

Technical Inference Problems in Non-Inferiority Trials

Nor Afzalina Azmee
&
Nick Fieller

Department of Probability & Statistics
University of Sheffield, UK

The 9th Islamic Countries Conference On Statistical Science
Shah Alam, Malaysia



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Talk Outline

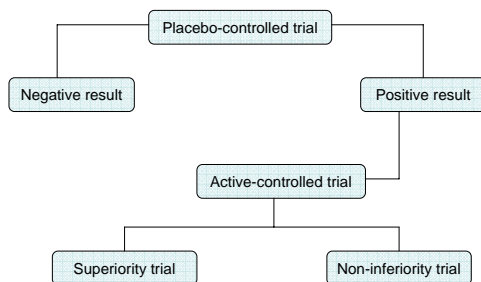
- Introduction
- Non-Inferiority Trials
- Assessment Method
- Ratio Estimation
- Examples
- Future work



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Introduction



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Introduction

- Superiority trial:
Is treatment A better than treatment B?
- Non-inferiority trial:
Is treatment A no worse than treatment B?



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Non-Inferiority Trials

- Aim: to show treatment E no worse than treatment R
- A predefined margin is specified
- Why is this trial important?
 - Public interest
 - Superiority trials become saturated



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Non-Inferiority Trials

- Types of non-inferiority trials:
 - 2 – arm ; E and R arms
 - 3 – arm; E, R and P arms
 - multi – arm; eg: different doses
- Reason: to eliminate assay sensitivity

(E-Experimental, R – Reference, P-Placebo)



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Non-Inferiority Trials

7

- Definition of assay sensitivity:-

“The ability of a study to distinguish between active and inactive treatments”

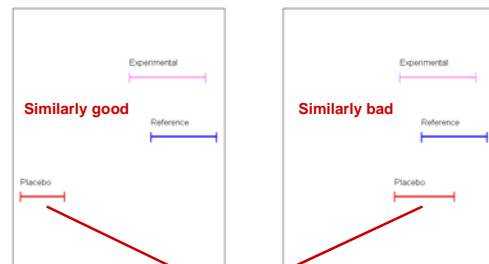


Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Non-inferiority Trials

8



2 POSSIBILITIES



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Non-Inferiority Trials

9

- Justification when including placebo
 - R is weak
 - R is traditional
 - R is volatile
 - Disease not understood
 - Delaying R is acceptable



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Non-Inferiority Trials

10

- CHMP (2005) declared:
 - 3 – arm non-inferiority trial should be used wherever possible.
- Also known as the “GOLD STANDARD” design.



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Assessment Method

11

- Naïve approach:
 - $H_0 : \mu_A = \mu_B$
 - $H_1 : \mu_A \neq \mu_B$

- H_0 not rejected \neq non-inferior

Absence of evidence of a difference

IS NOT

Evidence of absence of a difference



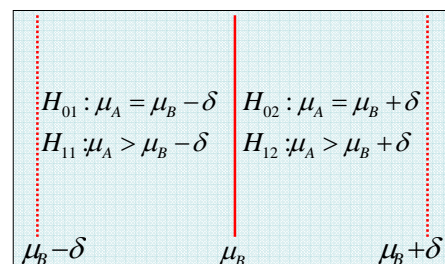
Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Assessment Method

12

- Equivalence approach:



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Assessment Method

13

• Non-inferiority approach: $\delta = f\mu_B$

• So, $H_0 : \mu_A \leq \mu_B - f\mu_B$

$H_1 : \mu_A > \mu_B - f\mu_B$

• Algebraic manipulation shows:-

$H_0 : \frac{\mu_A}{\mu_B} \leq \theta$ versus $H_1 : \frac{\mu_A}{\mu_B} > \theta$

$$\theta = 1 - f$$

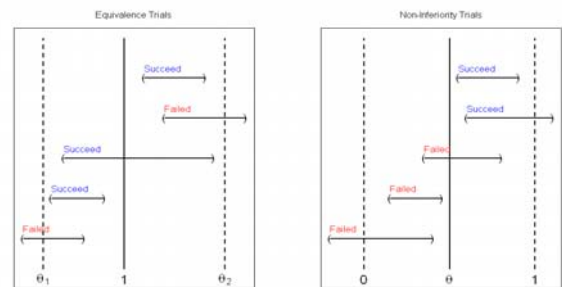


Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Assessment Method

14

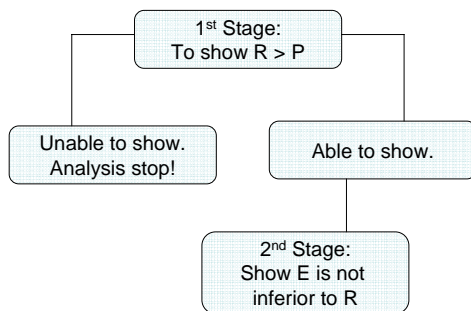


Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Assessment Method

15



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Ratio Estimation

16

• 2nd stage: Find the intervals for the ratio

• 3 methods to assess non-inferiority:

- Fieller's method (1944, 1954)

- The delta method

- Modified t – test (Pigeot, 2003)

Peculiar confidence intervals



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Ratio Estimation

17

• Assume that \bar{x}_A and \bar{x}_B are (possibly correlated) means of two samples with expectations μ_A and μ_B and variances $v_{11}\sigma^2$ and $v_{22}\sigma^2$ and covariance $v_{12}\sigma^2$



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Fieller's Method

18

• Define : -

$$g = \frac{t_{1-\alpha, r}^2 s^2 v_{22}}{\bar{x}_B}$$

And

$$E = v_{11} - 2 \frac{\bar{x}_A}{\bar{x}_B} v_{12} + \left(\frac{\bar{x}_A}{\bar{x}_B} \right)^2 v_{22} - g \left(v_{11} - \frac{v_{12}^2}{v_{22}} \right)$$



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Fieller's Method

19

- The upper and lower limits are :-

$$m_U, m_L = \frac{1}{1-g} \left[\frac{\bar{x}_A}{\bar{x}_B} - g \frac{v_{12}}{v_{22}} \pm \frac{t_{1-\alpha, r} S}{\bar{x}_B} \sqrt{E} \right]$$

-Exclusive
-Infinite

-Imaginary

POTENTIAL PROBLEMS



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Fieller's Method

20

- Easily implemented in 3 groups: E, R and P groups.
- Ratio of interest is:-

$$\frac{\mu_E - \mu_P}{\mu_R - \mu_P} > \theta$$

$$\theta = 0.5$$

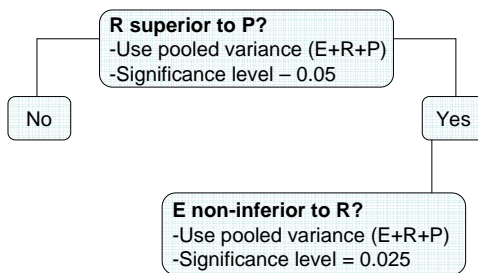


Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Example 1

21



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Example 1

22

Data

	Experimental	Reference	Placebo
Mean	1.4	1.53	1.15
Standard Deviation	0.74	0.82	0.72
Sample size	25	25	25

Result

Lower CI 1st Test	Upper CI 1st Test	Lower CI 2nd Test	Upper CI 2nd Test
0.02	0.74	IM	IM

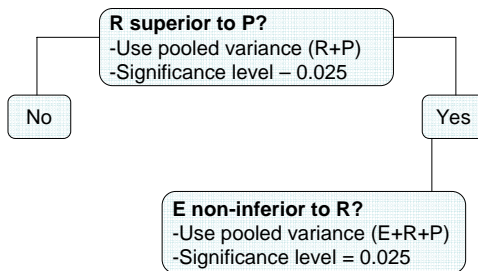


Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Example 2

23



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Example 2

24

Data

	Experimental	Reference	Placebo
Mean	1.81	1.01	0.55
Standard Deviation	1.18	0.77	0.79
Sample size	25	25	25

Result

Lower CI 1st Test	Upper CI 1st Test	Lower CI 2nd Test	Upper CI 2nd Test
0.02	0.91	1.34	-16.17



Technical Inference Problems in Non-Inferiority Trials, ICCS-IX, 12-14th December 2007



Future Works

- What are the meanings of exclusive and imaginary confidence intervals?
- Is two-stage testing really needed?
- Is there a better way of assessing non-inferiority?



Reference

Pigeot, I., Schäfer, J., Röhmel, J. and Hauscke, D. (2003). Assessing non-inferiority of a new treatment in a three-arm trial including a placebo. *Statistics in Medicine*, 22:883-899.

Koch, A. and Röhmel, J. (2004). Hypothesis testing in the "Gold Standard" design for proving the efficacy of an experimental treatment relative to placebo and a reference. *Journal of Biopharmaceutical Statistics*, 14: 315-325

Fieller, E.C. (1954). Some problems in interval estimation. *Jour. Roy. Statist. Soc., B*, 16:175-185

