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Transparency in Reporting Results From Randomized Clinical Trials

Robert Kaplan[1], Veronica Irvin[2]

[1]Corresponding author. Stanford University. Stanford, California, United States of America. Bob.Kaplan@stanford.edu
[2]Oregon State University. Corvallis, Oregon, United States of America. veronica.irvin@gmail.com

The interpretation of randomized clinical trials has been hindered by selective reporting bias[1]. In the USA, nearly 90% of industry sponsored trials report positive results, in comparison to only about half of government supported trials. Even in government sponsored studies, only about 46% of US NIH funded studies were published within 30 months of completion. Clinicians want to know the percentage of studies that support the use of a particular treatment[2]. But, it is difficult to calculate this percentage because the denominator for the analysis is unknown.

To address this problem, we examined all of the large randomized clinical trials funded by the US National Heart, Lung, and Blood Institute (NHLBI) over the 40 years ending in 2013[3]. Results from large trials (budget > US$ 500,000/year) are known to be more likely to be published[2]. We were particularly interested in whether the trials reported a significant benefit of treatment for the primary outcome that the investigators used to justify the study. For example, the primary outcome variable might be death from myocardial infarction or death from any cause. 55 large trials on heart disease treatments met the inclusion criteria.

We found that trials were more likely to produce a positive result if they were published prior to the year 2000. Prior to the 2000 positive results occurred in 57% of the published studies. Following the year 2000, the success rate plunged to just 8%.

Figure 1 plots the relative risks of the primary outcome by the publication year of the main outcome paper. The Cardiac Arrhythmia Suppression Trial (CAST) study was excluded from the Figure because it was an outlier in which there was an abruptly high mortality rate among those receiving the active treatment. Studies published prior to 2000 frequently reported that treatments were effective in comparison to control conditions. One important deviation was the CAST trial, which demonstrated significant harm of arrhythmia suppression. There was a significant change in the probability or reporting positive results after 2000. As shown in Figure 1, nearly all studies, reported null effects, The two exceptions were PREVENT and the SANDS trials which reported benefits and and the Women's Health Initiative which reported harm. Further, quantitative estimemates of treatment effect sizes declined for studies published after 2000. Of particular interest, following the year 2000, no study reported a significant benefit for all-cause mortality. After our review was reported in 2015, the SPRINT Trial became the first large NHLBI trial in 20 years to show a positive effect for all cause mortality[4].

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We do not know why there was a significant decline in the number of positive studies following the year 2000. We speculate, however, that it is associated with the implementation of a policy from the US Food and Drug (FDA) that created ClinicalTrials.gov[5], a service requiring prospective study registration. All studies evaluating pharmaceutical products , including biologics, must be registered. In addition evaluations of devices and treatments for serious or life threatening diseases require prospective registration[6,7]. Through the registration process, investigators must declare the study design, inclusion/exclusion criteria, and where the data will be collected. Of particular importance, they must pre-specified primary and secondary outcome variables. In addition to study registration, transparency has been enhanced through enforcement of reporting using The Consolidated Standards of Reporting Trials (CONSORT) guidelines. Introduced in 1996 and later expanded in 2001, CONSORT guidelines require reporting of all details for Randomized Clinical Trials (RCTs)[8]. Beginning around 2001, the International Committee of Medical Journal Editors started to enforce prospective registration of RCTs as a condition for publication. These changes required researchers to record their trial methods and specify the primary outcome measures prior to starting data collection.

Prior to year 2000, investigators had the opportunity to measure many outcome variables and then select for reporting those that offered statistically significant benefits. We believe the rate of finding some significant effect did not change. For example, 12 of 25 papers (48%) published after 2000 found at least one significant positive outcome for a variable other than the prespecified primary outcome. In the pre 2000 era, when a primary outcome had not been identified in advance, it is likely these would have been identified as positive studies. With prospective declaration of the primary outcome variables, the door to taking advantage of possible multiple comparisons was shut.

We considered alternative hypotheses, including use of active comparator versus placebo and author conflicts of interest. Analyses failed to support any of these alternative explanations. In summary, since 2000, there has been a significant decline in the number of RCTs reporting positive results. Although we can not say for certain, we believe that enforcement of transparent reporting standards by journal editors and trial registration that requires prospective identification of primary and secondary outcome variables may explain the trend toward publication of more null studies.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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