An R-Shiny Application for Design of Comparative Clinical Endpoint Bioequivalence Studies

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♦ Background

- For certain drug products such as complex locally acting drugs, bioequivalence (BE) to a reference listed drug (RLD) may be evaluated via comparative clinical endpoint BE studies.
- The design of a comparative clinical endpoint BE study is generally a blinded, randomized, and parallel study with various statistical test methods (Fig 1).
- A placebo arm is usually included in order to demonstrate that the study is sufficiently sensitive to detect product differences in the patient population enrolled in the study.
- However, these studies could be challenging due to a large sample size, insensitiveness (e.g., small effect size), and cost and time associated with conducting such studies.

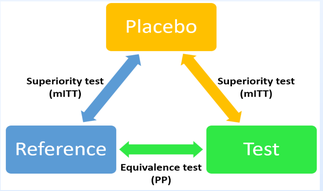


Fig 1. Statistical tests in comparative clinical endpoint bioequivalence studies.
mITT: Modified Intention to Treat; PP: Per Protocol

♦ Objective

- To facilitate the design of a comparative clinical endpoint BE study in terms of
  - Estimate sample size and power
  - Determine study duration, such as the time point to assess BE
  - Evaluate the study sensitivity
  - Streamline the study design to save time and budget

♦ Methods

- An R-Shiny based application (app) was developed to facilitate the design of BE studies with clinical endpoints in terms of sample size and study duration.
- The R and RStudio were used for programming and app testing.
- For continuous endpoints, the *PowerTOST* package was used for a sample size and power determination. For binary endpoints, published statistical equations were used. [1]
- For illustrative purpose, two hypothetical case studies were used.

♦ Results

Case #1 : **Sample** Size/Power Estimation for BE Assessment with Clinical Endpoints at a Prespecified Timepoint

Table 1. Input Values for Case #1

Type of Input	Contents	Value
Efficacy	Proportion of success for RLD	63%
	Proportion of success for Test	63%
	Proportion of success for Placebo	27%
Design features	Enrolled subjects qualified for the mITT	67%
	mITT subjects qualified for the PP	82%
	Desired Power	80%
	Acceptable Type I error rate	5%

Fig 2. Screenshot of Shiny Application for Input Values (left) and Final Sample Size Tab Output (right) in Case #1

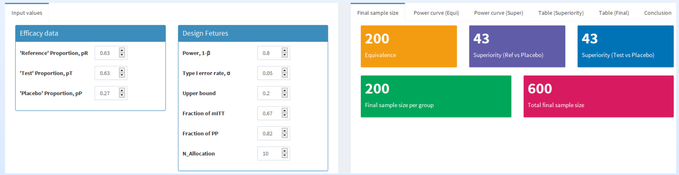
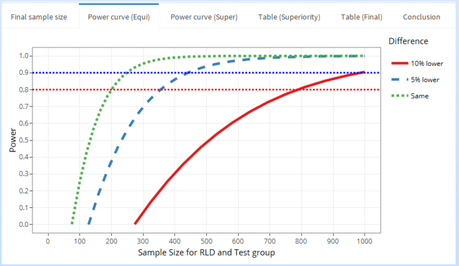
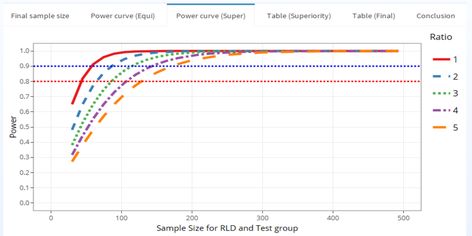


Fig 3. Power Curve of Equivalence Test in Case #1



- Explore the study power based on differences of treatment response rate between the RLD and Test products.
- Assuming the same, 5% and 10% lower response rate for the test product as compared to the RLD, sample size were estimated to be 200, 355, 789 per group for 80% power of study, respectively.
- Based on the assumption of same efficacy, sample size for 80%, 85%, 90% of power were 200, 220, 250 per group, respectively.

Fig 4. Power Curve of Superiority Test in Case #1



Ratio 1: RLD:Test:Placebo=1:1:1; Ratio 2: RLD:Test:Placebo=2:2:1; Ratio 3: RLD:Test:Placebo=3:3:1
Ratio 4: RLD:Test:Placebo=4:4:1; Ratio 5: RLD:Test:Placebo=5:5:1

- Due to the large effect size (RLD 0.63 vs Placebo 0.27), superiority test is easy to pass.
- Imbalanced designs (i.e., smaller placebo arm as compared to active treatment arms) are explored.

Table 2. Summary of Sample Size with Different Allocation Ratio and Power in Case #1

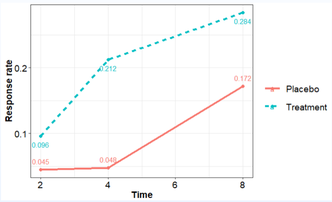
	Allocation	Power	Active	Placebo	Total	Sample_size
1	9	0.8	224	25	473	RLD:Test:Placebo = 224:224:25
2	10	0.8	239	24	502	RLD:Test:Placebo = 239:239:24

	Allocation	Power	Active	Placebo	Total	Sample_size
1	8	0.9	269	34	572	RLD:Test:Placebo = 269:269:34
2	9	0.9	299	34	632	RLD:Test:Placebo = 299:299:34
3	10	0.9	329	33	691	RLD:Test:Placebo = 329:329:33

- Final sample size and allocation ratio were determined to satisfy both the equivalence and superiority test.
- Final sample size recommendation was based on the total sample size to pass BE.
- Final recommended sample size were RLD:Test:Placebo = 224:224:25 and 269:269:34 when power was 0.8 and 0.9, respectively.

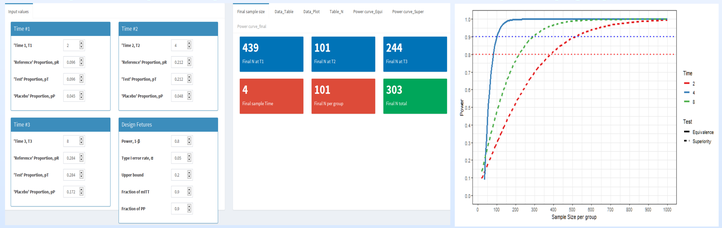
Case #2 : How to Determine the Time Point to Assess BE

Fig 5. Treat Response Rate at Various Timepoints (Days, Case #2)



	time	ref	test	placebo
1	2	0.096	0.096	0.045
2	4	0.212	0.212	0.048
3	8	0.284	0.284	0.172

Fig 6. Screenshot of R-Shiny Application for Input Values (left), Final Sample Size (middle) and Power Curve at Each Timepoint (right)



- Final sample size at each timepoint was determined by combined superiority and equivalence tests.
- Best timepoint and sample size were 101 per group at Day 4 in this case study.

♦ Conclusion

- The developed R-Shiny app could be used an efficient tool to assist comparative clinical endpoint BE study design.

♦ References

[1] Tu D. *J Stat Comput Simul*. 1997;59(3):271-290.

♦ Acknowledgements & Disclaimer

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