Editors' Note: WriteClick correspondence this week includes an instructive exchange between author, commenter, and biostatistician regarding the need to control for type I error. In reference to the recent article by Newhouse et al., "Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial," Dr. Gold warns of the possibility of type I error in the article's secondary outcomes analyses and against reading too much into the significant p values reported. The authors agree that, as an exploratory study, type I error was not controlled for as multivariate analysis would have been impractical. Our own biostatistician, Dr. Kryscio, lends his expert opinion and agrees that type I error would not necessarily need to be considered in this case but advises caution as the study was underpowered to detect significant differences within subsets.

Megan Alcauskas, MD, and Robert C. Griggs, MD

NICOTINE TREATMENT OF MILD COGNITIVE IMPAIRMENT: A 6-MONTH DOUBLE-BLIND PILOT CLINICAL TRIAL

Michael Gold, Vancouver, BC, Canada: Newhouse et al. report the results of what appears to be a prospectively powered study of transdermal nicotine in a relatively small population of patients with amnesic MCI.¹ The article appropriately reports the outcome of the primary outcome measure but provides no context for the control of type I error for the multitude of additional analyses and p values reported. There are 17 separate p values in the report: some from the intent-to-treat population, some from the per protocol population, and some from a post hoc analysis of *APOE* data. It is disingenuous to think that all these analyses carry the same inferential

value, yet the authors make no effort to control type I error. In absence of some sort of control over type I error, the slew of nominally significant p values needs to be approached with a great deal of caution, something that the authors also fail to mention.

Author Response: Paul A. Newhouse, Diantha Howard, Burlington, VT: As an exploratory study, we thought it was important to note any potential areas for efficacy as a guide for future studies. While we did not control for type I error on secondary outcomes, we reported the actual p values so that readers could draw their own conclusions about their importance. Adjusting p values across univariate analyses for different tasks utilizing different strategies would be inappropriate for the exploratory nature of the study. Multivariate analyses, which would control for effects across tasks, would be ideal but we were looking for particular areas for efficacy.

Editor's Note from Associate Editor of Biostatistics: Richard J. Kryscio, Lexington, KY: Since the results for the secondary outcomes are in agreement with the positive results for the primary outcome, I see no reason to adjust the type I error rate in this situation. Usually we expect to see some adjustment when the primary endpoint yields a negative result. However, Dr. Gold is correct in pointing out that since the study is not powered to detect differences on such a large number of endpoints assessed for several different subsets of the study participants, the readers of this article should employ caution when interpreting the results for these secondary endpoints.

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1. Newhouse P, Kellar K, Aisen P, White H. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. *Neurology* 2012;78:91–101.

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Nicotine Treatment of Mild Cognitive Impairment: a 6-Month Double-Blind Pilot Clinical Trial

Michael Gold, Paul A. Newhouse, Richard J. Kryscio, et al.

Neurology 2012;78;1895

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