

## Development of a Methodology for Indirect Treatment Comparisons in Meta-Analysis: Application to Treatments for Heart Failure

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**Background:** Statistical methodologies for indirect treatment comparisons (ITC) in meta-analyses have been proposed to evaluate the comparative efficacy of two treatments in situations where they have not been evaluated in head-to-head clinical trials. Popular methodologies include the Bucher method, network meta-analysis and mixed treatment comparisons. In the Bucher method, when there are studies for the direct comparison between A versus C and B versus C, the existence of a common comparator or linking treatment, C, forms the basis of a model that generates an indirect comparison between A versus B. The odds ratio was the effect measure for which this model was developed. We have extended the Bucher method for more than three treatments and have included a number of effect measures for dichotomous and continuous outcomes. **Objectives:** To describe the model for the odds ratio and relative risk and to illustrate these models by calculating indirect estimates for the effectiveness of the cardiac device implantable cardioverter defibrillator (ICD) combined with cardiac resynchronization therapy (CRT) versus ICD alone in patients with heart failure. **Methods:** We developed a model for situations when there is interest in obtaining indirect estimates for two treatments,  $A_1$ ,  $A_k$  in the set of treatments  $A_1, A_2, \dots, A_k$ , given that a direct comparison exists between each consecutive pair of treatments  $A_{i-1}, A_i$  ( $i=2, \dots, k$ ). An indirect effect estimate for ICD/CRT versus ICD was determined by considering different linking treatments used for heart failure: CRT alone and optimal medical therapy (OMT). The outcome of interest was mortality. For various parameter settings, simulations were conducted to determine the bias and mean square error (MSE) for the indirect treatment estimates, in particular for the three treatment setting. **Results:** For the odds ratio, comparing ICD/CRT versus ICD for the risk of mortality, the indirect OR was  $OR=0.97$  (95% CI: 0.62, 1.53) using a single linking treatment OMT (so called 'star' design). When two linking treatments were considered, CRT alone and OMT (so called 'ladder' design),  $OR=0.84$  (95% CI: 0.53, 1.35). Based on the simulated results for the three treatment model, the bias of this estimate was determined to be 0.062 and the MSE was determined to be 0.196. Both these values are reasonable values indicating that the indirect OR was clinically acceptable. The simulation results indicate that the bias and MSE associated with the indirect odds ratio are expected to be lower if the event rate, 0.3, in the group of patients receiving the common comparator increases to 0.5. The simulation results also indicate that the observed value of the bias and MSE would increase if the true value of the indirect estimate had been larger. Similar results were obtained for the relative risk. As well, comparison of our indirect odds ratio results were made with those using other ITC methods such as network meta-analysis and mixed treatment comparisons. **Limitations:** The primary assumption underlying the statistical model for the indirect estimate of  $A_1$  versus  $A_k$  is that the effect of the common comparator treatment, say  $A_i$ , for linking the two direct pairwise comparisons  $A_{i-1}, A_i$  and  $A_i, A_{i+1}$  is the same. Differences may arise when there is heterogeneity between the patient groups from which each of the direct estimates was obtained. In this situation, the indirect effect estimate may not be a valid estimate of the true relative efficacy of  $A_1$  versus  $A_k$ . It is important to check this model assumption in light of the data to which the model will be applied.

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