Novel approaches in adaptive designs and α adjustment, e.g., with futility criteria and for parallel design studies

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Simulation-based (2×2×2 crossover)

No futility criteria, unlimited stage 2 sample size

Reference	Type	Method	GMR	Power (%)	*CV* (%)	α_{adj}	TIE_{max}
Potvin *et al.* [3]	1	B	0.95	80	10 – 100	0.0294	0.0489
	2	C					0.0512*
Montague *et al.* [4]	2	D	0.90			0.0280	0.0517*
Fuglsang [5]	1	B	0.95	90	10 – 80	0.0284	0.0497
	2	C/D				0.0274	0.0501
	2	C/D	0.90			0.0269	0.0503

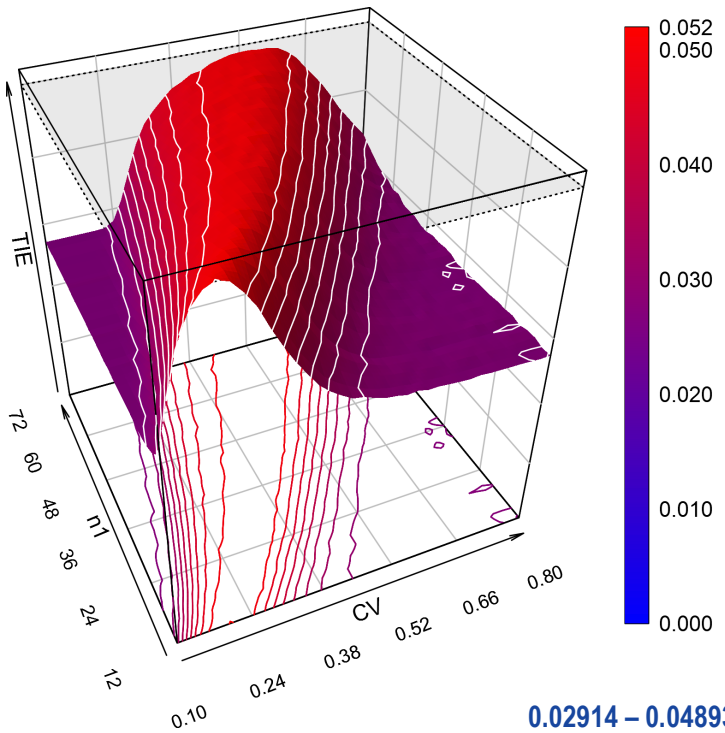
Futility criteria on CI, N_{max} 42 (low *CV*), 180 (high *CV*)

Reference	Type	Method	GMR	Power (%)	*CV* (%)	Futility region	α_{adj1}	α_{adj2}	TIE_{max}
Xu *et al.* [11]	1	E	0.95	80	10 – 30	0.9374 – 1.0667	0.0249	0.0363	0.0490
	2	F				0.9492 – 1.0535	0.0248	0.0364	0.0496
	1	E			30 – 55	0.9305 – 1.0747	0.0254	0.0357	0.0453
	2	F				0.9350 – 1.0695	0.0259	0.0349	0.0455

Operating Characteristics (Type 1 TSD [3])

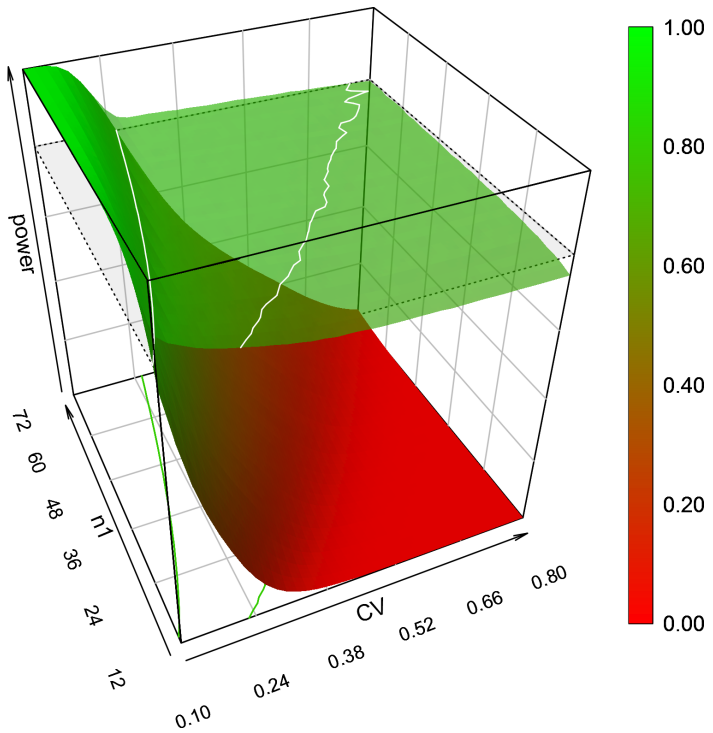
GMR 0.95, power 80%, α_{adj} 0.0294 (Potvin *et al.* 'Method B')

Type I Error



0.02914 – 0.04893

Power



Exact (2×2×2 crossover)

Repeated Confidence Intervals / Inverse Normal Method [15–18] **adapted for BE** [19–21]; **aka »Maurer's method«** [21]

- **Controls the Type I Error in the strict sense**
  - **Analytically proven**
  - **Confirmed in simulations**
- **Two approaches**
  - **Standard Combination Method**
  - **Maximum Combination Test (recommended** [20,21])
- **Weights of the stages have to be pre-specified**
  - **The adjusted α depends on the weights**
    - **The more weights differ, the more adjustment**
    - **Robust against misspecification**
    - **The same adjusted α is used in both stages**
  - **Simulations can be performed to find suitable weights**

Exact (2×2×2 crossover)

»Maurer's method« [21]

- My recommendations
  - Stage 1 sample size
    - 80% of fixed sample design for assumed GMR and *CV*
      - » Reasonably high probability to stop already in stage 1 for BE
      - » Overall power higher than fixed sample design
  - If *CV* expected to be not more than 75% larger than assumed
    - Standard Combination Method more powerful, requires less adjustment [22]
- Sample size re-estimation
  - A fixed GMR is used by default
  - Can be fully adaptive, i.e., based on the GMR of stage 1
- Minimum and maximum stage 2 sample sizes can be pre-specified
  - At least four subjects in two sequences are required in stage 2
  - Too small stage 2 negatively affects power

Exact (2×2×2 crossover)

»Maurer's method« [21]

- Optional futility criteria for stopping in the interim
  - GMR outside specified limits (default 0.80 – 1.25)
  - 90% confidence interval of the GMR entirely outside specified limits (default 0.95 – 0.95^{-1})
  - Maximum total sample size (default $4 \times n_1$)
- Futility criteria
  - Combinations are possible
  - Reduce the Type I Error
  - Negatively affect power
    - Fairly robust on GMR or CI
    - Very sensitive on N_{max}
  - Simulations highly recommended

Operating Characteristics (Exact [21])

Fixed GMR 0.95 (*CV* 0.1–0.8, n_1 12–72)

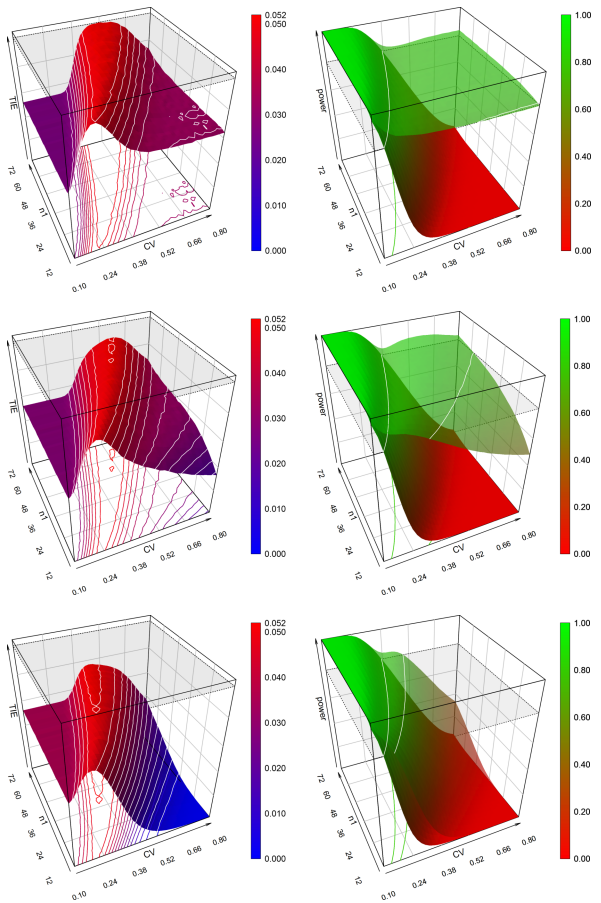
- No futility
- Type I Error 0.02598 – 0.04995

Adaptive GMR (*CV* 0.1–0.8, n_1 12–72)

- Futility on CI (outside 0.95 – 0.95^{-1})
- Type I Error 0.01678 – 0.04523

Adaptive GMR (*CV* 0.1–0.8, n_1 12–72)

- Futility on CI (outside 0.95 – 0.95^{-1})
- Futility on N_{max} ($> 4 \times n_1$)
- Type I Error 0.00006 – 0.03838



Exact (2×2×2 crossover)

»Maurer's method« [21]

- Contrary to simulation-based methods, data are not pooled
  - Stages are evaluated separately and assessed by (repeated) confidence intervals
    - ANOVA (EMA and most other juridictions)
    - Mixed-effects model (FDA, Health Canada, China's CDE)
    - Additional factors, e.g., for multi-group or multi-site studies can be incorporated in the model
  - Required in the interim analysis by Power2Stage [35]
    - GMR_1, CV_1, n_1, assumed GMR for sample size re-estimation, target power
    - If additional factors in the model: df_1, SEM_1
  - Required in the final analysis by Power2Stage [35]
    - GMR_1, CV_1, n_1
    - GMR_2, CV_2, n_2
    - If additional factors in the model: df_1, SEM_1, df_2, SEM_2

Simulation-based (parallel design [14])

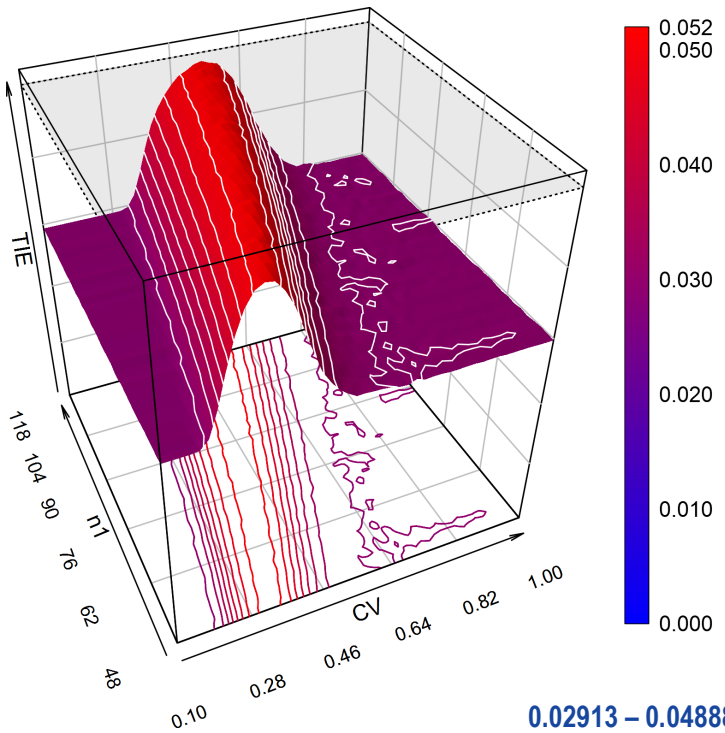
Two methods implemented in Power2Stage [35]

- ANOVA
  - Incorporates a term for stage in the final analysis
    - In line with the EMA's Q&A-document [28]
  - Assumes equal variances
    - Liberal and hence, not recommended
- Welch-Satterthwaite test
  - Approximates degrees of freedom for unequal group sizes and variances
    - No stage term possible; contradicts the EMA's Q&A-document [28]
    - In line with the FDA's guidance [33]
    - Highly recommended
- Modifications (simulations recommended)
  - Fully adaptive, i.e., based on the GMR observed in stage 1
  - Futility criterion on N_{max}

Operating Characteristics (Type 1 TSD [14])

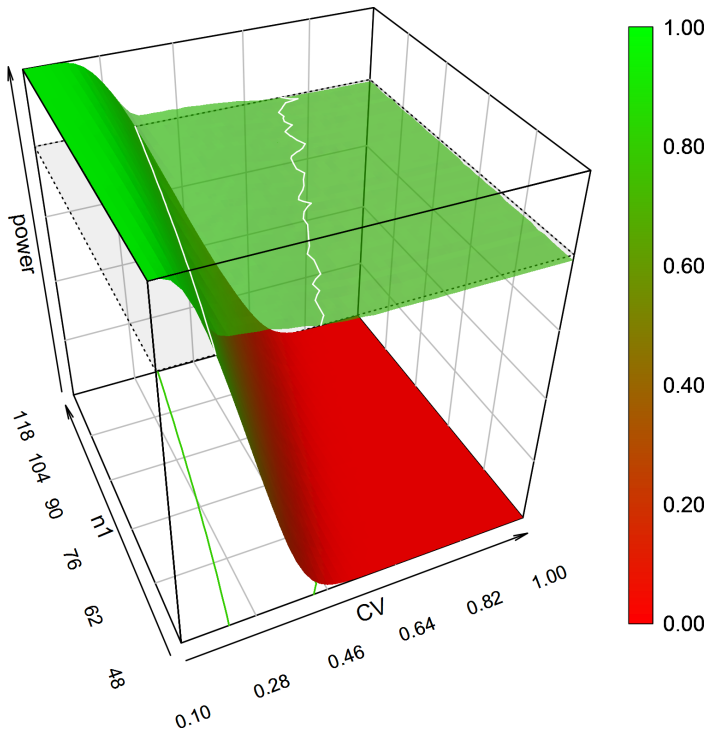
GMR 0.95, power 80%, α_{adj} 0.0294, Welch-Satterthwaite test

Type I Error



0.02913 – 0.04888

Power



State of Affairs

Simulation-based methods for 2×2×2 crossovers [3–13]

- **Ambiguous description in the EMA's guideline, regrettably incurred in other jurisdictions**
  - **Resulted in – unsubstantiated – deficiency letters**
  - **Wariness in the industry about application of adaptive designs**

    There are actually more articles describing the theoretical and statistical base for the application of the two-stage design than there are reported studies. [26]
  - **Type 2 TSD recommended by the FDA and Health Canada** [23,32]

Exact method for 2×2×2 crossovers [21] preferable

- **Strict Type I Error control**
- **Flexible (fully adaptive, futility criteria)**

Simulation-based method for parallel designs [14]

- **At the time being the only available**

Outlook

Expand the exact method for 2×2×2 crossovers

- If a PK metric in the first stage is highly variable, perform the second stage in a replicate design intended for reference-scaling
  - Scaling based on CV_{wR} in the second stage

Development of an exact method for parallel designs

- Not trivial because unequal sample sizes and variances have to be taken into account

Simulation-based methods for RSABE/ABEL

- Practically impossible
  - Stable sample size estimation requires 10^5 simulations taking conditions of the regulatory frameworks into account
  - 10^6 simulations to demonstrate control of the Type I Error
  - With a reasonable narrow grid of n_1 / CV-combinations estimated runtime ≈50 years 24 / 7 on a current workstation

Novel approaches in adaptive designs and α adjustment, e.g., with futility criteria and for parallel design studies

Thank You!

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Simulation-based sequential Two-Stage Designs

- **2×2×2 crossover design**

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- **Parallel design**

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Adaptive designs

- **Conditional power, repeated confidence intervals**

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- **2×2×2 crossover design**

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Packages for the open-source software R https://www.r-project.org/

- **Simulation-based (2×2×2 crossover** [3–12] **and parallel design** [14]**),**
  Exact (2×2×2 crossover design [21]**)**

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- **Simulation-based (2×2×2 crossover design** [13]**)**

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Maximum empiric Type I Error (10^6 simulations under the Null)

```
library(Power2Stage)
# Simulation-based (2×2×2 crossover, no futility); References 3, 4, 5
# Exact Power estimation by Owen's Q-function
method <- c("B", "C", "C", "B", "C", "C")
CV.loc <- c(0.24, 0.22, 0.20, 0.22, 0.10, 0.18)
n1.loc <- c(12, 12, 12, 12, 16, 12)
a      <- data.frame(Ref    = c(rep("[3]", 2), "[4]", rep("[5]", 3)),
                     Type   = c(1, 2, 2, 1, 2, 2),
                     Method = c("B ", "C ", "D ", "B ", "C/D", "C/D"),
                     GMR    = c(0.95, 0.95, 0.90, 0.95, 0.95, 0.90),
                     Power  = c(rep(80, 3), rep(90, 3)),
                     CV     = c(rep("10 - 100%", 3), rep("10  - 80%", 3)),
                     adj    = c(rep(0.0294, 2), 0.028, 0.0284, 0.0274, 0.0269))
for (i in 1:6) {
  a$TIE.max[i] <- power.tsd(method = method[i], alpha0 = 0.05, alpha = rep(a$adj[i], 2),
                            CV = CV.loc[i], n1 = n1.loc[i], GMR = a$GMR[i],
                            targetpower = a$Power[i] / 100, pmethod = "exact",
                            theta0 = 1.25)$pBE
}
a$Power   <- sprintf("%.0f%%", a$Power)
a$TIE.max <- round(a$TIE.max, 4)
print(a, row.names = FALSE)
```

Maximum empiric Type I Error (10^6 simulations under the Null)

```
library(Power2Stage)
# Simulation-based (2×2×2 crossover, futility criteria); Reference 11
# Exact Power estimation by Owen's Q-function
method  <- rep(c("B", "C"), 2)
CV.loc  <- c(rep(0.3, 2), rep(0.55, 2))
n1.loc  <- c(rep(18, 2), rep(48, 2))
fClower <- c(0.9374, 0.9305, 0.9492, 0.9350) # different futilities on CI
max.n   <- c(rep(42, 2), rep(180, 2))        # different futilities on Nmax
b       <- data.frame(Ref    = rep("[11]", 4), Type = c(1, 2, 1, 2),
                      Method = c("E  ", "F  ", "E  ", "F  "), GMR = rep(0.95, 4),
                      Power  = rep(80, 4), CV = c(rep("10 – 30%", 2), rep("30 – 55%", 2)),
                      adj1   = c(0.0249, 0.0248, 0.0254, 0.0259), # different alphas
                      adj2   = c(0.0363, 0.0364, 0.0357, 0.0349)) # in the stages
for (i in 1:4) {
  b$TIE.max[i] <- power.tsd.fC(method = method[i], alpha0 = 0.05,
                               alpha = c(b$adj1[i], b$adj2[i]), CV = CV.loc[i], n1 = n1.loc[i],
                               GMR = b$GMR[i], targetpower = b$Power[i] / 100,
                               max.n = max.n[i], fCrit = "CI", fClower = fClower[i],
                               pmethod = "exact", theta0 = 1.25)$pBE
}
b$Power   <- sprintf("%.0f%%", b$Power)
b$TIE.max <- round(b$TIE.max, 4)
print(b, row.names = FALSE)
```

Maximum empiric Type I Error (10^6 simulations under the Null)

```
library(Power2Stage)
# Exact (2×2×2 crossover): Maximum Combination Test, no futility criteria; Reference 21
# Exact Power estimation by Owen's Q-function
x       <- power.tsd.in(CV = 0.46, n1 = 62, weight = c(0.5, 0.25),
                        max.comb.test = TRUE, ssr.conditional = "error_power",
                        fCrit = "No", GMR = 0.95, targetpower = 0.8,
                        pmethod = "exact", theta0 = 1.25)
c       <- data.frame(Ref = "[21]", Method = "Maurer's", GMR = 0.95, Power = 80,
                      CV = "10 - 80%", adj = round(x$alpha[1], 5), TIE.max = x$pBE)
c$Power <- sprintf("%.0f%%", c$Power)
print(c, row.names = FALSE)

# Exact (2×2×2 crossover): Standard Combination Method, no futility criteria; Reference 21
# Exact Power estimation by Owen's Q-function
x       <- power.tsd.in(CV = 0.50, n1 = 70, weight = 0.5,
                        max.comb.test = FALSE, ssr.conditional = "error_power",
                        fCrit = "No", GMR = 0.95, targetpower = 0.8,
                        pmethod = "exact", theta0 = 1.25)
d       <- data.frame(Ref = "[21]", Method = "Maurer's", GMR = 0.95, Power = 80,
                      CV = "10 - 80%", adj = round(x$alpha[1], 5), TIE.max = x$pBE)
d$Power <- sprintf("%.0f%%", d$Power)
print(d, row.names = FALSE)
```

Exact (2×2×2 crossover)

Evaluation by Power2Stage [35]: Subjects 1–12 [3]

- **Interim analysis with fixed GMR 0.95**

```
interim.tsd.in(GMR1 = 1.0876, CV1 = 0.18213, n1 = 12, GMR = 0.95)
TSD with 2x2 crossover
Inverse Normal approach
 - Maximum combination test with weights for stage 1 = 0.5 0.25
 - Significance levels (s1/s2) = 0.02635 0.02635
 - Critical values (s1/s2) = 1.93741 1.93741
 - BE acceptance range = 0.8 ... 1.25
 - Observed point estimate from stage 1 is not used for SSR
 - With conditional error rates and conditional estimated target power
Interim analysis after first stage
 - Derived key statistics:
   z1 = 3.10000, z2 = 1.70344
   Repeated CI = (0.92491, 1.27891)
   Median unbiased estimate = NA
 - No futility criterion met
 - Test for BE not positive (not considering any futility rule)
 - Calculated n2 = 6
 - Decision: Continue to stage 2 with 6 subjects
```

Exact (2×2×2 crossover)

Evaluation by Power2Stage [35]: Subjects 1–12 | 13–18 [3]

- **Final analysis**

```
final.tsd.in(GMR1 = 1.0876, CV1 = 0.18213, n1 = 12,
             GMR2 = 1.0893, CV2 = 0.16776, n2 =  6)
TSD with 2x2 crossover
Inverse Normal approach
 - Maximum combination test with weights for stage 1 = 0.5 0.25
 - Significance levels (s1/s2) = 0.02635 0.02635
 - Critical values (s1/s2) = 1.93741 1.93741
 - BE acceptance range = 0.8 ... 1.25
Final analysis after second stage
 - Derived key statistics:
   z1 = 3.70299, z2 = 2.06106
   Repeated CI = (0.95672, 1.23796)
   Median unbiased estimate = 1.0953
 - Decision: BE achieved
```

  - Same conclusion as Potvin *et al.* 'Method B' [3] but slightly more conservative than its 94.12% CI with 0.9664 – 1.2252

Example: Weights and power in stages (minimum $n_2 = 6$, futility $N_{max} = 5 \times n_1$)

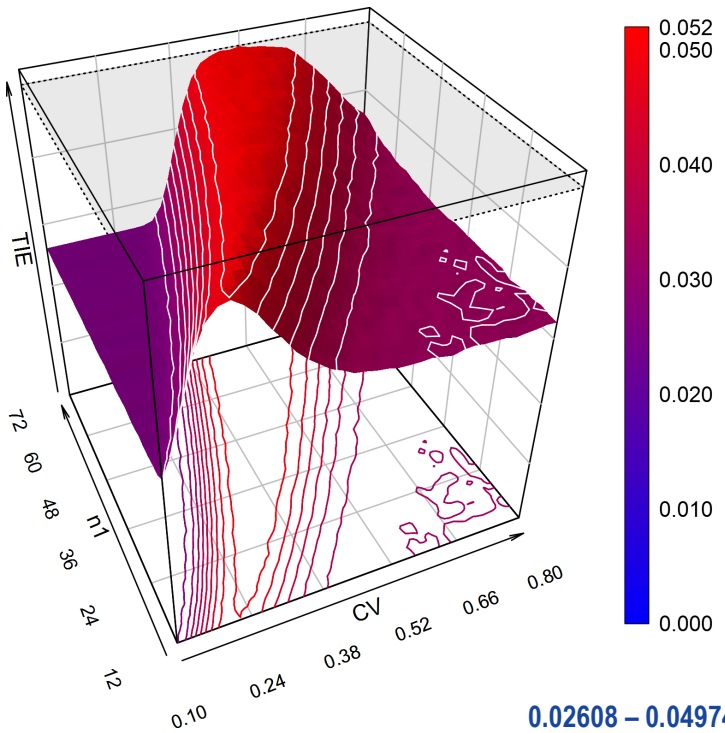
```
library(PowerTOST); library(Power2Stage)
CV  <- 0.3
n1  <- 0.8 * sampleN.TOST(CV = CV, print = FALSE)[["Sample size"]] # my recommendation
w1  <- w <- c(seq(0.9, 0.5, -0.1), 0.50)
w2  <- c(seq(0.1, 0.5, 0.1), 0.25)
MCT <- data.frame(Approach = "Maximum Combination Test",  w1 = w1, w2 = w2, n1 = n1)
SCM <- data.frame(Approach = "Standard Combination Method", w = w, n1 = n1)
for (i in seq_along(w1)) { # nmean is the expected average total sample size E[N]
  x           <- power.tsd.in(CV = CV, n1 = n1, weight = c(w1[i], w2[i]), GMR = 0.95,
                              min.n2 = 6, fCrit = "Nmax", fCNmax = 5 * n1)
  MCT$n2[i]   <- ceiling(x$nmean) - n1; MCT$adj[i] <- round(x$alpha[1], 5)
  MCT$pBE1[i] <- x$pBE_s1; MCT$pBE2[i] <- x$pBE
  x           <- power.tsd.in(CV = CV, n1 = n1, weight = w[i], max.comb.test = FALSE,
                              GMR = 0.95, min.n2 = 6,fCrit = "Nmax", fCNmax = 5 * n1)
  SCM$n2[i]   <- ceiling(x$nmean) - n1; SCM$adj[i] <- round(x$alpha[1], 5)
  SCM$pBE1[i] <- x$pBE_s1; SCM$pBE2[i] <- x$pBE
}
SCM <- SCM[-nrow(SCM), ]; MCT$Approach[2:nrow(MCT)] <- ""; SCM$Approach[2:nrow(SCM)] <- ""
print(MCT, row.names = FALSE, right = FALSE)
print(SCM, row.names = FALSE, right = FALSE)
```

- Similar average total sample sizes like in a fixed sample design
- Always higher power than fixed sample design
- ≈60% chance to stop in the interim for BE

Operating Characteristics (Exact [21])

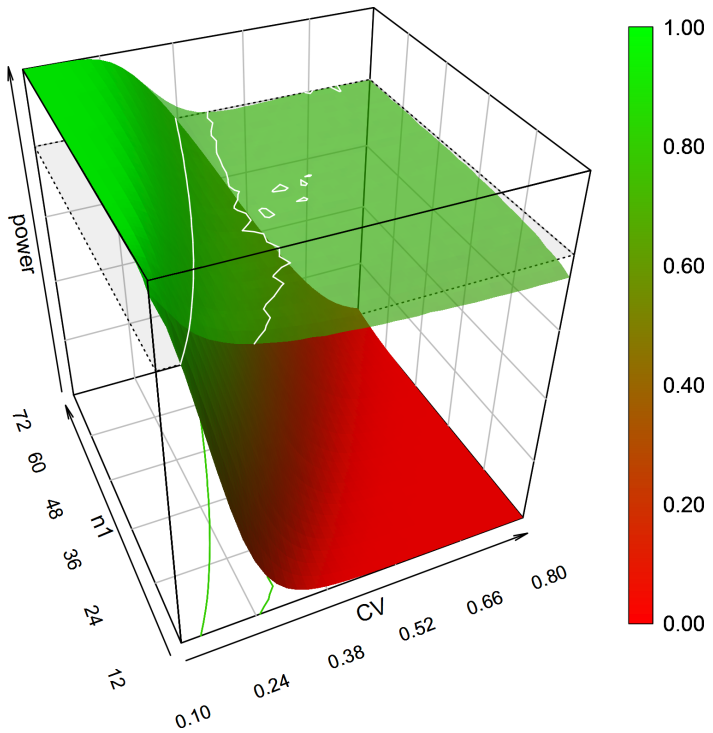
MCT: weights (0.25, 0.5) instead of the default (0.5, 0.25)

Type I Error



0.02608 – 0.04974

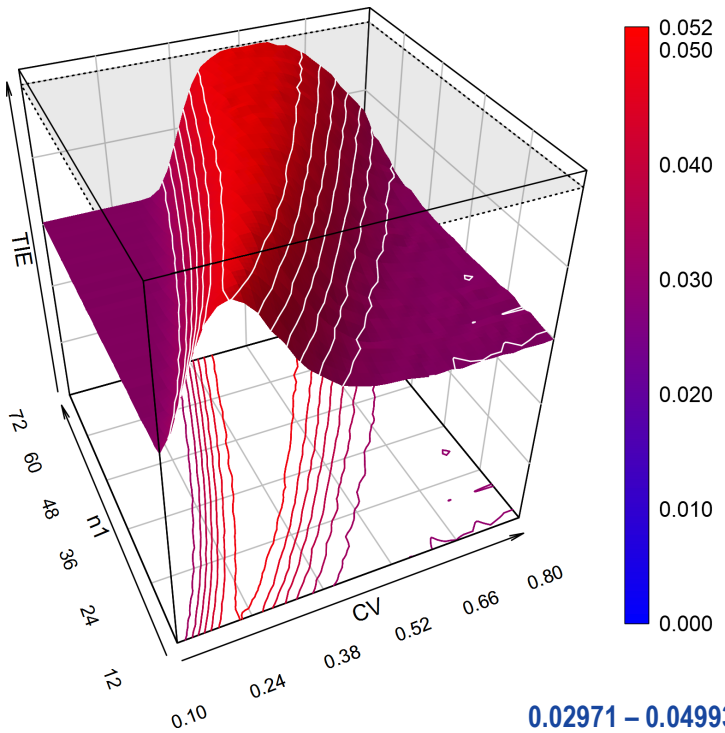
Power



Operating Characteristics (Exact [21])

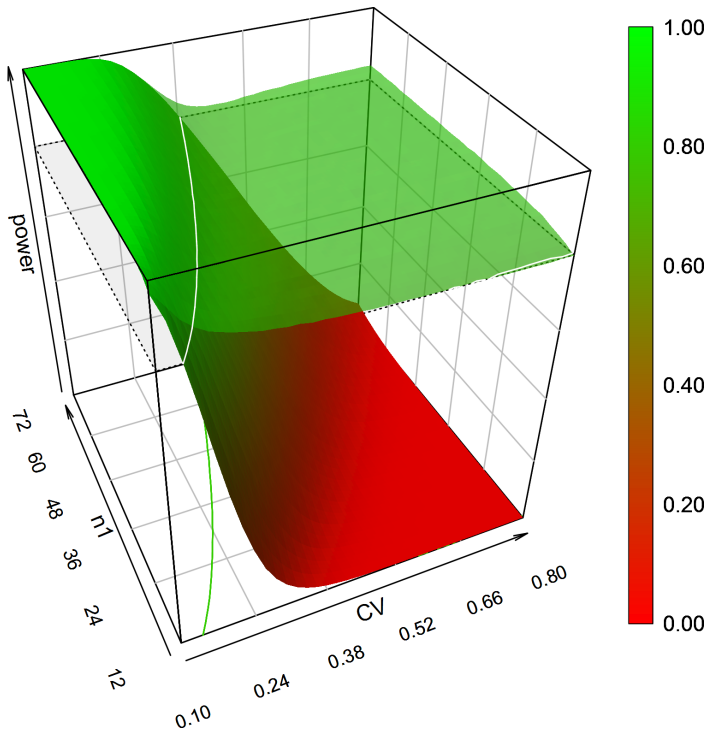
GMR 0.95, power 80%, α_{adj} 0.03037 (Standard Combination)

Type I Error



0.02971 – 0.04993

Power



Standard Combination Method
Minimum six subjects in stage 2

- **Interim analysis with fixed GMR 0.95**

```
interim.tsd.in(max.comb.test = FALSE, min.n2 = 6,
               GMR1 = 1.0876, CV1 = 0.18213, n1 = 12, GMR = 0.95)
TSD with 2x2 crossover
 Inverse Normal approach
  - Standard combination test with weight for stage 1 = 0.5
  - Significance levels (s1/s2) = 0.03037 0.03037
  - Critical values (s1/s2) = 1.87542 1.87542
  - BE acceptance range = 0.8 ... 1.25
  - Observed point estimate from stage 1 is not used for SSR
  - With conditional error rates and conditional estimated target power
Interim analysis after first stage
 - Derived key statistics:
    z1 = 3.10000, z2 = 1.70344
    Repeated CI = (0.92491, 1.27891)
    Median unbiased estimate = NA
 - No futility criterion met
 - Test for BE not positive (not considering any futility rule)
 - Calculated n2 = 6
 - Decision: Continue to stage 2 with 6 subjects
```

Standard Combination Method
Minimum six subjects in stage 2

- **Final analysis**

```
final.tsd.in(max.comb.test = FALSE,
             GMR1 = 1.0876, CV1 = 0.18213, n1 = 12,
             GMR2 = 1.0893, CV2 = 0.16776, n2 =  6)
TSD with 2x2 crossover
 Inverse Normal approach
  - Standard combination test with weight for stage 1 = 0.5
  - Significance levels (s1/s2) = 0.03037 0.03037
  - Critical values (s1/s2) = 1.87542 1.87542
  - BE acceptance range = 0.8 ... 1.25
Final analysis after second stage
 - Derived key statistics:
    z1 = 3.70299, z2 = 2.06106
    Repeated CI = (0.96127, 1.23210)
    Median unbiased estimate = 1.0884
 - Decision: BE achieved
```

  - Same conclusion as Maximum Combination Test; slightly less conservative than its CI 0.9567 – 1.2380 due to α_{adj} 0.03037 instead of 0.02635

Maximum empiric Type I Error (10^6 simulations under the Null)

```
library(Power2Stage)
# Simulation-based (parallel design): Welch-Satterthwaite test; Reference 14
# Exact Power estimation by Owen's Q-function
TIE.max <- power.tsd.p(method = "B", alpha = rep(0.0294, 2),
                       CV = 0.52, n1 = 116, GMR = 0.95,
                       targetpower = 0.8, test = "welch",
                       pmethod = "exact", theta0 = 1.25)$pBE
e       <- data.frame(Ref = "[14]", Type = 1, Method = "B ", GMR = 0.95, Power = 80,
                      CV = "10 - 100%", adj = 0.0294, TIE.max = TIE.max)
e$Power <- sprintf("%.0f%%", e$Power)
print(e, row.names = FALSE)
```

Example: Power (parallel design [14])

```
library(PowerTOST); library(Power2Stage)
CV <- 0.45 # total (pooled from within- and between-subject) CV
n1 <- floor(0.8 * sampleN.TOST(CV = CV, design = "parallel",
                               print = FALSE)[["Sample size"]]) # my recommendation
power.tsd.p(method = "B", alpha = rep(0.0294, 2), CV = CV, n1 = n1,
            pmethod = "exact", test = "welch", npct = c(0.05, 0.25, 0.5, 0.75, 0.95))
TSD with 2 parallel groups
Method B: alpha (s1/s2) = 0.0294 0.0294
CIs based on Welch's t-test
Target power in power monitoring and sample size est. = 0.8
Power calculation via exact method
CV1 and GMR = 0.95 in sample size est. used
No futility criterion
BE acceptance range = 0.8 ... 1.25
CV = 0.45; ntot(stage 1) = 128 (nT, nR = 64, 64); GMR = 0.95

1e+05 sims at theta0 = 0.95 (p(BE) = 'power').
p(BE)    = 0.82637
p(BE) s1 = 0.59414
Studies in stage 2 = 40.55%
Distribution of n(total)
- mean (range) = 155.5 (128 ... 316)
- percentiles
 5% 25% 50% 75% 95%
128 128 128 188 224
```

- 100,000 simulations by default
- Probability to stop in the interim for success ≈59%
- Probability to procees to second stage ≈41%
- Expected average total sample size E[N] 156
- Final power larger than fixed sample design's 80% with 160 subjects

Example: Empiric Type I Error (parallel design [14])

```
library(PowerTOST); library(Power2Stage)
CV <- 0.45 # total (pooled from within- and between-subject) CV
n1 <- floor(0.8 * sampleN.TOST(CV = CV, design = "parallel",
                               print = FALSE)[["Sample size"]]) # my recommendation
power.tsd.p(method = "B", alpha = rep(0.0294, 2), CV = CV, n1 = n1,
            pmethod = "exact", test = "welch", npct = 0.5, theta0 = 1.25)
TSD with 2 parallel groups
Method B: alpha (s1/s2) = 0.0294 0.0294
CIs based on Welch's t-test
Target power in power monitoring and sample size est. = 0.8
Power calculation via exact method
CV1 and GMR = 0.95 in sample size est. used
No futility criterion
BE acceptance range = 0.8 ... 1.25
CV = 0.45; ntot(stage 1) = 128 (nT, nR = 64, 64); GMR = 0.95

1e+06 sims at theta0 = 1.25 (p(BE) = TIE 'alpha').
p(BE)    = 0.044659
p(BE) s1 = 0.029288
Studies in stage 2 = 96.94%
Distribution of n(total)
- mean (range) = 190.5 (128 ... 330)
- percentiles
50%
190
```

- At the limits of the BE range one million simulations by default
- Probability to pass in the interim close to the level of the test
- Type I Error controlled (<0.05, significance limit of the binomial test 0.05036)