



RESEARCH NEWS

Transparency rules lead to large fall in positive trial results, analysis finds

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Fewer large clinical trials are reporting positive findings since the introduction of measures designed to improve transparency, shows a study that analysed results from trials funded by the US National Heart, Lung, and Blood Institute (NHLBI).

The study, published in *PLoS One*,¹ analysed 55 large randomised controlled trials carried out from 1970 to 2012 evaluating drugs or dietary supplements for treating or preventing cardiovascular disease. Trials were included if they had direct costs of over \$500 000 (£322 000; €458 000) a year and were carried out in human adults with a primary outcome of cardiovascular risk, disease, or death.

Researchers analysed the trials on the basis of whether they were published before 2000, when all trials funded by the NHLBI were registered prospectively with ClinicalTrials.gov before publication. They looked at whether trials reported a positive, negative, or null result on the primary outcome and total mortality.

Results showed that 57% of studies (17/30) published before 2000 showed a significant benefit in the primary outcome with the intervention they were testing. By contrast, only two of the 25 trials (8%) published after 2000 showed significant benefit ($\chi^2=12.2$; degrees of freedom=1; $P=0.0005$).

The researchers were Robert Kaplan, of the Agency for Healthcare Research and Quality at the US Department of Health and Human Services, and Veronica Irvin, of Oregon State University, USA. They said, "Beginning in approximately 2000, the likelihood of showing a significant benefit in large NHLBI funded studies declined. Among the explanations we evaluated, the requirement of prospective registration in ClinicalTrials.gov is most strongly associated with the observed trend toward null clinical trials."

They said that the prospective declaration of the primary outcome variable required when registering trials may eliminate the possibility of researchers choosing to report on other measures included in a study. "Almost half of the trials

[published after 2000] might have been able to report a positive result if they had not declared a primary outcome in advance," they noted. "Had the prospective declaration of a primary outcome not been required, it is possible that the number of positive studies post-2000 would have looked very similar to the pre-2000 period."

Further analysis showed that neither industry sponsorship nor improvement in clinical trial design and management explained the trend towards null results. Publication bias, in which journals favour results with positive findings, was also found not to explain this trend. Most (88%) of the trials were published, although there seemed to be a slight delay in the publication of null trials.

The researchers concluded, "Null findings in large randomised controlled trials may be disappointing to investigators, but they are not negative for science. Transparent and impartial reporting of clinical trial results will ultimately identify the treatments most likely to maximise benefit and reduce harm."



1 Kaplan RM, Irvin VL. Likelihood of null effects of large NHLBI clinical trials has increased over time. *PLoS One* 2015; doi:10.1371/journal.pone.0132382.

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