# Users' Guide

# Ratio Estimation for Meta-Analysis of Randomized Clinical Trials.

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## Introduction

This User's Guide provides information on how to obtain point estimates, 95% confidence limits, and two-sided P-values for meta-analysis of a complete set of randomized clinical trials based upon References 1 and 2 below.

The types of trials that these methods can be applied to are limited to two treatment randomized clinical trials with primary outcome either (A) Relative risks for binary (yes/no) outcomes or (B) Differences in Means or Proportions. It is presumed that you have assembled

the data in tabular form, either failure and sample size for each study by treatment combination (Relative Risk) or study means or proportions and sample sizes (Mean differences and Proportions). But see below for extended uses.

The first order of business is to download and save this guide and the two blank Excel templates rr_template_2022 and diff_template_2022 to a permanent folder on your computer. You will never edit these files.

**Quick Four-Step Process for getting the results**

Step 1: Download the Excel template you wish to use (rr or Diff) and save it to a folder on your computer under a recognizable name (e.g Example_1).

Step 2: Enter (or copy/paste) the tabular data into columns B, D, F, and H. Data for Example 1 from reference 1 or the application to mean differences are tabulated below for those who wish to kick the tires. Data go into consecutive rows 3+ (leave no gaps). A maximum of 50 studies can be included and the outcome data will appear in lines 53+.

Step 3. Delete all entries from Columns J and L below the end of the data. This can be done by highlighting the rows and pressing the Delete key or just highlighting all rows in columns J to L below the data and press the delete key.

Step 4: Save the file.

The key outcomes are highlighted in blue on lines 53+.

**Kick Tires for Results from Relative Risk Study** Example to input into Relative Risk Template

| Row# | Column B Deaths Experimental | Column D Sample Size Experimental | Column F Deaths Control | Column H Sample Size Control |
|---|---|---|---|---|
| 3 | 2 | 26 | 1 | 26 |
| 4 | 3 | 23 | 2 | 13 |
| 5 | 27 | 163 | 69 | 212 |
| 6 | 13 | 558 | 15 | 533 |
| 7 | 24 | 76 | 23 | 74 |
| 8 | 3 | 154 | 1 | 75 |
| 9 | 1 | 75 | 2 | 74 |
| 10 | 0 | 50 | 1 | 50 |
| 11 | 1 | 20 | 1 | 20 |

Source: Neto AS, Cardosa SO, Manetta JA, Galvao V , Esposito D, et al. (2012) Association Between Use of Lung-Protective Ventilation with Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome: A Meta-Analysis, *JAMA.* 2012, 308 (16):1651-1659. PMID: 23093163.

Table 1: Results from template Neto Study

| | Estimated Relative Risk RX: control (95% CI) | P-Value: Two-sided | Ratio of 95% Confidence Lengths Method: Inv Var |
|---|---|---|---|
| Ratio (Survey Sampling) | 0.70 (0.44,1.11) | 0.11 | 1.49 |

**Kick tires for Results from a Mean Difference Study**

Input Published Data for Mean Difference Study

| Row # | Column B | Column D | Column F | Column H |
|---|---|---|---|---|
| | Mean or Proportion Experimental | N-Experimental | Mean or Proportion Control | N-Control |
| 3 | -1.7 | 13 | -1.7 | 10 |
| 4 | -3.0 | 42 | -2.5 | 51 |
| 5 | -7.91 | 42 | -2.4 | 38 |
| 6 | 0.0 | 17 | 1.0 | 16 |
| 7 | -2.45 | 80 | -0.08 | 83 |

| Method | Estimated mean Diff RX-Control | P-Value: Two-sided | Ratio of 95% Confidence Lengths Method: Inv Var |
|---|---|---|---|
| Inverse Variance Weights (Published) | -2,31(-4.15,-0.47) | 0.01 | 1.00 |
| Unweighted | -1.73(-4.43,+0.97) | 0.15 | 1.47 |
| Ratio (Survey Sampling) | -2.31(-4.75, +0.12) | 0.057 | 1.32 |

The template only gives you the Ratio results. The unweighted was calculates separately using the mainstream random effects model. Using only mainstream calculations, the estimated coverage of the claimed 95% confidence interval is at best 73%.

**Expedited Use for Other Scenarios**

(1) Actuarial Survival Data. The role of sample size can be played by years at risk if all studies in the meta-analysis have these data. The relative risk here is the mean hazard ratio.

(2) Matched pair studies can also be included along with completely randomized studies if you are willing to consider each subject as two observations in the universe for those studies.

(3) With 51-100 studies a biostatistician will be needed. They should randomly split the analysis into two virtually equal sized sets of studies. (Equal with an even number or within one with an odd number of studies) Conduct the analysis on each. For relative risk, work in the log scale. For differences use raw scales.

Estimate=mean of the 2 log(RR) =(a+b)/2.

SE=sqrt ($Se_a^2$+ $Se_b^2$ )/sqrt(2)

Use a normal approximation.

Quality Assurance for Excel software.

These templates have undergone intensive quality assurance. Note that every calculated field in each spreadsheet has been triply proofed. Of interest to methodologists, the formula for every calculated field can be displayed in the top window of the sheet if you click on its entry.

**How Ratio Estimation Works (For Biostatisticians)**

More detail can be found in Shuster [1] cited below [under] How to Cite this paper.

Two types of Ratio Estimates are described below, with or without a natural log transform.

Let $(Y_j, Z_j)$ be M independent identically distributed random vectors with mean $(\mu_y, \mu_z)$ randomly sampled from a large population.

From classical single stage cluster sampling methods, the following are true for large M:

(A) If the $(Y_j, Z_j)$ are **certain to be non-negative**, (Relative Risk application) then based on smooth transformations of asymptotically bivariate normal estimators, the **natural** log of the ratio of sample means $(\bar{Y}/\bar{Z})$ has the following property.

Log $(\bar{Y}/\bar{Z})$ has an asymptotic t-distribution with M-2 degrees of freedom, with mean Log $(\mu_y/\mu_z)$ and asymptotic variance

$$V^2 = \{(\sigma_y/\mu_y)^2 + (\sigma_z/\mu_z)^2 - 2\rho\,(\sigma_y/\mu_y)\,(\sigma_z/\mu_z)\}/M \qquad (1)$$

$\sigma_y$, $\sigma_z$ and $\rho$ are the population standard deviations of Y and Z and the correlation between Y and Z.

A consistent estimate of $V^2$, $\hat{V}^2$ is obtained by replacing the parameters in equation (1) by their sample moments.

An asymptotic t-distribution implies that for large M, the estimate minus its asymptotic mean divided by its asymptotic standard deviation is approximately central t-distributed with M-2 degrees of freedom.

Of course, asymptotic normality and asymptotic t with large degrees of freedom are equivalent limiting distributions, but at least in the Relative Risk rare context, it has been found that the t-approximation worked well while the normal approximation produced considerable under coverage of the purported 95% confidence intervals, when the number of trials was small (ranging from 5-20).

One can use this information to obtain point estimates, confidence intervals, and P-values for $\text{Log}(\mu_y/\mu_z)$ and by natural antilogs, for $(\mu_y/\mu_z)$. Note that the point estimate for $(\mu_y/\mu_z)$ is $(\bar{Y}/\bar{Z})$. So, although a log transformation is used, the point estimate is in its original scale.

(B) If either of $Y_j$ or $Z_j$ can take on negative values, (differences in means or proportions) we cannot use logs and are forced to work with the raw values as follows, again using classical survey sampling methods.

$(\bar{Y}/\bar{Z})$ has an asymptotic t-distribution with M-2 degrees of freedom with mean $(\mu_y/\mu_z)$ and asymptotic variance

$$V^2 = \{(\sigma_y/\mu_z)^2 + (\mu_y \sigma_z/\mu_z^2)^2 - 2\rho(\mu_y \sigma_y \sigma_z/\mu_z^3)\}/M \qquad (2)$$

A consistent estimate of $V^2$, $\hat{V}^2$ is obtained by replacing the five population parameters by their sample moments in equation (2).

As in (A) above, the point estimate and asymptotic variance can be used to make inferences about the targeted parameter $(\mu_y/\mu_z)$.

Two-sided P-values can be calculated from the standardized score, absolute value of the estimate less the null hypothesized value, divided by $\hat{V}$, and calculated as the probability that the absolute value of a central T-distributed random variable with (M-2) degrees of freedom

exceeds this standardized score. Confidence intervals are obtained via the estimate +/- the product of the T-value from the central T-tables (M-2 degrees of freedom) and $\hat{V}$

**Application Scenarios.**

(i) Estimation of Relative Risk: In the log transformation method for non-negative values (A), the roles of $Y_j$ and $Z_j$ are played by $N_j \hat{P}_{1j}$ and $N_j \hat{P}_{2j}$ respectively. The $\hat{P}_{ij}$ are the sample proportions for Treatment i, (1=treatment and 2=control) study j while $N_j$ is the combined sample size for study j. Shuster and Walker [8] for details. The interpretation is that we are projecting the failure rate ratio of giving all patients in the urn Experimental Therapy to that of giving all patients Control therapy. The estimate is the projected ratio in the actual sample of studies. The population value corresponds to the sample value if all studies in the population were included. Note that by estimating proportions and not individual study relative risk, we do not have problems when the event rates are low.

(ii) Estimation of a difference in means or proportions from a collection of randomized clinical trials: Here, $Yj = N_j \Theta_j$ and $Z_j=N_j$ with $\Theta_j$ the mean difference in treatment means or proportions (Treatment - Control), and $N_j$ the combined sample size for study j. The global parameter projects what the true mean difference would be in the urn if all patients receive Treatment vs. that if all patients receive the control. We use (B) since negative values in the numerator are possible. The population parameter (consistent) would be identical to the estimate if all trials in the population were sampled.

**How to cite articles in publications and reports.**

Please cite both of the following articles:

1: Shuster JJ. Meta-Analysis 2020: A Dire Alert and a Fix. *Biostatistics and Biometrics* 2021; 10 (3): 73-78.

Meta-Analysis of Clinical Trials in the 2020s and beyond: A paradigm shift needed

To be added when finalized.