MEMORANDUM

To: Heinz Schneider

From: Michael Stoto

Re: Phenylephrine meta-analysis

Date: January 27, 2007

I have reviewed the January 23 draft of the CHPH Phenylephrine Task Group's "Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults with Acute Nasal Congestion due to Common Cold" and am pleased to report that I find that the task group has addressed all of the issues raised in the December 20, 2006 conference call, and that in my judgment the analysis meets professional standards. As a result, I believe that the conclusions are justified.

There are, however, a number of aspects of the written report that I believe can be improved. They are the following:

p. 6 — In presenting the study objectives, it should be noted that (a) individual studies will be reanalyzed in a parallel fashion and (b) a pooled (individual-level) meta analysis will be performed.

p. 12 — The footnote to Table 2 is an important point to make, but it should be made in the conclusions section rather than here.

p. 13 — The discussion of logs and ratios is overly complicated and confusing. It is well known that the log transformation is appropriate for ratio measures, and that the results of analyses done in the log scale should be transformed back to the original scale for presentation. A geometric mean is indeed equivalent to the re-transformed mean of the logs, but this not actually being done in this analysis, so the term "geometric mean" should not be used.

p. 14 — The results of study #8, now discussed in the pooled analysis section, should be moved to the conclusions section of the paper.

p. 15, l. 2 — Add s to "statistical models"

p. 15 — I would have labeled the second model as #1 and visa versa since that way the three would be increasingly complex.

p. 16 — The second complete paragraph, beginning with "The results …", is a result and should be moved to the results section.

pp. 17 & 18 Tables 3 and 4 should present the estimated difference or summary difference and a 95% confidence interval, i.e. the information in Figures 1-8.

Figures 1-8 Units should be given for the horizontal scale.

Comments on Phenylephrine Meta-analysis
M. A. Stoto, December 17, 2006

1. Choice of studies
    a. Why limit studies to before '76?
    b. Did you search for other studies, before or after '76?
    c. Complete references should be given for all studies
    d. "Site" looks like it might be the company performing some of the trials
2. Non-included studies
    a. Should list references and specific reason for exclusion
    b. Were results qualitatively consistent with the included studies?
    c. Was lack of individual-level data a reason for exclusion?
3. A priori choices
    a. should be made clear, including reason, at the start
    b. Rationale for excluding study #8 seems to depend on knowing that results would be significant without it
    c. Was choice of ΔNAR vs. ΔlnNAR a priori?
    d. Model for individual study and M-A
    e. 30 and 60 minute time points as most important output?
4. Time line
    a. Note at the start that studies tested outcomes at different points
    b. Were there results at other time points not reported here?
5. Data entry
    a. Note more clearly that individual-level data were used.
6. Outcome measure
    a. ln-ratio NAR = ΔlnNAR, which seems like a reasonable measure if NAR is a ratio; why was transformation used instead?
    b. ΔlnNAR might help with the departure from normality noted
7. Statistical model
    a. make more clear that this is a **pooled** meta-analysis (MA-P)
    b. List in text and tables as Model 1.a, 1.b, 2.a, 2.b, 3
8. Results
    a. If ΔNAR was chosen vs. ΔlnNAR a priori, it would be better to present it as such, with the alternative as a sensitivity analysis
    b. Report effect sizes and 95% C.I., not P-values
    c. Table 2 is hard to read since it does not make clear which studies has results at which levels and which didn't
    d. Better to present Table 2 in tabular form (e.g. rows = time points, columns = study) with effect and 95% C.I. for each available effect estimate. Base on a priori choice of statistical model, then indicate differences where they appear
    e. Table 2 (M-A results): Use same format as suggested above, with columns for Model 2 and Model 3
    f. Note that time scale on graphs is not equally spaced
    g. Show a forest plot for each key time point, with major analysis only

Abbreviated Curriculum Vitae

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EDUCATION

Harvard University: Ph.D. in Statistics, 1979; A.M. in Statistics, 1977; recipient of National Science Foundation Graduate Fellowship.
Princeton University: A.B. in Statistics with High Honors, 1975.

EMPLOYMENT

2006-	Professor of Health Services Administration and Population Health, School of Nursing and Health Studies, Georgetown University
2001-2006	Senior Statistical Scientist, RAND
1998-2001	Professor and Chair, Department of Epidemiology and Biostatistics, School of Public Health and Health Services, George Washington University
1997-	Adjunct Professor of Biostatistics, Harvard University
1983-1998	Senior Staff Officer, Institute of Medicine, National Academy of Sciences
1979-1987	Assistant, then Associate Professor of Public Policy, J. F. Kennedy School of Government, Harvard University (on leave, 1983-1984)

TEACHING EXPERIENCE

Pardee RAND Graduate School

2003- Research Synthesis and Meta-Analysis

Harvard School of Public Health, Harvard University

1997- Research Synthesis and Meta-Analysis for Public Health and Clinical Medicine

George Washington School of Public Health and Health Services

2000-2001 Research Synthesis and Meta-Analysis for Public Health and Clinical Medicine

SELECTED PUBLICATIONS

1. Emerson JD, Stoto MA. Exploratory methods for choosing power transformations. *Journal of the American Statistical Association* 1982; 77: 103-108.
2. Hoaglin DC, Light RJ, Mosteller F, McPeek B, Stoto MA. *Data for decisions: Information strategies for policymakers*, Cambridge, MA: Abt Books, 1982.
3. Stoto MA. The accuracy of population projections. *Journal of the American Statistical Association* 1983; 78: 13-20.

4. Blumenthal D, Gluck ME, Louis KS, Stoto MA, Wise D. University-industry relationships in biotechnology: Implications for the university. *Science* 1986; 232:1361-1366.
5. Stoto MA. Statistics for an aging population: Dealing with uncertainty. *American Statistician* 1988; 42:103-10.
6. Stoto MA. From data to analysis to conclusions: A statistician's view. In Bailar JC et al., eds. *Ethics and policy in scientific publication.* Council of Biology Editors, Washington, 1990.
7. Stoto MA. Public health assessment for the 1990s. *Annual Review of Public Health* 1992; 13:59-78.
8. Stoto MA, Durch JS. Forecasting survival, health, and disability: Report of a workshop. *Population and Development Review* 1993; 19:557-582.
9. Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. *Veterans and agent orange: Health effects of herbicides used in Vietnam.* Washington: National Academy Press, 1994.
10. Leveton LB, Sox HC, Stoto MA, eds. *HIV and the blood supply: An analysis of crisis decisionmaking.* Washington: National Academy Press, 1995.
11. Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. *Veterans and agent orange: Update 1996.* Washington: National Academy Press, 1996.
12. Stoto MA. Doing and understanding meta-analysis and not being misled by the results (Meeting summary). *Current Drugs*, 1997.
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18. Stoto MA, Cleary SD, Foster VB. Epidemiologic studies of MMR vaccine and autism. Prepared for the IOM Immunization Safety Review Committee, 2001.
19. Stoto MA. The precautionary principle and emerging biological risks: Lessons from swine flu and HIV in blood products. *Public Health Reports* 2002; 117:546-52.
20. Bozzette SA, Boer R, Bhatnagar V, Brower JL, Keeler EB, Morton SC, Stoto MA. A model for a smallpox vaccination policy. *New England Journal of Medicine* 2003; 348:416-425.
21. Berlin JA, Normand SL, Stoto MA, Flaig RB, Lemeshow AR, Colditz GA. Protocol for a meta-analysis of epidemiologic studies of the association between alcohol consumption and health outcomes. Deliverable #2 under NIAAA contract #: N01AA21011, 2003.
22. Colditz GA, Berlin JA, Stoto MA, Flaig RB, Lemeshow AR. Proposed protocol for population fractions estimation. Deliverable #3 under NIAAA contract #: N01AA21011, 2003.

23. Colditz GA, Normand S-L, Rimm EB, Stoto MA, Flaig RB, Lee R, Howe E. Estimating alcohol attributable fractions for U.S. morbidity and mortality based on meta-analyses of epidemiologic studies. Interim Final Report under NIAAA contract #: N01AA21011, 2005.
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30. Bhatnagar V, Stoto MA, Morton SC, Boer R, Bozzette SA. Transmission patterns of smallpox: systematic review of natural outbreaks in Europe and North America since World War II. *BMC Public Health*, 2006, 6:126.
31. Stoto MA, Combining results from independent studies: Systematic reviews and meta-analysis in clinical research, forthcoming in *Medical Uses of Statistics*, 3rd Edition, Bailar JC and Hoaglin D, eds., NEJM Books.
32. Stoto MA, Cosler LE. Evaluation. Forthcoming in Novick L, Mays G, eds. *Public health administration: Organization and strategy for population-based management*, 2nd Edition, 2006.

Institute of Medicine/National Research Council reports (with contributions from M. A. Stoto, in addition to those listed above)

1. *Adverse Effects of Pertussis and Rubella Vaccines* (1991).
2. *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (1993).
3. *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* (1994).
4. *Research Strategies for Assessing Adverse Events Associated with Vaccines* (1994).
5. *The Children's Vaccine Initiative: Continuing Activities. A Summary of Two Workshops* (1995).
6. *Detecting and Responding to Adverse Events Following Vaccination: Summary of a Workshop* (1997)
7. *Research To Identify Risks For Adverse Events Following Vaccination: Biological Mechanisms and Possible Means of Prevention: Summary of a Workshop* (1997)
8. *Vaccines for the 21st Century: A Tool for Decisionmaking* (2001)