Meta-analyses involving cross-over trials: methodological issues

From MARGARET R STEDMAN,[1*] FRANÇOIS CURTIN,[2] DIANA R ELBOURNE,[3] AARON S KESSELHEIM[1,4] and M ALAN BROOKHART[1,4]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA, [2]Merck Serono SA, Geneva, Switzerland, [3]Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK and [4]Department of Medicine, Harvard Medical School, Boston, MA, USA.

[*]Corresponding author. Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. E-mail: mstedman2@partners.org

We would like to make a correction to the description of the Becker–Balagtas method found in the 2002 *International Journal of Epidemiology* article by Elbourne *et al.*[1] The article describes methods of combining parallel and cross-over trials for the purposes of meta-analysis. In the following summary, we will provide a revised description of the Becker–Balagtas approach with an example of how to implement it.

The Becker–Balagtas approach is an estimation method used in the meta-analysis of cross-over trials with binary outcomes.[1] It is considered a marginal method because it relies on the marginal probabilities of the outcome to estimate the odds ratio (OR).[2] Typically, a conditional approach, such as the Mantel–Haenszel odds ratio (of the discordant pairs), is the usual effect estimate for cross-over trials.[3] However, when summarizing results across study designs the Becker–Balagtas approach is the preferred method.[3]

To compute the Becker–Balagtas estimates, we first define the observed cell quantities from a cross-over trial. In the cross-over design, all subjects participate in all treatments in successive periods where the sequence of treatments is determined by randomization.[1] For example, some subjects are randomized to receive placebo for the first period followed by the active treatment in the second period, others are randomized to receive the active treatment in the first period followed by the placebo in the second period. Each subject contributes two results for the active and placebo treatment periods.

Binary outcomes from a cross-over trial may be summarized as displayed in Table 1. Here, the outcome from the trial is either success or failure and the treatment is either active or placebo. Let s be the number of subjects that had a success with both treatments. Let v be the number of subjects that experienced failure with both treatments. Let t and u represent the number of subjects that had a success with one treatment, but failed with the other. Let a and c represent the row totals, b and d the column totals and n the total number of subjects.[1]

Table 1 2 × 2 table for a cross-over trial

	Placebo treatment period		
	Success	Failure	
Active treatment period			
Success	s	t	a
Failure	u	v	c
	b	d	n

According to the Becker–Balagtas method, we compute the marginal odds ratio and variance as follows:[3]

$$\mathrm{OR}_{\mathrm{Marginal}} = \frac{ad}{bc}$$

$$\mathrm{var}(\mathrm{In}(\mathrm{OR}_{\mathrm{marginal}})) = \frac{1}{a}+\frac{1}{c}+\frac{1}{b}+\frac{1}{d}-\frac{\Delta}{2n}$$

where $\frac{\Delta}{n}$ is the within subject covariance and Δ is defined as:[3]

$$\Delta = n^2\left(\frac{ns-ab}{abcd}\right)$$

Additionally, the correlation coefficient (a ratio of the covariance and the variance) can be estimated from the table as:[3]

$$\rho = \frac{ns-ab}{\sqrt{abcd}}$$

The Becker–Balagtas estimation method is applied when combining data from different designs in a meta-analysis.[1] For example, consider a meta-analysis of two trials of the effect of brand name and generic anti-epileptic drugs on seizure outcomes. The first trial has a parallel design (independent outcomes) and the second trial has a cross-over design (correlated outcomes). Our objective is to combine the results of these two trials into a single summary estimate of the odds ratio of uncontrolled seizures for generic anti-epileptic drugs compared with brand-name anti-epileptic drugs.

Table 2 presents results from a trial with a parallel design.[4] A total of 60 newly diagnosed patients were randomized to either a brand name or generic anti-epileptic drug. Of the 45 patients randomized to generic anti-epileptic drugs, 6 had uncontrolled seizures as did 5 of the 15 allocated to brand-name drugs.[4]

We compute the odds ratio and variance according to the usual methods. For estimates of uncontrolled seizures in generic versus brand name drugs, the

Table 2 Results from Kishore *et al.* (parallel design)

	Drugs		
	Generic	Brand name	
Seizures			
Uncontrolled	6	5	11
Controlled	39	10	49
Total	45	15	60

Table 3 Results from Oles *et al.* (cross-over design)

	Brand name drugs		
	Uncontrolled seizures	Controlled seizures	
Generic drugs			
Uncontrolled seizures	2	0	2
Controlled seizures	2	16	18
Total	4	16	20

calculations are performed as follows:[3]

$$\mathrm{OR} = \frac{6 * 10}{5 * 39} = 0.31$$
$$\mathrm{var}(\mathrm{In}(\mathrm{OR})) = \frac{1}{6} + \frac{1}{5} + \frac{1}{39} + \frac{1}{10} = 0.49$$

Table 3 presents results from a different trial with a cross-over design.[5] In this case, all 20 participants received both treatments and the order of treatment was randomly assigned. Of the 20 participants, 2 experienced uncontrolled seizures with both the generic and brand-name anti-epileptic drugs.[5]

We apply the Becker–Balagtas method by computing the odds ratio from the marginal quantities. The variance is adjusted for the within-patient correlation ($\rho = 0.67$).[3]

$$\mathrm{OR}_{\mathrm{Marginal}} = \frac{2 * 16}{4 * 18} = 0.44$$
$$\mathrm{var}(\mathrm{In}[\mathrm{OR}_{\mathrm{Marginal}}]) = \frac{1}{2} + \frac{1}{18} + \frac{1}{4} + \frac{1}{16} - 2\frac{5.56}{20} = 0.31$$

$$\Delta = 20^2\left(\frac{(20 * 2) - (2 * 4)}{2 * 4 * 18 * 16}\right) = 5.56$$
$$\rho = \frac{(20 * 2) - (2 * 4)}{\sqrt{2 * 4 * 18 * 16}} = 0.67$$

Assuming there are no other methodological concerns or between study heterogeneity, we can then combine these two estimates into one summary estimate. The estimates from the two trials may be combined by the usual inverse variance method for meta-analysis.[6] The summary estimate ($\mathrm{OR}_{\mathrm{pool}}$) is a weighted average of the two odds ratios where the weights (w_1, w_2) are determined by the precision of the estimates. The variance of the pooled estimate is a function of the inverse of the sum of the weights.[6]

$$\begin{aligned}
\mathrm{OR}_{\mathrm{pool}} &= \exp(w_1 * \mathrm{In}(\mathrm{OR}_1) + w_2 * \mathrm{In}(\mathrm{OR}_2)) \\
&= \exp(0.39 * -1.18 + 0.61 * -0.81) \\
&= 0.39 \\
\mathrm{var}(\mathrm{In}(\mathrm{OR}_{\mathrm{pool}})) &= 1/(\mathrm{var}(\mathrm{In}[\mathrm{OR}_1])) \\
&\quad + 1/(\mathrm{var}(\mathrm{In}[\mathrm{OR}_2])) \\
&= \frac{1}{0.49} + \frac{1}{0.31} \\
&= 0.19 \\
\mathrm{In}(\mathrm{OR}_1) &= -1.18 \\
\mathrm{In}(\mathrm{OR}_2) &= -0.81 \\
w_1 &= \frac{\frac{1}{0.49}}{\frac{1}{0.49} + \frac{1}{0.31}} = 0.39 \\
w_2 &= \frac{\frac{1}{0.31}}{\frac{1}{0.49} + \frac{1}{0.31}} = 0.61
\end{aligned}$$

A confidence interval (CI) for the pooled estimate is then:

$$\begin{aligned}
95\%\ \mathrm{CI} &= \exp(\mathrm{In}(\mathrm{OR}_{\mathrm{pool}}) \pm 1.96 * \sqrt{\mathrm{var}(\mathrm{In}(\mathrm{OR}_{\mathrm{pool}}))} \\
&= (0.16, 0.91)
\end{aligned}$$

To conclude this example, we report with 95% confidence that the odds of seizure for generic anti-epileptic drugs compared with brand-name anti-epileptic drugs is between 0.16 and 0.91. Based on these two trials, we find that the generic medications in these studies show a significantly reduced odds of uncontrolled seizure compared with the brand-name medications.

Note the following corrections to the formulae for Δ and s given in the appendix of the original article.[1] The formula for s may be applicable when the frequency is unknown but the correlation is reported. Assuming the same notation, the original formula for Δ and s are:

$$\Delta = \left(\frac{s - ab}{abcd}\right)$$
$$s = ab + \rho\sqrt{\frac{abcd}{n}}$$

The correct formulae are as follows:

$$\Delta = n^2\left(\frac{ns - ab}{abcd}\right)$$
$$s = \frac{\rho\sqrt{abcd} + ab}{n}$$

Correct application of the Becker–Balagtas method is important to ensure accurate estimation of summary estimates for meta-analysis. When including various

trial designs in a meta-analysis, it is best to select a common measurement that does not favour one design over the other.[1] Of the currently available methods, the marginal approach (or Becker–Balagtas method[2]) introduces the least bias when the meta-analysis combines cross-over trials with parallel trials.[3]

References

[1] Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV. Meta-analysis involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;**31:** 140–49.

[2] Becker MP, Balagtas CC. Marginal modeling of cross-over data. *Biometrics* 1993;**49:**997–1009.

[3] Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over trials. II: binary outcomes. *Stat Med* 2002;**21:**2145–59.

[4] Kishore K, Jailakhani BL, Sharma JN, Ahuja GK. Serum phenytoin levels with different brands. *Indian J Physiol Pharmacol* 1986;**30:**171–76.

[5] Oles KS, Penry JK, Smith LD, Anderson RL, Dean JC, Riela AR. Therapeutic bioequivalency study of brand name versus generic carbamazepine. *Neurology* 1992;**42:**1147–53.

[6] Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis*. San Diego: Academic Press Inc., 1985.

doi:10.1093/ije/dyp345
Advance Access publication 21 December 2009

When size presents problems

From PETER MORFELD[1,2]* and THOMAS C ERREN[2]

[1]Institute for Occupational Epidemiology and Risk Assessment (IERA) of Evonik Industries AG, Essen and [2]Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research, University Hospital of Cologne, University of Cologne, Germany

*Corresponding author. Institute for Occupational Epidemiology and Risk Assessment (IERA) of Evonik Industries AG, Rellinghauser Str.1-11, 45128 Essen, Germany. E-mail: peter.morfeld@evonik.com

With interest we read the Editorial by Dr Hense[1] headed 'When size matters'. We wish to compliment Dr Hense for pointing to several problems that mega-projects may generate. Most importantly, we certainly agree that mega-cohorts are not a solution to identifying and establishing causality per se.[2] Moreover, we wish to complement a potential pitfall of mega-studies, namely with regard to 'bias', a term which was not mentioned in the Editorial. Importantly, in view of the anticipated enormous visibility of 'these lighthouse projects of epidemiology',[1] it is a must to avoid the publication and dissemination of possibly biased findings.

In 2005, Ioannidis provided a convincing rationale as to 'why most published research findings are false'.[3] Having shown that small study group sizes can be a reason for distorted results, he argued also that 'claimed research findings may often be simply accurate measures of the prevailing bias' (p. e124).[3] Now, the probability that biased results may be reported uncritically as valid findings actually increases when precision is maximized because random error no longer has relevant effects and is, thus, expected to no longer mask small biases involved. In particular, observational studies of very large sizes—designed to measure small effects—are prone to this type of error and have to be analysed with extra diligence via bias estimation and adjustment procedures.[4,5]

Overall, a danger of sizeable studies is that large numbers may be misunderstood as a sufficient tool to identify truth and as an insurance against errors that plague researchers in small(er) investigations. Disconcertingly, the opposite may be true: indeed, due to the lack of random error, likely involved but uncovered biases may become a driving force for erroneous findings and misinterpretations in mega-studies that are conducted to measure small effects.

References

[1] Hense H-W. When size matters. *Int J Epidemiol* 2011;**40:** 5–7.

[2] Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*, 3rd edn. Philadelphia: Lippincott Williams & Wilkins, 2008.

[3] Ioannidis JPA. Why most published research findings are false. *PLoS Med* 2005;**2:**696–701.

[4] Greenland S. Multiple-bias modelling for analysis of observational data. *J R Stat Soc A* 2005;**168:**267–306.

[5] Morfeld P, McCunney R. Bayesian bias adjustments of the lung cancer SMR in a cohort of German carbon black production workers. *J Occup Med Toxicol* 2010;**5**(1). http://www.occup-med.com/content/5/1/23 (23 March 2011, date last accessed).

doi:10.1093/ije/dyr066
Advance Access publication 30 March 2011