# Faculté de pharmacie

## Séminaire de l'axe

## «Médicament et santé des populations»

Université de Montréal

# «Marginal Meta-Analysis for Combining Multiple Randomized Clinical Trails with Rare Events – Lessons Learned from Avandia Story»


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*À l'invitation de la professeure Mireille Schnitzer*


Meta analysis (MA) is commonly used in the post-marketing safety studies for FDA regulated medical products, including drugs, medical device, and etc. Avandia Studies (Nissen et al, 2007, 2010) is a powerful example to show how important MA is in real life for quantifying the safety concerns with policy impacts. However, the fact that the re-analysis of same Avandia data could reach different conclusions showed clearly the statistical challenges and difficulties associated with standard fixed effect and random effect MA methods. Specifically, the inclusion and exclusion of zero trials, changing the effect estimand to risk difference, and/or using other fixed effect MA methods rather than Peto, would all lead to different results. Lesson learned from Avandia studies inspired our discovery of the problems associated with "homogeneous effects" or "effect at random" assumption – the validity assumption underlying standard MA approaches, and led to a set of more relaxed Study at Random assumptions. Additionally, two more concerns motivated our research on this marginal meta analysis: (1), rare events in safety studies often lead to low power in homogeneity test associated with standard MA approaches. Even though they may bias the results, various types of add-hoc continuation corrections were proposed and widely used to improve the performance of standard MA estimators. (2) Non-collapsibility issues associated with odds ratio limit the interpretability of many popular MA estimators too. As a result, based on the new flexible study homogeneity assumption, we proposed a marginal meta analysis approach with natural weights which provided a consistent treatment effect estimate for marginal causal effects combining randomized clinical trials in safety studies. This estimator is particularly useful when the outcome is rare, and double zero trials are naturally accounted in the estimation without any add-doc continuity correction. Systematic simulation studies show that the proposed estimator performs reasonably well under different rationales. This method is re-applied in Avandia safety evaluation as a real case application. This is a joint work with my students, Elande Baro, Yun-Yu Cheng, and colleague from FDA, Guoxing Soon.