Bioequivalence trials designed using adaptive methodologies

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BASS XIII

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Objective

- To share an exact method for design and evaluation of two stage sequential designs for bioequivalence hypothesis
- To discuss how this method compares to existing designs

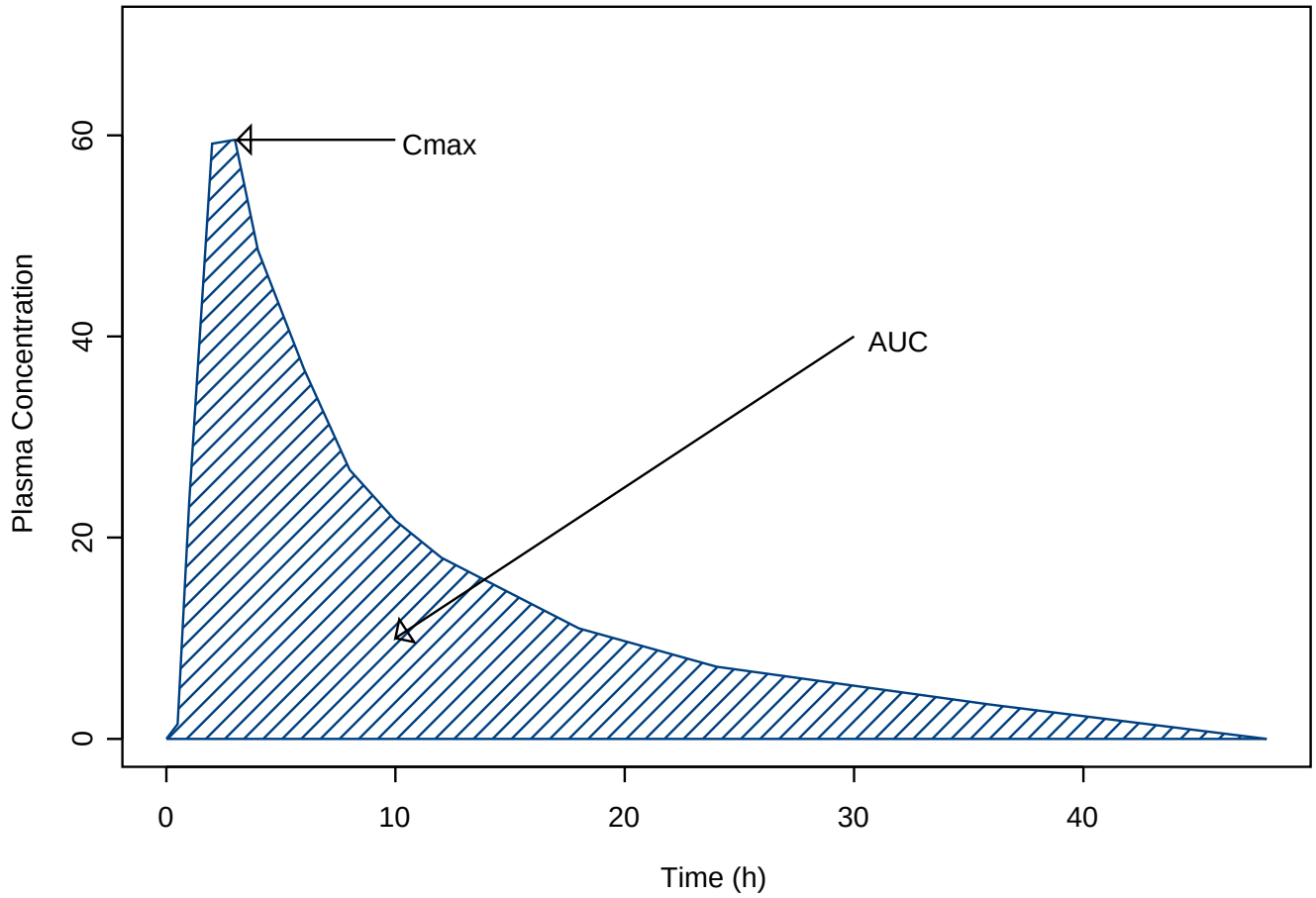
Outline

- Introduction to Bioequivalence Trials
- Motivation
- Two-Stage Sequential Design
- Exact Methods
- Comparisons to Current Methodologies
- Other Work
- Summary

Bioequivalence trials

- Clinical study to compare a new formulation and current formulation of drug product
- Objective is to demonstrate *bioequivalence (BE)* of pharmacokinetic (PK) profile
  - PK - drug concentration in the blood
  - surrogate for efficacy and safety
  - PK measures: AUC and Cmax
- Conducted to gain market access for new formulation

Figure of PK profile and measures



Crossover Designs and Model

- **Study Design:** A randomized, open-label, period-balanced, two period crossover design. Formulatoins: **C**: current and **T**: test
- **Model:** $y_{ijk} = \mu + \pi_j + \tau_{\mathbf{d[i,j]}} + s_{ik} + \mathbf{e_{ijk}}$

  for the kth subject in the jth period of the ith sequence

  between-subject: $s_{ik} \sim N(0, \sigma_b^2)$

  within-subject: $e_{ijk} \sim N(0, \sigma_e^2)$

  – sequence 1 be CT, sequence 2 be TC:

  $d[1,1] = d[2,2] \Rightarrow$ regimen C

  $d[1,2] = d[2,1] \Rightarrow$ regimen T

Effect and Variance Estimates from Crossover Trial

- **Treatment Difference:** $\tau_d = \tau_T - \tau_C$
- estimated by: $\hat{\tau}_d = \frac{1}{2}(\bar{y}_{12.} - \bar{y}_{11.} + \bar{y}_{21.} - \bar{y}_{22.}) \quad \sim N(\tau_d, 2\sigma_e^2/N)$
- **Within-subject variance:** σ_e^2

  estimated by: $s^2 = \sum_{i=1}^{2} \sum_{k=1}^{N/2} ((d_{ik} - \bar{d}_{i.})^2/(N-2))$

where

$\bar{y}_{ij.} = \sum_{k=1}^{N/2} y_{ijk}/(N/2)$

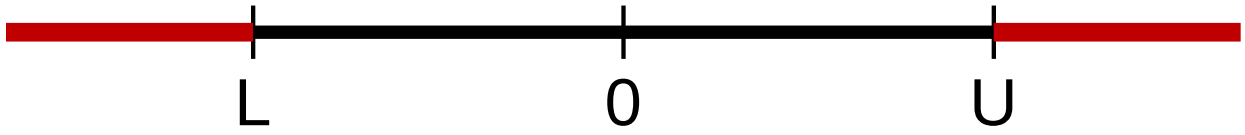
$d_{ik} = y_{i2k} - y_{i1k}$

$\bar{d}_{i.} = \sum_{k=1}^{N/2} d_{ik}/(N/2)$

Bioequivalence Hypotheses

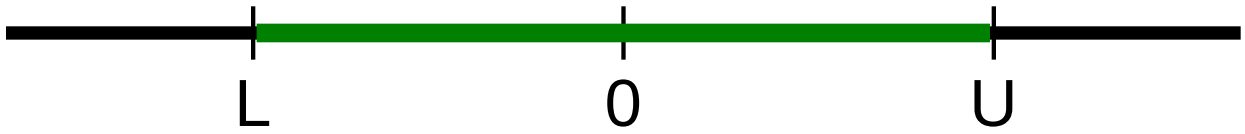
The null hypothesis of "Not bioequivalent" is expressed as:

$$H_0^- : \tau_d \leq L \quad \text{or} \quad H_0^+ : \tau_d \geq U$$



The alternative hypothesis of "Bioequivalent" is expressed as:

$$H_a^- : \tau_d > L \quad \text{and} \quad H_a^+ : \tau_d < U$$



L and U define the bioequivalence criteria. For this talk, it $L = -U$ (symmetric BE criteria).

Type I and II Error Probabilities

- Type I error probabilities:

$$\alpha^- = \text{Prob}[\text{Claim BE}|\ \tau_d = \text{L}]$$

$$\alpha^+ = \text{Prob}[\text{Claim BE}|\ \tau_d = \text{U}]$$

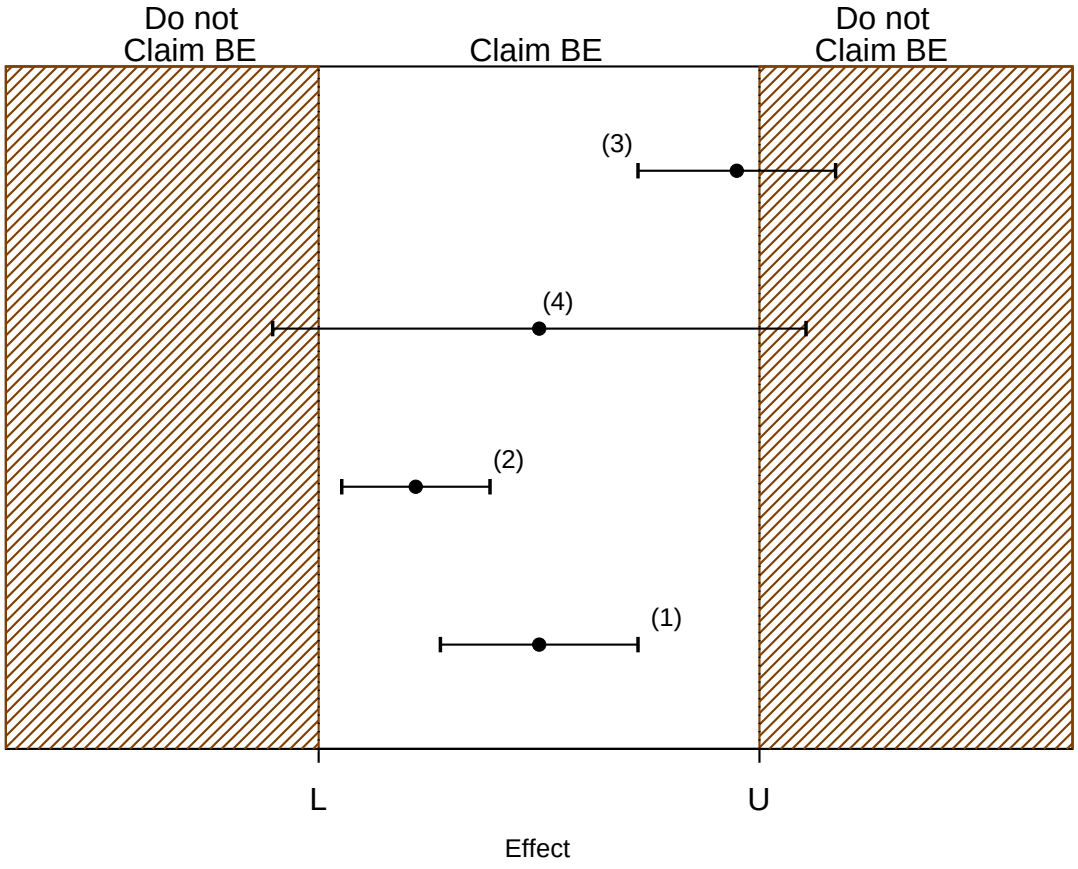
$$\alpha = \alpha^- = \alpha^+, \text{ when } L = -U$$

- Type II error probabilities:

$$\beta = 1 - \text{Prob}[\text{Claim BE}|\tau_d = 0]$$

Claim BE when both H_0^- and H_0^+ are rejected.
Or when the $100(1-2\alpha)\%$ confidence intervals $\in (U, L)$

Claiming BE



Motivation for Research

- Sample size:

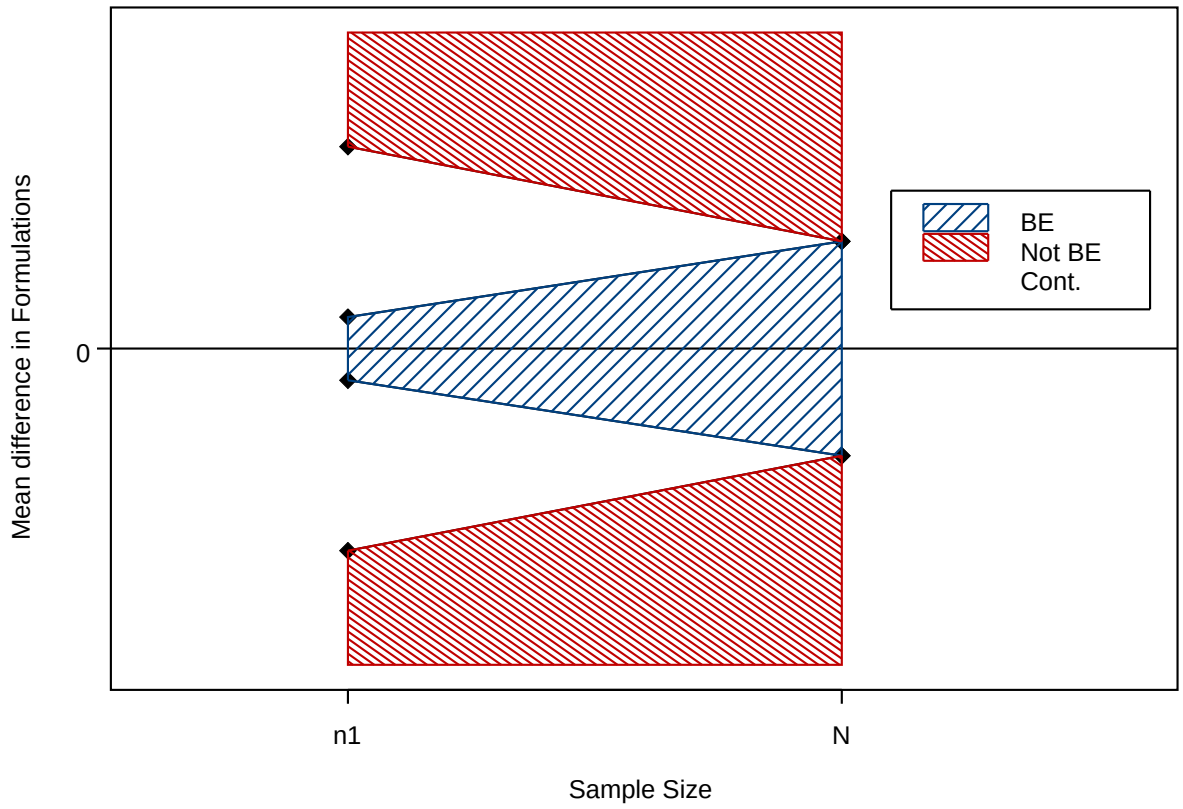
$$N_0 = \frac{2\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta/2)\right)^2 \boldsymbol{\sigma_0^2}}{(U - |\boldsymbol{\tau_{d0}}|)^2}$$

- Under estimates of the within-subject variance (e.g.; $\sigma_0^2 < \sigma_e^2$) can result in an **inconclusive** study
  - delay market access for drug product and/or formulation
- **Adaptive** designs can help mitigate any uncertainty
  - Sample size re-estimation
  - **Group sequential designs**
  - Group sequential design with sample size re-estimation

Two stage group sequential design

- Two-stage group sequential design with **interim** look after n_1 subjects complete and **final** look after N $(= n_1 + n_2)$ subjects complete
- At interim: 3 potential decisions (i) stop and claim BE, (ii) stop and do not claim BE and (iii) continue trial.
  - Defined by rejection region criteria
    - in terms of difference in formulations, $\hat{\tau}_d$
    - in terms of test statistics, t^- and t^+

Two-stage sequential design defined in terms of difference in formulations, τ_d



Test Statistics: Interim

- At interim look will calculate (based on n_1 subjects)

$$t_1^- = \frac{\hat{\tau}_{d1} - L}{s_1\sqrt{2/n_1}} \quad \text{and} \quad t_1^+ = \frac{U - \hat{\tau}_{d1}}{s_1\sqrt{2/n_1}}$$

  - mean difference in treatments, $\hat{\tau}_{d1}$
  - estimated within-subject variance, s_1^2
  - test statistics, t_1^- and t_1^+
    - follow a Student's T distribution, if $\tau_d = L$ or U, respectively

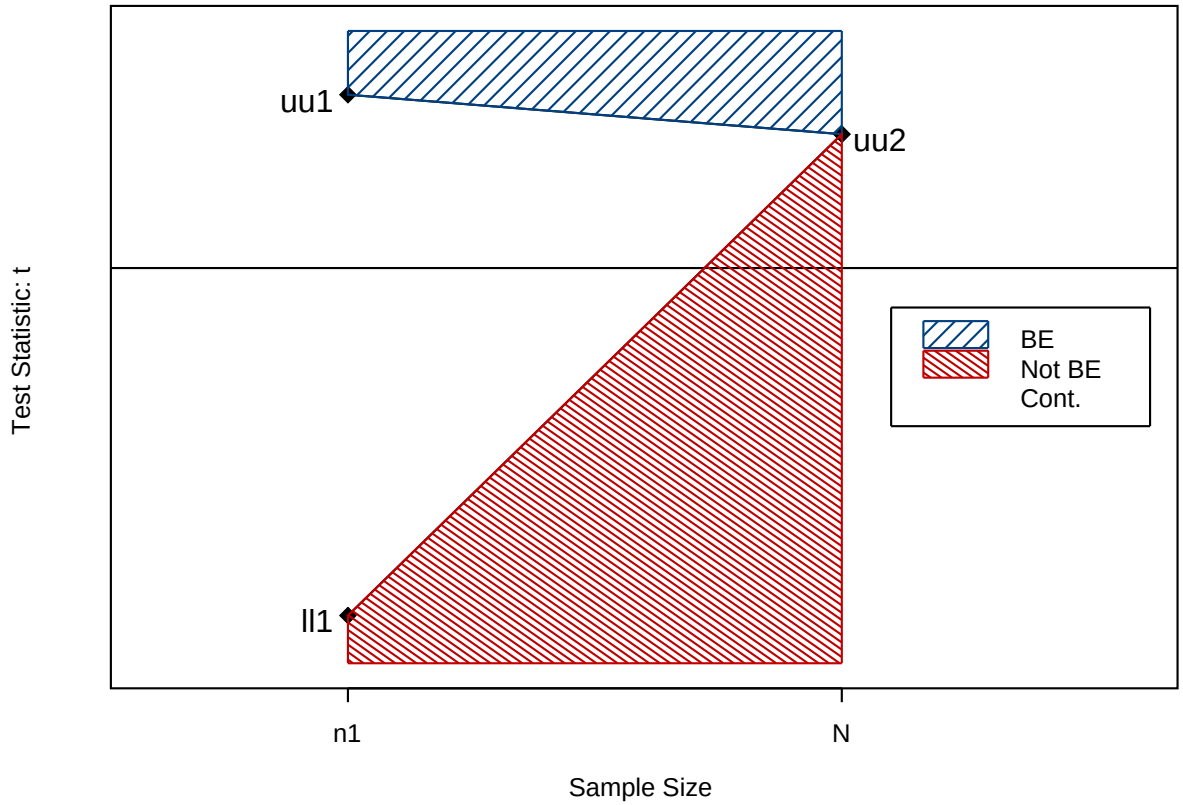
Test Statistics: Final Look

- At final look will calculate (based on $n_1 + n_2$ subjects)

$$t^- = \frac{\hat{\tau}_d - L}{s\sqrt{2/N}} \quad \text{and} \quad t^+ = \frac{U - \hat{\tau}_d}{s\sqrt{2/N}}$$

  - mean difference in treatments, $\hat{\tau}_d$
  - estimated within-subject variance, s^2
  - test statistics, t^- and t^+
    - **do not** follow a Student's T distribution, only calculate if study "continues" following interim analysis
    - t^- and t^+ are dependent on t_1^- and t_1^+,

Two-stage sequential design defined in terms of test statistics, t^- and t^+



Note: Both t^- and t^+ must be in blue area to Claim BE.
And either t^- and t^+ can be in the red to not claim BE.

Dependence between interim and end analysis

- $\hat{\tau}_d$ is dependent on $\hat{\tau}_{d1}$ $\qquad (n_1/N)\hat{\tau}_{d1} + (n_2/N)\hat{\tau}_{d2} = \hat{\tau}_d$

- s^2 is dependent on s_1^2 $\qquad s^2 = \frac{(n_1-2)s_1^2+(n_2-2)s_2^2+SS}{n_1+n_2-2}$

where $\qquad SS = \frac{n_1 n_2}{2N}[(\bar{d}_{1.}^{(1)} - \bar{d}_{1.}^{(2)})^2 + (\bar{d}_{2.}^{(1)} - \bar{d}_{2.}^{(2)})^2],$

where $d_i^{(1)}$ and $d_i^{(2)}$ are the average difference in formulations for the ith sequence based on n_1 and n_2 subjects, respectively.

Type I and II Error Probabilities and Futility Probabilities for Two-Stage Sequential Design

Decision	$\tau_d = L$	$\tau_d = U$	$\tau_d = 0$
Claim BE at interim *	α_1^-	α_1^+	ρ_1
Claim BE at end **	α_2^-	α_2^+	ρ_2
Claim BE	$\alpha^- = \alpha_1^- + \alpha_2^-$	$\alpha^+ = \alpha_1^+ + \alpha_2^+$	$\rho = \rho_1 + \rho_2$
Do not claim BE at interim *	α_0^-	α_0^+	

* study is also stopped at this point

** implies study continued following interim look

- All probabilities can be evaluated using the density functions of test statistics, t_1^-, t_1^+, t^- and t^+.
- Which are functions of the independent statistics, $\hat{\tau}_{d1}$, $\hat{\tau}_d$, s_1^2, s_2^2 and the $d_i^{(j)}$'s

Defining the density functions of t_1^-

Density of t_1^-

- $\hat{\tau}_{d1} \sim N(\tau_d,\ 2\sigma_e^2/n_1)$
- Let $w_1 = (n_1 - 2)s_1^2/\sigma_e^2 \quad \sim \chi^2_{n_1-2}$
- Then $z_1^- = t_1^-\ \sqrt{w_1/(n_1-2)}$, which is distributed normally
- The density of t_1^- can be expressed as the joint density of z_1^- and w_1:
  - product of normal and a chi-square density function

Defining the density functions of t^-

Density of t^-

- Let $w = (N-2)s^2/\sigma_e^2 = w_1 + w_2^* \quad \sim \chi^2_{N-2}$
- $w_2^* = (n_2)(s_2^*)^2/\sigma_e^2 \quad \sim \chi^2_{n_2}$
  - $(s_2^*)^2 = (n_2 - 2)s_2^2 + SS$
- Let $z_2^- = t^- \sqrt{(w_1 + w_2^*)/(N-2)} - \sqrt{N/n_1} z_1^-$, which is distributed normally
  - which is a function of $\hat{\tau}_{d2}$ and $(s_2^*)^2$
- The density of t^- can be expressed as the joint density of z_1^-, w_1, z_2^- and w_2^*:
  - product of 2 normal and 2 chi-square density functions
  - an improper density

Calculating Error Probabilities

Let,

$\pi_1(\Delta) = Prob[\text{Claim BE at interim} \mid \tau_d = \Delta]$

$\pi_2(\Delta) = Prob[\text{Continue at interim and Claim BE at end} \mid \tau_d = \Delta]$

The probabilities can be defined in terms of π_1 and π_2 as follows:

$$\alpha^- = \alpha_1^- + \alpha_2^- = \pi_1(L) + \pi_2(L)$$

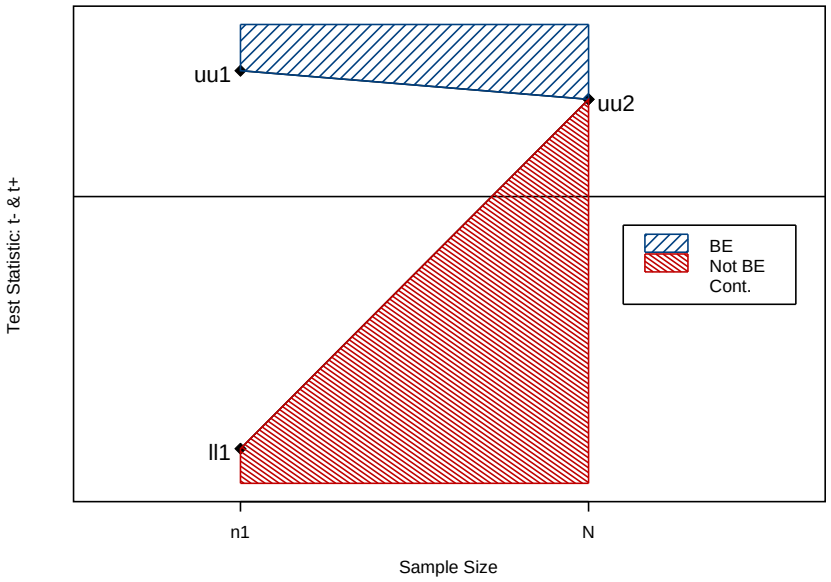
$$\alpha^+ = \alpha_1^+ + \alpha_2^+ = \pi_1(U) + \pi_2(U)$$

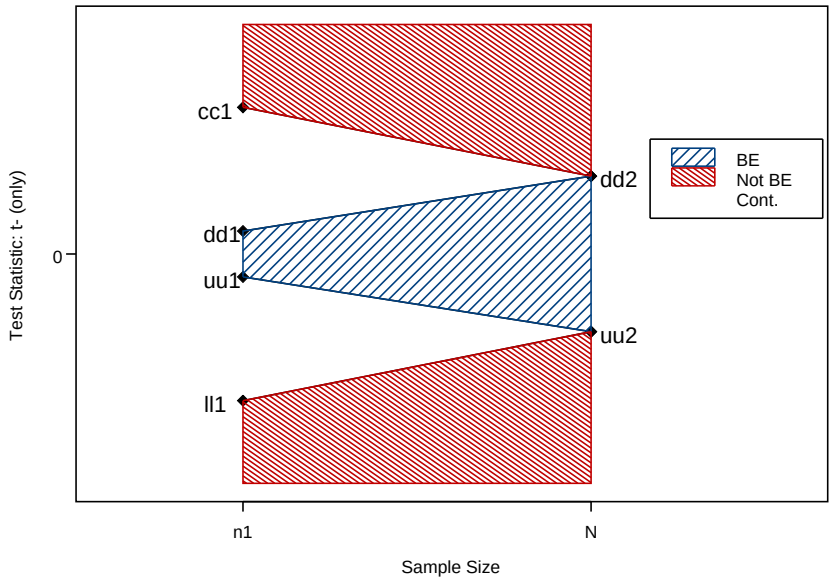
$$\beta = 1 - \rho = 1 - \rho_1 - \rho_2 = 1 - \pi_1(0) - \pi_2(0)$$

$\pi_1(\Delta)$ and $\pi_2(\Delta)$ can be evaluated by integrating over the densities t_1^- and t^-, respectively.

The futility probabilities, α_0^- and α_0^+, will be defined later in the talk.

Defining integration limits





$$dd_1 = 2U/(s_1\sqrt{2/n_1}) - uu1$$
$$cc_1 = 2U/(s_1\sqrt{2/n_1}) - ll1$$
$$dd_2 = 2U/(s\sqrt{2/N}) - uu_2$$

Defining integration limits (continued)

Decision	**only t^-**
Claim BE at interim	$t_1^- \in (uu_1, dd_1)$
Do not Claim BE at interim	$t_1^- < ll_1$ or $t_1^- > cc_1$
Continue	$t_1^- \in (ll_1, uu_1)$ or $t_1^- \in (dd_1, cc_1)$
Claim BE at end	$t^- \in (uu_2, dd_2)$
Do not Claim BE at	$t^- \leq uu_2$ or $t^- cc_2$

Note: uu_1 is less than dd_1 when $w_1 < \theta^2(n_1/2)(n_1 - 2)/uu_1^2$.

And uu_2 is less than dd_2 when w_2^* is less than $\theta^2(N/2)(N_1 - 2)/uu_2^2$.

Defining $\pi_1(\Delta)$ and $\pi_2(\Delta)$

$$\pi_1(\Delta) = \int_0^{bb_1} \int_{d_1}^{cc_1} \phi(y_1^-)\psi_{n_1-2}(w_1)\; dy_1^- dw_1$$

$$\pi_2(\Delta) =$$
$$\int_0^{bb_1} \int_{c_1}^{d_1} \int_0^{bb_2} \int_{c_2}^{d_2} \phi(y_1^-)\psi_{n_1-2}(w_1)\phi(y_2^-)\psi_{n_2}(w_2^*)\; dy_2^- dw_2^* dy_1^- dw_1$$
$$+ \int_0^{bb_1} \int_{cc_1}^{dd_1} \int_0^{bb_2} \int_{c_2}^{d_2} \phi(y_1^-)\psi_{n_1-2}(w_1)\phi(y_2^-)\psi_{n_2}(w_2^*)\; dy_2^- dw_2^* dy_1^- dw_1$$
$$+ \int_{bb_1}^{\infty} \int_{c_1}^{dd_1} \int_0^{bb_2} \int_{c_2}^{d_2} \phi(y_1^-)\psi_{n_1-2}(w_1)\phi(y_2^-)\psi_{n_2}(w_2^*)\; dy_2^- dw_2^* dy_1^- dw_1.$$

Integration limits for $\pi_1(\Delta)$ and $\pi_2(\Delta)$

$$
\begin{aligned}
bb_1 &= \theta^2(n_1/2)(n_1-2)/uu_1^2 \\
c_1 &= ll_1\sqrt{w_1/(n_1-2)} - (\mathbf{\Delta - L})/(\sigma_{\mathbf{e}}\sqrt{\mathbf{2/n_1}}) \qquad \mathbf{\Delta}/\sigma_{\mathbf{e}} = (\mathbf{\Delta}/\sigma_{\mathbf{0}})(\sigma_{\mathbf{0}}/\sigma_{\mathbf{e}}) \\
d_1 &= uu_1\sqrt{w_1/(n_1-2)} - (\Delta - L)/(\sigma_e\sqrt{2/n_1}) \\
cc_1 &= \frac{2U}{\sigma_e\sqrt{2/n_1}} - uu_1\sqrt{w_1/(n_1-2)} - (\Delta - L)/(\sigma_e\sqrt{2/n_1}) \\
dd_1 &= \frac{2U}{\sigma_e\sqrt{2/n_1}} - ll_1\sqrt{w_1/(n_1-2)} - (\Delta - L)/(\sigma_e\sqrt{2/n_1}) \\
bb_2 &= \theta^2(N/2)(N_1-2)/uu_2^2 \\
c_2 &= \frac{uu_2\sqrt{(w_1+w_2^*)/(N-2)} - y_1^-\sqrt{n_1/N} - (\Delta - L)/(\sigma_e\sqrt{2/N})}{\sqrt{n_2/N}} \\
d_2 &= \frac{2U/(\sigma_e\sqrt{2/N}) - uu_2\sqrt{(w_1+w_2^*)/(N-2)} - y_1^-\sqrt{n_1/N} - (\Delta - L)/(\sigma_e\sqrt{2/N})}{\sqrt{n_2/N}}
\end{aligned}
$$

Futility Probabilities

The futility probability is the probability of do not claim BE at the interim, which occurs when $t_1^- < ll_1$ and $t_1^- \geq 2U/(s_1\sqrt{2/n_2}) - ll_1$.

$$\begin{aligned}\alpha_0^- &= Prob[\text{Do not claim BE at interim } \mid \tau_d = L] \\ &= 1 - \int_0^\infty \int_{c_1}^\infty \phi(y_1^-)\psi_{n_1-2}(w_1)\, dy_1^- dw_1 \\ &\quad + \int_0^\infty \int_{dd_1}^\infty \phi(y_1^-)\psi_{n_1-2}(w_1)\, dy_1^- dw_1\end{aligned}$$

where $c1$ and $dd1$ are defined above, with $\Delta = L$.

Generating a design

- Set α and β
- Provide σ_0^2 and τ_{d0}
- Set equivalence criteria, L and U

- Further constraints are needed
  - When interim look will occur, defined in terms of ratio of n_1/N
  - How much of α to be spend at the interim look, α_1
  - Futility criteria, defined in terms of α_0.

- Using $\pi_1(\Delta)$ and $\pi_2(\Delta)$ can solve for rejection region parameters, ll_1, uu_1 and uu_2 for any choice of constraints

Example Designs

Let

- $\alpha = 0.05$ and $\beta = 0.10$
- σ_0 be values such that $\theta_0 = (U/\sigma_0) = 0.2628, 0.5343$ and 0.9254
- $\tau_d = 0$, $U = -L = 0.2231$, $n_1/N = 0.5$
- $\alpha_1 = 0.008821$ and $\alpha_0 = 0$ (No stopping for futility)

θ_0	N (R)	n_1	ll_1	uu_1	uu_2
0.2628	321.39 (1.03)	160.69	-4.3964	2.1963	1.6960
0.5343	78.99 (1.04)	39.50	-4.8579	2.2876	1.7108
0.9254	27.44 (1.09)	13.72	-6.5718	2.5918	1.7547

NOTE: R is the ratio of maximum sample size for the sequential design and the sample size for a fixed design.

More example Designs

Now consider the following changes:

- $n_1/N = 0.75$ (design 2)
- $\alpha_1 = 0.0303964$ (design 3)
- $\alpha_0 = 0.25$ (design 4)
- all three changes (design 5)

For $\theta_0 = 0.9254$, new designs are:

Design	θ_0	N (R)	n_1	ll_1	uu_1	uu_2
1	0.9254	27.44 (1.09)	13.72	-6.5718	2.5918	1.7547
2	0.9254	27.19 (1.08)	20.39	-5.6327	2.5816	1.7150
3	0.9254	30.19 (1.19)	15.09	-6.3268	2.0247	1.9678
4	0.9254	27.44 (1.09)	13.72	-0.6949	2.5918	1.7525
5	0.9254	28.23 (1.12)	21.17	-0.6885	1.9911	1.8404

Summary of Exact Methods

- the Exact Method is specific to:
  - bioequivalence hypothesis
  - two stage sequential design
- the exact Method provides:
  - *exact* Type I and II error probabilities
  - means to evaluate any 2 stage sequential design
- Is generalizable to
  - more than one interim look
    - computationally exhaustive
  - superiority hypotheses

Question: What methods for designing a two stage sequential design for BE already exist?

Other group sequential designs

- Many designs in the literature
  - All are based on similar principles (dependence of the later looks on earlier looks)
- Differences
  - Assume variance is known
  - Hypothesis is one or two sided superiority ($H_0 : \tau_d = 0$)
- There are approximations to account for these.

- Another alternative: Combining p-values of adaptive designs

Question: How do these compare to the exact method?

Approximations from Jennison and Turnbull[2]:

- Assumption of known variance
  - Transformation of rejection region parameters (l_1, u_1 and u_2) using the quantiles of the t-distribution ($t_{\nu,p}$):
  - $ll_1 = t_{n_1-2,1-\Phi(l_1)}$, $uu_1 = t_{n_1-2,1-\Phi(u_1)}$ and $uu_2 = t_{N-2,1-\Phi(u_2)}$
- Bioequivalence: design as a superiority trial
  - Equate: Claim different (superiority) to Do not claim BE and vice-versa

    α: is desired Type II probability of the bioequivalence trial

    β: is desired Type I probability of the bioequivalence trial
  - Transformation of the rejection region parameters, (b_1, a_1 and b_2)

$$l_1 = -b_1 + U/(\sigma_e\sqrt{2/n_1}) \qquad u_1 = -a_1 + U/(\sigma_e\sqrt{2/n_1})$$
$$u_2 = -b_2 + U/(\sigma_e\sqrt{2/N})$$

p-Value designs[3-8]

- Proposed in the context of adaptive designs
- Based on: Independence of cohorts and thus, their corresponding p-values
- p-values $\sim U[0,1]$, with z-score $(z_i = \Phi^{-1}(1-p_i))$ are $\sim N[0,1]$ (under null hypothesis)
- The combination of the p-values, $C(p_1, p_2)$ is also $N[0,1]$:

$$C(p_1, p_2) = 1 - \Phi[w_1\Phi^{-1}(1-p_1) + w_2\Phi^{-1}(1-p_2)].$$

- Compare p_1 verse α_1 and α_0 and $C(p_1, p_2)$ verse c
- For BE, p-values for both Hypotheses (H_0^- and H_0^+)are needed
- Power and sample sizes are approximate
  - z-scores are not distribute $N[0,1]$ under the alternative.

Comparison of designs

- Under the assumption of variance known, $n_1 = n_2$ and $w_i = \sqrt{(n_i/N)}$, all three designs are identical
- However, they differ under assumption of the variance being unknown
- For combination p-value designs:

  \+ error probabilities are exact under the null

  \- not all the information is used if trial continues to the end
- For approximations

  \+ uses all the information

  \- the dependence of between looks is partially ignored
- **The exact method has both advantages!!**

Question: How do they compare in terms of controlling α and β?

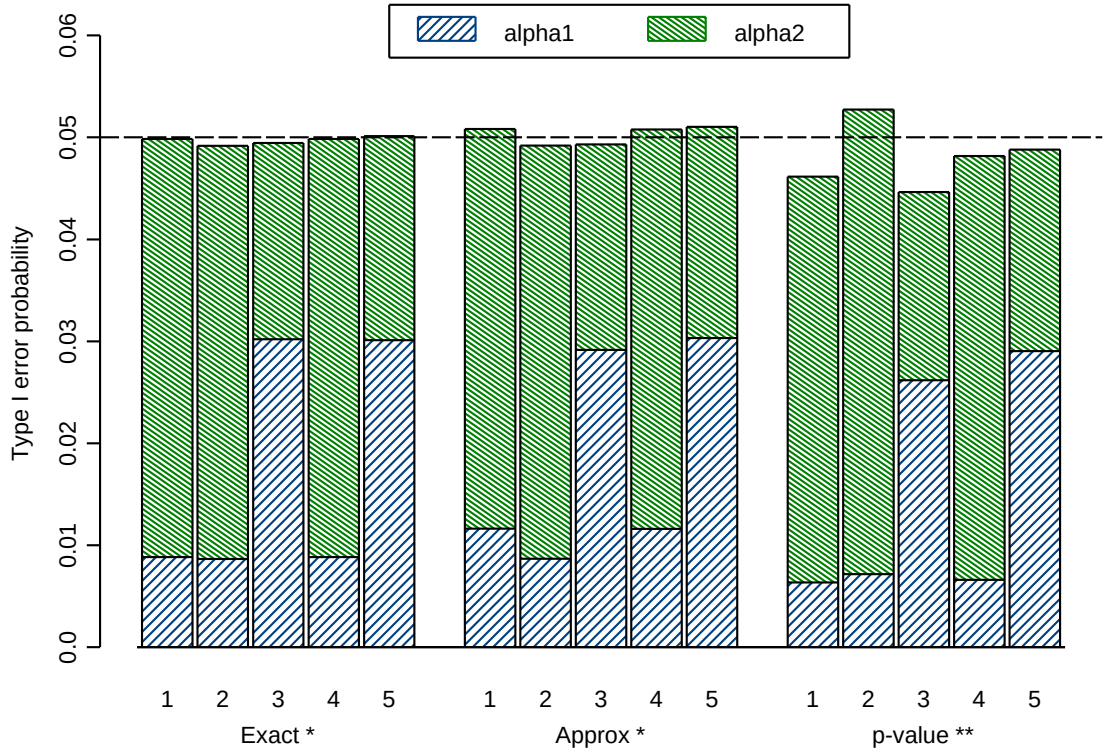
Comparison of designs: Design parameters

Parameter	**Exact Design**	**Approx. Design***	**p-value Design****
N	27.44	26	25.78
n_1	13.72	14	12.89
ll_1 or a_0	-6.5718	-6.7663	1.0
uu_1 or a_1	2.5918	2.4722	0.00882
uu_2 or c	1.7547	1.7625	0.04536

$*$ Sample sizes rounded to nearest even integer, prior to transformation of rejection region. Superiority design generated using exact methods

$**$ Rejection region parameters defined in terms of p-values (a_0, a_1 and c)

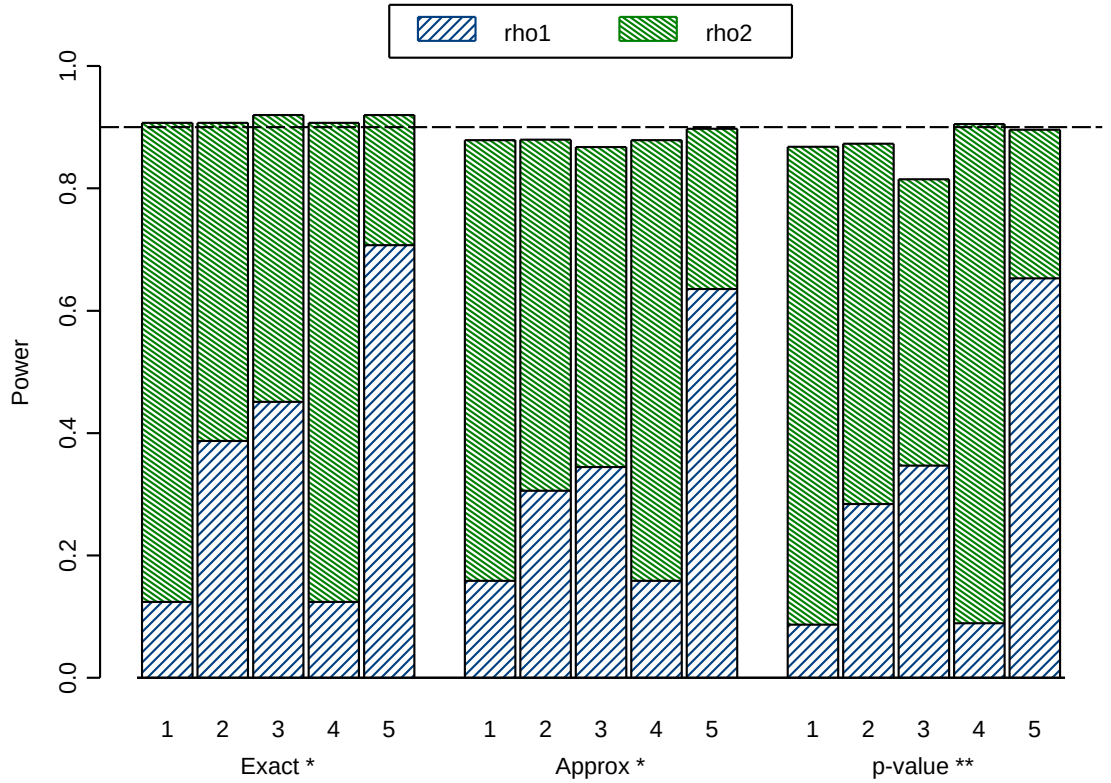
Comparison of designs: Type I error probabilities



$*$ Exact methods used to calculate probability

$**$ Monte Carlo/Importance sampling (1000 reps) used to calculate probability

Comparison of designs: Type II error probabilities



$*$ Exact methods used to calculate probability

$**$ Monte Carlo/Importance sampling (1000 reps) used to calculate probability

Other Work

- Sample size re-estimation
  - Similar methods can be used
  - Summation of integrals, each one corresponding to re-estimated value of n_2
- Two stage sequential designs with sample size re-estimation

  Fixed Sequential Design only re-estimate n_2

  Partially fixed sequential design re-estimate n_2 and uu_2

  Fully flexible sequential design re-estimate n_2, uu_1, ll_1 and uu_2

Summary

- The exact Method provides:
  - ability to design trials with *exact* Type I and II error probabilities
  - great flexibility in design constraints
  - a means to evaluate the properties of any 2 stage sequential design
- Is superior to other designs which either do not provide exact probabilities or do not utilize all information gathered in the trial
- The exact method is generalizable to
  - other hypotheses (e.g.; superiority)
  - more than one interim look
    - ∗ although computationally exhaustive

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