Detailed statistical analysis

Notation

Without loss of generality, the number of adverse events of a given type (e.g., hospitalization) is denoted by y for y = 0,1, …, M. It was assumed that the same study can contribute with different estimates for different treatment groups, which are considered independent and indexed by i for i = 1,2,…, k.

Approximation of the number of person-years of exposure

Typically, follow-up time in studies was reported in weeks. However, clinical interpretation is facilitated by the use of person-years monitored (11). Thus, for each treatment group i, the sum of the number of years that the randomized participants were under observation was approximated by:

Equation (1) ➔ $T_1 = \frac{follow\text{-}up_i \times n_i - (follow\text{-}up_i \times p_i \times 0{,}5)}{52.143}$

...where $follow\text{-}up_i$ represents the follow-up time in weeks, n_i denotes the number of participants analyzed, and p_i represents the number of participants who discontinued or were lost during follow-up in study i. Based on equation (1), it is possible to infer that the premise is that participants lost over time contributed to half of the total follow-up time.

Model

The Poisson distribution is the natural choice for modeling data in the form of counts. Thus, a Bayesian meta-analytic model was implemented assuming a Poisson distribution and random effects. Assuming the treatment groups are independent, the number of adverse events in treatment group i, y_i, during total follow-up time in person-years, T_i, for i = 1, 2, …, k was considered as:

Equation (2) ➔ $y_i \sim \text{Poisson}(\lambda_i)$

Equation (3) ➔ $\lambda_i = \theta_i \times T_i$

Equation (4) ➔ $\log(\theta_i) \sim \text{N}(d, \tau^2)$

...where λ_i is the mean of the distribution and θ_i is the incidence rate in the ith study. As can be seen in equation (4), the model assumes that the incidence rates (on the log scale) are random samples from a normal distribution, whose true mean is d with variance τ^2. Both d and τ^2 are unknown entities and need to be estimated based on observed data. From the point of view of the meta-analysis, the estimates of d and τ^2 represent the logarithm of the summary incidence

rate across treatment groups (random-effects model) and the inter-treatment-group variance, respectively.

The model was specified with non-informative a priori distributions:

$$d \sim \mathrm{N}(0, 10^4)$$

$$\tau \sim \mathrm{Unif}(0, 5)$$

To facilitate the interpretation, summary results have been shown as $\hat{d} \times 1000$, denoting the summary incidence rate per 1000 person-years.

Implementation

The model parameters were estimated by the Monte Carlo method coupled to Markov chains (MCMC) using the Gibbs sampler implemented in the MultiBUGS program (12). The first 50,000 simulations were discarded (burn-in period) and the model was continued for another 166,667 iterations through three independent chains, totaling 500,000 simulations. Convergence and autocorrelation were verified graphically in the Stata program (version 16, StataCorp, Texas, USA) as described by Thompson; Palmer; Moreno (13). The summary results of the meta-analyses were calculated by the median of the posterior distribution, and the 95% credibility intervals by the 2.5th and 97.5th percentiles of the posterior distributions.