A Bayesian Framework to Account for Uncertainty Due to Missing Data in Meta-Analysis

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Aims: Missing outcome data is a common threat to the validity of the results from Randomised Controlled Trials (RCTs) which, if not analysed appropriately, can lead to misleading treatment effect estimates. Studies with missing outcome data also threaten the validity of any meta-analysis that includes them. We propose a conceptually simple Bayesian framework to combine study results with missing binary outcome data within a meta-analysis. The framework allows one to reflect the uncertainty introduced by the missing data either making minimal assumptions or incorporating external prior information about missingness mechanism.

Methods: We fit a pattern-mixture model that includes the prob(missing) and the prob(event given missing) within the meta-analysis likelihood statement. Prior information on the probability of an event in missing individuals can be introduced in several ways. Priors can be put directly on the probability of success given a subject was missing, on the Informative Missingness Odds Ratio (IMOR), on the success probability ratio, on the success probability difference or on the Response Probability Ratio, all within the same modelling framework. All models are fitted in the freely available Bayesian software WinBUGS.

Results: We use as an illustrative example a meta-analysis of 17 RCTs comparing haloperidol with placebo in the treatment of schizophrenia. This meta-analysis contains a fairly small amount of missing data with proportionately more missingness in the placebo group. The models in our missing data framework tended to have only a relatively small effect on the size of the point estimate (due to there being quite a small amount of missing data in most of the trials), however the level of uncertainty associated with the point estimate is increased compared to the standard Complete Case (CC) or Intention To Treat models, reflecting the uncertainty introduced by the missing outcomes. A fixed effect CC meta-analysis gives an Odds-Ratio (OR) of 3.82 with 95% CrI (2.66, 5.37), compared with an OR of 3.90 with 95% CrI (2.66, 5.62) using our framework where priors are put on the probability success difference. Similarly a random effects CC meta-analysis gives an OR of 10.70 with 95% CrI (3.63, 30.66), compared with an OR of 11.32 with 95% CrI (3.26, 37.45) using our framework where priors are put on the probability success difference.

Conclusion: The proposed Bayesian framework is conceptually and computationally simple. It allows the incorporation of prior information on the probability of an event in missing individuals to be introduced in different formats, and for the propagation of uncertainty due to missingness through

the model parameters. Our method allows one to make the best use of evidence produced from RCTs with missing outcome data in a meta-analysis, accounts for any uncertainty induced by missing data, and fits easily into the wider evidence synthesis framework for medical decision making.