Author's response to reviews

Title: What differences are detected by superiority trials or ruled out by noninferiority trials? A cross-sectional study on a random sample of two-hundred two-arms parallel group randomized clinical trials.

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Author's response to reviews: see over
Dear Dr Norton,

We wish to submit to BMC Medical Research Methodology a manuscript entitled “What differences are detected by superiority trials or ruled out by noninferiority trials? A cross-sectional study on a random sample of two-hundred two-arms parallel group randomized clinical trials”.

We think that our work might interest the readers of the BMC Medical Research Methodology. Although it is generally admitted that sample size determination should be done prior to any randomized controlled trial\(^1\), the rules to determine the smaller clinical difference in superiority and the larger in noninferiority trials, are unclear and justifications of the choice are rarely given\(^2,3\). While it is often considered that noninferiority trials should rule out smaller clinical differences compared to superiority trials, there is no real consensus regarding the determination of the difference to use to estimate sample size. Reaching a consensus is an important challenge for clinical researchers. In this framework, we decided first to describe the current practices of researchers and to verify whether superiority margins used in planning clinical trials are indeed larger on average than non-inferiority margins, and to examine the variability between studies in these parameters. Our second goal was to identify study-related factors that may influence the choice of the difference, such as the nature of the study outcome, the clinical field, the type of treatments compared, etc.

In order to be representative of the current published literature in high-quality journals\(^4\), we conducted a cross-sectional study based on a random sample of two hundred two-arm, parallel group superiority (100) and noninferiority (100) randomized clinical trials published between 2004 and 2009, after the publication of the revised CONSORT statement\(^1\), in 27 leading medical journals\(^4\).

We confirmed that differences to be detected in superiority trials are larger than those to be ruled out in noninferiority trials. The variability between trials is considerable and partly explained by the type of outcome (differences to be detected or ruled out are smaller for a mortality outcome) and the medical context. But even within a medical context, the variability remains important. We believe our results are of interest to the community of clinical researchers, particularly those involved in clinical trials, but might also interest clinicians not involved in clinical research. We finally point out two lines for further research in order to better explore the determinants of minimal or maximum clinical important difference values in focusing on specific medical area. Once this survey is done, maybe we could propose guidelines regarding best practices in determining the difference to be detected by a clinical trial.

We look forward to hearing from you in the near future.
Yours sincerely,

Angèle Gayet-Ageron


