Why should noninferiority clinical trials be performed?

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PRACTICAL SCENARIO

A double-blind, randomized, placebo-controlled, noninferiority clinical trial assessed the efficacy of adding five extra days of β-lactam treatment (amoxicillin plus clavulanate) versus placebo after three days of that therapy on clinical cure among clinically stable, moderately severe, community-acquired pneumonia adult patients admitted to 16 hospitals in France.[1] Results showed that 77% of the participants in the placebo group and 68% of the participants in the β-lactam group were considered clinically cured—the between-group difference was 9.4% (95% CI: −0.38 to 20.04). The authors concluded that treatment for three days was noninferior to treatment for eight days, and that these results could lead to important reductions in antibiotic consumption and decrease hospital costs.

NONINFERIORITY TRIALS

Among the types of randomized controlled trials, superiority trials are the most common. However, sometimes it is important to evaluate whether a new intervention is noninferior (equal or not worse) than an existing treatment in terms of efficacy, but exhibits other additional benefits, such as lower costs, fewer side/adverse effects, easier administration, or improved adherence.[2]

In our example, the authors chose a noninferiority clinical trial because their goal was to assess whether a shorter antibiotic regimen was not worse than the standard therapy, within a predefined noninferiority margin (NIM). The NIM is defined as an acceptable clinically difference in efficacy that is a trade-off for other advantages of the new treatment, such as shorter duration in our example. As long as the new treatment is not worse than the standard of care by this margin, the new treatment is considered noninferior.

The NIM is the largest reduction in efficacy of the new treatment compared with the standard of care that is acceptable to the expert community, and can be challenging to establish. If the width of the NIM is too narrow, a clinically acceptable alternative intervention might be considered inferior, and if it is too wide, an inferior intervention might be considered noninferior. Choosing the NIM requires both statistical and clinical consideration, and it is defined a priori and reported in the study protocol. Guidelines recommend defining the NIM based on a comprehensive review of the historical evidence of the efficacy of the current standard of care, which must also be the comparator.

Once the NIM is set (< 10% in our example),[1] the study hypothesis is described. The null hypothesis (H0) states that the between-group difference is larger than

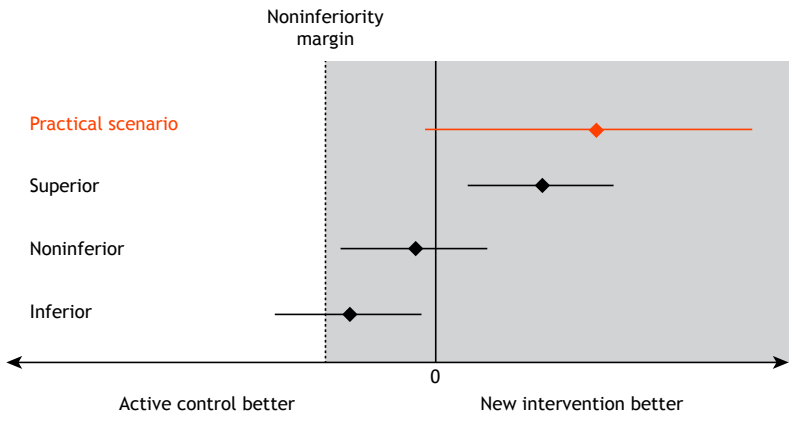

Figure 1. The figure shows possible result scenarios of a noninferiority clinical trial. The mean between-group differences (black circles) and respective 95% CIs (black error bars) for three potential scenarios comparing the new intervention with the active control are shown. The null hypothesis is that the difference between the new intervention and the active control is beyond the noninferiority margin, shown in the shadowed area. In our example (in red)[1], the lower bound of the 95% CI is within the noninferiority margin; therefore, the null hypothesis is rejected and noninferiority can be claimed.

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the noninferiority margin (i.e., the new intervention is inferior) and the alternative hypothesis (H1) is that the between-group difference is smaller than the noninferiority margin (i.e., the new intervention is at least not worse). The statistical approach involves calculating the 95% CI of the mean difference (in our example)[1] in efficacy between the groups and evaluating if the lower bound of the 95% CI is greater than the noninferiority margin (Figure 1). The null hypothesis is rejected, and noninferiority can be claimed, when the lower bound of the 95% CI is smaller than this margin.

KEY POINTS

1) A noninferiority trial is the appropriate design to answer a research question when a new intervention is not expected to be superior to the standard of care in terms of efficacy, but it is not unacceptably inferior either, and offers additional advantages.

2) The noninferiority margin is the largest reduction in efficacy of the new treatment compared with the standard of care that is acceptable, so that the new treatment is not "unacceptably worse." This predefined margin should be based on clinical and statistical considerations.

REFERENCE

1. Dinh A, Ropers J, Duran C, Davido B, Deconinck L, Matt M, et al. Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial [published correction appears in Lancet. 2021 Jun 5;397(10290):2150]. Lancet. 2021;397(10280):1195-1203. https://doi.org/10.1016/S0140-6736(21)00313-5
2. Kaji AH, Lewis RJ. Noninferiority Trials: Is a New Treatment Almost as Effective as Another?. JAMA. 2015;313(23):2371-2372. https://doi.org/10.1001/jama.2015.6645