Commentary: Avoiding type II errors—simulation studies?

Type II errors abound in the medical literature. However, a confidence interval in this case would have helped the reader to know how much confidence to put in a negative result. Unfortunately, the situations encountered in practice are complex, and power is difficult to achieve. This is especially true of studies that involve prognostic factors. Fortunately, advances in computer technology have made simulation studies more accessible. Simulation studies using computer-intensive procedures to provide estimates to quantitative problems are becoming more frequent. These computer-based evaluations can be extremely useful, because they provide estimates that cannot be achieved with studies of real data alone (1). High-quality simulation studies require the same rigor as any real data study. Keep your eyes peeled for the different situations where simulation studies can be used, their design, and their reproducibility (2).

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Designing bioequivalence studies—how much of a difference is acceptable?

To the Editor:

Alleyassin et al. (1) should be congratulated on their recent article on methotrexate (MTX). However, we should be cautious in assuming that a single dose of MTX is equivalent to multiples doses. Equivalence trials have a different design and null hypothesis formulation (2, 3). In an equivalence trial, the conventional significance test has little relevance: Failure to detect a difference does not imply equivalence; a difference that is detected may not have any clinical relevance and may correspond to practical equivalence (4). The relevance of the confidence interval, however, is easier to see. The confidence intervals, calculated from the data shown in their article, demonstrate that single-dose treatment has a 95% confidence interval (CI) of 0.77–0.95, whereas multiple doses have a 95% CI of 0.82–0.97. From these figures, we conclude that a multiple-dose treatment may be equivalent to a single-dose treatment, but not the opposite. These results are similar to those reported by Barnhart et al. (5). The authors’ conclusion that a “multidose regimen is more effective than the single-dose regimen” seems to be more appropriate.

In addition, Dr. Alleyassin and colleagues note the clinical importance of an absolute difference of 2.7% between both treatments. This is a paramount question. One of the fundamental methodologic features in equivalence trials is the accepted range of difference between treatments. The authors should predefine a range of equivalence as an interval from −δ to +δ so that we can simply check whether the confidence interval centered on the observed difference lies entirely between −δ and +δ, if it does, equivalence is demonstrated, but if it does not, there is still room for doubt (4). If we decide to use a 3% range for δ, instead of 21%, which I believe is unacceptable, the sample size to show equivalence would increase up to 292 patients in each group, considering an α error of 0.05 and a β error of 0.2. Therefore, we are not able to reach any hard evidence of equivalence from the paper.

I agree with the authors that the multiple-dose protocol is more cumbersome to administer, and we tend to use the single-dose treatment. However, the choice of treatment must be based on initial serum β-hCG. It would be interesting if the authors present their success rates according to initial β-hCG levels. A cut-off, derived from a receiver operating characteristic (ROC) curve, would help us to establish which treatment protocol should be used.

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Reply of the Authors:

Thank you for your letter and your insightful comments regarding our paper (1). The aim of our study was to investigate the effectiveness of two methods of methotrexate (MTX) treatment for ectopic pregnancy (EP) in routine clinical