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# Random-effects model for meta-analysis of clinical trials: An update

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**Abstract**

The random-effects model is often used for meta-analysis of clinical studies. The method explicitly accounts for the heterogeneity of studies through a statistical parameter representing the inter-study variation. We discuss several iterative and non-iterative alternative methods for estimating the inter-study variance and hence the overall population treatment effect. We show that the leading methods for estimating the inter-study variance are special cases of a general method-of-moments estimate of the inter-study variance. The general method suggests two new two-step methods. The iterative estimate is statistically optimal and it can be easily calculated on a spreadsheet program, such as Microsoft Excel, available on the desktop of most researchers. The two-step methods approximate the optimal iterative method better than the earlier one-step non-iterative methods.


*Keywords:* Clinical trials; Meta-analysis; Random effects model; Restricted maximum likelihood; Variance components

## 1. Introduction

Meta-analysis is a statistical technique for combining estimated treatment effects from independent comparable clinical trials (studies). Such analyses have become increasingly popular in medical research where information about treatment efficacy is available from a number of clinical trials with inconclusive or inconsistent results.

A major difficulty in integrating the findings from various studies stems from the sometimes diverse nature of the studies being combined. The studies may differ, for example, in terms of patient characteristics or methods employed. To account for such inter-study differences, DerSimonian and Laird [1] proposed a simple random effects model which allows for treatment effects to vary across studies and uses a simple non-iterative method to estimate the inter-study treatment effect variance. Because it incorporates inter-study differences into the analysis of overall treatment efficacy, and because of its simplicity, the method [1] continues to be widely used. Nevertheless, indiscriminate or inappropriate use of any approach to meta-analysis of clinical trials can lead to misleading inferences about treatment effects [2], and

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the need for careful consideration of methods in drawing statistical inferences from comparable but heterogeneous studies remains critical.

In this paper, we first review the random-effects model for meta-analysis of clinical trials and introduce a general method-of-moments estimate for the inter-study variance which includes several existing estimates as special cases. In addition to the non-iterative method proposed by DerSimonian and Laird [1], an iterative estimate of the inter-study variance based on a random effects model was proposed by Paule and Mandel [3] for inter-laboratory studies. This estimate was subsequently shown to be statistically optimal [4] and can be easily calculated on a spreadsheet program. Another non-iterative estimate of the inter-study variance component based on a random-effects model was proposed by Cochran [5]. In contrast to the non-iterative DerSimonian and Laird as well as the iterative Paule and Mandel estimates, the estimate based on Cochran's ANOVA assumes that each study provides equal information and is of equal sample size.

We show that the inter-study variance estimates based on the methods of Cochran, DerSimonian and Laird, and Paule and Mandel are all special cases of a general method-of-moments estimate for the inter-study variance with slightly different weights assigned to the studies. The general method-of-moments estimate suggests two-step alternatives to the one-step non-iterative procedures based on Cochran's ANOVA and the DerSimonian and Laird methods. We illustrate and compare the estimates from the five methods in several examples, and based on the empirical evidence, suggest improvements to the commonly used one-step non-iterative random-effects model estimates.

## 2. Methods

We consider the problem of combining estimated treatment effects from a series of $k$ comparative clinical studies, where the data from each study consist of the number of patients in treatment and control groups, $n_{Ti}$ and $n_{Ci}$, and the proportion of patients with some event in each of the two groups, $r_{Ti}$ and $r_{Ci}$. A random effects model for meta-analysis stipulates that the observed treatment effect, $y_i$, from the $i$-th clinical study is made up of two additive components: the true treatment effect for the study, $\theta_i$, and the sampling error, $e_i$. That is, $y_i=\theta_i+e_i$ for $i=1,\ldots,k$. The variance of $e_i$, $\sigma_i^2$, is the sampling variance reflecting within-study variance and the sample size of the study. The sampling variance, $\sigma_i^2$, is usually unknown and is estimated from the data of the $i$-th observed study. For instance, when the observed effect in the $i$-th study is a difference in proportions, $r_{Ti}-r_{Ci}$, the sampling variance can be estimated [1] by

$$s_i^2 = r_{Ti}(1-r_{Ti})/n_{Ti} + r_{Ci}(1-r_{Ci})/n_{Ci.}$$

In addition to the sampling error associated with each study, the random effects model assumes the true treatment effect in each trial will be influenced by several factors, including patient characteristics as well as design and execution of the study. The model explicitly accounts for this possible heterogeneity in the true treatment effects and stipulates that $\theta_i=\mu+\delta_i$, where $\theta_i$ is the true treatment effect in the $i$-th study, $\mu$ is the overall treatment effect for a population of possible treatment evaluations, and $\delta_i=\theta_i-\mu$ is the deviation of the $i$-th study's effect from the overall effect $\mu$. The variance of $\delta_i$, $\tau^2\geq 0$, is the inter-study variance and represents both the degree to which true treatment effects vary across experiments as well as the degree to which individual studies give biased assessments of treatment effects. The special case $\tau^2=0$ represents lack of heterogeneity among the true treatment effects; i.e., the true treatment effects $\theta_i$ are all equal and the common value is $\mu$.

With this formulation, the model assumes that the observed treatment effects, $y_1,\ldots, y_k$, are realizations of independent random variables from a distribution with overall value $\mu$ and variances $\tau^2+\sigma_1^2,\ldots, \tau^2+\sigma_k^2$, respectively, where $\sigma_1^2>0,\ldots, \sigma_k^2>0$ and $\tau^2\geq 0$. The variances reflect the two components of variance assigned to each observed effect: an inter-study variance $\tau^2$ which reflects treatment effects heterogeneity and an intra-study variance $\sigma_i^2$ (or its approximation $s_i^2$) which reflects within-study sampling variance.

### 2.1. Estimation of the overall population treatment effect $\mu$

Given the observed effects, $y_1,\ldots, y_k$, and the sampling variances, $\sigma_1^2,\ldots, \sigma_k^2$, the first step in meta-analysis based on a random effects model is to calculate an estimate for the inter-study variance $\tau^2$ and then estimate the overall population treatment effect $\mu$ and its standard error.

If $\sigma_1^2,\ldots, \sigma_k^2$ and $\tau^2$ were known, a weighted estimator of $\mu$ would be $\mu_W=\Sigma_i W_i y_i/\Sigma_i W_i$, where $W_i=1/(\tau^2+\sigma_i^2)$, and its standard error would be s.e.$(\mu_W)=1/(\Sigma_i W_i)^{1/2}$. In practice, the variances $\sigma_1^2,\ldots, \sigma_k^2$, and $\tau^2$ are usually unknown and