SEMI-PARAMETRIC APPROACHES FOR THE INDIVIDUAL PATIENT DATA META-ANALYSIS OF TIME-TO-EVENT OUTCOMES

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Systematic reviews which include a meta-analysis of individual patient data (IPD) from randomised controlled trials are often described as the 'yardstick' against which all systematic reviews should be measured. IPD offers several advantages which include the standardisation of outcome definitions, the possibility of undertaking a more complete, possibly updated analysis based on all randomised patients, the analysis of any previously unreported outcomes and the ability to more fully investigate the influence of covariates on heterogeneity of treatment effects. In particular, IPD is especially useful for time-to-event outcomes since the poor reporting of suitable summary data in trial reports may preclude reliable aggregate data meta-analysis.

A number of alternative methods for IPD meta-analysis of time-to-event outcomes have been established and used in practice. The most common approach for this type of data is a stratified log-rank analysis (Simmonds et al 2005) however a simulation study suggested that this method may not always be the most appropriate and consideration of alternative methods was recommended (Tudur Smith et al 2007).

In the Cox regression model stratified by trial with random treatment effects (Tudur Smith et al 2005), the hazard function for the *ith* individual in the *jth* trial is written as

$$\lambda_{ij}(t) = \lambda_{0j}(t)\exp(\beta_{1j}x_{1ij})$$
$$\beta_{1j} = \beta_1 + b_{1j}$$
$$b_{1j} \sim N(0, \tau^2)$$

where λ_{0j} is the baseline hazard function in the *jth* trial. The hazards are only assumed to be proportional within each trial. The coefficient β_1 can be interpreted as the average log hazard ratio for a population of possible treatment effects, and b_{1j} is the deviation of the *log hazard ratio* in the *jth* trial from this population average. The random quantities b_{1j} are assumed to follow a Normal distribution with mean zero and variance τ^2 which is a measure of the between trial variability in treatment effect i.e. a measure of the degree of statistical heterogeneity.

We will show how the model can be fitted, describe an application to explore the evidence for heterogeneity in pairwise meta-analysis of anti-epileptic drug trials, and extend the model to allow multiple treatment comparisons.