The Special Case of Clinically Meaningful Similarity

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Outline

- Contrast Superiority and Non-inferiority hypotheses
- **Choice of non-inferiority margin**
- Challenges of non-inferiority trials -- including required sample sizes

Leon AC. Comparative Effectiveness Clinical Trials in Psychiatry: Superiority, Non-inferiority and the Role of Active Comparators. *J Clinical Psychiatry* 2011

Comparative Effectiveness Research

The US Agency for Healthcare Research and Quality (AHRQ) issued RFAs for comparative effectiveness research (CER)

CER: "the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in 'real world' settings …"

Possible CER Questions

Superiority

Is Investigational Agent superior to Active Comparator?

Non-inferiority

Is Investigational worse than Active Comparator?

Superiority Trial Hypotheses

H_0 : Investigational = Active Comparator

H_1: Investigational ≠ Active Comparator

If H_0 is not rejected,

No difference can mean either:

- *Both* treatments are effective *or*
- *Neither* treatment is effective

Superiority Trial

Design trial to have sufficient power to detect a *clinically meaningful effect*.

Meta-analysis of placebo-controlled SGA trials for schizophrenia: *d=.51* *(Leucht et al, 2009)*

Assume PANSS sd=20:

10 PANSS units; d=.50 (64/grp; 80% power)

8 PANSS units; d=.40: (100/grp; 80% power)

CER: Expect smaller *d* with active comparator *(larger N)*

How small an effect is still meaningful?

Non-significant Superiority Result

A negative superiority trial does not demonstrate equivalence or non-inferiority.

Result could stem from problems with design or implementation.

Evidence of non-inferiority comes from well-designed and well-conducted non-inferiority trial.

Non-Inferiority Trials

Research Question: Is an inexpensive generic inferior to a more costly, novel intervention?

Non-inferiority design not widely used in psychopharm.

Non-inferiority trials could play fundamental role in CER.

Non-Inferiority Trial Hypotheses

H_0: Active – Investigational ≥ Non-Inferiority Margin

*Active comparator is **superior** to Investigational*

H_1: Active – Investigational < Non-Inferiority Margin

*Investigational is **not inferior** to Active comparator*

Choosing Non-Inferiority Margin (δ)

- Defining "not worse than":
  Largest difference that is *clinically acceptable* or *clinically indifferent*

- Margin (δ) should be:
  < smallest effect of active vs. placebo

  << clinically meaningful dif. (d) of superiority RCT

- NI margin (δ) must be stated in protocol

Choosing Non-Inferiority Margin (δ)

- Meta-analysis of placebo controlled RCTs of SGAs for schizophrenia (Leucht, 2009): d =0.51
- If PANSS sd=20, d =.50… 10 PANSS units
- If 5 PANSS units corresponds with non-inferiority, δ =.25
- Is 5 PANSS points clinically *acceptable* difference? 3 PANSS points? 2 points?

Involve clinicians and patients

Choosing Non-Inferiority Margin (δ)

Meta-analysis RCTs of fluox for MDD: d =.38 (DeBrota, NCDEU)

- If HAMD sd=8, d =.40… 3.2 HAMD units
- If HAMD difference of 2 represents non-inferiority, δ =.25
- Is 2 HAMD points clinically *acceptable* difference?
  1 point?

Non-Inferiority Sample Sizes

Required NI Sample Size > Superiority N

If non-inferiority margin is half of the difference expected in superiority RCT, non-inferiority N is fourfold higher (binary & continuous outcomes)

Note: ½ is used for illustration. It is not a guideline.

Non-Inferiority Sample Sizes: Continuous Outcome

N/group	Delta (sd units)
6280	0.05
1570	0.10
698	0.15
393	0.20
252	0.25

NCSS/PASS

Assumes: $\alpha = .025$; $\beta = .20$

Another Challenge: Assay Sensitivity

Interpretation of NI trials problematic if Active Comparator inconsistently separates from placebo

Precludes use of NI design for depression and anxiety

FDA Draft Guidance: Non-Inferiority Clinical Trials, 2010

Summary

- Choosing the Non-Inferiority Margin (δ)
  - Small enough δ to convince clinicians/researchers that investigational intervention is therapeutic

- Other challenges of Non-Inferiority Trials:
  - Feasibility of NI sample size
  - Evidence of assay sensitivity in the absence of placebo.