A NON-LINEAR HIERARCHICAL MODEL FOR EVIDENCE SYNTHESIS OF SAFETY DATA

[1]Tim Friede, [2]Beat Neuenschwander, [2]Alan Moore

[1]*Warwick Medical School, The University of Warwick, Coventry, UK*
[2]*CIS, Novartis Pharma AG, Basel, Switzerland*

In drug development safety analyses combining the evidence across clinical trials are increasingly important in order to detect even small risks of adverse reactions to the experimental drug under investigation. However, regulatory guidelines are vague regarding the methods to be used to summarize data across trials and simple pooling of the data is not uncommon (McEntegart 2000). Furthermore, unlike in standard meta-analysis the contrasts of interest usually cannot be estimated in every single study. Therefore for evidence synthesis in the context of indirect comparisons random effects models allowing for between-trial variation are used (see for example Spiegelhalter et al 2004, Whitehead 2002, Lumley 2002, Lu and Ades 2004). Safety events are often defined as pathological levels of blood or urine parameters with the samples routinely taken at discrete time points, say every three months, during the course of the study. Based on a discrete time-to-event model as described for example by Clayton and Hills (1993) we develop a hierarchical model synthesizing the evidence across trials. Model fitting is considered from a maximum likelihood perspective as well as from a Bayesian perspective. In a simulation study motivated by real-life data we investigate the properties of the proposed procedures.

References

Clayton D, Hills M (1993) Statistical models in epidemiology. Oxford University Press, Oxford. Chapter 4.

Lu G, Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine 23: 3105–3124.

Lumley T (2002) Network meta-analysis for indirect treatment comparisons. Statistics in Medicine 21: 2313–2324.

McEntegart DJ (2000) Pooling in integrated safety databases. Drug Information Journal 34: 495–499.

Spiegelhalter D, Abrams KR, Myles JP (2004) Bayesian approaches to clinical trials and health-care evaluation. Wiley, Chichester. Chapter 8.

Whitehead A (2002) Meta-analysis of controlled clinical trials. Wiley, Chichester. Chapter 10.