

### Can We Believe the Positive Results of RCTs?

Paul Tornetta III, MD; Justin J. Koh, MD; Jean Kang, MD  
Boston University Medical Center, Boston, MA, United States

**Purpose:** Randomized control trials (RCTs) inform changes in practice. We sought to evaluate a series of RCTs from the orthopaedic trauma (Tr) literature as well as in general surgery (GS) and medicine (M) to determine: (1) the calculated risk of a false positive outcome, and (2) the actual error rate in multiple outcome reporting (alpha error).

**Methods:** 25 RCTs in 25 journals from June 2018 backwards were chosen. The presence of a specified primary outcome was evaluated. All others considered secondary outcomes. If no primary outcome was specified, all outcomes were considered equal. For studies reporting a difference (a positive finding) we used a published equation to calculate the risk of alpha error (incorrectly concluding a treatment difference) due to multiple reporting via multiple time points or intergroup comparisons without appropriate correction. Each trial was tested for alpha error in each statistically positive outcome. Comparisons of orthopaedic trauma were made with general surgery and medical trials.

**Results:** 295 studies met criteria (53 Tr, 119 GS, 123 M). Explicit statement of the primary outcome was present in 70%, 69%, and 99% of Tr, GS, and M studies, respectively ( $P < 0.0001$ ). Multiple time points or intergroup comparisons were present in 58% (Tr), 62% (GS), and 81% (M) of studies. Corrections for the multiple evaluations were performed in only 11% (Tr), 9% (GS), and 7% (M) of trials and statements about adjustments were made in 11% (Tr), 10% (GS) and 23% (M). The calculated per paper risk of alpha error was  $62\% \pm 25\%$ ,  $66\% \pm 27\%$ , and  $69\% \pm 25\%$  for Tr, GS, and M trials, respectively. For Tr trials with a primary outcome identified, the calculated risk of alpha error was  $21\% \pm 18\%$  for primary outcomes and  $55\% \pm 28\%$  for secondary outcomes. The actual rates of alpha error when determined were 30% for primary outcomes, 78% for secondary outcomes, and 89% for any outcome. For all Tr trials, the actual alpha error rate per paper was 88%. The actual alpha error rate was always within the 95% confidence interval of the calculated risk. Of the 1566 total outcomes in the 53 Tr papers, 366 were reported as positive and of these, 164 (45%) remained statistically significant after appropriate adjustments were made.

**Conclusion:** The majority of RCTs in all fields identify a primary outcome. The vast majority of RCTs in all fields report multiple outcomes, but an average of only 10% make adjustments for them. The theoretical calculated rate of alpha error accurately predicted the actual alpha error rate in orthopaedic trauma trials for primary, secondary, and all outcomes, supporting the value of the calculation to predict random chance resulting in a positive outcome in RCTs. Adjustments for multiple evaluations are not being performed in the majority of RCTs in orthopaedic trauma. Potentially inaccurate positive findings exist in all fields. Finally, 45% of individual outcomes remained positive after adjustments for multiple outcomes although 89% of the papers had at least 1 positive result that was in error.

The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or medical device he or she wishes to use in clinical practice.