Delfini Pearls
Comparative Study Designs of Clinical Trials

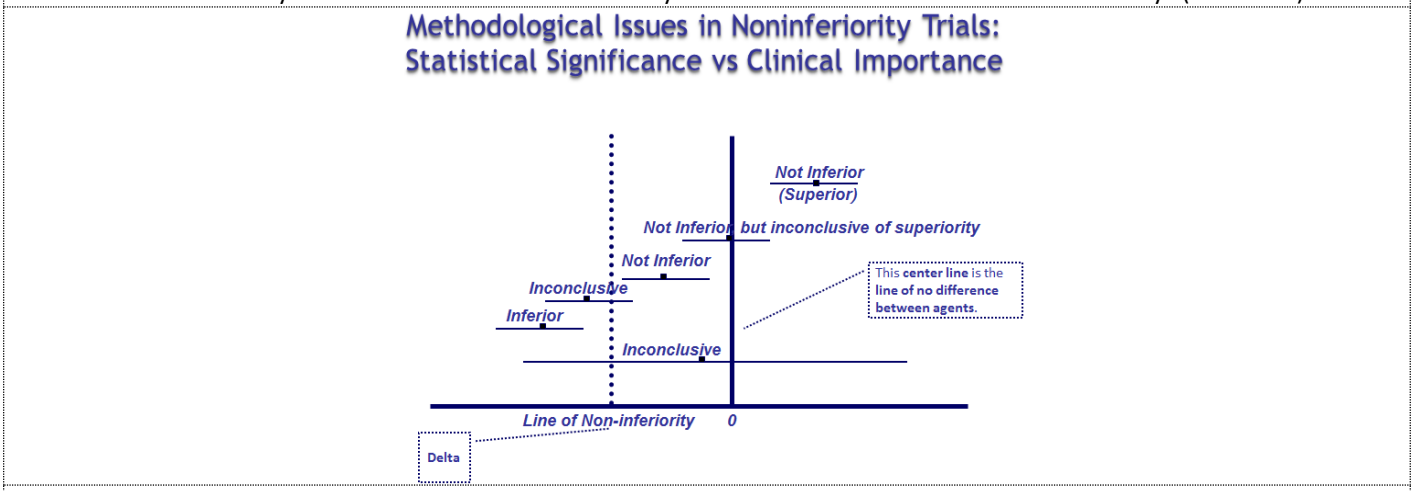
Healthcare Information & Decision Equation: **Information➔Decision ➔Action➔Outcome**
Is it true➔Is it useful ➔Is it usable?

Superiority is the typical aim of an RCT. Ideally, a non-inferiority test is included in superiority trials.
Equivalence trials aim to determine whether one (typically new) intervention is therapeutically similar to an existing treatment.
Non-inferiority trials seek to determine whether a new treatment is no worse than a reference treatment.
Delta: Because proof of exact equality is impossible, a margin of non-inferiority or equivalence ("Delta") for the treatment effect is defined. Establishing Delta requires statistical and/or clinical judgment. (GraphPad: "…determine your zone of scientific or clinical indifference…")

- 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.
- For **non-inferiority trials**, one line is established which represents the smallest amount of clinical benefit acceptable: the smallest boundary of the confidence interval (CI) for the comparison of the new treatment to the old must be above this line. (Pictured below)

Terminology

- "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 study" (or studies).



Considerations & Critical Appraisal Issues For Non-Inferiority and Equivalence Trials

- Is the reference treatment truly efficacious in area studied? Strongly recommended to obtain the referent study and critically appraise it as well as determine if the study of the new agent is sufficiently similar to the referent study. Review key details such as population, dosing, duration, co-interventions, adherence, endpoints, etc. Comparison is limited to the specific outcomes chosen—"equivalence" does not equate with "me too." Even if studies are well-done, true equivalence or non-inferiority cannot be directly established—there may be unaccounted for differences between agents.
- If the new agent has not been compared to placebo, then superiority to placebo can only be indirectly assumed even if the referent agent is superior to placebo.
- Superiority claim may, in a noninferiority or equivalence trial, be valid using an appropriate test with confidence intervals (not just point estimate): groups that agree superiority can be claimed under the right circumstances include CONSORT 06, FDA, EMEA. Multiplicity adjustment is not needed. Population should be ITT.
- Lacking direct comparison to placebo risks creating confusion about benefits and harms.
- Time may have affected efficacy for even the referent agent—such as changes in resistance patterns to antibiotics or in patient behaviors such as dietary changes due to public health interventions.
- Anything that diminishes effect size favors equivalence and non-inferiority (e.g., conservative application of ITT (i.e., per protocol analysis should be included); insufficient power, which is determined by CIs, that result in "inconclusive" or "uncertain" outcomes, not blinded to study design without hard outcomes, etc.)
- Is the Delta clinically reasonable?
- **IMPORTANT: Claims of equivalence or non-inferiority may not be appropriate in superiority trials where delta is established *post hoc*. If prespecified and valid, claims can ONLY be made for the outcomes compared.**