Model-based network meta-analysis for time-course relationships: A union of two methodologies

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Background: Model-based meta-analysis (MBMA) is a technique increasingly used in drug development for synthesising results from multiple studies, allowing pooling of information on treatment, dose-response and time-course characteristics, which are often non-linear. Such analyses are used in drug development to inform future trial designs. Network meta-analysis (NMA) is used in Health Technology Appraisals and by reimbursement agencies for simultaneously comparing effects of multiple treatments. Recently, a framework for dose-response model-based network meta-analysis (MBNMA) has been proposed that draws strengths from both MBMA and NMA.

Methods: We expand the MBNMA framework for modelling of time-course functions that allows for the inclusion of observations from multiple study time points using a Bayesian approach. This methodology preserves randomisation by aggregating within-study relative effects and, by modelling consistency equations on the time-course parameters, it allows for testing of inconsistency between direct and indirect evidence. Residual correlation between observations can be accounted for using a multivariate likelihood. We demonstrate our modelling framework using an illustrative dataset of 24 trials investigating treatments for pain in osteoarthritis.

Results: Of the time-course functions that we explored in our dataset, an E_{max} function allowed for the greatest degree of flexibility, both in the time-course shape and in the specification of time-course parameters (E_{max} and ET_{50}), and it also has strong biological plausibility. Our final model had a posterior mean residual deviance of 291.4 (compared to 345 data points), indicating a good fit to the data. Some simplifying assumptions were needed to identify ET_{50}, as studies contained few observations at earlier follow-up times. Treatment estimates were robust to the choice of likelihood (univariate/multivariate), suggesting that accounting for residual correlation between time points may not be essential if the time-course function has been appropriately modelled and the parameters of interest are summary treatment estimates.

Conclusions: Time-course MBNMA provides a statistically robust framework for synthesising evidence on multiple treatments at multiple time points whilst preserving randomisation and allowing for testing of inconsistency. The methods can inform drug-development decisions, and provide the rigour needed in the reimbursement decision-making process, thereby acting as a bridge between early phase clinical research and Health Technology Appraisal.