



臨床試験のデザインと解析用 R パッケージ【 rpact 】

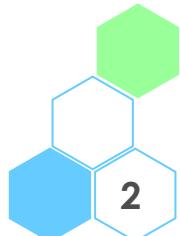
舟尾 暢男



パッケージ「*ract*」



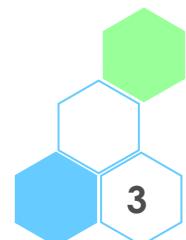
- Adaptive design の名著:Wassmer and Brannath (2016) で紹介された手法を実装
- 連続量、二値データ、生存時間データに関する検証的試験デザインのシミュレーションと解析手法を網羅
- GUI での操作も可能
<https://ract.shinyapps.io/public/>



充実の vignettes : <https://www.rpact.org/vignettes>



1. Defining group-sequential boundaries
2. Designing group-sequential trials with two groups and a continuous endpoint
3. Designing group-sequential trials with a binary endpoint
4. **Designing group-sequential trials with two groups and a survival endpoint** ← 生存関数の設定
5. Simulation-based design of group-sequential trials with a survival endpoint
6. **An example to illustrate boundary re-calculations during the trial** ← 計画例数からの変更時
7. Analysis of a group-sequential trial with a survival endpoint
8. **Defining accrual time and accrual intensity** ← 観察期間に関する詳細な設定
9. How to use R generics with rpact
10. How to create admirable plots with rpact
11. Comparing sample size and power calculation results for a group-sequential trial with a survival endpoint: rpact vs. gsDesign
12. Supplementing and enhancing rpact's graphical capabilities with ggplot2
13. Using the inverse normal combination test for analyzing a trial with continuous endpoint and potential sample size reassessment
14. Planning a trial with binary endpoints
15. Planning a survival trial
16. Simulation of a trial with a binary endpoint and unblinded sample size re-calculation
17. How to create summaries
18. How to create analysis result (one- and multi-arm) plots
19. How to create simulation result (one- and multi-arm) plots
20. Simulating multi-arm designs with a continuous endpoint
21. Analysis of a multi-arm design with a binary endpoint





- Fixed Design での例数設計
- Group Sequential Design での棄却限界値
- Group Sequential Design での例数設計
- その他





Fixed: 平均値の比較①

- 群間差=0.5、両群共通の標準偏差=2、 $\alpha = 0.025$ (片側)、 $1 - \beta$ (検出力)=80%
 - 1群あたり 252.1 例、2群合計 504.3 例(実際は整数や偶数等に丸める)
 - 非劣性試験の場合(例: $H_0: \text{difference} \leq \Delta = -1$)は、`thetaH0=-1` 等とする

```
> getSampleSizeMeans(thetaH0=0, alternative=0.5, stDev=2, alpha=0.025, beta=0.2, sided=1)
Design plan parameters and output for means:
```

Design parameters:

```
Significance level : 0.0250
Type II error rate : 0.2
Test : one-sided
```

User defined parameters:

```
Alternatives : 0.5
Standard deviation : 2
```

Default parameters:

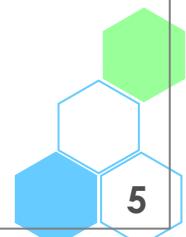
```
Normal approximation : FALSE
Mean ratio : FALSE
Theta H0 : 0
Treatment groups : 2
Planned allocation ratio : 1
```

Sample size and output:

```
Number of subjects fixed : 504.3
Number of subjects fixed (1) : 252.1
Number of subjects fixed (2) : 252.1
Critical values (effect scale) : 0.350
Local one-sided significance levels : 0.0250
```

Legend:

(i): values of treatment arm i





Fixed: 平均値の比較②

- 後の準備のため、先に変数 `design` に「デザインに関する設定」を格納した上で例数設計を行う
- 群間差 = 0.5、両群共通の標準偏差 = 2、 $\alpha = 0.025$ (片側)、 $1 - \beta$ (検出力) = 80%
 - 2 群合計 505 例(実際は偶数に丸めることも)

```
> design <- getDesignGroupSequential(kMax=1, alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeMeans(design, thetaH0=0, alternative=0.5, stDev=2)
> summary(designPlan)
```

Sample size calculation for a continuous endpoint

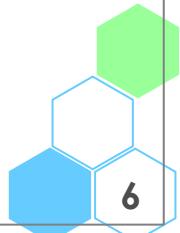
Fixed sample analysis.

The sample size was calculated for a two-sample t-test (one-sided),
alternative = 0.5, standard deviation = 2, allocation ratio = 1, and power 80%.

Stage	Fixed
Efficacy boundary (z-value scale)	1.960
<u>Number of subjects</u>	<u>505</u>
One-sided local significance level	0.0250
Efficacy boundary (t)	0.350

Legend:

(t): approximate treatment effect scale





Fixed:割合の比較①

- 被験群の割合=0.5、対照群の割合=0.4、 $\alpha = 0.025$ (片側)、 $1 - \beta$ (検出力)=80%
 - 1群あたり 387.3 例、2 群合計 774.7 例(実際は整数や偶数等に丸める)
 - 非劣性試験の場合(例: $H_0: \pi_1 - \pi_2 \leq \Delta = -0.1$)は、`thetaH0=-0.1` 等とする

```
> getSampleSizeRates(thetaH0=0, pi1=0.5, pi2=0.4, sided = 1, alpha = 0.025, beta = 0.2)
```

Design plan parameters and output for rates:

Design parameters:

Significance level	:	0.0250
Type II error rate	:	0.2
Test	:	one-sided

User defined parameters:

pi (1)	:	0.500
pi (2)	:	0.400

Default parameters:

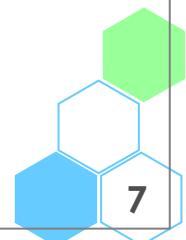
Normal approximation	:	TRUE
Risk ratio	:	FALSE
Theta H0	:	0
Treatment groups	:	2
Planned allocation ratio	:	1

Sample size and output:

Direction upper	:	TRUE
<u>Number of subjects fixed</u>	:	<u>774.7</u>
<u>Number of subjects fixed (1)</u>	:	<u>387.3</u>
<u>Number of subjects fixed (2)</u>	:	<u>387.3</u>
Critical values (effect scale)	:	0.0698
Local one-sided significance levels	:	0.0250

Legend:

(i): values of treatment arm i





Fixed: 割合の比較②

- 後の準備のため、先に変数 `design` に「デザインに関する設定」を格納した上で例数設計を行う
- 被験群の割合=0.5、対照群の割合=0.4、 $\alpha = 0.025$ (片側)、 $1 - \beta$ (検出力)=80%
 - 2 群合計 775 例(実際は偶数に丸めることも)

```
> design <- getDesignGroupSequential(kMax=1, alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeRates(design, thetaH0=0, pi1=0.5, pi2=0.4)
> summary(designPlan)

Sample size calculation for a binary endpoint
```

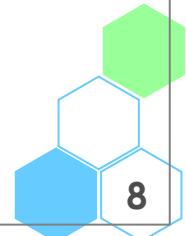
Fixed sample analysis.

The sample size was calculated for a two-sample test for rates (one-sided), treatment rate π (1) = 0.5, control rate π (2) = 0.4, allocation ratio = 1, and power 80%.

Stage	Fixed
Efficacy boundary (z-value scale)	1.960
Number of subjects	775
One-sided local significance level	0.0250
Efficacy boundary (t)	0.070

Legend:

(t): approximate treatment effect scale





Fixed: 生存時間の比較①

- 被験群のハザード=0.04462、対照群の割合=0.08615、登録期間=無し、観察期間=5(年)、両群とも5(年)あたりの脱落率=0%、 $\alpha=0.025$ (片側)、 $1-\beta$ (検出力)=80%、Freedman の方法
 - 1群あたり141.5例、2群合計283例(実際は偶数に丸めることも)
 - 非劣性試験の場合(例: $H_0 : \text{hazard ratio} \geq 1.2$)は、`thetaH0=1.2`等とする

```
> getSampleSizeSurvival(typeOfComputation="Freedman", # "Schoenfeld",
+   thetaH0=1, lambda1=0.04462, lambda2=0.08615, accrualTime=1e-8, followUpTime=5,
+   dropoutRate1=0, dropoutRate2=0, dropoutTime=5, alpha=0.025, beta=0.2, sided=1)
```

Design plan parameters and output for survival data:

Design parameters:

Significance level	: 0.0250
Type II error rate	: 0.2
Test	: one-sided

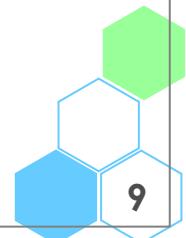
(中略)

Sample size and output:

Direction upper	: FALSE
pi (1)	: 0.415
pi (2)	: 0.644
median (1)	: 15.5
median (2)	: 8.0
Hazard ratio	: 0.518
Number of events	: 77.8
Calculate follow up time	: FALSE
<u>Number of subjects fixed</u>	: <u>283.0</u>
<u>Number of subjects fixed (1)</u>	: <u>141.5</u>
<u>Number of subjects fixed (2)</u>	: <u>141.5</u>
Analysis times	: 5.00
Study duration	: 5.00
Critical values (effect scale)	: 0.641
Local one-sided significance levels	: 0.0250

Legend:

(i): values of treatment arm i





Fixed: 生存時間の比較②

- 後の準備のため、先に変数 design に「デザインに関する設定」を格納した上で例数設計を行う
- 被験群のハザード=0.04462、対照群の割合=0.08615、登録期間=無し、観察期間=5(年)、両群とも 5 (年)あたりの脱落率=0%、 $\alpha = 0.025$ (片側)、 $1 - \beta$ (検出力)=80%、Freedman の方法
 - 2 群合計 284 例

```
> design <- getDesignGroupSequential(kMax=1, alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeSurvival(design, typeOfComputation="Freedman", # "Schoenfeld",
+   thetaH0=1, lambda1=0.04462, lambda2=0.08615, accrualTime=1e-8, followUpTime=5,
+   dropoutRate1=0, dropoutRate2=0, dropoutTime=5)
> summary(designPlan)
Sample size calculation for a survival endpoint

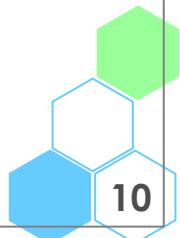
Fixed sample analysis.

The sample size was calculated for a two-sample logrank test (one-sided),
treatment lambda (1) = 0.045, control lambda (2) = 0.086, allocation ratio = 1, and power 80%.
```

Stage	Fixed
Efficacy boundary (z-value scale)	1.960
<u>Number of subjects</u>	<u>284</u>
Number of events	77.8
Analysis time	5.0
One-sided local significance level	0.0250
Efficacy boundary (t)	0.641

Legend:

(t): approximate treatment effect scale





Fixed: 生存時間の比較③

- 後の準備のため、先に変数 design に「デザインに関する設定」を格納した上で例数設計を行う
- 被験群のハザード=0.04462、対照群の割合=0.08615、[登録期間=2\(年\)](#)、観察期間=5(年)、両群とも5(年)あたりの脱落率=0%、 $\alpha=0.025$ (片側)、 $1-\beta$ (検出力)=80%、Freedman の方法
 - 2群合計 245 例(実際は偶数に丸めることも)

```
> design <- getDesignGroupSequential(kMax=1, alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeSurvival(design, typeOfComputation="Freedman", # "Schoenfeld",
+   thetaH0=1, lambda1=0.04462, lambda2=0.08615, accrualTime=2, followUpTime=5,
+   dropoutRate1=0, dropoutRate2=0, dropoutTime=5)
> summary(designPlan)
Sample size calculation for a survival endpoint

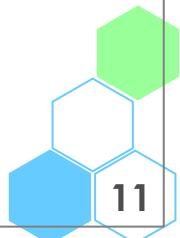
Fixed sample analysis.

The sample size was calculated for a two-sample logrank test (one-sided),
treatment lambda (1) = 0.045, control lambda (2) = 0.086, allocation ratio = 1, and power 80%.
```

Stage	Fixed
Efficacy boundary (z-value scale)	1.960
<u>Number of subjects</u>	<u>245</u>
Number of events	77.8
Analysis time	7.0
One-sided local significance level	0.0250
Efficacy boundary (t)	0.641

Legend:

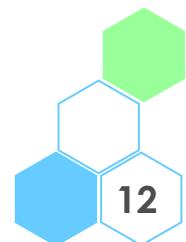
(t): approximate treatment effect scale





メニュー

- Fixed Design での例数設計
- Group Sequential Design での棄却限界値
- Group Sequential Design での例数設計
- その他



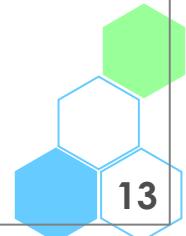


Boundary: 有効中止のみのデザイン

- 情報分数 $t=0.5, 1$ で解析、 $\alpha = 0.025$ (片側)、 $1-\beta$ (検出力) = 80%
 - 前者: O'Brien & Fleming の方法("asOF" で O'Brien & Fleming 型の α 消費関数に変更)
 - 後者: Pocock の方法("asP" で Pocock 型の α 消費関数に変更)

```
> design <- getDesignGroupSequential(typeOfDesign="OF", # "asOF"
+   informationRates=c(0.5,1), alpha=0.025, beta=0.2, sided=1)
> summary(design)
Sequential analysis with a maximum of 2 looks (group sequential design)
Stage          1      2
Information rate    50% 100%
Efficacy boundary (z-value scale) 2.797 1.977
Cumulative alpha spent 0.0026 0.0250
One-sided local significance level 0.0026 0.0240

> design <- getDesignGroupSequential(typeOfDesign="P", # "asP"
+   informationRates=c(0.5,1), alpha=0.025, beta=0.2, sided=1)
> summary(design)
Sequential analysis with a maximum of 2 looks (group sequential design)
Stage          1      2
Information rate    50% 100%
Efficacy boundary (z-value scale) 2.178 2.178
Cumulative alpha spent 0.0147 0.0250
One-sided local significance level 0.0147 0.0147
```





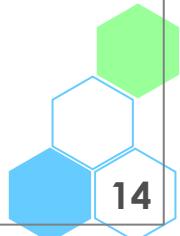
Boundary: 無効中止のみのデザイン

- 情報分数 $t=0.25, 0.5, 0.75, 1$ で解析、 $\alpha=0.025$ (片側)、 $1-\beta$ (検出力)=80%
 - 最終解析以外での有効中止:なし(引数 typeOfDesign、userAlphaSpending で指定)
 - 中間解析時の無効中止:O'Brien & Fleming 型の β 消費関数

```
> design <- getDesignGroupSequential(typeOfDesign="asUser",
userAlphaSpending=c(0,0,0,0.025),
+   informationRates=(1:4)/4, alpha=0.025, beta=0.2, sided=1,
+   typeBetaSpending="bsOF", bindingFutility=FALSE)
> summary(design)

Sequential analysis with a maximum of 4 looks (group sequential design)

Stage          1      2      3      4
Information rate 25%    50%    75%   100%
Efficacy boundary (z-value scale) Inf    8.000  8.000  1.960
Futility boundary (z-value scale) -0.829  0.598  1.387
Cumulative alpha spent <0.0001      0      0    0.0250
One-sided local significance level     0 <0.0001 <0.0001  0.0250
```



Boundary: 有効&無効中止のデザイン



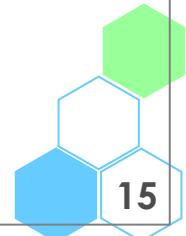
- 情報分数 $t=0.5, 1$ で解析、 $\alpha = 0.025$ (片側)、 $1-\beta$ (検出力) = 80%
 - 前者: 有効中止は O'Brien&Fleming 型の α 消費関数、中間解析の z 値が負なら無効中止
 - 後者: 有効中止は O'Brien&Fleming 型の α 消費関数、無効中止は Pocock 型の β 消費関数

```
> design <- getDesignGroupSequential(typeOfDesign="asOF", informationRates=c(0.5,1),
+   alpha=0.025, beta=0.2, sided=1, futilityBounds=c(0), bindingFutility=FALSE)
> summary(design)

Sequential analysis with a maximum of 2 looks (group sequential design)
Stage           1      2
Information rate      50%    100%
Efficacy boundary (z-value scale) 2.963  1.969
Futility boundary (z-value scale)      0
Cumulative alpha spent      0.0015  0.0250
One-sided local significance level 0.0015  0.0245

> design <- getDesignGroupSequential(typeOfDesign="asOF", informationRates=c(0.5,1),
+   alpha=0.025, beta=0.2, sided=1, typeBetaSpending = "bsP")
> summary(design)

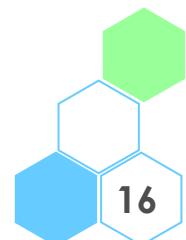
Sequential analysis with a maximum of 2 looks (group sequential design)
Stage           1      2
Information rate      50%    100%
Efficacy boundary (z-value scale) 2.963  1.969
Futility boundary (z-value scale)  0.985
Cumulative alpha spent      0.0015  0.0250
One-sided local significance level 0.0015  0.0245
```





メニュー

- Fixed Design での例数設計
- Group Sequential Design での棄却限界値
- Group Sequential Design での例数設計
- その他





GSD: 平均値の比較

- 群間差=0.5、両群共通の標準偏差=2、 $\alpha = 0.025$ (片側)、 $1-\beta$ (検出力)=80%
- 中間解析 1 回(情報分数 $t=0.5$ にて)、O'Brien & Fleming 型の α 消費関数
 - 2 群合計 507 例(実際は偶数に丸めることも)

```
> design <- getDesignGroupSequential(typeOfDesign="asOF",
+   informationRates=c(0.5,1), alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeMeans(design, thetaH0=0, alternative=0.5, stDev=2)
> summary(designPlan)
```

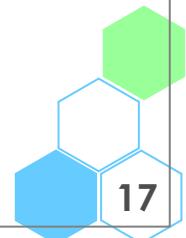
Sample size calculation for a continuous endpoint

Sequential analysis with a maximum of 2 looks (group sequential design).
The sample size was calculated for a two-sample t-test (one-sided),
alternative = 0.5, standard deviation = 2, allocation ratio = 1, and power 80%.

Stage	1	2
Information rate	50%	100%
<u>Efficacy boundary (z-value scale)</u>	2.963	1.969
<u>Number of subjects</u>	254	507
Cumulative alpha spent	0.0015	0.0250
<u>Cumulative power</u>	0.1641	0.8000
One-sided local significance level	0.0015	0.0245
Efficacy boundary (t)	0.752	0.351
Exit probability for efficacy (under H0)	0.0015	
Exit probability for efficacy (under H1)	0.1641	

Legend:

(t): approximate treatment effect scale





GSD:割合の比較

- 被験群の割合=0.5、対照群の割合=0.4、 $\alpha = 0.025$ (片側)、 $1 - \beta$ (検出力)=80%
- 中間解析 1 回(情報分数 $t=0.5$ にて)、O'Brien & Fleming 型の α 消費関数
 - 2 群合計 778 例

```
> design <- getDesignGroupSequential(typeOfDesign="asOF",
+   informationRates=c(0.5,1), alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeRates(design, thetaH0=0, pi1=0.5, pi2=0.4)
> summary(designPlan)
```

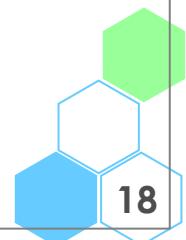
Sample size calculation for a binary endpoint

Sequential analysis with a maximum of 2 looks (group sequential design).
The sample size was calculated for a two-sample test for rates (one-sided),
treatment rate pi (1) = 0.5, control rate pi (2) = 0.4, allocation ratio = 1, and power 80%.

Stage	1	2
Information rate	50%	100%
<u>Efficacy boundary (z-value scale)</u>	2.963	1.969
<u>Number of subjects</u>	389	778
Cumulative alpha spent	0.0015	0.0250
<u>Cumulative power</u>	0.1641	0.8000
One-sided local significance level	0.0015	0.0245
Efficacy boundary (t)	0.150	0.070
Exit probability for efficacy (under H0)	0.0015	
Exit probability for efficacy (under H1)	0.1641	

Legend:

(t): approximate treatment effect scale



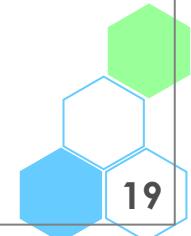


GSD: 生存時間の比較

- 被験群のハザード=0.04462、対照群の割合=0.08615、登録期間=2(年)、観察期間=5(年)、両群とも5(年)あたりの脱落率=0%、 $\alpha=0.025$ (片側)、 $1-\beta$ (検出力)=80%、Freedman の方法
- 中間解析1回(情報分数 $t=0.5$ にて)、O'Brien & Fleming 型の α 消費関数
 - 2群合計 246 例

```
> design <- getDesignGroupSequential(typeOfDesign="asOF",
+   informationRates=c(0.5,1), alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeSurvival(design, typeOfComputation="Freedman", # "Schoenfeld",
+   thetaH0=1, lambda1=0.04462, lambda2=0.08615, accrualTime=2, followUpTime=5,
+   dropoutRate1=0, dropoutRate2=0, dropoutTime=5)
> summary(designPlan)

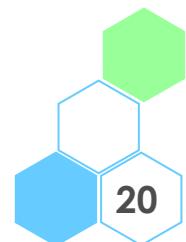
Sample size calculation for a survival endpoint
Sequential analysis with a maximum of 2 looks (group sequential design).
The sample size was calculated for a two-sample logrank test (one-sided),
treatment lambda (1) = 0.045, control lambda (2) = 0.086, allocation ratio = 1, and power 80%.
Stage          1      2
Information rate    50%   100%
Efficacy boundary (z-value scale) 2.963  1.969
Number of subjects        246   246
Cumulative number of events 39.1   78.1
Analysis time       3.7    7.0
Cumulative alpha spent 0.0015 0.0250
Cumulative power        0.1641 0.8000
One-sided local significance level 0.0015 0.0245
Efficacy boundary (t)           0.387  0.641
Exit probability for efficacy (under H0) 0.0015
Exit probability for efficacy (under H1) 0.1641
```





メニュー

- Fixed Design での例数設計
- Group Sequential Design での棄却限界値
- Group Sequential Design での例数設計
- その他



Simulation-based Designing



<https://cran.r-project.org/web/packages/rpact/rpact.pdf>

- シミュレーションベースでの試験デザインの検討を行うことも出来る
 - 1～2 群、連続応答: getSimulationMeans()
 - 1～2 群、二値応答: getSimulationRates()
 - 1～2 群、生存時間: getSimulationSurvival()
 - 多群、連続応答: getSimulationMultiArmMeans()
 - 多群、二値応答: getSimulationMultiArmRates()
 - 多群、生存時間: getSimulationMultiArmSurvival()
- 解析例は以下を参照
 - 上記関数のヘルプの例
 - Simulating multi-arm designs with a continuous endpoint
https://vignettes.rpact.org/html/rpact_multi_arm_simulation_means_examples.html
 - Simulation of a trial with a binary endpoint and unblinded sample size re-calculation
https://vignettes.rpact.org/html/rpact_sample_size_reassessment_examples.html
 - Simulation-based design of group-sequential trials with a survival endpoint
https://vignettes.rpact.org/html/rpact_survival_simulation_examples.html



試験終了後の解析



<https://cran.r-project.org/web/packages/rpact/rpact.pdf>

- `getDesignXXX()` + `getDataset()` + `getAnalysisResults()` にて条件付き検出力、統計量、Repeated CIs、final stage p-values、median unbiased point estimates、final CI 等を計算
 - 参考: `getConditionalPower()`、`getFinalConfidenceInterval()`、`getFinalPValue()`、`getRepeatedConfidenceIntervals()`、`getRepeatedPValues()`
- 解析例は以下を参照
 - `getAnalysisResults()` のヘルプの例
 - Using the inverse normal combination test for analysing a trial with continuous endpoint and potential sample size reassessment
https://vignettes.rpact.org/html/rpact_continuous_analysis_example.html
 - Analysis of a multi-arm design with a binary endpoint
https://vignettes.rpact.org/html/rpact_multi_arm_analysis_rates_examples.html
 - Analysis of a group-sequential trial with a survival endpoint
https://vignettes.rpact.org/html/rpact_analysis_examples.html





例：例数再算定を伴う GSD + 平均値の比較

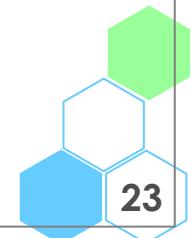
- 群間差=0.5、両群共通の標準偏差=2、 $\alpha = 0.025$ (片側)、 $1-\beta$ (検出力)=80%
- 中間解析 1 回(情報分数 $t=0.5$)、O'Brien & Fleming 型消費関数、最終解析は Inverse Normal 法
 - 計画例数は stage 1 が 256、合計 511 例

```
> design <- getDesignInverseNormal(typeOfDesign="asOF", futilityBounds=c(0),
+   informationRates=c(0.5,1), alpha=0.025, beta=0.2, sided=1)
> # print(design)
> # getDesignCharacteristics(design)
> designPlan <- getSampleSizeMeans(design, thetaH0=0, alternative=0.5, stDev=2)
> summary(designPlan)

Sample size calculation for a continuous endpoint
Sequential analysis with a maximum of 2 looks (inverse normal design).
The sample size was calculated for a two-sample t-test (one-sided),
alternative = 0.5, standard deviation = 2, allocation ratio = 1, and power 80%.

```

Stage	1	2
Information rate	50%	100%
Efficacy boundary (z-value scale)	2.963	1.969
Futility boundary (z-value scale)	0	
Number of subjects	256	511
Cumulative alpha spent	0.0015	0.0250
Cumulative power	0.1660	0.8000
One-sided local significance level	0.0015	0.0245
Efficacy boundary (t)	0.749	0.349
Futility boundary (t)	0	
Overall exit probability (under H0)	0.5015	
Overall exit probability (under H1)	0.1892	
Exit probability for efficacy (under H0)	0.0015	
Exit probability for efficacy (under H1)	0.1660	
Exit probability for futility (under H0)	0.5000	
Exit probability for futility (under H1)	0.0232	

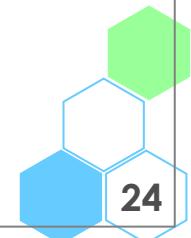




例：例数再算定を伴う GSD + 平均値の比較

- Stage 1 の結果(被験群と対照群の順)
 - 平均 = 0.3 と 0.0、標準偏差 = 2.5 と 2.2、例数 = 130 と 126
 - 中間解析の結果は「継続」、条件付き検出力は 22.67%

```
> MyData1 <- getDataset(  
+   means1  = c(0.3), means2  = c(0.0),  
+   stDevs1 = c(2.5), stDevs2 = c(2.2),  
+   n1      = c(130), n2      = c(126))  
> ( results <- getAnalysisResults(design=design, dataInput=MyData1, nPlanned=256, stage=1) )  
Analysis results (inverse normal design):  
  Stages          : 1, 2  
  Information rates    : 0.500, 1.000  
  Critical values       : 2.963, 1.969  
  Futility bounds (non-binding) : 0.000  
  Cumulative alpha spending : 0.001525, 0.025000  
  Stage levels          : 0.001525, 0.024500  
  Effect sizes           : 0.3  
  Test statistics         : 1.018, NA  
  p-values                : 0.1548, NA  
  Combination test statistics : 1.016, NA  
  Actions             : continue, NA  
  Theta H0              : 0  
  Cond. rejection probability : 0.03853, NA  
  Planned sample size     : NA, 256  
  Planned allocation ratio : 1  
  Assumed effect          : 0.3  
  Assumed standard deviation : 2.357  
  Conditional power        : NA, 0.2267  
  RCIs (lower)           : -0.5815, NA  
  RCIs (upper)            : 1.181, NA  
  Repeated p-values       : 0.3144, NA  
  Final stage             : NA  
  Final p-value           : NA, NA  
  Final CIs (lower)       : NA, NA  
  Final CIs (upper)       : NA, NA  
  Median unbiased estimate : NA, NA
```





例：例数再算定を伴う GSD + 平均値の比較

- Stage 1 の結果より例数再算定(被験群と対照群の順)
 - 元々の想定値(群間差=0.5、両群共通の標準偏差=2)より、stage 2 の例数を 436 例(2群合計)とすることで条件付き検出力が 80% を超える

```
> stageResults <- getStageResults(design=design, dataInput=MyData1)

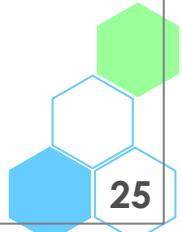
> rpact::::getConditionalPowerMeans(design=design, stageResults=stageResults,
+   nPlanned=436, thetaH1=0.5, assumedStDev=2)
```

\$nPlanned

```
[1] NA 436
```

\$conditionalPower

```
[1] NA 0.8001298
```

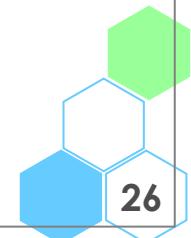




例：例数再算定を伴う GSD + 平均値の比較

- Stage 1 + 2 の結果(被験群と対照群の順)
 - 最終解析の結果は「棄却(成功)」
 - 統計量、Repeated CIs、final stage p-values、median unbiased estimates、final CI 等が計算

```
> MyData2 <- getDataset(  
+   means1 = c(0.3, 0.5), means2 = c(0.0, 0.1),  
+   stDevs1 = c(2.5, 2.4), stDevs2 = c(2.2, 2.3),  
+   n1      = c(130, 220), n2      = c(126, 216))  
> ( results <- getAnalysisResults(design=design, dataInput=MyData2) )  
Analysis results (inverse normal design):  
  Stages : 1, 2  
  Information rates : 0.500, 1.000  
  Critical values : 2.963, 1.969  
  Futility bounds (non-binding) : 0.000  
  Cumulative alpha spending : 0.001525, 0.025000  
  Stage levels : 0.001525, 0.024500  
  Effect sizes : 0.3000, 0.3626  
  Test statistics : 1.018, 1.776  
  p-values : 0.1548, 0.0382  
  Combination test statistics : 1.016, 1.971  
  Actions : continue, reject  
  Theta H0 : 0  
  Cond. rejection probability : 0.03853, NA  
  Planned sample size : NA, NA  
  Planned allocation ratio : 1  
  Assumed effect : 0.3626  
  Assumed standard deviation : 2.351  
  Conditional power : NA, NA  
  RCIs (lower) : -0.5814864, 0.0005159  
  RCIs (upper) : 1.1815, 0.7129  
  Repeated p-values : 0.31440, 0.02483  
  Final stage : 2  
  Final p-value : NA, 0.02484  
  Final CIs (lower) : NA, 0.0005016  
  Final CIs (upper) : NA, 0.7088  
  Median unbiased estimate : NA, 0.3551
```





おまけ: BE 試験の場合

- BE 試験の解析と例数設計

http://nfunao.web.fc2.com/files/be_study.pdf

- スライド中のプログラム:http://nfunao.web.fc2.com/files/be_study.zip

- 後発医薬品の生物学的同等性試験ガイドライン(令和 2 年 3 月 19 日改正)での要件に従った試験デザインの検討例

- 2 劑 2 期クロスオーバーデザインでの解析方法
- 各種試験デザインでの例数設計

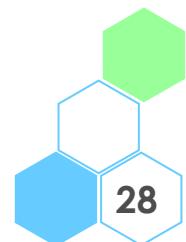
- Fixed Design
- Group Sequential Design
- Adaptive Design





メニュー

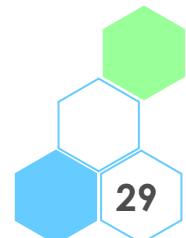
- Fixed Design での例数設計
- Group Sequential Design での棄却限界値
- Group Sequential Design での例数設計
- その他

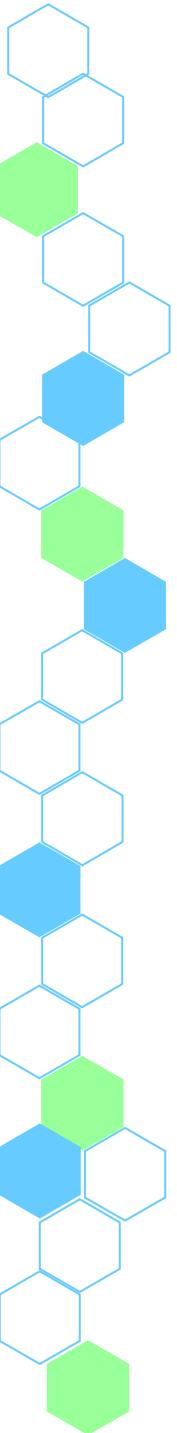




参考文献

- Gernot Wassmer and Werner Brannath (2016) "Group Sequential and Confirmatory Adaptive Designs in Clinical Trials", Springer
- rpact – R Programming for Adaptive Clinical Trials
<https://www.rpact.com/>
<https://www.rpact.org/vignettes>
- CRAN – rpact
<https://cran.r-project.org/web/packages/rpact/rpact.pdf>
https://cran.r-project.org/web/packages/rpact/vignettes/rpact_getting_started.html
- Graphical user interface for rpact package
<https://rpact.shinyapps.io/public/>
- 大橋 靖雄 他著(2016)「生存時間解析 応用編」東京大学出版会





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