Understanding Design of Randomized Controlled Trials: Non-inferiority, Equivalence, Superiority Design

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The rapid development of medical science and clinical research method enables new therapies with higher efficacy than the standard of care. The three most common designs of clinical researches are uncontrolled clinical trials, nonrandomized controlled trials and randomized controlled trials (RCTs). In an RCT, each patient is assigned to receive a specific treatment intervention by a chance, results of RCT considered more definitive than the results of any other type of clinical trials. Traditionally two sided comparative RCTs aim to determine whether new treatment is superior to current therapy or placebo. By contrast, the goal of many current researches is to determine if novel therapies have equivalent or non-inferior efficacies to the current, established ones.

Superiority tests

The null hypothesis of a superiority trial is that new treatment is equally effective to the current one and the alternative hypothesis is that they differ. With a significant result, one concludes in a superiority trial that new treatment is different in efficacy from current one, and when the observed result is in favor of new treatment, we conclude that new treatment is statistically, significantly better performing than current one

Equivalence tests

In equivalence trials, alternative hypothesis is that the new treatment is equivalent to the current therapy. The conventional method of testing equivalence hypotheses is to perform two, one-sided tests (TOST) of hypotheses. Using TOST, equivalence is established at the α significance level if a $(1–2\alpha)$ x 100% confidence interval for the difference in efficacies (new – current) is contained within the prestated margin interval $(-\delta, \delta)$, a range of values for which the efficacies are considered equivalent.

Noninferiority tests

For noninferiority studies, the alternative hypothesis is that the new treatments is not much worse (either equivalent or superior) than the current therapy. Noninferiority trials are often wrongly called equivalence trials. Noninferiority trials are intended to show whether a new treatment has at least as much efficacy as the standard or is worse by an amount less than prestated margin of noninferiority (δ). The observed treatment effect is not by itself sufficiently informative. Interpretation of results depends on where the confidence interval for the treatment effect lies relative to both the margin of noninferiority (δ) and a null effect.

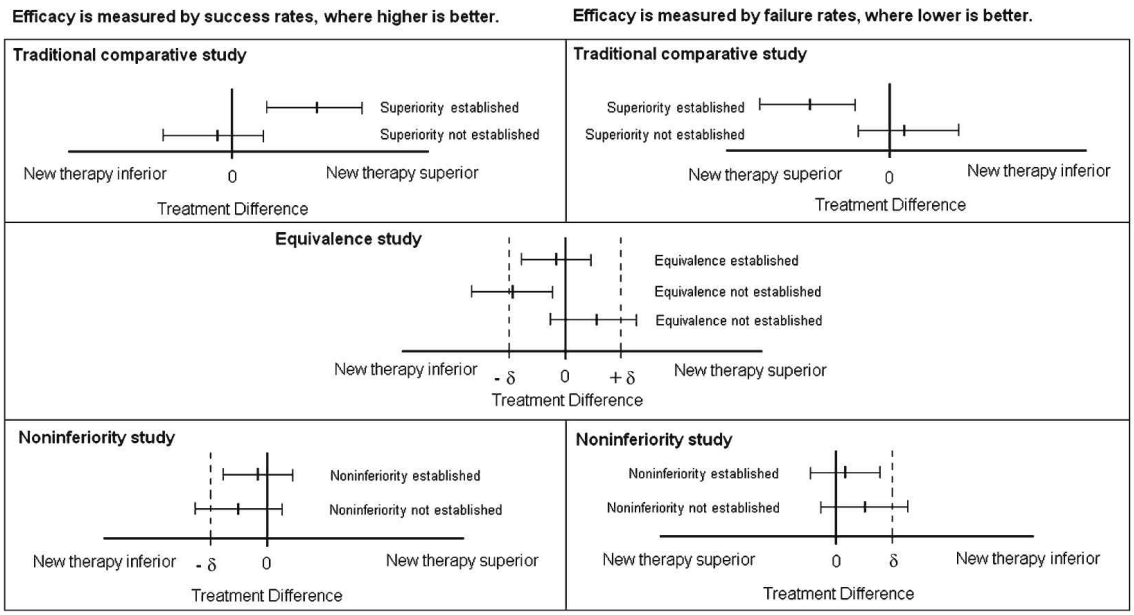

Figure 1. Two one-sided test procedure (TOST) and the equivalence margin in equivalence/noninferiority testing.