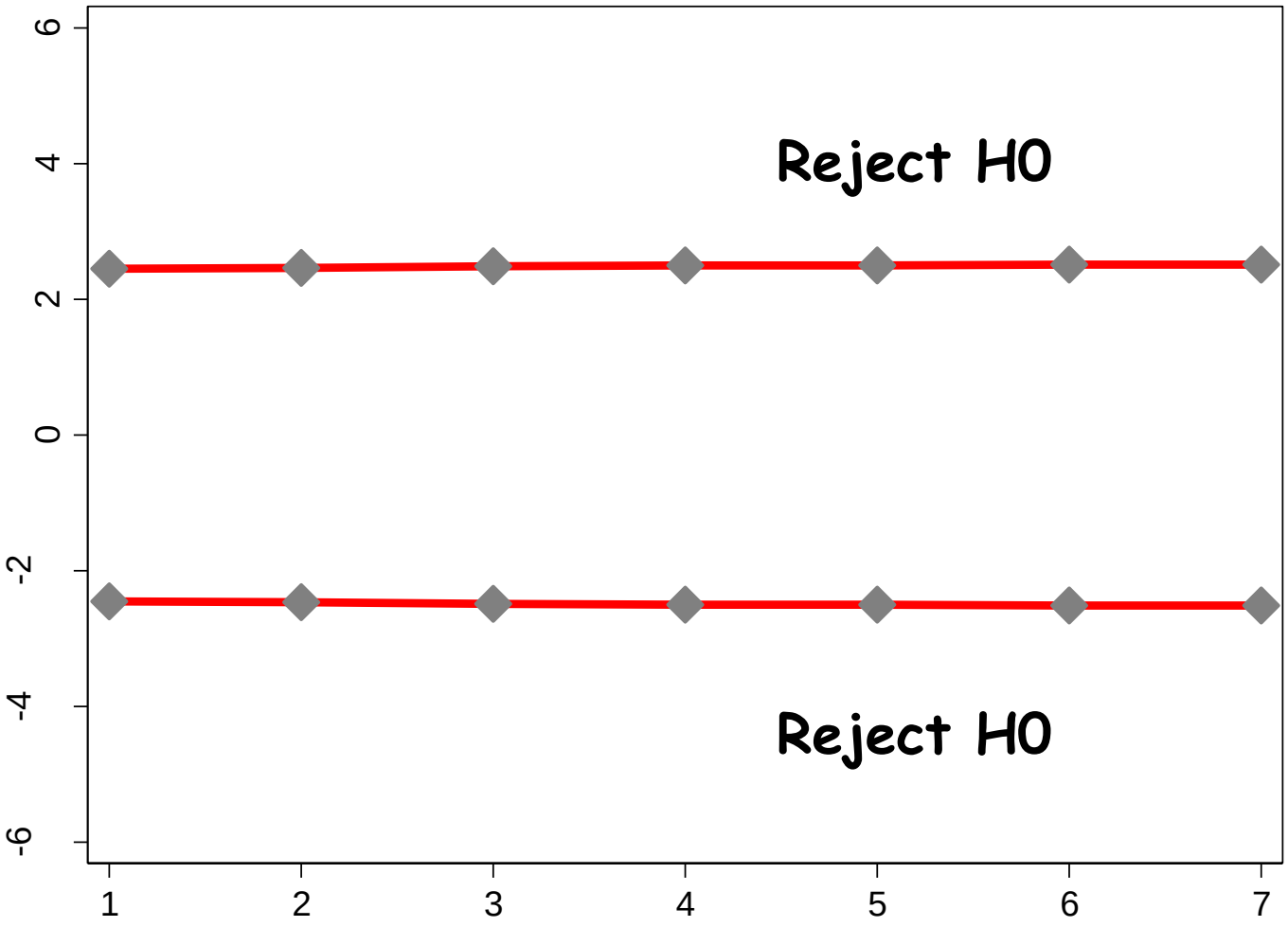
A more stringent nominal significant level for each repeated test, to keep overall significant level at some reasonable value.

# Group sequential tests boundaries

- Pocock (1977)
  - Divides ***equally*** the overall significance levels
- O'Brien and Fleming (1979)
  - Slightly increase in the significance level on each following test

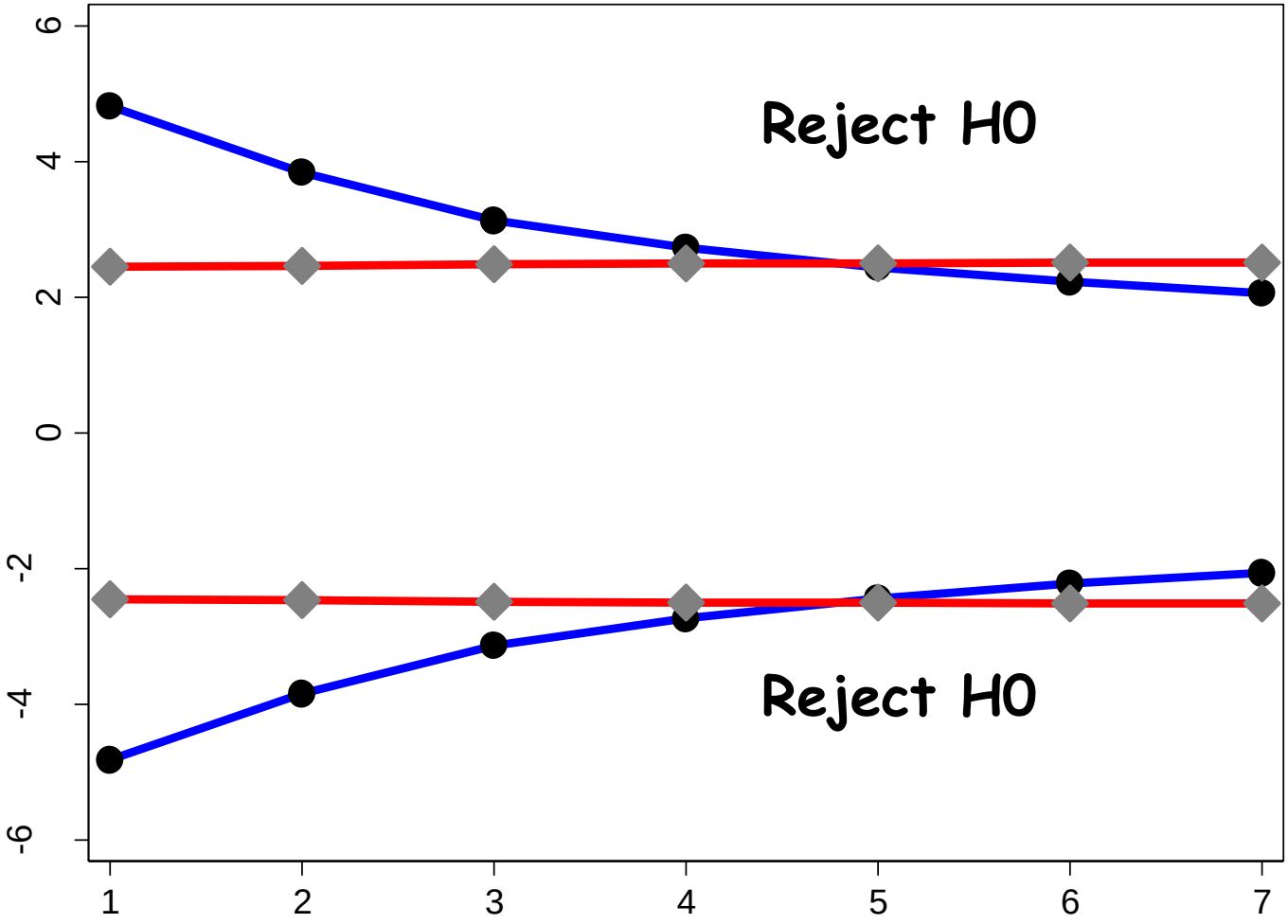
- Alpha Spending approach (Lan deMets, 1994)
  - To allow investigators to determine how they want to "spend" the type-I error or alpha during the course of the trial.
  - The alpha spending function guarantees that at the end of the trial, the overall type I error will be the pre-specified value of $\alpha$.

# Critical Values (z) for 2-sided Group Sequential Design with .05 Overall Significance and 7 Looks




Pocock

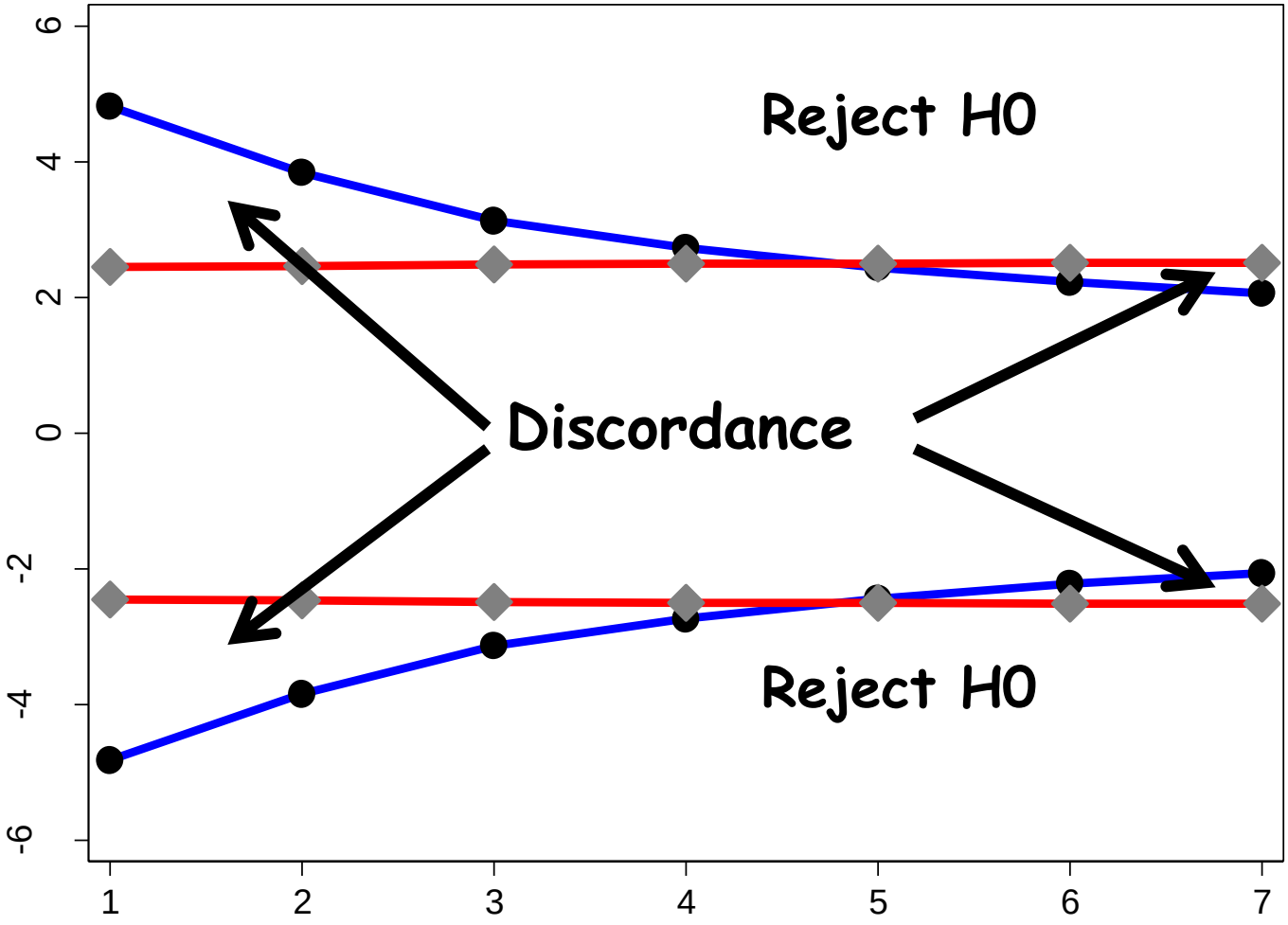
# Critical Values (z) for 2-sided Group Sequential Design with .05 Overall Significance and 7 Looks




O'Brien Flemming

Pocock

# Critical Values (z) for 2-sided Group Sequential Design with .05 Overall Significance and 7 Looks




O'Brien Flemming

Pocock

- **"An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial"**

- **"Because the number, methods, and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol."**

*(from ICH-E9)*

# Software to design group sequential randomized clinical trials with time to event endpoint

- Commercial
  - East
  - PEST
  - PASS
  - S+ seqtrial
- R package
  - gsdesign

**`plansurvct.func`**: an add-on to the **gsDesign** package

sample size for time to event endpoints in clinical trials with or without group sequential testing in both the superiority and non-inferiority settings.

**Designing group sequential randomized clinical trials with time to event end points using a R function**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COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 108 (2012) 113–128

# Plansurvct.func: Input

- **`plansurvct.func(design,Survhyp,pe,alfa,beta,duraccrual, durstudy,look,fup,dropout)`**
  - Type of trial (Superiority [one or two sided] non inferiority, equivalence)
  - Survival Hypothesis (Survival rate or Hazard ratio)
  - Proportion of patients assigned to the experimental arm
  - Type I error rate
  - Type II error rate (1-power)
  - Accrual duration,
  - Study duration
  - Interim Analysis (Number, Timing, Efficacy / Futiliy)
    - Pocock Boundaries
    - O'Brien Fleming Boundaries
    - Land deMets boundaries
  - Follow-up duration
  - Drop out information

# Plansurvct.func: Output

- **`plansurvct.func(design,Survhyp,pe,alfa,beta,duraccrual, durstudy,look,fup,dropout)`**

  - Hazard ratio under the alternative hypothesis
  - Hazard ratio under the null hypothesis (only for noninferiority trials)
  - The required number of events
  - The total sample size
  - The number of patients to be included in each arm
  - If there are interim analyses, the information fraction at each interim analysis, the number of events, the p-value and boundary to reject H0 and the analysis time under H0 and H1.

# Example: Superiority Trial without interim Analysis

- Hypothesis :
  - Superiority two sided
  - OS at 5 years:
    - 65% control arm vs 75 % Exprimental arm
  - 50% randomized in experimental arm
  - Alpha= 5% / Type II Error: 10%
  - Accrual duration: 2 years
  - Study duration : 6 years
  - No interim Analysis
  - No fixed follow-up
  - No drop out

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,1,0,0)
```

# Example: Superiority Trial without interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,1,0,0)
```

```
+--------------------+
|     Data Check     |
+--------------------+
+ Parameters OK
+ Packages OK
+-----------------------------------------------------+
| Survival Superiority Trial: Two-Sample Test         |
+-----------------------------------------------------+
+ Test Parameters
  - 1-Sided or 2-Sided Test: 2-Sided
  - Significance level alpha: 0.05
  - Power: 0.9
+ Study parameters
  - Accrual Duration (duraccrual): 2
  - Follow-up: No Fixed Follow-up
  - Study Duration (durstudy): 6
  - Assigned Fraction Experimental Arm: 0.5
  - Drop Out: No Drop Out
+ Analysis
  - Number of Planned Analysis: 1
```

# Example: Superiority Trial without interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,1,0,0)
```

```
+-------------------------------------------------+
| Survival Superiority Trial: Two-Sample Test     |
+-------------------------------------------------+

.... ....
+ Survival Parameters
  - Times (times): 5
  - Survival Control (Sc): 0.65
  - Survival Experimental (Se): 0.75
  - Hazard Ratio under Alternative Hypothesis (HR): 0.668
+ Sample Size
  - Number of Events: 258
  - Total Number of Subjects: 862
  - Number of Subjects (Arm Exp., Arm Contr.): (431,431))
```

# Example: Super n Analysis

```
EX11 <- plansu:                                  75,0.65),
0.5,c(0.025,0.(
+-----------------------------------------------------+
| Survival Superi                                     |
+-----------------------------------------------------+
.... ....
+ Survival Parame
  - Times (times)
  - Survival Cont
  - Survival Expe
  - Hazard Ratio                                (HR): 0.668

+ Sample Size
  - Number of Events: 258
  - Total Number of Subjects: 862
  - Number of Subjects (Arm Exp., Arm Contr.): (431,431)
```

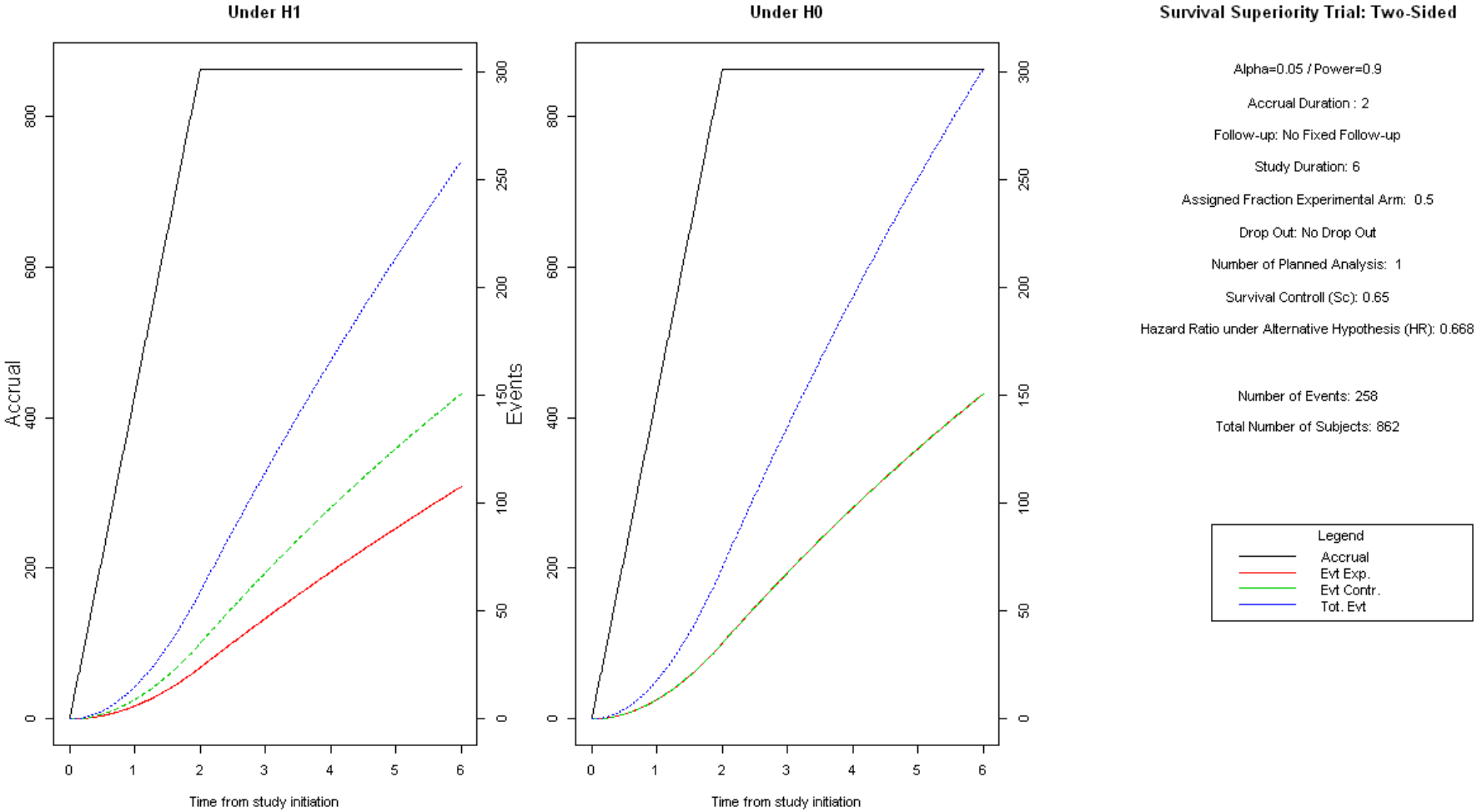
**Survival Superiority Trials: Two Sample Test - Logrank Test: G**

| Plan ID | Plan1 | | |
|---|---|---|---|
| **Test Parameters** | | | |
| 1-Sided or 2-Sided Test | 2-Sided | | |
| Significance Level (Alpha) | 0.05 | | |
| Power (1 - Beta) | 0.9 | | |
| Assigned Fraction (Treatment) | 0.5 | | |
| **Boundary Parameters** | | | |
| Planned Number of Looks | 1 | | |
| Spacing of Looks | | | |
| Hypothesis to be Rejected | | | |
| Boundary Family | | | |
| Boundary to Reject H0 | | | |
| Boundary to Reject H1 | | | |
| **Survival Parameters** | | | |
| -Log-hazard Ratio | 0.4037 | | |
| Number of Hazard Pieces | 1 | | |
| Number of Accrual Periods | 1 | | |
| Variance of -Log-hazard Ratio | Null | | |
| **Committed Accrual** | | | |
| Committed Accrual (Duration) | 2.0 | | |
| Committed Accrual (Subjects) | 861 | | |
| **Max. Duration and Events** | | | |
| Maximum Study Duration | 6.0 | | |
| Maximum Number of Events | 258 | | |
| **Expected Values under...** | H0 | H1 | H ½ |
| Expected Accrual (Subjects) | 861 | 861 | 861 |
| Expected Study Duration | 5.144 | 6.0 | 5.524 |
| Expected Number of Events | 258 | 258 | 258 |

Variable Follow-up Design
Maximum study duration 6 time units. Subjects are followed from randomization until dropout, failure or study termination.

# Example: Superiority Trial without interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,1,0,0)
```



# Example: Superiority Trial with interim Analysis

- Hypothesis :
  - 5 Analysis: 4 Interim Analysis + 1 Final
    - Lan deMets O'Brien Fleming / Efficacy H0
    - Equally spaced
  - No fixed follow-up
  - No drop out

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,
c(5,c(1,1),c(1:4)/5),0,0)
```

# Example: Superiority Trial with interim Analysis

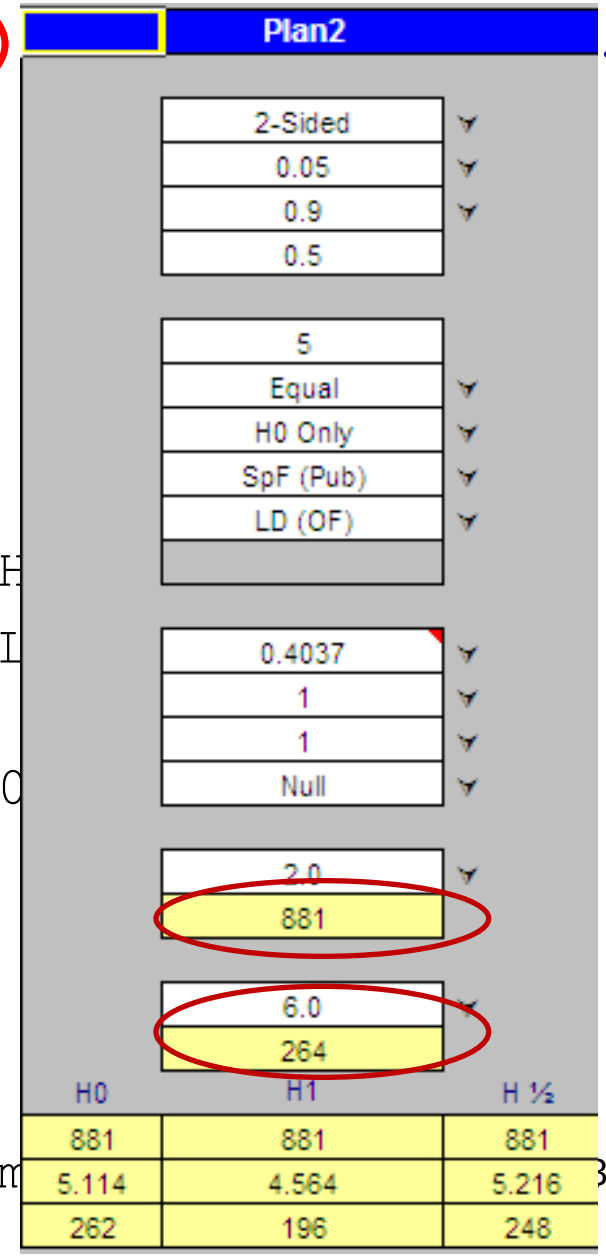
```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,
c(5,c(1,1),c(1:4)/5),0,0)
```

```
+ Analysis
  - Number of Planned Analysis: 5
  - Spacing of analysis: 0.2 0.4 0.6 0.8 1
  - Hypothesis to be rejected: Only H0
  - Boundary to reject (H0- / H0+): Lan deMets O'Brien
Fleming / Lan deMets O'Brien Fleming
  - Symmetric Boundary Alpha: Lower=0.025/ Upper=0.025
... ...
+ Sample Size
  - Number of Events: 264
  - Total Number of Subjects: 882
  - Number of Subjects (Arm Exp., Arm Contr.): (441,441)
```

# Example: Superiority Trial with interim Analysis

```
EX11 <- plansurvct.func(c(1,2)                                    5),
0.5,c(0.025,0.025),0.10,2,6,
c(5,c(1,1),c(1:4)/5),0,0)
```

```
+ Analysis
  - Number of Planned Analysis: 5
  - Spacing of analysis: 0.2 0.4 0.6
  - Hypothesis to be rejected: Only H
  - Boundary to reject (H0- / H0+): L
Fleming / Lan deMets O'Brien Fleming
  - Symmetric Boundary Alpha: Lower=0
... ...
+ Sample Size
  - Number of Events: 264
  - Total Number of Subjects: 882
  - Number of Subjects (Arm Exp., Arm                                3)
```



# Example: Superiority Trial with interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,
c(5,c(1,1),c(1:4)/5),0,0)
```

```
[1] "+ Boundaries"
  Information  Events pvalue reject H0 Boundary reject H0- Boundary reject H0+ Analysis Time Under H0 Analysis Time Under H1
1         0.2  52.756            0.000              -4.877               4.877                   1.71                   1.87
2         0.4 105.512            0.001              -3.357               3.357                   2.50                   2.80
3         0.6 158.269            0.007              -2.680               2.680                   3.31                   3.78
4         0.8 211.025            0.022              -2.290               2.290                   4.19                   4.84
5         1.0 263.781            0.042              -2.031               2.031                   5.14                   6.00
[1] "+-------------------------------------------------------------------+"
```

# Example: Superiority Trial with interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,
c(5,c(1,1),c(1:4)/5),0,0)
```

| | | P-value | Boundaries Reject | | Analysis Time | |
|---|---|---|---|---|---|---|
| Info. | evt | reject H0 | H0- | H0+ | H0 | H1 |
| 0.2 | 52 | <0.001 | -4.877 | 4.877 | 1.68 | 1.83 |
| 0.4 | 105 | 0.001 | -3.357 | 3.357 | 2.43 | 2.72 |
| 0.6 | 158 | 0.007 | -2.680 | 2.680 | 3.21 | 3.65 |
| 0.8 | 211 | 0.022 | -2.290 | 2.290 | 4.04 | 4.66 |
| 1 | 264 | 0.042 | -2.031 | 2.031 | 4.94 | 5.98 |

# Example: Superiority Trial with interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,
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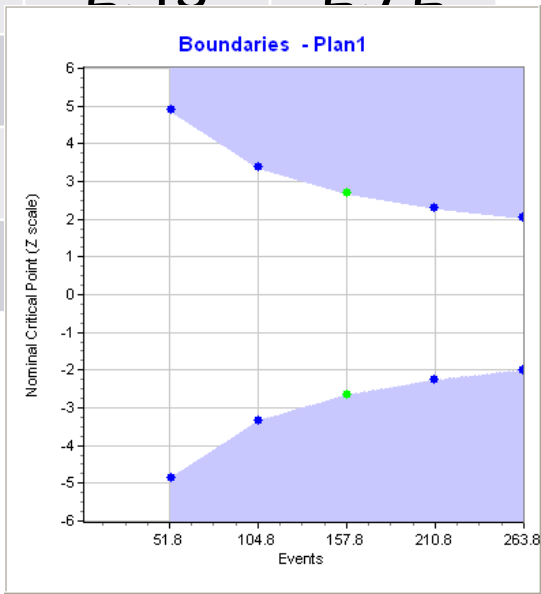
| | | P-value | Boundaries Reject | | Analysis Time | |
|---|---|---|---|---|---|---|
| Info. | evt | reject H0 | H0- | H0+ | H0 | H1 |
| 0.2 | 52 | <0.001 | -4.877 | 4.877 | 1.68 | 1.83 |
| ( | | | -3.357 | 3.357 | 2.43 | 2.72 |
| ( | | | -2.680 | 2.680 | | |
| ( | | | -2.290 | 2.290 | | |
| | | | -2.031 | 2.031 | | |

| Boundaries | |
|---|---|
| H0- | H0+ |
| -4.877 | 4.877 |
| -3.357 | 3.357 |
| -2.680 | 2.680 |
| -2.290 | 2.290 |
| -2.031 | 2.031 |



# Example: Superiority Trial with interim Analysis

```
EX11 <- plansurvct.func(c(1,2),c(1,5,0.75,0.65),
0.5,c(0.025,0.025),0.10,2,6,
c(5,c(1,1),c(1:4)/5),0,0)
```

| | | P-value | Boundaries Reject | | Analysis Time | |
|---|---|---|---|---|---|---|
| Info. | evt | reject H0 | H0- | H0+ | H0 | H1 |
| 0.2 | 52 | [illegible] | [illegible] | [illegible] | 1.68 | 1.83 |
| 0.4 | 105 | | | | 2.43 | 2.72 |
| 0.6 | 158 | | | | 3.21 | 3.65 |
| 0.8 | 211 | | | | 4.04 | 4.66 |
| 1 | 264 | | | | 4.94 | 5.98 |

| Under H0 | Under H1 |
|---|---|
| 1.673 | 1.829 |
| 2.431 | 2.716 |
| 3.210 | 3.656 |
| 4.045 | 4.666 |
| 4.945 | 6.000 |

# Other Options

- Interim Analysis
  - Superiority 2-sided: Interim analysis with asymetric boundaries
  - Superiority one sided / Non Inferiority: Interim analysis for efficacy and/or futility

- Possibility to graph
  - Duration study against the number of patients to be included
  - Sample size according to the hazard ratio
  - ...

# In summary

- Plansurvct.func is an add-function of gsdesign
- Possibility to design group sequential trials with time to event endpoint
- Results similar to those obtained using East
- Future works:
  - Variable accrual rate
  - different distribution function to modelling the occurrence of the event of interest

**Thank your for your attention!**