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Response to: Vance W. Berger's letter to the editor regarding "Simpson's Paradox and Confounding"

Overall we agree with most of Berger's points and are therefore somewhat curious that the tone of his letter suggests otherwise. In the following paragraphs we clarify point by point our areas of agreement and disagreement.

We disagree with Berger's suggestion that there is a clear distinction between the terms "blocking" and "stratification". Many authors use these terms interchangeably and even those who make a distinction specify that the distinction is for clarity. Consider for example, "Blocked randomization is, as described previously, a special kind of stratification. However, this text will restrict use of the term blocked randomization to mean stratifying over time, and use of stratified randomization to refer to stratifying on factors other than time (Friedman, Furberg, and DeMets (1998, p. 67)."

Alternatively, we agree that blocking has an inherent problem, at least theoretically, in that in some circumstances investigators could predict the group to which a subject would be allocated. In other words, blocking

can lead to randomization being subverted. But the fact that a researcher can, on occasion, intentionally or unintentionally misapply a valid methodology should not result in the methodology being abandoned. As to the maximal procedure, this is an alternative approach to randomization for reducing selection bias (Berger, 2005), if that is a concern. But does the maximal procedure, compared to a randomized block design, ensure a more proportional distribution of subjects on a known confounding variable as is the issue with Simpson's paradox? No. We agree that minimization in its pure form is not randomization.

As to the issue of when stratified and unstratified analyses can be misleading, we agree that there are other situations (beyond Simpson's Paradox) in which these analyses could lead to erroneous conclusions, such as when a covariate is a pseudo-covariate (Berger, 2004), but full discussions of those situations, which are related to different internal validity issues, were beyond the scope of this paper. Further, we heartily agree that covariates should be measured before randomization. In closing, for readers who wish a more in-depth analysis of the issues that Berger raised, issues that were beyond the scope of our article, his book focuses specifically on those topics (Berger, 2005).

#### References:

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- Berger, V. W. (2005). *Selection bias and covariate imbalances in randomized clinical trials*. Chichester, England: Wiley.
- Friedman, L. M., Furberg, C. D., & DeMets, D.L. (1998). *Fundamentals of clinical trials* (3rd ed.) New York: Springer-Verlag.