

Rejoinder

William DuMouchel

Many thanks to all of the discussants for their observations and suggestions and encouraging words. My response is quite short because I agree with all of their comments.

Professor Evans points out the importance and potential difficulty of selecting which set of issues or adverse event definitions to include in the analysis. They need to be approximately exchangeable in terms of prior belief as to their expected associations with Treatment and with covariates. Prior belief refers to your expert opinion before looking at the data to be analyzed—it would not be appropriate to just select issues that are observed to have high odds ratios with treatment, for example, which might tend to bias the estimation of variance components in the model, making them appear too small. His suggestion of selecting SMQs that are formed from terms in a local region of the MedDRA hierarchy seems reasonable, or of using other knowledge or data that seem to point to plausible exchangeability. I also agree with Professor Evans on the need for more experience with how MBLR works with varying numbers of issues (K) and numbers of covariates (J) and varying sample sizes. My intuition is that the model should be robust to a wide range of K and sample sizes, but that it is probably not a good idea to allow J to be too large, on the rationale that collinearity often leads to problems in any regression model having many covariates. Perhaps J should be kept in the range of 1 to 5, and I suspect that it would be a mistake, leading to spurious results, to think of MBLR as a data mining technique, where you search for the best 5 covariates out of 50 available, for example. Better to just use a few prespecified covariates that have some prior justification for potential effects or interactions with treatment.

Professor Berry provides a nice overview of the inferential and medical difficulties raised by drug safety issues. Many of these difficulties are beyond the reach of any mere statistical model, of course. But in as much as consideration of multiplicities due to analyses of

related medical events and to subgroup analyses contribute to these problems, perhaps the MBLR model, or similar approaches using Bayesian shrinkage, can help researchers see the forest through the trees.

Special thanks go to Brad McEvoy and Ram Tiwari for their collaborations and discussions during the later development of MBLR, and now for their acute comments here. First, they provide an insightful and enlightening discussion of the relationship of the MBLR model to meta-analysis modeling in general, assuming that the data at hand come from multiple studies. My choice, made for simplicity, was to treat the Study ID as just another categorical variable like patient age or sex. This should eliminate certain biases like those due to Simpson's paradox, and does allow the treatment effect to vary by Study, but does not treat Study as an independent random effect that could potentially interact with all other covariates. It also makes it difficult to build into the analysis the fact that patients were independently randomized within each study, which does not play much of a role in a Bayesian model, but is an important aspect of the classical paradigm. McEvoy and Tiwari define an extended meta-analytic MBLR model that allows for Study (trial) to be a higher level of a hierarchical model and fit it to the data in the paper using the Markov chain Monte Carlo (MCMC) approach. That model is much more complex, since instead of just 4 prior standard deviations to estimate, there are $(2K + 4) = 24$ such hyperparameters, which would make it impossible to fit using the simpler methodology of the present paper. Much more research would be needed to assess the relative validity and reliability of this more complicated methodology. An alternative approach might be to fit the current MBLR model separately to the data from each study, and then using a more traditional meta-analysis approach as a post-processing step applied to the coefficients and standard errors so obtained.

Drs. McEvoy and Tiwari also focus on the decision to borrow strength across different issues (AEs), in that if your prior belief that the issues are exchangeable is incorrect, then the shrinkage may not help and could possibly lead to extraneous variability. They point out that careful interpretation is especially needed when a rare but severe issue is analyzed in conjunction with

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