Appendix 1.

Calculation methods and a practical example: topical azelaic acid versus topical metronidazole for rosacea

The calculation methods used in this study have all been described in previous studies.[1-3] To illustrate the methods, we consider a trial-network, using data from a Cochrane review (CD003262)[4] that provided sufficient data to make a direct and adjusted indirect comparison of topical azelaic acid (intervention *A*) and topical metronidazole (intervention *B*) in patients with rosacea. Note that the indirect comparison was not actually performed in the original review.

Direct and indirect comparisons

A single head-to-head comparison trial[5] with 251 patients provided an odds ratio of 0.55 (95% CI 0.33 to 0.91) in favour of azelaic acid. Placebo-controlled trials revealed that topical azelaic acid and topical metronidazole were both more efficacious than placebo, but the pooled effect size from the topical metronidazole vs. placebo trials (OR=0.17, 95% CI 0.09 to 0.32) was greater than that from the azelaic acid vs. placebo trials (OR= 0.45, 95% CI 0.34 to 0.61) (Table A1).

Let $lnOR'_{AB}$ denote log odds ratio of the adjusted indirect comparison of topical azelaic acid (A) and topical metronidazole (B). Based on the results from the two sets of placebo controlled trials ($lnOR_{AC}$ and $lnOR_{BC}$), we use Bucher et al's method[1] to make an adjusted indirect comparison of topical azelaic acid and metronidazole:

$$\ln OR'AB = \ln ORAC - \ln ORBC = -0.7978 - (-1.7824) = 0.9846 \quad .$$

Its standard error is estimated by:

$$SE(\ln OR'AB) = \sqrt{SE(lnORAC)^2 + SE(lnORBC)^2} = \sqrt{0.1511^2 + 0.3309^2} = 0.3638 \quad .$$

Therefore, the adjusted indirect comparison based on six trials suggested that topical azelaic acid is less efficacious than topical metronidazole (OR 2.68, 95% CI: 1.31 to 5.46), which is opposite to the result of the direct comparison (OR 0.55, 95% CI: 0.35 to 0.91) (Table A1).

Inconsistency between direct and indirect estimates

The inconsistency (Δ) is defined as the difference in log odds ratios between direct and indirect estimates together with its standard error. It can also be expressed as the ratio of odds ratios (ROR) after an antilog transformation.

The inconsistency between the direct and indirect estimate is calculated by:

$$\Delta = \ln OR_{AB} - \ln OR'_{AB} = -0.6057 - 0.9847 = -1.5904 ,$$

and its standard error by:

$$SE(\Delta) = \sqrt{SE(\ln OR_{AB})^2 + SE(\ln OR'_{AB})^2} = \sqrt{0.2629^2 + 0.3638^2} = 0.4488 .$$

The 95% confidence interval of the estimated inconsistency (in log scale) is calculated by $\Delta \pm 1.96 \times SE(\Delta) = -1.5904 \pm 1.96 \times 0.4488$. That is, the 95% confidence interval of the inconsistency is from -2.4700 to -0.7108.

The above inconsistency can also be expressed as a ratio of odds ratios (ROR) by an antilog transformation (for example, $ROR = EXP(\Delta) = EXP(-1.5904) = 0.2038$). Expressed as the ratio of odds ratios, the inconsistency between the direct and indirect estimates is 0.204 (95% CI: 0.085 to 0.491).

Test of statistical significance of the estimated inconsistency:

Then we calculate a *z* statistic for testing the null hypothesis that Δ=0,

$$z = \frac{\Delta}{SE(\Delta)} = \frac{-1.5904}{0.4488} = -3.54 .$$

This *z* value is corresponding to a P value of 0.0004 that is much smaller than 0.05. Therefore, the null hypothesis of *Δ=0* is rejected, and the inconsistency between the direct and indirect estimates is statistically significant.

Because of the statistically significant inconsistency, the combination of the direct and indirect comparison results (also called mixed treatment comparison), concern is expressed in the validity of this combined analysis. (The two inconsistent estimates are combined in Table A1 for purposes of illustration of the methods only.) This combination of indirect and direct evidence can be achieved in standard meta-analysis software by "pretending" the two estimates are the results (log odds ratios and corresponding standard errors) from two primary studies (e.g. the calculation may be carried out using Generic Inverse Variance Method in Review Manage 5[a]). In this case, the combination of the direct and indirect evidence provides an odds ratio of 0.94 (95% CI 0.62 to 1.43), with significant heterogeneity (I^2 =92%, P=0.0004).

[a] Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Table A1. Results of different methods to compare topical azelaic acid and topical metronidazole for rosacea. Outcome: lack of improvement according to physician's global evaluation

Comparisons	**No. of trials**	**lnOR (SElnOR)** **OR (95% CI)**	**Heterogeneity** **I^2% (P)**
Direct comparison of topical azelaic acid (A) and topical metronidazole (B)	1	$lnOR_{AB}$ = -0.6057 (0.2629) OR: 0.55 (0.35 to 0.91)	N.A.
Topical azelaic acid (A) versus placebo (C)	3	$lnOR_{AC}$ = -0.7978 (0.1511) OR: 0.45 (0.34 to 0.61)	0% (P=0.62)
Topical metronidazole (B) versus placebo (C)	3	$lnOR_{BC}$ = -1.7824 (0.3309) OR: 0.17 (0.09 to 0.32)	0% (P=0.74)
Adjusted indirect comparison of topical azelaic acid and metronidazole	3/3	$lnOR'_{AB}$ = 0.9846 (0.3638) OR: 2.68 (1.31 to 5.46)	
Combination of direct and indirect comparison	1 // 3/3	-0.0601 (0.2131) OR: 0.94 (0.62 to 1.43)	92% (Z=-3.54; P=0.0004)

References to Appendix 1

1. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50(6):683-91.
2. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326(7387):472-475.
3. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. *J Clin Epidemiol* 2008;61(5):455-63.
4. van Zuuren EJ, Graber MA, Hollis S, Chaudhry M, Gupta AK, Gover M. Interventions for rosacea. *Cochrane Database Syst Rev* 2005(3):CD003262.
5. Elewski BE, Fleischer AB, Jr., Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol* 2003;139(11):1444-50.