Sample size determination in clinical trials with multiple co-primary endpoints

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Outline

- Background and objectives
- Statistical settings
- Derivation of power formula
- Behavior of sample sizes
- Conclusion

Background

- Clinical trials often employ two or more primary endpoints.
  - A major concern is whether or not clinical trials should achieve statistical significance on all of the multiple primary endpoints (i.e., co-primary endpoints).
- Statistical Principles for Clinical Trials ICH (1998)
- Multiple Endpoint Expert Team (PhRMA) listed 20 diseases where regulatory agencies have required co-primary endpoints.

Offen et al. (2007)

Common solutions for the multiplicity

- Composite variable ICH (1998)
  - ○ This approach addresses the multiplicity problem without requiring adjustment to multiplicity.
  - ✕ A clinically meaningful and validated variable is not always available.
  - ✕ Interpretation of the variable is not easy.

- Assuming the independency among endpoints and increasing the power for each endpoint
  - ○ The power is simply defined. Eaton and Muirhead (2006)
  - ✕ The power would be under-evaluated. (The sample size is over-sized.)

Existing approaches for power and sample size determination

Continuous (Normal)

Xiong et al. (2005)
Sozu et al. (2006, 2011)
Eaton, Muirhead (2006)
Sugimoto et al. (2011)

IBC 2010
(2010.12.6)
Sozu et al.
(submitted)

Binary

Song (2009)
Sozu et al. (2010, 2011)
Hamasaki et al.
(submitted)

MCP 2011 (2011.8.31)

MCP 2011 (2011.8.31)
Hamasaki et al.
(submitted)

Ordinal

Time-to-event

Objective

We discuss the power and sample size determination for superiority comparative clinical trials with multiple co-primary endpoints (for achieving statistical significance for all of the endpoints).

Continuous (Normal)

Cont. and Binary

Binary

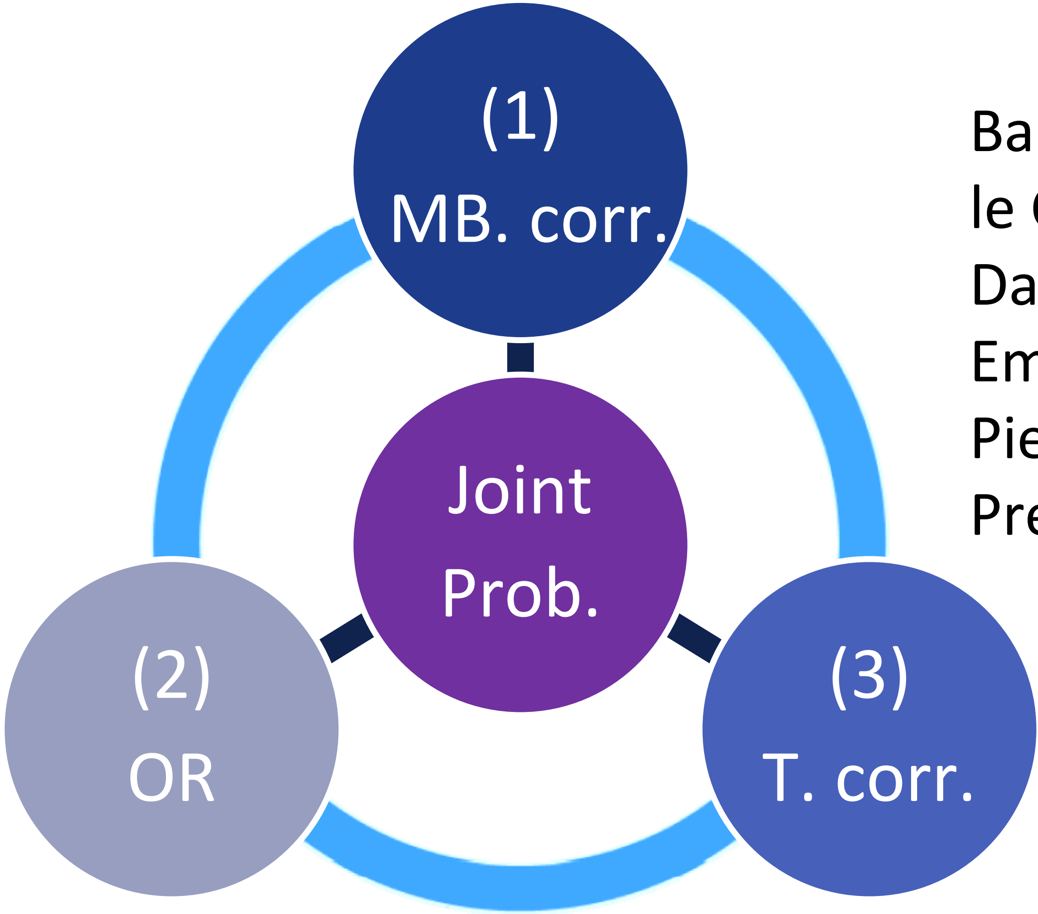
Common steps of our research

- Define the response variables and association measures (correlations) among them
- Calculate the correlation coefficients among the test statistics to derive a power formula
- Evaluate the behaviors of sample sizes

Association measures among endpoints

Scale	Distribution	Association measure(s)
Cont. (Normal)	Multivariate Normal (MN)	Correlation coefficient (r)
Binary	Multivariate Bernoulli (MB)	(1) r of MB dist. (MB. corr.) (2) Odd ratio (OR) (3) r of a latent MN dist. (Tetrachoric corr.)
Cont. and Binary	MN (latent distribution)	r of a latent MN dist. (Biserial corr.)

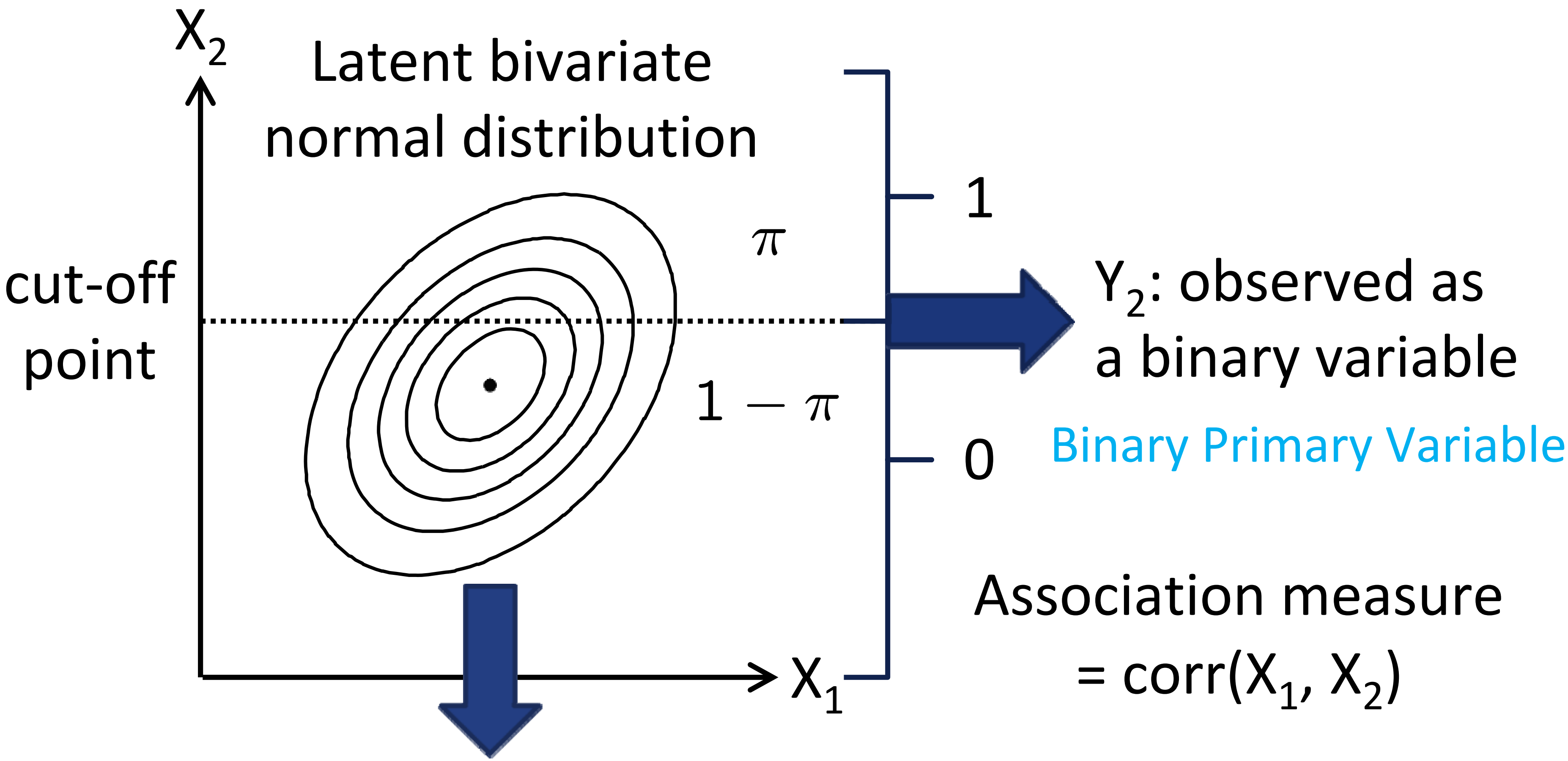
Relationships among association measures for binary variables



Bahadur (1961)
le Cessie (1994)
Dale (1986)
Emrich, Piedmonte (1991)
Prentice (1988)

A joint probability can be estimated
if the individual data of endpoints are available.

Biserial model for mixed cont. and binary variables



Y_1: observed as a normal variable
Normal Primary Variable

Pearson (1909)
Tate (1955a, 1955b)

Hypothesis testing

- $\delta_k = \begin{cases} \text{Difference in means for Normal Primary Variable} \\ \text{Difference in success probabilities for Binary Primary Variable} \end{cases}$

  $(k = 1, \ldots, K)$

  - $\delta_k > 0$ means an improvement

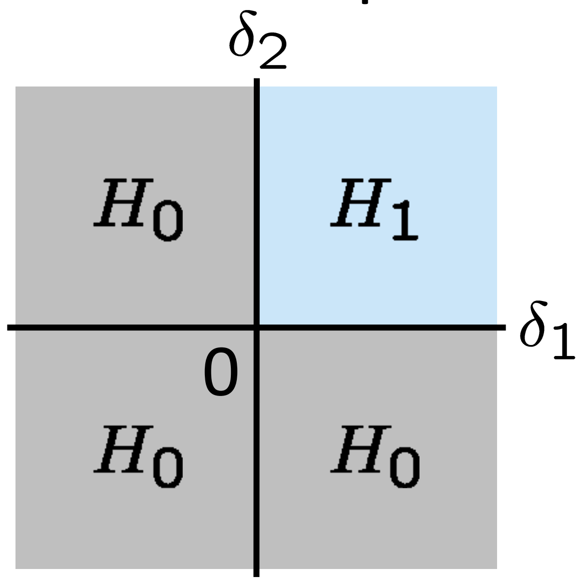
- $H_0 : \delta_k \leq 0$ for at lest one $\boldsymbol{k}$

  $(\iff \max \delta_k \leq 0)$

- $H_1 : \delta_k > 0$ for all $\boldsymbol{k}$

  $(\iff \min \delta_k > 0)$

Parameter space for two endpoints



Testing methods

- Normal Primary Variable

(1) Z-test: Known variance — Xiong et al. (2005)

(2) T-test: Unknown variance — Sozu et al. (2006, 2011)

- Binary Primary Variable

(1)(2) Chi-square test without/with cc

(3)(4) Arcsine transformation without/with cc

(5) Fisher's exact test (cc: continuity correction)

(6) Test based on log-transformed relative risks

(1-5) Sozu et al. (2010) (6) Hamasaki et al. (submitted)

Power formula:
Asymptotic normal test (except for T-test)

- Overall power = $1 - \beta = \Pr\left(\bigcap_{k=1}^{K} \{Z_k > z_\alpha\}\right)$
  - Z_k : Test statistic
  - z_α : Critical value (α : Significance level)
- Transform Z_k into the standardized statistics Z_k^* .
  - $(Z_1^*, \ldots, Z_K^*)^\top \sim N_K(\mathbf{0}, \mathbf{\Sigma})$
  - $\mathbf{\Sigma}$: diagonal = 1, off diagonal is given by a function of the association measure of the response variables.
- The power can be calculated from the CDF of $N_K(\mathbf{0}, \mathbf{\Sigma})$.

Sozu et al. (2010, 2011)

Power formula: T-test

- Overall power = $1 - \beta = \Pr\left(\bigcap_{k=1}^{K} \{T_k > t_\alpha\}\right)$
  - T_k : Test statistic
  - t_α : Critical value
- Calculate the power using a Monte Carlo integration
  - Generate Wishart random numbers for variance-covariance matrix
  - Calculate the conditional power
  - Repeat the above steps and calculate the mean of the conditional power

Sozu et al. (2006, 2011)

Power formula: Fisher's exact test

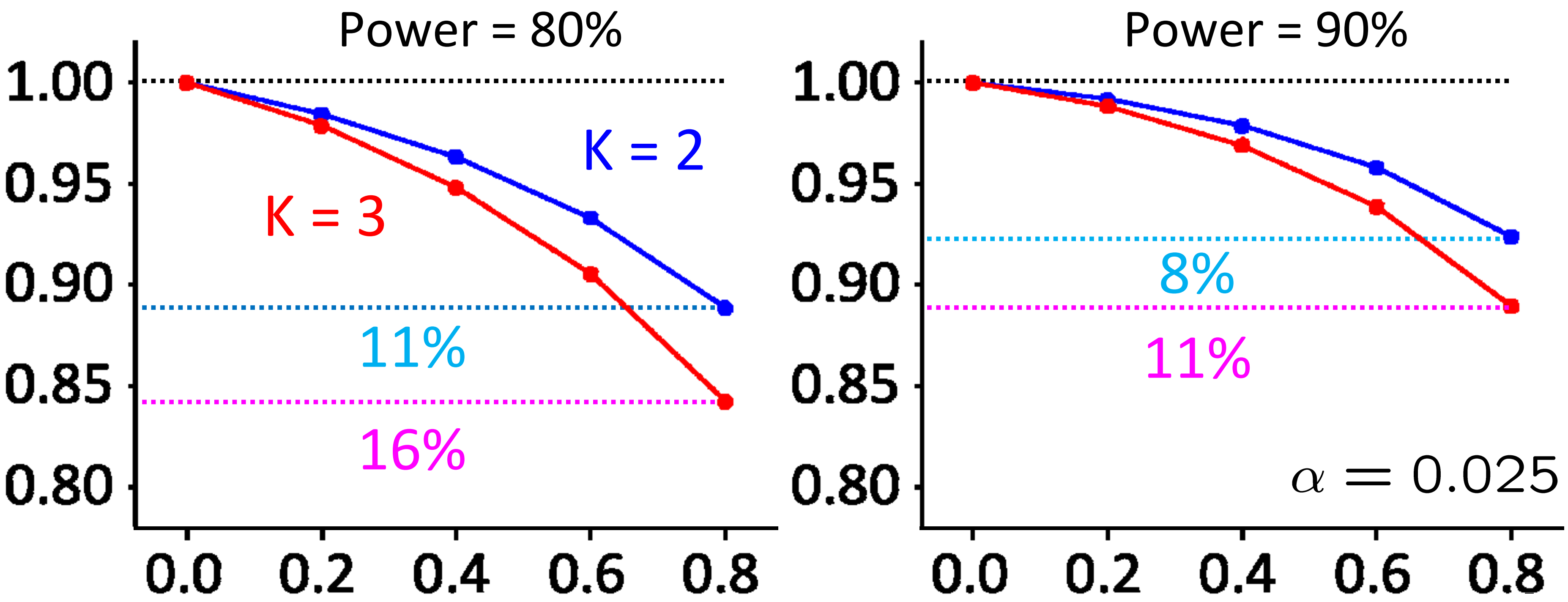
- Overall power = $1 - \beta = \Pr\left(\bigcap_{k=1}^{K} \{P_k < \alpha\}\right)$
  - P_k : one-sided p-value

- Calculate the power using a Monte Carlo integration.
  - Generate random numbers for the response variables from the assumed distribution

Sozu et al. (2010, 2011)

Behavior of sample sizes for $\delta_1 = \delta_2 (= \delta_3)$ Normal Primary Variables: Z-test

$$\text{Decrease in sample size} = \frac{\text{sample size at each r}}{\text{sample size at r = 0.0}}$$



r : correlation coefficient (compound symmetry)

Behavior of sample sizes for Normal Primary Variables

Sozu et al. (2006, 2011)

- The sample size ↘ the correlation ↗
  - when the effect sizes are approximately equal among endpoints
- The decrease in SS is determined by the following four design parameters:

  (1) Significance level of alpha (α)

  (2) Target power $(1-\beta)$

  (3) Effect size ratios of endpoints

  (4) Correlations among endpoints

  Sugimoto et al. (2011)
- The sample size (SS) based on T-test (unknown variance) + 1 $\simeq$ the SS based on Z-test (known variance).

Behavior of sample sizes for other Primary Variables

- **Binary Primary Variables:** Sozu et al. (2010, 2011)
  - The features of the testing methods are similar to the case of single endpoint (K=1).
    - e.g. The Arcsine transformation with CC provides sample sizes approximately equal to those obtained by Fisher's exact test.
- **Mixed Normal and Binary Variables:**
  - The decrease in the sample size is relatively small as compared to the case of Normal Primary Variable.

Convenient formula for sample size

- Sample size formula for Normal Primary Variables

$$n = \frac{(C_K + z_\alpha)^2}{\kappa_p \cdot \min(\delta_k)^2} \xrightarrow[\text{endpoints (K=1)}]{\text{Single}} \frac{(z_\beta + z_\alpha)^2}{\kappa_p \cdot \delta_1^2}$$

  - C_K is the function of the four design parameters
    - A Value can be obtained from the numerical table.
  - $\kappa_p = p/(1+p),\ \ p = n_C/n_T$
    - n_T, n_C : The number of subjects of each group
- A required sample can be calculated without using a statistical software.

Sugimoto et al. (2011)

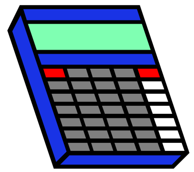
An numerical example: K = 2

- $\gamma_1 = \delta_1/\delta_2 = 0.5/0.4 = 1.25$
- $\rho_{12} = 0.5$ (Correlation between two endpoints)
- $\alpha = 0.025$
- $\beta = 0.2$

Numerical table → $C_2 = 0.925$

$$n = \frac{(C_2 + z_\alpha)^2}{\kappa_p \cdot \delta_2^2} = \frac{(0.925 + 1.96)^2}{(1/2) \cdot 0.4^2} = 104.04 \to 105$$

$$n_T = n_C \to p = 1 \to \kappa_p = p/(1+p) = 1/2$$

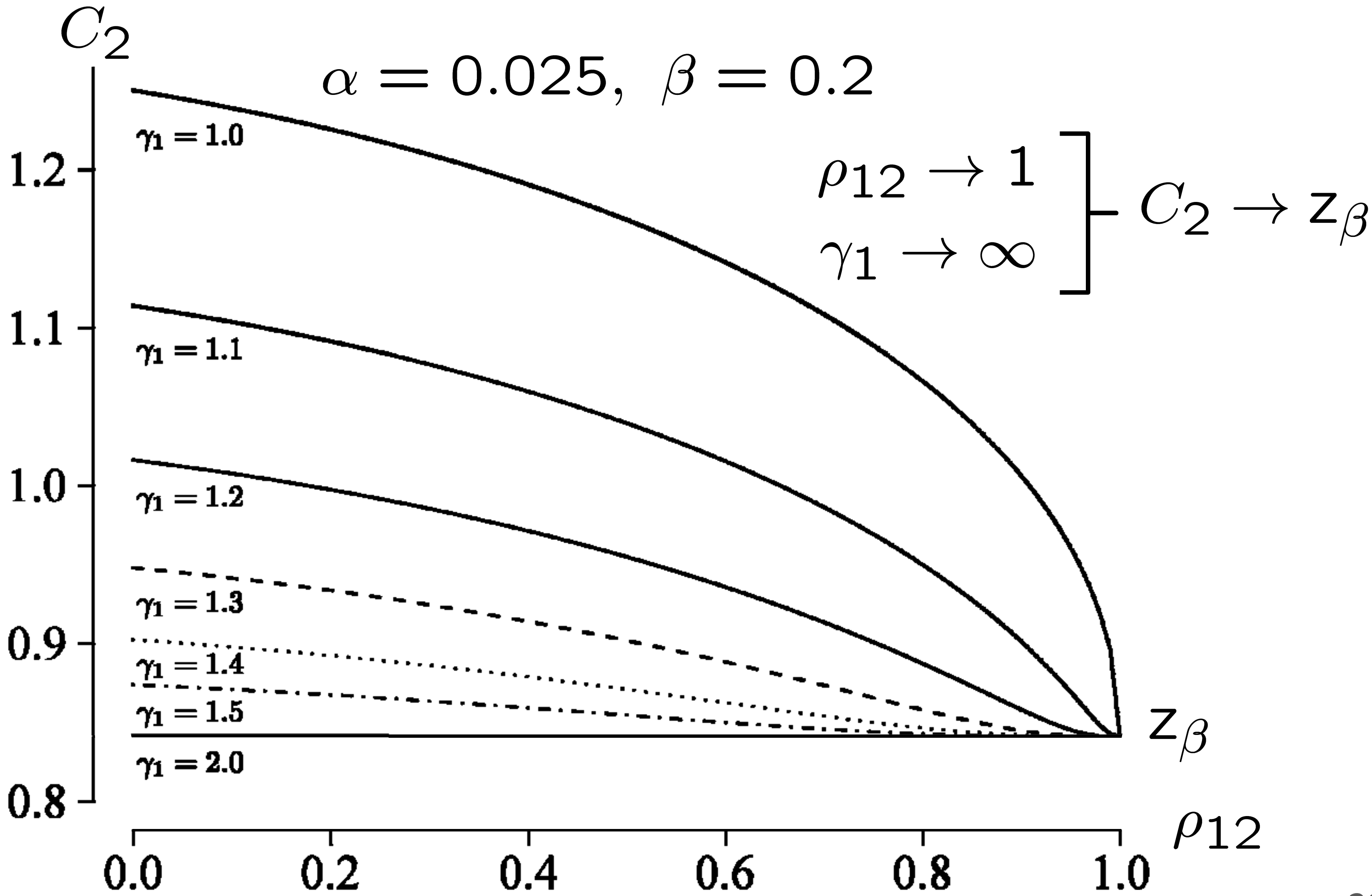


Example of numerical table for C_2

$$K = 2,\ \alpha = 0.025,\ \beta = 0.2$$

γ_1	ρ_{12} 0.0	0.2	0.3	0.5	0.7	0.8	0.95
1.00	1.250	1.226	1.210	1.168	1.109	1.066	0.961
1.02	1.219	1.195	1.179	1.138	1.079	1.038	0.934
⋮				⋮			
1.25	0.979	0.962	0.952	0.925	0.890	0.870	0.843
⋮				⋮			
2.00	0.842	0.842	0.842	0.842	0.842	0.842	0.842

Curve of C_2



C_2
$\alpha = 0.025,\ \beta = 0.2$
$\rho_{12} \to 1$
$\gamma_1 \to \infty$
$C_2 \to z_\beta$
$\gamma_1 = 1.0$
$\gamma_1 = 1.1$
$\gamma_1 = 1.2$
$\gamma_1 = 1.3$
$\gamma_1 = 1.4$
$\gamma_1 = 1.5$
$\gamma_1 = 2.0$
z_β
ρ_{12}
1.2
1.1
1.0
0.9
0.8
0.0
0.2
0.4
0.6
0.8
1.0

Conclusions

- We introduced the method of power and sample size calculations for multiple co-primary endpoints for achieving statistical significance for all of the endpoints.
- It is important to consider associations among endpoints into sample size calculation when
  - the endpoints are (positively) correlated and
  - the effect sizes (i.e., the corresponding individual powers) are approximately equal among the endpoints.

Thank you very much for your attention

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Backup

Why multiple endpoints are required?

(1) Lack of a consensus on a single most important variable from the medical perspective

(2) No clear aetiology of diseases

(3) A disease condition is characterized in multi-dimensional ways

Pocock (1997)

Pong and Shein-Chung (1997)

Sankoh et al. (2003)

Chuang-Stein et al. (2007)

Statistical Principles for Clinical Trials

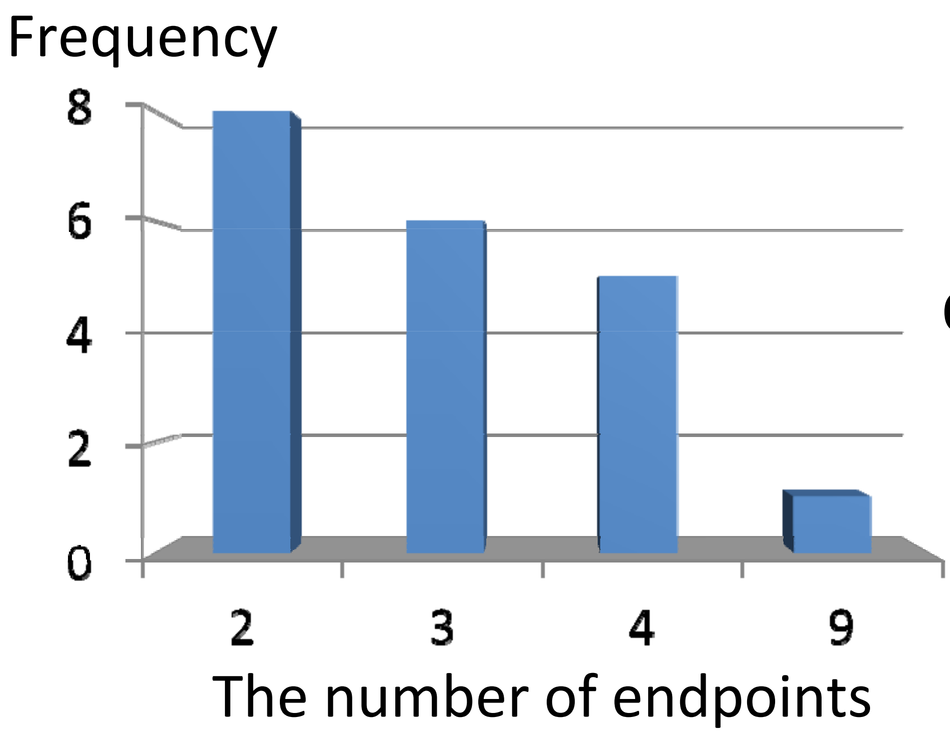
- 2.2.2 Primary and Secondary Variables
  - There should generally be only one primary variable.

- 2.2.5 Multiple Primary Variables
  - It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies.

ICH (1998)

Examples of co-primary endpoints

- Multiple Endpoint Expert Team (PhRMA) listed 20 diseases where regulatory agencies have required co-primary endpoints.



Offen et al. (2007)

Example of a clinical trial

- A randomized, parallel-treatment, placebo-controlled, double-blind trial
- Acute migraine
- Five co-primary endpoints are considered.

(1) pain freedom

(2) pain relief

(3) phonophobia

(4) photophobia

(5) nausea

Ho et al. (2008)

Example of guidance

- Irritable Bowel Syndrome
- Primary endpoint

FDA (2010)

(1) Abdominal pain (11-points: 0 to 10)

(2) IBS-C (Constipation): stool frequency

(2) IBS-D (Diarrhea): stool consistency

- The Bristol stool Form Scale (seven levels)

http://www.e-chiken.com/shikkan/kabinsei.htm

Rösler et al. (1999; BMJ)

Statistical methods

The study sample population of about 200 in each group was planned to enable achievement of 90% power with $\alpha = 0.05$ for detecting at least a 3.0 point improvement on the Alzheimer's disease assessment scale and an increase from 15-30% among patients scoring < 4 on the clinician impression of change scale.

Three possible clinical scenarios

- Showing significance for

Sankoh et al. (2003)

(1) all primary variables

- co-primary endpoints
  - reverse multiplicity problem

Offen et al. (2007)

(2) majority of the primary variables

(The constitution of the majority is defined in the protocol)

(3) one or more of the primary variables

- alternative primary endpoints

Offen et al. (2007)

Feature of three association measures

	Pros	Cons
B. corr	▪ Parameter of the assumed distribution	▪ Restricted range
OR	▪ No restricted range from 0 to infinity ▪ A direct extension to a global cross-ratio	▪ A scale depends strongly on response probabilities
L. corr	▪ No restricted range from -1 to 1	▪ Iterative calculations are necessary to specify the value from a value of other measure

Assumptions for response variables

- Biserial model
  - NPV (X) is observed as X (X = X)
  - BPV (Y) is obtained by a dichotomized of X (X -> Y)

Pearson (1903)

- Point-biserial model
  - NPV (X) is distributed as a mixed normal distribution
  - BPV (Y) is distributed as a Bernoulli distribution

Standardized test statistics

$$1-\beta = \mathrm{P}\left(\bigcap_{k=1}^{K}\{Z_k > z_\alpha\}\right) \simeq \mathrm{P}\left(\bigcap_{k=1}^{K}\{Z_k^* > c_k^*\}\right)$$

$$Z_k^* = \begin{cases} \dfrac{\bar{Y}_{\mathrm{T}k} - \bar{Y}_{\mathrm{C}k} - \delta_k}{\sigma_k\sqrt{\dfrac{1+\kappa}{\kappa n}}}, & k \le k_m \\ \dfrac{p_{\mathrm{T}k} - p_{\mathrm{C}k} - \delta_k}{\sqrt{\dfrac{\kappa\pi_{\mathrm{T}k}\theta_{\mathrm{T}k} + \pi_{\mathrm{C}k}\theta_{\mathrm{C}k}}{\kappa n}}}, & k > k_m, \end{cases},$$

$$c_k^* = \begin{cases} z_\alpha - \dfrac{\delta_k}{\sigma_k}\sqrt{\dfrac{\kappa n}{1+\kappa}}, & k \le k_m \\ \dfrac{1}{\sqrt{\kappa\pi_{\mathrm{T}k}\theta_{\mathrm{T}k} + \pi_{\mathrm{C}k}\theta_{\mathrm{C}k}}}\left\{\sqrt{\dfrac{(\pi_{\mathrm{T}k} + \kappa\pi_{\mathrm{C}k})(\theta_{\mathrm{T}k} + \kappa\theta_{\mathrm{C}k})}{1+\kappa}}\, z_\alpha - \sqrt{\kappa n}\,\delta_k\right\}, & k > k_m. \end{cases}$$

Correlation between standardized test statistics

$$
\gamma^{kk'} = \begin{cases}
\text{two continuous variables } (k, k' \leq k_m): \\
\dfrac{\kappa \operatorname{Corr}(Y_{\mathrm{T}jk}, Y_{\mathrm{T}jk'}) + \operatorname{Corr}(Y_{\mathrm{C}jk}, Y_{\mathrm{C}jk'})}{1+\kappa}, \\
\text{continuous and binary variables } (k \leq k_m, \text{ and } k' > k_m): \\
\dfrac{\kappa \operatorname{Corr}(Y_{\mathrm{T}jk}, Y_{\mathrm{T}jk'})\sqrt{\pi_{\mathrm{T}k'}\theta_{\mathrm{T}k'}} + \operatorname{Corr}(Y_{\mathrm{C}jk}, Y_{\mathrm{C}jk'})\sqrt{\pi_{\mathrm{C}k'}\theta_{\mathrm{C}k'}}}{\sqrt{1+\kappa}\sqrt{\kappa\pi_{\mathrm{T}k'}\theta_{\mathrm{T}k'} + \pi_{\mathrm{C}k'}\theta_{\mathrm{C}k'}}}, \\
\text{two binary variables } (k, k' > k_m): \\
\dfrac{\kappa \operatorname{Corr}(Y_{\mathrm{T}jk}, Y_{\mathrm{T}jk'})\sqrt{\pi_{\mathrm{T}k}\theta_{\mathrm{T}k}\pi_{\mathrm{T}k'}\theta_{\mathrm{T}k'}} + \operatorname{Corr}(Y_{\mathrm{C}jk}, Y_{\mathrm{C}jk'})\sqrt{\pi_{\mathrm{C}k}\theta_{\mathrm{C}k}\pi_{\mathrm{C}k'}\theta_{\mathrm{C}k'}}}{\sqrt{\kappa\pi_{\mathrm{T}k}\theta_{\mathrm{T}k} + \pi_{\mathrm{C}k}\theta_{\mathrm{C}k}}\sqrt{\kappa\pi_{\mathrm{T}k'}\theta_{\mathrm{T}k'} + \pi_{\mathrm{C}k'}\theta_{\mathrm{C}k'}}}.
\end{cases}
$$

Sample size calculation

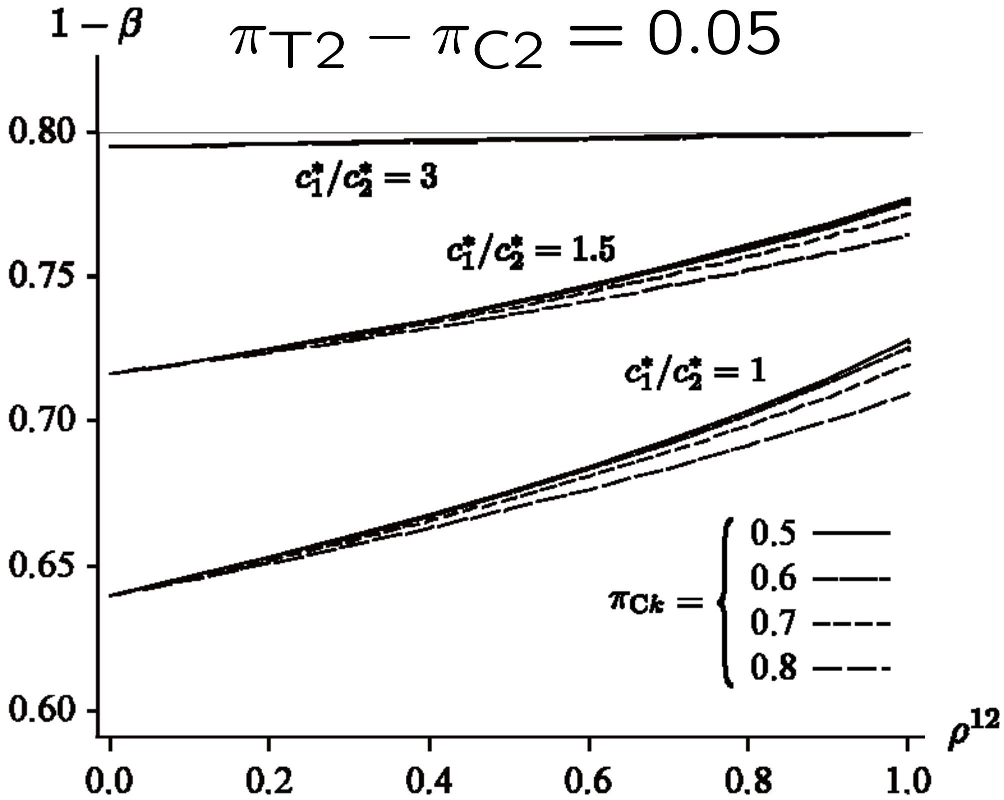
- Specify the value of parameters.
  - NPV: mean μ_{ik} and variance σ_k^2
  - BPV: success probability π_{ik}
- Specify the value of $\rho_{kk'} = \text{corr}(X_{ijk}, X_{ijk'})$.

  (Consider equal sample sizes: $n_1 = n_2 = n$)
- Choose a starting value of n and calculate the power.
- Repeat the above steps by gradually increasing n .
  - End the operation when the calculated power exceeds the desired $1 - \beta$, and select n as the minimum value of sample size.

Behavior of overall power (mixed)

one continuous and one binary variable (K=2)

$\pi_{T2} - \pi_{C2} = 0.05$



individual power = 0.8

Behaviors of sample sizes

c_1^*/c_2^*	δ_1^*	Proportions $(\pi_{T2}\ \pi_{C2})$	Correlation ρ^{12} 0.0	0.3	0.5	0.8	E_1	E_2
1	0.100	(0.55 0.50)	2055 (80.1)	2016 (79.9)	1980 (80.0)	1904 (80.0)	1565	1565
	0.103	(0.65 0.60)	1931 (80.0)	1895 (80.1)	1862 (80.1)	1793 (80.0)	1471	1471
	0.112	(0.75 0.70)	1643 (80.1)	1614 (80.1)	1588 (80.0)	1534 (80.0)	1251	1251
	0.132	(0.85 0.80)	1189 (80.0)	1171 (80.1)	1154 (80.1)	1122 (80.0)	906	906
	0.201	(0.60 0.50)	509 (79.8)	499 (80.3)	490 (80.9)	472 (80.2)	388	388
	0.210	(0.70 0.60)	468 (80.1)	459 (80.0)	451 (80.0)	435 (80.1)	356	356
	0.231	(0.80 0.70)	385 (80.1)	379 (80.1)	373 (80.2)	361 (80.2)	294	294
	0.281	(0.90 0.80)	262 (80.7)	258 (80.6)	254 (80.5)	248 (80.4)	199	199
1.5	0.115	(0.55 0.50)	1819 (79.8)	1789 (80.0)	1760 (79.8)	1702 (79.7)	1183	1565
	0.119	(0.65 0.60)	1710 (80.0)	1682 (80.1)	1656 (80.1)	1603 (80.1)	1112	1471
	0.129	(0.75 0.70)	1454 (80.0)	1432 (80.1)	1411 (80.1)	1370 (80.0)	946	1251
	0.151	(0.85 0.80)	1053 (80.1)	1038 (80.0)	1025 (80.1)	1000 (80.2)	685	906
	0.232	(0.60 0.50)	451 (79.7)	443 (79.9)	436 (80.4)	422 (79.8)	293	388
	0.242	(0.70 0.60)	414 (80.0)	407 (80.1)	401 (80.0)	389 (80.1)	270	356
	0.266	(0.80 0.70)	341 (80.2)	336 (80.0)	331 (80.1)	322 (80.2)	222	294
	0.323	(0.90 0.80)	232 (80.6)	229 (80.7)	226 (80.7)	221 (80.7)	151	99

Behaviors of sample sizes (cont.)

3	0.160	(0.55 0.50)	1583 (79.7)	1578 (80.1)	1574 (80.4)	1568 (80.3)	611	1565
	0.165	(0.65 0.60)	1487 (80.1)	1483 (80.2)	1479 (80.1)	1474 (80.1)	574	1471
	0.179	(0.75 0.70)	1265 (80.1)	1262 (80.1)	1259 (80.1)	1254 (80.0)	489	1251
	0.211	(0.85 0.80)	916 (80.1)	914 (80.1)	912 (80.2)	909 (80.2)	354	906
	0.322	(0.60 0.50)	392 (79.6)	391 (79.6)	390 (79.6)	388 (79.5)	152	388
	0.336	(0.70 0.60)	360 (80.0)	359 (80.2)	358 (80.1)	357 (80.0)	139	356
	0.370	(0.80 0.70)	297 (80.3)	296 (80.3)	295 (80.2)	294 (80.2)	115	294
	0.450	(0.90 0.80)	202 (80.7)	201 (80.6)	201 (80.6)	200 (80.9)	78	199

Summary of the results

- The behaviors of sample sizes are in agreement with the results in the continuous case.
- π_{ik} is not close to 1
  - AS = AN << ASc = Fi = ANc
- π_{ik} is close to 1
  - AS < AN << ASc = Fi < ANc
- The behaviors of achieved sample sizes for K=3 are similar to those for K=2.
- The empirical power attains a pre-specified power.
  - The performance of ASc and Fi is better.

An illustration: PREMIER study

- Early aggressive rheumatoid arthritis
- ACR50
  - The percentage of patients in whom an ACR50 response was achieved
- mTSS
  - The mean change from baseline in the modified total Sharp score.
- Adalimumab + Methotrexate v.s. Methotrexate

Breedveld (2006)

An illustration: PREMIER study

Sample sizes per group with $\alpha = 0.025, 1 - \beta = 0.8$

mTSS		ACR50	Correlation ρ^{12}						
δ_1	σ_1	$(\pi_{T2}\ \pi_{C2})$	0.0	0.3	0.5	0.8	E_1	E_2	c_1^*/c_2^*
4.4	19.0	(0.59 0.46)	346	340	334	323	294	231	0.72
4.4	20.0	(0.59 0.46)	369	363	358	347	326	231	0.63
4.4	21.0	(0.59 0.46)	394	389	384	374	359	231	0.56
4.4	22.0	(0.59 0.46)	422	417	413	404	394	231	0.50

E_1, E_2: Sample size separately calculated for each endpoint so that the individual power is at least 0.8.

Breedveld (2006)

Joint density function of test statistics