AN APPLICATION OF A BIVARIATE RANDOM EFFECTS META-ANALYSIS IN A COST-EFFECTIVENESS ANALYSIS OF TREATMENT FOR SLEEP APNOEA

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Introduction
Systematic reviews to identify the current evidence for health technologies often form the basis for an economic evaluation. Where multiple trials provide information on the same outcome measure a meta-analysis may be conducted to synthesise the available evidence. Often more than one clinical outcome will be of interest in determining overall health outcomes. Frequently multiple outcomes are synthesised individually in a series of univariate meta-analyses. This paper explores the use of multivariate meta-analysis as an evaluative tool for the treatment of continuous positive airways pressure (CPAP) for the treatment of sleep apnoea.

Case study
Sleep apnoea describes a disorder where repeated collapse of the upper airway during sleep causes a reduction/obstruction of respiratory airflow. When accompanied by clinical symptoms such as excessive daytime sleepiness it is known as obstructive sleep apnoea-hypopnoea syndrome (OSAHS). The main treatment goal is to reduce daytime sleepiness. Treatments include the administration of CPAP during sleep, the use of dental devices to reposition the tongue or mandible and lifestyle modifications. The National Institute for Health and Clinical Excellence (NICE) in the UK requested an evaluation of CPAP in comparison to best supportive care, placebo and dental devices. This evaluation forms the basis for a comparison of alternative methods to synthesise the available data on clinical outcomes.

Systematic review
The primary outcome measure was subjective daytime sleepiness (Epworth Sleepiness Scale (ESS)) and objective sleepiness (e.g., Maintenance of Wakefulness Test (MWT)). The secondary outcome measures included blood pressure (BP), cardiovascular events (CVEs), road traffic (RTAs) and occupational accidents, quality of life. The review identified 38 RCTs comparing CPAP to placebo, of which 23 reported information on ESS, 5 on MWT, 16 on BP. The measures of daytime BP included those taken by ambulatory measurement (7 studies) and during office visits (3 studies). No RCTs reported information on CVEs, occupational accidents or RTAs.

Decision-analytic model
The primary outcome measure was the cost per quality-adjusted life-year (QALY) gained. A Markov model was developed which estimated QALY’s as a function of survival, daytime sleepiness, CVEs and RTAs. A set of individual patient data were used to map ESS scores to utility values. The Framingham risk equations predicted risk of CVEs as a function of BP; the utility decrement for CVEs was obtained from published studies. Thus from the range of outcomes identified in the systematic review, mean difference in ESS score and mean difference in systolic BP at follow-up were selected for input into the decision-analytic model.

Bivariate random effects meta-analysis
We first set out the framework for a bivariate random effects meta-analysis, which has been reported in Riley et al. (Riley et al., 2007a,b), among others. We then compare the results of bivariate approach to separate univariate analyses, and test the sensitivity of the model to alternative values for the within- and between-study correlation in treatment effects. A random effects analysis was performed where it was assumed that each study’s sample statistics for mean difference in ESS (ess) and mean difference in BP (bp) represented an estimate of different underlying true values (essReMu, bpReMu), and these underlying true values were assumed to be drawn from a distribution with particular mean (essReMu, bpReMu) and variance (essReSD2, bpReSD2).

Results
In URMAs endpoints are assumed missing completely at random (MCAR). Data may be considered MCAR if the mechanism for missingness:
i) is completely random; ii) does not depend on the missing values themselves; iii) does not depend on other variables in the dataset.

In BRMAs missing endpoints are assumed to be missing at random (MAR) Data may be considered MAR if the mechanism for missingness:
i) does not depend on the missing values themselves; ii) but can be explained by other variables in the dataset.

If treatment effects on multiple outcomes are thought to be correlated missing data will be MAR; the MCAR assumption is violated and applying a univariate approach can result in biased pooled estimates. In CPAP missing outcomes may be explained by the observed between-study correlation in treatment effects as well as the individual pooled estimates.

Meta-analysis may be considered to be observational as they synthesise data from those RCTs that are published. This issue of publication bias, where positive or statistically significant results may be more likely to be published may have a corollary in that only those secondary outcomes on which the treatment effect is positive or statistically significant may get reported. If this is the case then the missing assumption could be violated, as the missing data could depend on the missing value itself. However in the case of CPAP statistical significance does not seem to be important in reporting treatment effects on BP.

Often the number of studies available to inform the between-study correlation may be limited. In this case study the 95% credible interval was wide with seven studies providing both outcomes (0.78 to 0.96). In many cases, no information on the within-study correlation but even then it is still possible to employ a multivariate approach (Riley et al. 2007b).

The bivariate model described in this paper could be extended to incorporate more than two outcomes. A benefit of the approach is that the same set of studies is used to inform the pooled estimates for all of the outcomes. Any correlation between parameters can be incorporated in subsequent analyses. By using the 10,000 iterations from which the pooled estimates are derived (i.e. the WinBUGS output) directly in the probabilistic decision-analytic model correlation between treatment effects was maintained. This in turn can affect the estimates of decision uncertainty and value of information analysis.

Conclusions
In general systematic reviews may focus on more than one outcome of interest. The model described here is generalisable to any number of outcome measures.

Advantages of multivariate meta-analysis:
1)Accounts for correlation when estimating mean effects if there is missing data; 2) Allows correlation in population parameter estimates to be incorporated in decision-analytic models; 3)Potentially allows for correlation between variables to be accounted for.

The difference between the URMAs and BRMAs may have important consequences when the results are used to inform a cost-effectiveness analysis, particularly in terms of characterising uncertainty and estimating the value of further research.

References
Riley RD, Thompson JR and Abrams KR: An alternative model for bivariate random-effects meta-analysis when the within-study correlations are unknown. Biostatistics 2007b 0(0).

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