DESIGN AND ANALYSIS OF BIOSIMILAR STUDIES

3-part Course instruted by

Shein-Chung Chow, PhD

at the 1st
Annual Biosimilars Forum
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Assessing Biosimilarity: Issues and Recent Development

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Assessing Interchangeability: Issues, Designs and Statistical Methods

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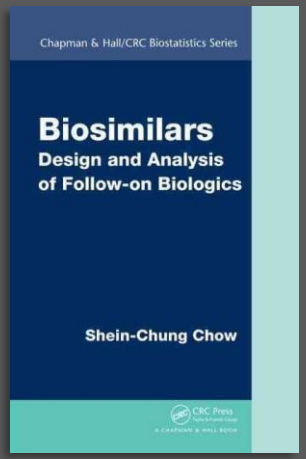
Lecture 3 (*soon*):

Analytical Similarity Assessment in Biosimilar Studies

DESIGN AND ANALYSIS OF BIOSIMILAR STUDIES

Annual Biosimilars Forum

This material includes the 2nd Lecture (entitled: **Assessing Interchangeability: Issues, Designs and Statistical Methods**) of the scientific course presented by ***Professor Shein-Chung Chow*** at the **1st Biosimilars Forum** in Budapest. The first and third parts of the course will be available to download separately, courtesy of Annual Biosimilars Forum event series at the Forum's official website: www.biosimsforum.com.



The materials of the course are developed based on

- the book entitled "**Biosimilars: Design and Analysis of Follow-on Biologics**" by *Chow SC* published in 2013 by Chapman and Hall/CRCPress, Taylor & Francis, New York,
- and the 3rd edition of the book entitled "**Design and Analysis of Bioavailability and Bioequivalence Studies**" by *Chow SC* and *Liu JP* published in 2008 by Chapman and Hall/CRC Press, Taylor & Francis, New York.

THE FIRST ANNUAL BIOSIMILARS FORUM
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Design and Analysis of Biosimilar Studies

Lecture 1: Assessing Biosimilarity: Issues and Recent Development

Lecture 2: Assessing Interchangeability: Issues, Designs and Statistical Methods

Lecture 3: Analytical Similarity Assessment in Biosimilar Studies

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Design and Analysis of Biosimilar Studies

Lecture 2
Assessing Interchnageability: Issues, Designs, and Statistical Methods

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Outline

- Concept of interchangeability
  - Switching
  - Alternating
- Current issues
  - Produce same clinical results in any given patient
- Criteria for interchangeability
  - Adjust for variability of reference product
- Study designs
  - Switching designs
- Statistical methods
- Remarks

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Definition of interchangeability

The biological product to be *interchangeable* with the reference product if

(A) the biological product

(i) is *biosimilar* to the reference product; and

(ii) can be *expected* to produce the same clinical result *in any given patient*; and

(B) for a biological product that is administered more than once to an individual, the *risk* in terms of safety or diminished efficacy of *alternating* or *switching* between use of the biological product and the reference product is *not greater than* the risk of using the reference product without such *alternation* or *switch*.

US BPCI Act 2009

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Remarks

- There is a clear distinction between biosimilarity and interchangeability
- Biosimilarity does not apply interchangeability
- The concept of interchangeability include
  - Switching
  - Alternating

  which are different from the concept of interchangeability for generic drugs
  - Prescribability
  - Switchability

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Key questions raised at FDA Public Hearings

- In practice, it is not possible to show same clinical result in any given patient.
  - Sub-population?
  - Specific population?
  - For every patient, we need to show same clinical result
- However, it is possible to show same clinical result in any given patient with certain assurance (Chow, 2010; Chow et al., 2011)

Concept of switching

- Switching
  - Switch from one biologic product to another
  - Switch from a reference to a biosimilar
  - Switch from a biosimilar to a reference
  - Switch from a biosimilar to another biosimilar
- Narrower sense of switching
  - R->T, T->R
- Broader sense of switching
  - R->T, T->R, R->R, T->T
- Complications
  - There may be a number of biosimilar products

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Concept of switching

- Where there are more than one biosimilars
  - $T_i \rightarrow R$, $R \rightarrow T_i$
  - $T_i \rightarrow T_j$
- When there are multiple references
  - US-licensed and EU-approved reference products
  - Same reference product from different location of the manufacturing process
  - Same reference product from different lots

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Concept of alternating

- Alternating
  - Switch from one biologic product to another and then switch back to the original biologic product
- Narrow sense of alternating
  - R->T->R, T->R->T
- Broader sense of alternating
  - R->T->R, T->R->T, R->R->R, T->T->T
- In practice, there may be more than one reference product and more test products

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Concept of alternating

- In practice, there may be more than one reference product and more test products
  - $R_i \rightarrow T_j \rightarrow R_i,\ T_i \rightarrow R_j \rightarrow T_i$
  - $R_i \rightarrow T_j \rightarrow R_i,\ T_i \rightarrow R_j \rightarrow T_i\ , R_i \rightarrow R_j \rightarrow R_i,\ T_i \rightarrow T_j \rightarrow T_i$

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Current issue – criteria for interchangeability

- Past experience for assessing interchangeability
  - Individual bioequivalence
  - σ_D standard deviation due to subject-by-drug interaction
  - σ_D/σ_R standard deviation due to subject-by-drug interaction adjust for standard deviation of the reference product
  - Current (80.00%, 125.00%) criteria adjust for both σ_R (SABE) and σ_D/σ_R (new proposed criterion)

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FDA's recommended criterion for individual bioequivalence (IBE)

$$\theta = \frac{(\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_{WR}^2 - \sigma_{WT}^2)}{\max(\sigma_0^2, \sigma_{WR}^2)},$$

where σ_{WR}^2 and σ_{WT}^2 are intra-subject variances for the reference product and the test product, respectively, σ_D^2 is the variance component due to the subject-by-drug product interaction, and σ_0^2 is a regulatory constant.

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FDA's recommended criterion based on σ_D

Chen, M.L., Patnaik, R., Hauck, W.W., Schuirmann, D.F., Hyslop, T., and Williams, R. (2000). An individual bioequivalence criterion - regulatory considerations. *Statistics in Medicine*, 19, 2821-2842.

- Individual bioequivalence is to address drug switchability
- Variability due to the subject-by-formulation interaction is an indicator of drug switchability
- A value of 0.15 for the estimation of the standard deviation due to the subject-by-drug product may be considered to be important

FDA's recommended criterion based on σ_D

Endrenyi, L., Taback, N. and Tothfalusi, L. (2000). Properties of the estimated variance component for subject-by-formulation interaction in studies of individual bioequivalence. *Statistics in Medicine*, 19, 2867-2878.

- Positive bias observed for the estimation of the variability due to the subject-by-formulation interaction
  - About a quarter to one-third of estimates greater than 0.15
  - These estimates do not result from the true existence of the subject-by-formulation interaction rather than the large intrasubject variability of the reference formulation
- The results from the FDA data sets exhibit almost identical pattern.

Remarks

- It is wrong to conclude the existence of the subject-by-drug product interaction if the estimate of σ_D in numerically greater than a pre-specified value such as 0.15.
- It is then suggested that criterion for drug interchangeability should be developed based on σ_D/σ_{WR}.

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Reversed BE criteria

- FDA's current position
  - A generic drug can be used as a substitute of the brand-name drug if it has been shown to be bioequivalent to the brand-name drug
- Key concept
  - T is bioequivalent to R -> T can be a substitute of R
  - R is bioequivalent to T -> R can be a substitute of T
- Reversed BE criteria
  - If T is bioequivalent to R and R is bioequivalent to T, then T and R can be used interchangeably

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A proposed new criterion based on SABE adjust for σ_D/σ_R

Step 1: Unscaled ABE criterion

$$\frac{1}{BEL} \leq GMR \leq BEL$$

where BEL=1.25

Step 2: Scaled ABE (SABE) criterion

- adjust for σ_R

Step 3: Proposed scaled criterion for drug interchangeability (SCDI)

- adjust for σ_D/σ_R

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Step 1
for development of SCDI

$$\frac{1}{BEL} \leq GMR \leq BEL$$

This implies

$$-log(BEL) \leq log(GMR) \leq log(BEL),$$

or

$$-log(BEL) \leq \mu_T - \mu_R \leq log(BEL),$$

where μ_T and μ_R are logarithmic means.

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Step 2
for development of SCDI

$$-log(BELS) \leq \frac{\mu_T - \mu_R}{\sigma_W} \leq log(BELS),$$

or

$$-log(BELS)\,\sigma_W \leq \mu_T - \mu_R \leq log(BELS)\sigma_W,$$

where σ_W^2 is a within-subject variation and $BELS$ is the BE limit for SABE. In practice, σ_{WR}^2, the within-subject variation of the reference product is often considered.

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Step 3
for development of SCDI

$$\frac{(\mu_T-\mu_R)^2+\sigma_D^2}{\sigma_W^2} = \frac{2\delta\sigma_D+(\delta-\sigma_D)^2}{\sigma_W^2},$$

where $\delta = \mu_T - \mu_R$. When δ and σ_D are close, we observe that

$$\frac{\delta^2+\sigma_D^2}{\sigma_W^2} \approx \frac{2\delta\sigma_D}{\sigma_W^2}.$$

The assumption is reasonable when both δ and σ_D are small.

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Step 3
for development of SCDI

Thus, the proposed scaled criterion for drug interchangeability (SCDI) is:

$$-log(BELS) \leq \left(\frac{\mu_T - \mu_R}{\sigma_W}\right)\left(\frac{2\sigma_D}{\sigma_W}\right) \leq log(BELS).$$

Now, let $f = \sigma_W/(2\sigma_D)$, a correction factor for drug interchangeability. Then, the proposed SCDI criterion is given by:

$$-log(BELS)\, f\sigma_W \leq \mu_T - \mu_R \leq log(BELS) f\sigma_W$$

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Simulation study

- Conducted under a 2x2 replicated crossover design
  - i.e., 2x4 crossover design (TRTR, RTRT)
- The performance of the four criteria were evaluated in terms of percent passage.
- The parameters were specified to account for best and worst scenarios:
  1. $\mu_T - \mu_R = 0\%, 5\%,$ and 10% of μ_R;
  2. $\sigma_{WR} = 0.1, 0.2,$ and 0.3 and σ_{WT} was chosen to be smaller, similar, or larger than that of σ_{WR} (i.e., ± 0.1);
  3. $\sigma_D = 0.0, 0.15, and\ 0.3$.
  4. Fixed: σ_{BR}=σ_{BR}=0.2; P1=0.001=P2=P3=P4=Sequence effect; 20 patients per sequence.

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Remarks on criteria for drug interchangeability

- The passage probability of PBE/IBE criteria was not satisfactory due to the mask effects among $\Delta\mu$, σ_D, and σ_{WR} (σ_{WT}).
- The criterion based on σ_D is not sensitive to the change in $\Delta\mu$.
- The reversed ABE criterion fails to respond adequately to the changes in σ_D and σ_{WR}.
- The SCDI criterion appears to be the most satisfactory one for addressing drug interchangeability because of its sensitivity to the changes in $\Delta\mu$, σ_D, and σ_{WR}.

Current issue – study design for interchangeability

- Study design for interchangeability
  - Crossover design
  - Switching design
  - Alternating design
  - Switching/alternating design
- Hybrid parallel-crossover design
  - Parallel plus 2x2 crossover design
  - Parallel plus 2x3 dual crossover design
  - Parallel plus replicated 2x2 crossover design
  - Complete N-of-1 randomized design
- Physician's intuition design
  - (RRRR, RTRT)

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Study design for interchangeability

- Demonstration of same clinical result in any given patient
  - Crossover design
- Demonstration of alternating or switching
  - Balaam's design
  - Repeat design (i.e., repeat the second period in a 2x2 cross over design)
  - Extra-reference design
  - Complete design
  - Physician's intuition design

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Assessing interchangeability

- In any given patient
  - 2x2 crossover design

	Period	
Seq 1	T	R
Seq 2	R	T

- Subjects are randomly assigned to receive either the sequence of TR or RT
- Each subject at his/her own control
- Does address the risk of the switch from T to R and the switch from R to T

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Assessing interchangeability

- Disadvantages of the 2x2 crossover design
  - Does not provide independent estimates of intra-subject variabilities of the test and reference products
  - Does not address the risk of the switch from T to T and the switch from R to R
- To overcome the above drawbacks, one may consider to add two sequences: TT and RR, which leads to a 4x2 crossover design
  - This 4x2 crossover design is usually referred to as Balaam's Design

Assessing interchangeability

- Assessing risk of switching
  - 4x2 Balaam's crossover design
  - All possible combinations of R and T

Balaam's Design		
	Period	
Seq 1	**R**	**T**
Seq 2	**T**	**R**
Seq 3	**R**	**R**
Seq 4	**T**	**T**

- Seq 3 and seq 4 provide independent estimates of intra-subject variabilities for the reference and test product, respectively
- Balaam's design allow the assessment of the risk of switching in the broader sense.
- However, it does not allow the assessment of the risk of alternation

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Assessing interchangeability

- Assessing risk of alternation
  - 2x3 dual crossover design

Cross-over			
	Period		
Seq 1	T	R	T
Seq 2	R	T	R

- The 2x3 dual design provide independent estimates of intra-subject variabilities of the test and reference products
- The 2x3 dual design allows the assessment of the risk of the alternation of T->R->T and R->T->R.

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Assessing interchangeability

- Assessing risk of switching/alternation
  - Four sequences modified Balaam's design
  - All possible combinations of R and T

Modified Balaam's Design			
	Period		
Seq 1	**T**	**T**	
Seq 2	**R**	**R**	
Seq 3	**T**	**R**	**T**
Seq 4	**R**	**T**	**R**

- Modified Balaam's design allows independent estimates of intra-subject variabilities of the test and reference product, respectively.
- Modified Balaam's design can assess the risk of switching and alternation.

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Assess interchangeability

- Alternative designs being considered

Physician's choice			
	Period		
Seq 1	T	R	T
Seq 2	R	R	R

Repeat			
	Period		
Seq 1	T	R	R
Seq 2	R	T	T

Extra Ref			
	Period		
Seq 1	T	R	R
Seq 2	R	T	R

- The one on the left is physician's choice. Seq 2 allows the establishment of reference standard
- The one in the middle is a design repeats the second period which also allows independent estimates of intra-subject variabilities
- The one on the right is so-called extra-reference design, which the optimal design for assessing IBE among the 2x3 crossover design.

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Assess interchangeability

- Alternative designs being considered

Complete Design			
	Period		
Seq 1	T	R	R
Seq 2	R	T	R
Seq 3	R	R	T

- This design is nothing but adding Seq 3 to the extra-reference design. This design is balance in the sense that there is only on test product in each sequence. The performance of this design is very similar to that of the extra-reference design.

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Comparison of designs under IBE

	Design	Decomposition of γ	m	d.f of σ^2_{Wl}	$\mathrm{Var}(2\hat{\delta})$
Cross Over	TRT vs. RTR	$\delta^2 + 0.5(\sigma^2_{0.5,1} + \sigma^2_{1,0.5}) + 0.25\sigma^2_{WT} - 1.75\sigma^2_{WR} - c$	5	$n_1 - 1$ or $n_2 - 1$	$\frac{1}{n_1}\sigma^2_{0.5,1} + \frac{1}{n_2}\sigma^2_{1,0.5}$
Repeat Design	TRR vs. RTT	$\delta^2 + 0.5(\sigma^2_{0.5,1} + \sigma^2_{1,0.5}) + 0.25\sigma^2_{WT} - 1.75\sigma^2_{WR} - c$	5	$n_2 - 1$ or $n_1 - 1$	$\frac{1}{n_2}\sigma^2_{0.5,1} + \frac{1}{n_1}\sigma^2_{1,0.5}$
Jessica's Design	TRT vs. RRR	$\delta^2 + \sigma^2_{0.5,1} + 0.5\sigma^2_{WT} - 2\sigma^2_{WR} - c$	4	$n_1 - 1$ or $n_2 - 1$	$\frac{4}{n_2}\sigma^2_{0.5,1}$

Table 1: Comparison of Different Designs ($c = \theta_U max\{\sigma^2_0, \sigma^2_{WR}\}$)

	Design	Decomposition of γ	m	d.f of σ^2_{Wl}	$\mathrm{Var}(2\hat{\delta})$
Extra Reference	TRR vs. RTR	$\delta^2 + \sigma^2_{1,0.5} - 1.5\sigma^2_{WR} - c$	3	$n_1 + n_2 - 2$	$(\frac{1}{n_1} + \frac{1}{n_2})\sigma^2_{1,0.5}$
Complete Design	TRR vs. RTR vs. RRT	$\delta^2 + \sigma^2_{1,0.5} - 1.5\sigma^2_{WR} - c$	3	$n_1 + n_2 + n_3 - 3$	$\mathrm{Var}(3\hat{\delta}) = (\frac{1}{n_1} + \frac{1}{n_2} + \frac{1}{n_3})\sigma^2_{1,0.5}$

Table 2: Comparison of Different Designs ($c = \theta_U max\{\sigma^2_0, \sigma^2_{WR}\}$)

	Design	Decomposition of γ	m	d.f of σ^2_{Wl}	$\mathrm{Var}(2\hat{\delta})$
Balaam's Design	RT vs. TR vs. RR vs. TT	$\delta^2 + \sigma^2_{1,1} - 2\sigma^2_{WR} - c$	3	$n_3 - 1$ or $n_4 - 1$	$(\frac{1}{n_1} + \frac{1}{n_2})\sigma^2_{1,1}$

Table 3: Comparison of Different Designs ($c = \theta_U max\{\sigma^2_0, \sigma^2_{WR}\}$)

Hybrid parallel-crossover design

- Hybrid parallel plus crossover design
  - With 2 dosing periods
    e.g., parallel plus 2x2 crossover design
  - With 3 dosing periods
    e.g., parallel plus 2x3 dual crossover design
  - With 4 dosing periods
    e.g., parallel plus replicated 2x2 crossover design
- N-of-1 randomized design
  - Complete design
  - Partial design
    e.g., physician's intuition design

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Hybrid
parallel plus 2x2 crossover design

- Parallel part
  - Two parallel-group with replicates, i.e., (RR,TT)
- Crossover part
  - 2x2 crossover design, i.e., (RT,TR)
- Hybrid parallel plus crossover
  - The combination of parallel and crossover becomes a 4x2 crossover design (RR,TT,RT, TR)
  - This leads to Balaam 4x2 crossover design

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Hybrid
parallel plus 2x2 crossover design

(1) Comparisons by sequence;
(2) Comparisons by period;
(3) T *vs*. R based on sequence #3 and #4
  – this is equivalent to the analysis of a typical 2x2 crossover design;
(4) T vs R given T based on sequence #1 and #3;
(5) R vs T given R based on sequence #2 and #4;
(6) The comparison between (1) and (3) for the assessment of treatment-by-period interaction.
(7) This design may be useful for assessing drug interchangeability in terms of switching

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Hybrid parallel plus 2x3 dual crossover design

- Parallel part
  - Two parallel-group with replicates, i.e., (RRR,TTT)
- Crossover part
  - 2x3 crossover design, i.e., (RTR,TRT)
- Hybrid parallel plus crossover
  - The combination of parallel and crossover becomes a 4x3 crossover design

  (RRR,TTT,RTR, TRT)

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Hybrid parallel plus replicated 2x2 crossover design

- Parallel part
  - Two parallel-group with replicates, i.e., (RRRR,TTTT)
- Crossover part
  - Replicated 2x2 crossover design, i.e., (RTRT,TRTR)
- Hybrid parallel plus crossover
  - The combination of parallel and crossover becomes a 4x4 crossover design

    (RRRR,TTTT,RTRT, TRTR)

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Physician's intuition design

- Parallel part
  - Select a group from the two parallel-group with replicates, i.e., RRRR
- Crossover part
  - Select a group (sequence) from the replicated 2x2 crossover design, e.g., RTRT
- Hybrid parallel plus crossover
  - The combination of parallel and crossover becomes a 2x4 crossover design

    (RRRR,RTRT)

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Complete N-of-1 randomized design

Qualified subjects are randomly assigned to receive one of the sequences of treatments

Table 4: A Complete N-of-1 Randomized Trial Design with Four Periods

Group	Period I	Period II	Period III	Period IV
1	R	R	R	R
2	R	R	R	T
3	R	R	T	R
4	R	R	T	T
5	R	T	R	R
6	R	T	R	T
7	R	T	T	R
8	R	T	T	T
9	T	R	R	R
10	T	R	R	T
11	T	R	T	R
12	T	R	T	T
13	T	T	R	R
14	T	T	R	T
15	T	T	T	R
16	T	T	T	T

Physician's intuition design

- Physician's intuition design consists of two groups (sequences) of treatments
  - One group is selected from the parallel part, e.g., RRRR
  - The other group is selected from the crossover part, e.g., RTRT
  - Thus, the physician intuition design is given by (RRRR,RTRT)
- Physician's intuition design and its dual design constitute a hybrid parallel-crossover design
- Physician's intuition design has received much attention lately

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Physician's intuition design

- Advantages
  - Allow estimate of intra-subject variability of the reference product
  - Allow assessment of risk of switching for "R to T", "T to R", and "R to R"
  - Allow assessment of risk of alternation within individual subject, i.e., "R to T to R", "T to R to T", and "R to R to R"
- Limitations
  - Possible confounding and/or interaction effects
  - Does not allow estimate of intra-subject variability of the test product
  - Cannot fully address switching and/or alternation
  - By sequence analysis and/or by period analysis are not appropriate

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Remarks

- Hybrid parallel-crossover designs (with 2, 3, or 4 dosing periods) are special cases of complete N-of-1 randomized design
- Physician's intuition design is a partial design of the parallel plus replicated 2x2 crossover design which in turn is a partial design of the complete N-of-1 randomized design
- To have a complete assessment of switching and/or alternation for drug interchangeability, the complete N-of-1 randomized design is useful.

Statistical methods

- Concept of reproducibility probability
- Development of biosimilarity index
- Development of switching index
  - Based on reproducibility probability
- Development of alternating index
  - Based on reproducibility probability
- Similar idea can be applied to develop biosimilarity, switching, and alternating indices
  - Multiple principal component analysis approach

Statistical methods

We are interested in testing the following hypotheses:

H_0 : the study is not positive vs.

H_a : the study is positive

H_0 is rejected if and only if |T|>c, where c is a positive known constant and T is a test statistic.

The reproducibility probability of observing a significant clinical result when H_a is indeed true is given by

$$p = P(|T| > c \mid H_a) = P(|T| > c|\hat{\theta}),$$

where $\hat{\theta}$ is an estimate of θ, which is an unknown parameter or vector of parameters.

Development of biosimilarity index

- Probability-based indices
  - biosimilarity and switching index
  - alternating index for assessment of interchangeability are developed based on reproducibility probability.
- Moment-based indices

  For example, we may conside a standardized score

$$\hat{Z}_d = \frac{\hat{\mu}_T - \hat{\mu}_R}{\hat{\sigma}_d}$$

  In this case, the biosimilarity index can be defined as

$$\text{BI} = \hat{Z}_d \text{ or BI} = \Phi(\hat{Z}_d)$$

Local biosimilarity index

This biosimilarity index proposed by Chow et al. (2011) is illustrated based on the well-established bioequivalence criterion by the following steps:

Step 1: Assess average biosimilarity based on a given criterion, e.g. (80%, 125%) based on logtransformed data;

Step 2: Calculate the local biosimilarity index (i.e., reproducibility) based on the observed ratio

and variability;

Local biosimilarity index

Step 3: Claim local biosimilarity if the 95% confidence lower bound of the biosimilarity index is larger than p_0 , a pre-specified number.

Note that p_0 can be obtained based on an estimated of reproducibility probability for an R-R study comparing a reference product to itself (the reference product).

Zhang AJ, Tzeng JY, and Chow SC (2014). GaBI Journal, to appear.

Totality biosimilarity index

To address the totality-of-the-evidence, the biosimilarity index Chow; Chow et al. (2011) can be obtained at each domain by the following steps

Step 1: Obtain $\hat{p}_i$, the biosimilarity index for the ith domain;

Step 2: Define the totality biosimilarity index as

$$\hat{p}_T = \sum_{i=1}^{k} w_i \hat{p}_i,$$

where w_i is the weight for the *i* th domain, where *i* =1,…,*k* (number of domains);

Step 3: Claim local biosimilarity if the 95% confidence lower bound of $\hat{p}_T$ is greater than a pre-specified value

Advantages

- It is robust with respect to the selected study endpoint, biosimilarity criteria, and study design,
- It takes variability into consideration (one of the major criticisms in the assessment of average bioequivalence),
- It allows the definition and assessment the degree of similarity (in other words, it provides partial answer to the question that “how similar is considered similar?” and
- The use of biosimilarity index or totality biosimilarity index will reflect the sensitivity of heterogeneity in variance.

Switching index (SI)

Under a 4×2 Balaam's crossover design, define p_{Ti} the totality biosimilarity index for the ith switch, where *i* =

- 1 (switch from R to R),
- 2 (switch from T to T),
- 3 (switch from R to T), and
- 4 (switch from T to R).

Switching index (SI)

As a result, the switching index (SI) can be obtained as follows :

Step 1: Obtain $\hat{p}_{Ti}$, , i =1,…,4;

Step 2: Define switching index as ,

$$SI = \min_i \{\hat{p}_{Ti}\},$$

$i = 1, \ldots, 4$ which is the largest order of the biosimilarity indexes;

Step 3: Claim switchability if the 95% confidence lower bound of SI is greater than a pre-specified value p_{S0}

Switching index (SI)

- The probability density function of the defined switching index *SI* =$P_{T(4)}$

$$f_{SI}(p) = \frac{4!}{3!}\big(F(p)\big)^0\big(1-F(p)\big)^3 f(p) = 4\big(1-F(p)\big)^3 f(p).$$

- The expected value and the variance of *SI* can be given by

$$\mu_{SI} = E(SI) = 4\int p\big(1-F(p)\big)^3 f(p)dp$$

$$V(SI) = \mathrm{E}(SI^2) - (\mu_{SI})^2$$

where $\mathrm{E}(SI^2) = \int p^2\big(1-F(p)\big)^3 f(p)dp$

- The 95% CI lower bound of *SI* can be obtained

Alternating index (AI)

Under a modified Balaam's crossover design, i.e., (TT, RR, TRT, RTR), define p_{Ti} the totality biosimilarity index for the ith switch, where *i* =

- 1 (switch from R to R),
- 2 (switch from T to T),
- 3 (switch from R to T), and
- 4 (switch from T to R).

Alternating index (AI)

As a result, the alternating index (AI) can be obtained as follows:

Step 1: Obtain $\hat{p}_{Ti}$, , i =1,…,4;

Step 2: Define the range of these indexes,
$AI = \max_i\{\hat{p}_{Ti}\} - \min_i\{\hat{p}_{Ti}\}$, as the alternating index;

Step 3: Claim switchability if the 95% confidence lower bound of AI is greater than a pre-specified value p_{A0}

Alternating index (AI)

- The joint density function of $\max_i\{\hat{p}_{Ti}\}$ *and* $\min_i\{\hat{p}_{Ti}\}$, is given by

$$f_{(1,4)}(p) = 12f\left(p_{T(1)}\right)f\left(p_{T(4)}\right)\left[F\left(p_{T(4)}\right) - F\left(p_{T(1)}\right)\right]^2$$

The expected value and the variance of *SI* can be given by

$$\mu_{AI} = E(AI) = 12\iint (p_{T(4)} - p_{T(1)})$$
$$f\left(p_{T(1)}\right)f\left(p_{T(4)}\right)\left[F\left(p_{T(4)}\right) - F\left(p_{T(1)}\right)\right]^2 dp_{T(1)}dp_{T(4)}$$
$$V(AI) = \mathrm{E}(AI^2) - (\mu_{AI})^2$$

where $\mathrm{E}(AI^2) = 12\iint (p_{T(4)} - p_{T(1)})^2$
$$f\left(p_{T(1)}\right)f\left(p_{T(4)}\right)\left[F\left(p_{T(4)}\right) - F\left(p_{T(1)}\right)\right]^2 dp_{T(1)}dp_{T(4)}$$

Remarks

- Clinical/statistical interpretation of the concepts of interchangeability need to be clarified.
  - Prescribability versus switchability for generic drugs
  - Switching versus alternating for biosimilars
- Following similar idea, alternative switching and alternating indices can be developed under various switching/alternating designs.
  - Sample size estimation can be performed.
- However, regulatory guidance on the criteria for interchangeability in terms of switching and alternation are necessarily developed before valid statistical methods can be developed.

DESIGN AND ANALYSIS OF BIOSIMILAR STUDIES

Annual Biosimilars Forum

The third lecture of the course will be available soon to download separately courtesy of Annual Biosimilars Forum event series at the Forum's official website: www.biosimsforum.com.

1

Lecture 1:

Assessing Biosimilarity: Issues and Recent Development

2

Lecture 2:

Assessing Interchangeability: Issues, Designs and Statistical Methods

3

Lecture 3 (*coming soon*):

Analytical Similarity Assessment in Biosimilar Studies

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The **Viennese Section of the International Biometric Society** is part of the ROeS, the Austrian Swiss Region of the International Biometric Society (IBS). WBS is an independent, non-profit organization which provides a professional forum for discussions of how to apply statistical methods in biological and medical science.

The **Hungarian Society for Clinical Biostatistics** is a national group of International Society for Clinical Biostatistics (ISCB), and it was founded to stimulate research into the principles and methodology used in the design and analysis of clinical research and to increase the relevance of statistical theory to the real world of clinical medicine.

Accelsiors Ltd. – as a scientific driven CRO – has been a committed supporter of biosimilar drug development, many of their professionals were involved into biosimilar drug development from the early beginnings, guided and managed the first biosimilar drug development projects and professionally supporting clinical trials as well as registration in this innovative field and being active in the clinical research arena in the past two decades.