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**Meta-Analysis Workshop 2021 – Program**

**September 30th – October 1st**

"Exploring the limits of advanced meta-analysis"

**Thursday, September 30th**

**12:45 Welcome**

**13:00 Invited Talk by Sofia Dias (University of York) Network meta-analysis: making best use of the evidence for better decisions**

**Abstract:** Meta-analyses are often used to synthesize evidence from multiple studies in order to decide which treatment is most effective (or cost-effective) out of several alternatives but often more than two treatments are available for a condition of interest. Separate meta-analyses of each pair of treatments is data- and time-inefficient and can lead to conflicting conclusions. Network meta-analysis (NMA) is commonly used to compare multiple treatments by combining all the studies making comparisons of any two or more treatments of interest. Thus, NMA makes best use of the

available data by combining direct and indirect evidence on all comparisons

of interest, by simply extending the familiar assumptions in pairwise

(two-treatment) meta-analysis.

By jointly synthesizing evidence from multiple sources, a degree of

‘evidence redundancy’ can be created in a network of treatment comparisons,

and this can be used to inform additional parameters of interest. In

addition, the typical Bayesian hierarchical modelling framework used to

implement NMAs can also be used to mitigate some common issues caused when

treatment networks are sparse, e.g., when many treatments but few studies

are available for a particular decision-problem.

We will discuss the underlying assumptions in NMA and describe (1) models

that attempt to estimate and adjust for bias due to study design

characteristics and (2) “class models” where an overall relative treatment

effect for a class, or group, of treatments is assumed, whilst retaining

individual treatment effects which may have their own specific costs and

adverse events.

Data requirements, assumptions and limitations will be discussed with

reference to some real examples.

**13:45 Christian Röver (University of Göttingen)** **Using the bayesmeta R package for Bayesian random-effects meta-regression**

**Abstract:** The bayesmeta R package facilitates Bayesian meta-analysis within the simple normal-normal hierarchical model (NNHM). Using the same numerical approach, we extended the bayesmeta package to include several covariables instead of only a single "overall mean" parameter. We demonstrate the use of the package for several meta-regression applications, including modifications of regressor matrix and prior

settings to implement model variations. Possible applications include consideration of continuous covariables, comparison of study subgroups, and network-meta-analysis.

**14:10 Break / Discussions**

**14:30 Invited Talk by Wolfgang Viechtbauer (Maastricht University) A general workflow for complex meta-analysis with dependent effect sizes**

**Abstract:** Once the tedious steps of searching and screening the literature for relevant studies have been completed, the standard workflow for a meta-analysis is to quantify the phenomenon of interest (e.g., the effectiveness of a treatment, the association between two variables) in terms of some effect size measure for each study, calculate the sampling variances of the estimates, and then synthesize the estimates using fixed- or random-effects models (possibly in combination with an exploration of heterogeneity using meta-regression). However, in practice, the structure underlying the estimates is often more complex, for example, when multiple estimates were extracted from the same study, possibly based on the same or at least partially overlapping groups of study participants. In this case, the workflow needs to involve a consideration of the dependency in the estimates, computation of the sampling error covariances, the use of multilevel/multivariate models, and possibly the use of cluster-robust variance estimation. In this talk, I will describe this general workflow and illustrate its application using the metafor and the clubSandwich packages.

**15:15 Robbie C.M. van Aert (Tilburg University) Bayesian hypothesis testing and estimation under the marginalized random-effects meta-analysis model**

**Abstract:** Meta-analysis methods are used to synthesize results of multiple studies on the same topic. The most frequently used statistical model in meta-analysis is the random-effects model containing parameters for the overall effect, between-study variance in primary study’s true effect size, and random effects for the study-specific effects. I propose Bayesian hypothesis testing and estimation methods using the marginalized random-effects meta-analysis (MAREMA) model where the study-specific true effects are regarded as nuisance parameters which are integrated out of the model. I propose using a flat prior distribution on the overall effect size in case of estimation and a proper unit information prior for the overall effect size in case of hypothesis testing. For the between-study variance (which can attain negative values under the MAREMA model), a proper uniform prior is placed on the proportion of total variance that can be attributed to between-study variability. Bayes factors are used for hypothesis testing that allow testing point and one-sided hypotheses. I will illustrate the developed methods by applying it to two meta-analyses and introduce easy-to-use software in the R package BFpack to compute the proposed Bayes factors.

**15:40 Break / Discussions**

**16:00 Invited Talk by Daniel Jackson (AstraZeneca) Multi-step estimators of between-study variances and covariances and their relationship with the Paule-Mandel estimator**

**Abstract:** Moment based estimation methods for the between-study variance are well established in univariate meta-analysis but can perform poorly. Multi-step moment-based estimators have been proposed to improve performance, whilst retaining computational and conceptual simplicity. This talk will, in an "equation-light" way, explain how multi-step estimators are calculated. It will focus on univariate analyses but will also outline work in progress that explores the multivariate setting. The main aims are to disseminate some recently published findings that give greater credibility to multi-step estimators, that establish their relationship with the Paule-Mandel estimator, and to give an indication of the directions of our current unpublished work. We will illustrate the use of multi-step estimators using several different examples, both univariate and multivariate. We will outline the main findings from preliminary simulation studies in the multivariate setting (and will explain why extensive univariate simulation studies are not a priority). Our results illustrate the (recently published and proved mathematically) relationship between the multi-step estimator and the Paule-Mandel estimator in the univariate setting. This relationship becomes weaker for multivariate meta-analyses but will also tentatively propose how multi-step estimators could be used to define a multivariate Paule-Mandel estimator.

**16:45 Discussions / Closing Remarks**

**Friday, October 1st**

**09:00 Greeting**

**09:15 Invited Talk by Georgia Salanti (University of Bern) IPD Network meta-analysis seen as prediction model for heterogeneous treatment effects**

**Abstract:** Predicting individualized treatment effects is of great importance, so that a treatment might be targeted to individuals who will benefit from it and be avoided by those who won’t. We have developed a two-stage individualized prediction model for heterogeneous treatment effects, by combining prognostic research and network meta-analysis methods. We extend the idea of risk-modelling, that has been used to estimate heterogeneous treatment effects in a single randomized trial, in the context of network meta-analysis. We are also developing methods to evaluate the clinical relevance of the model, by extending the decision curve analysis idea. We apply the methodology in a network of trials that compare four treatments for patients with relapsing-remitting multiple sclerosis. We will also present an R-Shiny app that estimates the risk of relapse under the available treatments.

**10:00** **Thilo Welz (TU Dortmund University) Two new cluster robust covariance estimators for multivariate meta-regression**

**Abstract:** Multivariate meta-regression allows for the consideration of dependency structures between multiple effects of a study, which are based on the same study participants. Furthermore, robust estimators are generally desired for regression as they account for potential model misspecification without much loss of efficiency when model assumptions are correct. We suggest two new cluster robust variance-covariance estimators for multivariate meta-regression. We compare these with alternative cluster robust approaches, such as the bias reduced linearization approach as proposed by Tipton & Pustejowsky. We perform a comparative simulation study, focusing mainly on the empirical coverage of constructed confidence regions.

**10:25** **Break / Discussions**

**10:45 Invited Talk by Ian White (MRC Clinical Trials Unit at UCL, London) Precision-weighted bias: a new performance measure targeted at meta-analysis**

**Abstract:** Trials that are stopped early due to evidence of efficacy are often regarded as biased, and GRADE guidelines tend to favour excluding such trials from meta-analysis. However, such trials also have larger standard errors than if they had not been stopped early, and the consequent association between point estimate and standard error may also impact meta-analysis. I will introduce precision-weighted bias, a new performance measure for trial results that can be explored in simulation studies. Precision-weighted bias can help understanding the impact of trials on a meta-analysis and suggests that trials stopped early are not a source of bias in meta-analysis.

**11:30 Eric Knop (TU Dortmund University) Performance of robust confidence intervals for mixed-effects meta-regression with interaction**

**Abstract:** The power of statistical tests and confidence intervals in mixed-effects meta-regression models depends strongly on the method used for the

variance estimation of the parameters of interest. Since standard approaches perform poorly when basic assumptions like homogeneity or

normality are violated, robust methods are required. In previous research

such methods were compared to the commonly used Knapp-Hartung method for

models with one moderator. The Knapp-Hartung method usually turned out to

be the best, even when those basic assumptions were violated. In this work the performance of confidence intervals based on the Knapp-Hartung method is compared to confidence intervals based on robust heteroscedasticity consistent methods in a model where an interaction between two moderators is present. By a simulation study it could be shown that in absence of normality Knapp-Hartung method reaches its limits and a heteroscedasticity consistent method might be more adequate.

**12:00** **Discussions / Closing Remarks**