The generic inverse variance method

The new method of analysis that is available in Review Manager 4.2 (RevMan) is the 'generic inverse variance method' (GIVM). This method can be applied to a number of different situations that are encountered by Cochrane authors and this article aims to address three of these.

The data that are required for the GIVM are an estimate for the relative treatment effect and its standard error, for each of the studies that are to be included in the analysis. Each study estimate of the relative treatment is given a weight that is equal to the inverse of the variance of the effect estimate (i.e. one divided by the standard error squared).

It should be noted that this method should only be used when it is not possible to enter data in the usual form of dichotomous, continuous or individual patient data to ensure that the reader is able to see the data by treatment group whenever possible. The GIVM should not be used as an alternative to the methods that are currently available in RevMan 4.1 but rather in situations where it is not feasible to use them.

Described below are three situations where authors may need to use the GIVM:

(1) The outcome is **dichotomous** (i.e. the outcome can only take one of two possibilities) but the published paper reports only the odds ratio (OR) or relative risk (RR) and its standard error. Previously in RevMan 4.1, such results could not be included in a quantitative analysis and could only be described in the text of the review.

(2) The outcome is **continuous** and the published paper reports only the difference between the means for the two groups and the standard error of this difference. These data could not previously be included in a quantitative analysis in RevMan 4.1.

(3) The design of the trial is **cross-over**, the outcome is continuous, and the average difference between periods and its standard error are reported by the published paper. There are a number of different methods that could be used to analyse continuous data that have been reported in papers conducting cross-over trials. Elbourne discusses problems that arise in the meta-analysis of cross-over trials and other issues relating to these type of studies.

Each of these situations will be looked at in detail with examples that authors may come across.

Dichotomous Data

In this example there are five included studies that have all reported data on a dichotomous outcome. This outcome is not a favourable outcome (e.g. death) and therefore the treatment is more beneficial if there are fewer events.

The information that is provided for each trial is given below:

Study 1

		Event Present		
		Yes	No	Total
Intervention	Treatment A	16	9	25
	Treatment B	16	29	45
	Total	32	38	70

Study 2

RR 2.1 95% Confidence interval (0.83,5.3)

Study 3

		Event Present		
		Yes	No	Total
Intervention	Treatment A	21	15	36
	Treatment B	44	44	88
	Total	65	59	124

Study 4

		Event Present		
		Yes	No	Total
Intervention	Treatment A	6	5	11
	Treatment B	2	4	6
	Total	8	9	17

Study 5

RR 1.67 95% CI (0.74,3.75)

In the last edition of RevMan, studies 1,3 and 4 could be included in a meta-analysis, but not studies 2 and 5.The results from these latter two studies could only be included in the text of the review.

Using the GIVM it is now possible to combine these data to obtain one overall pooled estimate for the RR. To do this the following procedure can be followed once you are in RevMan 4.2:

- add an outcome as normal (click on the comparison of interest and then click add), you will be
- asked to 'Add outcome/category',

- click on 'generic inverse variance'.

- In the next screen a number of details will need to be entered.

- Enter the description and group labels as normal but two other details will need to be entered.

- The 'Name for effect measure' should be entered as 'Relative Risk' (as this is the effect estimate that we are interested in, in this particular example, this may be the odds ratio or the risk difference for dichotomous data in other examples).

- Next to 'entered data' there are two options that can be chosen, either 'Original Scale' or 'Logarithm'. Due to the fact that the standard error of the relative risk is on the natural log scale we need to highlight 'Logarithm' (for more information on logarithms *see* Bland and Altman).

Entering the required results for dichotomous outcomes is quite tricky and below there are two detailed examples based on the data that have already been discussed. We need to enter the log (from this point on were log is written the natural log is assumed, this can also be written as ln) of the RR and the standard error of the ln(RR).

For studies 1,3 and 4 we could proceed using the following method (based on study 1):

Construct a 2x2 table entering in all the cells as shown for study 1 below:

		Event Present		
		Yes	**No**	**Total**
Intervention	**Treatment A**	16 (a)	16 (b)	32 (a+b)
	Treatment B	9 (c)	29 (d)	38 (c+d)
	Total	25 (a+c)	45 (b+d)	70 (a+b+c+d)

Table 1: 2x2 table for study 1.

The RR is calculated as : $\dfrac{a/a+b}{c/c+d} = \dfrac{a(c+d)}{c(a+b)}$ (1)

Which is equal to 2.11 for study 1, we then take the log of this value to obtain 0.747.

The formula for calculating the SE of the ln(RR) is given as:

$$SE(\ln(RR)) \approx \sqrt{\dfrac{1}{a} - \dfrac{1}{a+b} + \dfrac{1}{c} - \dfrac{1}{c+d}}$$ (2)

The SE of the ln(RR) is equal to 0.341.

If these two values are entered as the effect estimate and standard error, from them RevMan 4.2 will calculate the RR and 95% CI (this is not on the log scale).

For studies 2 and 5 we are unable to do this as we do not have the information to construct a 2x2 table. Therefore we need to use the 95% CI to work backwards and calculate the SE of the ln(RR).

Note that the 95% CI for the ln(RR) is usually calculated as:

$$(\ln(RR) - [1.96 \times SE(\ln(RR))], \ln(RR) + [1.96 \times SE(\ln(RR))])$$ (3)

These figures are then exponentiated to give the CI of the relative risk.

To calculate the SE of the ln(RR) from the CI we can either use the upper or lower limit to work with. In this example the upper limit of the confidence interval will be used, a similar procedure can be used for the lower limit.

We know that the RR for study 2 is 2.1, the 95% CI for the RR is (0.83,5.3) and ln(RR) is 0.7419. If we take the log of this CI we obtain the 95% CI for the log of the RR, which is (-0.19,1.67).

If we fill in the information that we know in (3) we obtain:

$$(\ln(2.1) - 1.96 \times SE(\ln(RR)), \ln(2.1) + 1.96 \times SE(\ln(RR)))$$ (4)

We know that the upper limit of (4) is equal to ln(5.3), which equals 1.67, therefore

$$\ln(2.1) + (1.96 \times SE(\ln(RR))) = 1.67$$ (5)

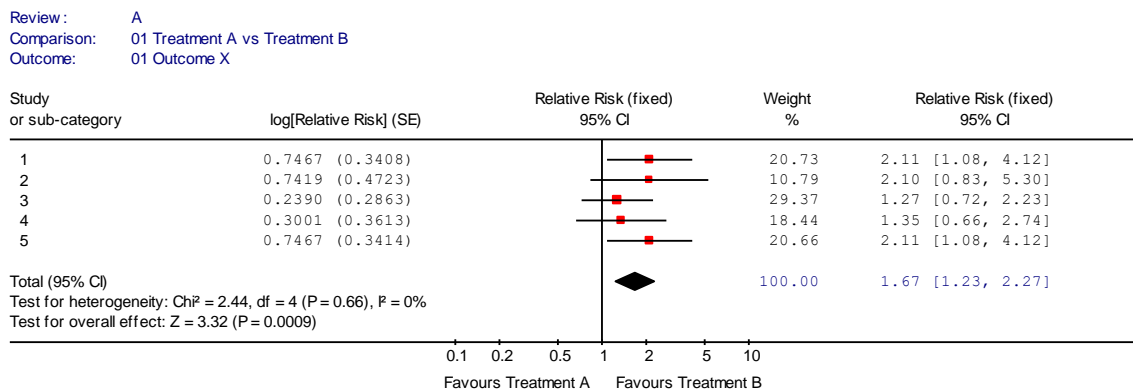Rearranging (5)

$$\ln(2.1) + (1.96 \times SE(\ln(RR))) = 1.67$$
$$1.96 \times SE(\ln(RR)) = 1.67 - \ln(2.1)$$
$$SE(\ln(RR)) = \dfrac{1.67 - \ln(2.1)}{1.96}$$

we obtain that the SE(ln(RR)) is equal to 0.4723.

We now have the two figures that can be entered into RevMan 4.2 to complete our analysis, ln(RR) = 0.7419 and SE(ln(RR)) = 0.4723.

The results of the analysis including data from all five studies can be seen overleaf:

Study or sub-category	log[Relative Risk] (SE)	Relative Risk (fixed) 95% CI	Weight %	Relative Risk (fixed) 95% CI
1	0.7467 (0.3408)		20.73	2.11 [1.08, 4.12]
2	0.7419 (0.4723)		10.79	2.10 [0.83, 5.30]
3	0.2390 (0.2863)		29.37	1.27 [0.72, 2.23]
4	0.3001 (0.3613)		18.44	1.35 [0.66, 2.74]
5	0.7467 (0.3414)		20.66	2.11 [1.08, 4.12]
Total (95% CI)			100.00	1.67 [1.23, 2.27]

Test for heterogeneity: Chi² = 2.44, df = 4 (P = 0.66), I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)

0.1 0.2 0.5 1 2 5 10
Favours Treatment A   Favours Treatment B

Figure 1: Forest plot for data in example 1

Details of the formulae for calculating the odds ratio and its standard error can be seen in the appendix .

Continuous Data

Similar to the previous example we will look at a hypothetical example which includes five studies, each of which has reported data on a particular outcome. This outcome is a favourable outcome (a higher result is better) and there are two treatment groups (A and B).

The information that each study reported can be seen in table 2:

Study	Treatment A	Treatment B	Difference (A-B)
6	Mean=16.3 sd=3.1 n=16	Mean=-0.9 sd=1.8 n=19	---------------
7	Mean=14.6 sd=4.6 n=12	Mean=1.9 sd=3.2 n=14	---------------
8	---------------------	--------------------	14.21 95% CI (12.45,15.97)
9	-----------------------	--------------------	7.6 95%CI (5.05,10.15)
10	Mean=12.9 sd=2.1 n=42	Mean=2.6 sd=1.6 n=40	-----------------

Table 2: Information reported by each study

Table 2 shows that studies 6,7 and 10 report information that could be traditionally entered in RevMan 4.1, namely the mean, standard deviation and the number of participants in each group. However the information given for studies 8 and 9 could not have been included in a quantitative-analysis due to the fact that the difference between the treatments and its standard error have been reported.

All of these studies can be combined using the GIVM in RevMan 4.2. The analysis should be set up as before, but the appropriate headings should be changed accordingly and the scale should be left on the default option which is 'Original Scale'.

The information that needs to be entered for each study is the difference in means and its standard error. For studies 6,7 and 10 we need to calculate the mean difference and standard error. This can be done using the following formulae for calculating the mean difference and its SE.

Mean difference = Mean response of Treatment A – Mean response Treatment B

$$se(Mean\ Difference) = \sqrt{\frac{sd_1^2}{n_1} + \frac{sd_2^2}{n_2}} \quad (6)$$
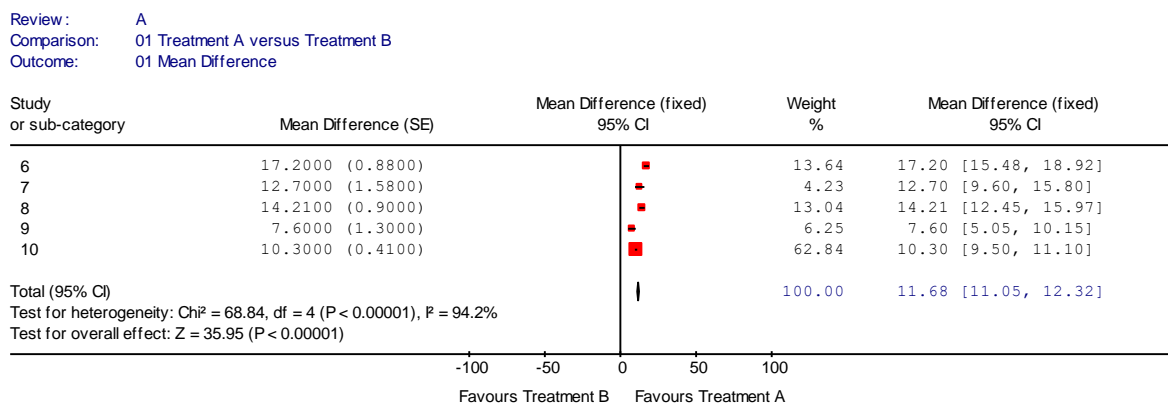
where

$sd_1^2\ and\ sd_2^2$ are the standard deviations squared for treatment groups 1 and 2 respectively

$n_1\ and\ n_2$ are the number of participants in treatment groups 1 and 2 respectively.

For studies 8 and 9 the mean difference is already given but we need to calculate the standard error from the 95 % confidence interval that is given. This can be done by subtracting the mean difference from the upper limit of the confidence interval and dividing by 1.96. For example, to calculate the standard error for study 8, the following calculation is used:

(15.97 – 14.21) divided by 1.96 = 0.9. Therefore, the standard error for this particular outcome is 0.9.

The analysis looks as follows:

Review: A
Comparison: 01 Treatment A versus Treatment B
Outcome: 01 Mean Difference

Study or sub-category	Mean Difference (SE)	Mean Difference (fixed) 95% CI	Weight %	Mean Difference (fixed) 95% CI
6	17.2000 (0.8800)		13.64	17.20 [15.48, 18.92]
7	12.7000 (1.5800)		4.23	12.70 [9.60, 15.80]
8	14.2100 (0.9000)		13.04	14.21 [12.45, 15.97]
9	7.6000 (1.3000)		6.25	7.60 [5.05, 10.15]
10	10.3000 (0.4100)		62.84	10.30 [9.50, 11.10]
Total (95% CI)			100.00	11.68 [11.05, 12.32]

Test for heterogeneity: Chi² = 68.84, df = 4 (P < 0.00001), I² = 94.2%
Test for overall effect: Z = 35.95 (P < 0.00001)

-100   -50   0   50   100
Favours Treatment B   Favours Treatment A
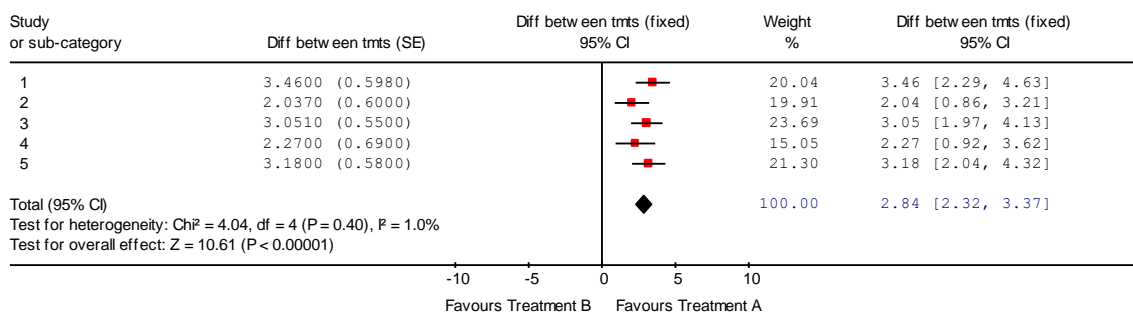
Figure 2: Meta-analysis of continuous data

It is important to note that the axis labels have been changed to ensure that they correspond with the correct meaning of the graph.

Cross-over trials

In this section we will only be looking at data from cross-over trials with a continuous outcome. Elbourne discusses methods that can be adopted to analyse data that have been reported in a cross-over trial. The three methods that Elbourne discusses will be looked using an example in which the data has been simulated.

(1) Conducting a meta-analysis using the results from a paired analysis, which entails looking at the difference between a person's results for the two periods. This takes into account the correlation between two results on the same person. This method uses the GIVM in RevMan 4.2 and the forest plot for this analysis can be seen below. For this method to be conducted within a review, the primary paper would need to report the mean difference of the participants and its standard error or we would need to estimate this by using formulae that are described later in this section.
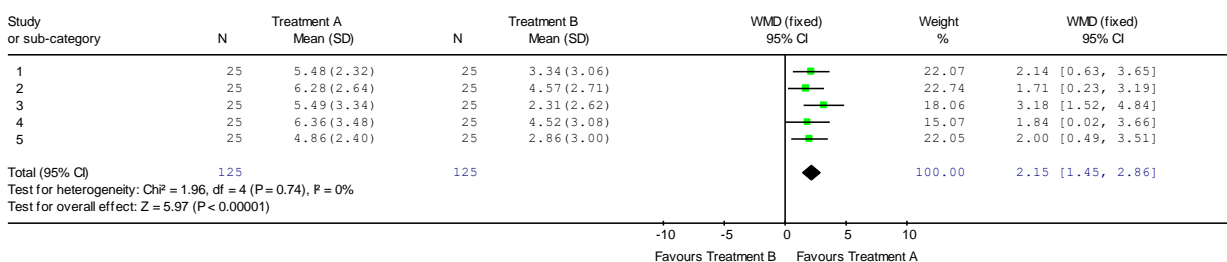
Study or sub-category	Diff between tmts (SE)	Diff between tmts (fixed) 95% CI	Weight %	Diff between tmts (fixed) 95% CI
1	3.4600 (0.5980)		20.04	3.46 [2.29, 4.63]
2	2.0370 (0.6000)		19.91	2.04 [0.86, 3.21]
3	3.0510 (0.5500)		23.69	3.05 [1.97, 4.13]
4	2.2700 (0.6900)		15.05	2.27 [0.92, 3.62]
5	3.1800 (0.5800)		21.30	3.18 [2.04, 4.32]
Total (95% CI)			100.00	2.84 [2.32, 3.37]

Test for heterogeneity: Chi² = 4.04, df = 4 (P = 0.40), I² = 1.0%
Test for overall effect: Z = 10.61 (P < 0.00001)

-10　-5　0　5　10
Favours Treatment B　Favours Treatment A

Figure 3: Meta-analysis of cross-over trial using GIVM

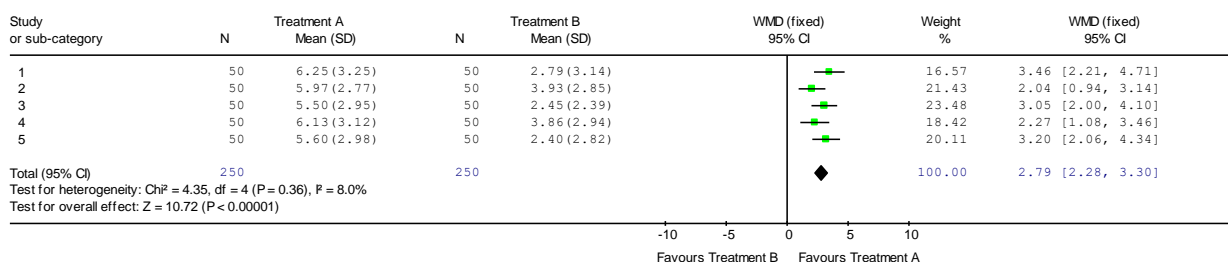(2) Analyse the data from the first period only, thus the results are taken from effectively a parallel group trial.

Study or sub-category	N	Treatment A Mean (SD)	N	Treatment B Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
1	25	5.48(2.32)	25	3.34(3.06)		22.07	2.14 [0.63, 3.65]
2	25	6.28(2.64)	25	4.57(2.71)		22.74	1.71 [0.23, 3.19]
3	25	5.49(3.34)	25	2.31(2.62)		18.06	3.18 [1.52, 4.84]
4	25	6.36(3.48)	25	4.52(3.08)		15.07	1.84 [0.02, 3.66]
5	25	4.86(2.40)	25	2.86(3.00)		22.05	2.00 [0.49, 3.51]
Total (95% CI)	125		125			100.00	2.15 [1.45, 2.86]

Test for heterogeneity: Chi² = 1.96, df = 4 (P = 0.74), I² = 0%
Test for overall effect: Z = 5.97 (P < 0.00001)

-10　-5　0　5　10
Favours Treatment B　Favours Treatment A

Figure 4: Meta-analysis of first period data only

(3) Ignore the cross-over and combining all the results from the treatment periods together and combining all the results from the control together. This creates two independent groups (although they are not truly independent) which are then analysed.

Study or sub-category	N	Treatment A Mean (SD)	N	Treatment B Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
1	50	6.25(3.25)	50	2.79(3.14)		16.57	3.46 [2.21, 4.71]
2	50	5.97(2.77)	50	3.93(2.85)		21.43	2.04 [0.94, 3.14]
3	50	5.50(2.95)	50	2.45(2.39)		23.48	3.05 [2.00, 4.10]
4	50	6.13(3.12)	50	3.86(2.94)		18.42	2.27 [1.08, 3.46]
5	50	5.60(2.98)	50	2.40(2.82)		20.11	3.20 [2.06, 4.34]
Total (95% CI)	250		250			100.00	2.79 [2.28, 3.30]

Test for heterogeneity: Chi² = 4.35, df = 4 (P = 0.36), I² = 8.0%
Test for overall effect: Z = 10.72 (P < 0.00001)

-10　-5　0　5　10
Favours Treatment B　Favours Treatment A

Figure 5: Meta-analysis ignoring the cross-over

These methods are discussed in more detail by Elbourne.

Methods 2 and 3 can be carried out using RevMan 4.1 but now method 1 (the recommended approach) can be applied using RevMan 4.2.

The method follows the same procedure as that in the continuous example before. For this method the data that need to be entered into RevMan are the mean person difference between the two treatment periods and the standard error of this mean.

Problems may arise if the standard error of the difference is not given in the primary paper but the standard errors for the mean of each treatment group separately are given. The formula that is used to calculate the standard deviation of the difference between the means is not the same as that described in (2). The formula in (2) is for calculating the standard error for the difference of two independent groups and does not take into account the correlation between the results.

To calculate the standard error of the mean difference within participants the following formulae can be used:

We first calculate the variance of the within participant difference:

$$[SD(Difference)]^2 = sd_1^2 + sd_2^2 - 2\rho sd_1 sd_2 \quad (7)$$

where sd_1 and sd_2 are the standard deviations from the two treatment groups, ρ is the correlation between the results from the two treatment periods.

We can then calculate the standard error of the mean difference using the result that we obtained in (7), using the following formula:

$$SE(mean\ difference) = \frac{SD(difference)}{\sqrt{n}} \quad (8)$$

where n is the number of participants within the trial.

Even using this formulae if the correlation between the treatment periods is not known then we are still not able to estimate the standard error of the within participant difference.

There are two possible solutions to this problem. The first solution is to use an estimate from work that has been done previously and to then use this estimate as the correlation. It is very unusual for correlations to be published and therefore it is extremely difficult to 'guess' what the correlation should be. The second solution is to conduct a sensitivity analysis (for more information on conducting a sensitivity analysis see chapter 8 of the Cochrane Reviewers' Handbook).

The best possible solution when analysing cross-over trials is to obtain the IPD so that a complete analysis can be performed, this may not be possible for a number of reasons and in this situation the results from individual cross-over trials should be reported qualitatively within the text and the data from the trial should not be included within the meta-analysis of the review.

The information required for the GIVM is the mean within-participant difference and the standard error of this mean.

Appendix

Using the notation described in table 1, the OR for an individual study is equal to:

$$\frac{a/b}{c/d} = \frac{ad}{bc}$$

The standard error of the log odds ratio is:

$$se\{\ln(OR)\} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

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