Delfini Group™, LLC

Evidence- & Value-based Solutions For Health Care
Clinical Improvement Consults, Content, Seminars, Training & Tools

Primer: RCT Design Goals - Superiority, Equivalence & Non-inferiority

Key Points

Randomized controlled trials are designed to compare two or more groups to determine superiority, equivalence or non-inferiority of one experiment to another (such as one treatment compared to another treatment or to placebo).

Caution ➔ **Evaluating equivalence and non-inferiority is complex and prone to pitfalls and Delfini discourages use of these designs**

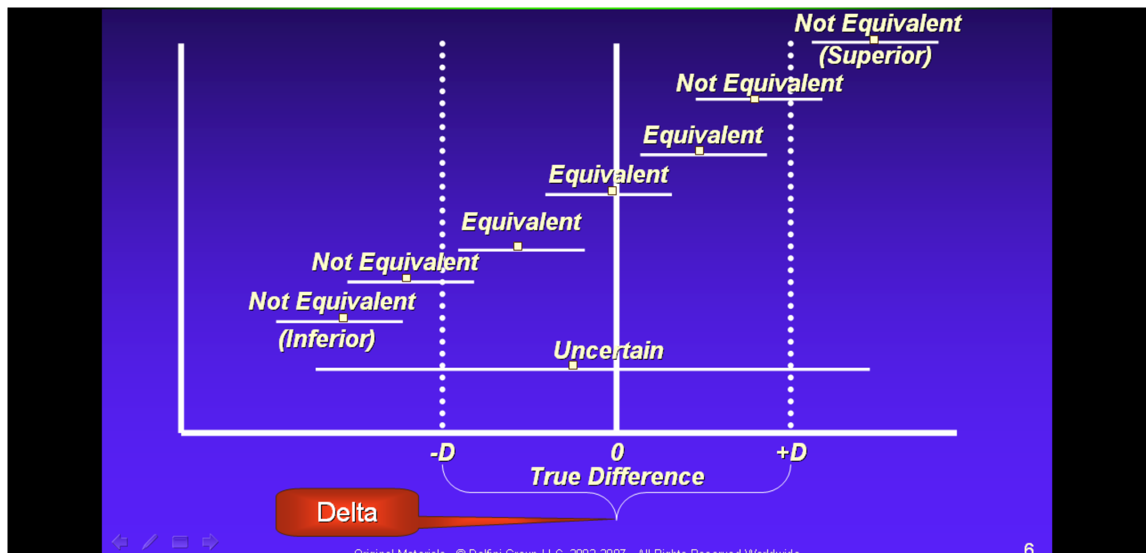
Recommended is to review considerations and potential pitfalls and Delfini advice below.

Background & Terminology

Trial Goals

- Aim of the classic RCT is to demonstrate superiority if it exists
- Equivalence trials aim to determine whether one (typically new) intervention is therapeutically similar to an existing treatment
- Noninferiority trial seeks to determine whether a new treatment is no worse than a reference treatment
- Because proof of exact equality is impossible, a prestated margin of noninferiority or equivalence ("Delta") for the treatment effect is defined
  - Establishing Delta requires statistical and/or clinical judgment
  - For noninferiority trials, one line is established which represents the smallest amount of clinical benefit acceptable: the smallest boundary of the confidence interval for the comparison of the new treatment to the old must not be lower than this line
  - For equivalence trials, two lines are established to define equivalence so that equivalence is defined as the treatment effect being between − delta and + delta: the confidence interval for the comparison of the new treatment to the old must be within this range

An Illustration of Delta and Conclusions from Varying Results



More Terms

- "New" refers to the treatment being tested
- The comparison or "reference treatment" is often called an "active control" or "positive control"
- We refer to the study or studies that determined efficacy of the "active control" as the "referent

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study" (or studies)

- Ideally, this is a systematic review

Considerations & Potential Pitfalls

What additional issues to worry about for equivalence and non-inferiority trials:

1. Is the referent treatment truly efficacious – establish this first
2. Has the new agent been compared to placebo? If not, then superiority to placebo can only be indirectly assumed if the referent agent is superior to placebo
3. Currently there is no clear agreement about how to set Delta
4. Was non-inferiority or equivalence prespecified? (It is okay to establish superiority from equivalence or non-inferiority trials; it is not okay to establish non-inferiority or equivalence from a superiority trial unless Delta has been prespecified)
5. Even if studies are well-done, true equivalence or non-inferiority cannot be directly established
    a. There may be unaccounted for differences between agents
    b. Time may have affected efficacy for even the referent agent – such as changes in resistance patterns to antibiotics or patient behaviors
    c. The comparison is limited to the specific outcomes chosen – "equivalence" does not equate with "me too"
6. Any bias that would tend to diminish an effect size would favor equivalence and non-inferiority (example: conservative application of ITT analysis, insufficient power, etc.)

Advice

Advice for how to approach equivalence and non-inferiority trials:

1. Is the referent truly efficacious? Get the study and critically appraise it.
2. Is the study of the new agent sufficiently similar to the referent study to make a comparison?
    - Review key details such as population, dosing, duration, co-interventions, adherence, etc.
    - Are the outcome measures the same in the studies? Inferiority or equivalence are truly relevant to that outcome ONLY
3. Critically appraise the new study
4. Look closely at the way missingness is handled in the new study since, depending upon how values are assigned, non-inferiority might be favored; sensitivity analyses might be helpful
5. ITT analysis performed in a conservative way must be guarded against, as what is conservative in a superiority trial, could be biased toward no difference, which will "favor" equivalence (or non-inferiority) falsely

Advice for evaluating Delta:

- Our advice to readers is to obtain valid referent study outcomes information to consider what might be an appropriate Delta
    - Inferiority: Review the confidence interval and determine what you would accept as the line of smallest clinical benefit
    - Equivalence: Review the confidence interval and determine what you would accept as clinically acceptable for Delta – a conservative choice is recommended with a narrow interval
    - In both instances, keep in mind that bias tends to favor an intervention and efficacy results might be smaller than effectiveness outcomes

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