Chapter 4. Conclusions

Meta-regression methods will be increasingly used in the future. Their attractiveness lies in their potential to explain differences between studies, thereby helping the clinician and decision-maker determine when, where, and for whom a treatment is beneficial. Our experts noted the usefulness and timeliness of this report.

Our panel had several general recommendations regarding meta-analysis and meta-regression. Foremost, the panel echoed the guidance given by others: measuring and incorporating heterogeneity in a meta-analysis is not sufficient. Meta-analysts should investigate and attempt to understand the causes of heterogeneity, and meta-regression is an appealing technique to use. The panel saw the need for outreach by the methodological community to the user community in advising how to conduct, interpret, and present meta-regression analyses. Further software development should include model diagnostics, and graphical approaches.

The panel made several recommendations that we were able to include in this report. Some recommendations are delegated to future research. The panel also addressed the next methodological topic for the Southern California Evidence-Based Practice Center given our role as technical support to the NCCAM. The panel recommended that if we undertake as our next methodological topic the quality assessment of observational studies, we focus on a specific clinical topic as a "case study." The panel recommended against developing a global scale, and also did not advise considering observational study quality in general.

Our simulation compared five meta-regression methods ranging from fixed effects to random effects, either including or not including covariates, to the control rate method. Our simulation results produced the following guidelines for the meta-regression practitioner:

- In general, failure to incorporate important covariates at either the study or person level, can bias the results of a meta-analysis.
- Despite the importance of including covariates, a model that includes a covariate that is an aggregate of a person-level characteristic rather than a study characteristic can produce biased results. The trade-off between the biases of incorporating an aggregated covariate versus excluding it requires further exploration.
- If the control rate affects treatment, the meta-analysis should incorporate the control rate. However, control rate meta-regression is susceptible to bias via the correlation between the control rate and other omitted covariates. This suggests that extensions of control rate meta-regression to include other covariates may prove useful.
- As always, larger number of studies and larger number of patients per study can reduce bias with proper modeling.

In summary, our key message to practitioners is they should explore the causes of heterogeneity via the inclusion of covariates at both the person level and study level. Either fixed effects or random effects methods can be used to support this exploration. Note that our work presented in this report has not addressed confidence interval construction and statistical significance testing. Further work in this dimension may reveal differences between fixed and random effects approaches.

The research to date has revealed promising directions for expanding the simulation. In particular, we need to further implement the expert panel's advice that more variability in sample sizes be included. Furthermore, correlations, both negative and positive, between study baseline outcome rates and covariates at both the study and person level need to be explored over an expanded range of values. Similarly, a broader range of within-study variation for the person-level covariate(s) should be evaluated. The ability of the various meta-regression methods to identify which covariates, study or person-level, are able to predict the treatment effect, and how well they can do so, should also be a question addressed by an expanded simulation study. We now have in place a simulation methodology, a common notation, and a supportive panel of national experts to enable and guide our continued work in this area.

NCCAM and AHRQ were especially interested in the topic of heterogeneity in meta-analysis given its relevance to alternative medicine literature. The challenges faced in synthesizing this literature are very different from those faced in for example the cardiovascular literature. The latter consists mainly of large randomized controlled trials. In contrast, the alternative medicine literature consists mainly of small trials, and nonrandomized studies. In addition to study design heterogeneity, the interventions are heterogeneous as well as the patient populations. Thus, methods for dealing with heterogeneity are particularly relevant.

Staff of the Southern California Evidence-Based Practice Center have applied meta-regression in the alternative medicine setting. In systematic review of the evidence on ephedra and ephedrine,[27, 28] we used meta-regression to compare weight loss efficacy between groups receiving ephedrine; ephedrine plus caffeine; and ephedra plus herbs containing caffeine versus placebo. In a meta-analysis of spinal manipulation,[29] we developed meta-regression models for acute and chronic back pain patients predicting short-term and long-term pain and function. These models took the unique approach of denoting the spinal manipulation group as the comparison group against which all other treatments, such as sham or physical therapy, were compared. The usual strategy would be to compare versus placebo or control. The knowledge gained via the research presented in this report impacted the application of meta-regression to these alternative medicine questions, and improved our ability to synthesize and understand these therapies.