The harmonic mean chi-squared test to substantiate scientific findings

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Statistical methodology plays a crucial role in drug regulation. Decisions by the FDA or EMA are typically made based on multiple primary studies testing the same medical product, where the two-trials rule is the standard requirement, despite a number of shortcomings. A new approach is proposed for this task based on the (weighted) harmonic mean of the squared study-specific test statistics. Appropriate scaling ensures that, for any number of studies, the null distribution is a chi-squared distribution with one degree of freedom. Further properties are discussed and a comparison with the two-trials rule is made, as well as with alternative research synthesis methods. An attractive feature of the new approach is that a claim of success requires each study to be convincing on its own to a certain degree depending on the significance level and the number of studies. A real example with 5 clinical trials investigating the effect of Carvedilol for the treatment of patients with moderate to severe heart failure patients is used to illustrate the methodology. As a by-product, the approach provides a calibration of the sceptical p-value recently proposed for the analysis of replication studies.