

Criteria for Evaluating Studies of Thimerosal Safety

1 March 2017

Studies assessing the safety of thimerosal (thiomersal) and its constituent, ethyl mercury, in humans will be evaluated using the criteria described below. The judges may request access to the raw data and clarification of study design, exposure and outcome measures, and any other items deemed relevant to making valid inferences from all available data pertaining to thimerosal safety, including study limitations and sources of uncertainty. For further details on such items please see Rothman et al¹; see also the ASA statement on P-values² and accompanying guidelines for interpretation³ which are available as free downloads. The submission should include:

1. All study protocols, including complete selection and exclusion criteria, all data-collection methods and the data-editing and analysis protocols (e.g., how were data inconsistencies detected and handled? how were missing data handled?).
2. All unselected original data, including data later excluded.
3. All measures of exposure to thimerosal and mercury, and their limitations, including why these measures form a complete assessment or, if not, how they may be incomplete.
4. A description of the outcome measures and rationale for the measures, including why these measures form a complete assessment or, if not, how they may be incomplete.
5. For every outcome measure, an explanation of what would

¹Rothman, K. J., Greenland, S., & Lash, T.L. (2008). *Modern Epidemiology*, 3rd ed. Philadelphia: Lippincott-Wolters-Kluwer.

²Wasserstein, R. L., & Lazar, N. A. (2016). The ASA's Statement on p-Values: Context, process, and purpose. *The American Statistician*, 70, at <http://amstat.tandfonline.com/doi/abs/10.1080/00031305.2016.1154108>

³Greenland, S., Senn, S.J., Rothman, K.J., Carlin, J.C., Poole, C., Goodman, S.N., & Altman, D.G. (2016). Statistical tests, confidence intervals, and power: A guide to misinterpretations. *The American Statistician*, 70, online supplement 1 at <http://www.tandfonline.com/doi/suppl/10.1080/00031305.2016.1154108>; reprinted in the *European Journal of Epidemiology*, 31, 337-350 at <http://link.springer.com/article/10.1007/s10654-016-0149-3>

constitute a clinically important effect.

6. For every outcome measure, a margin of safety (e.g., no effect, or one in 10 million effect) below that effect with rationale for that margin in terms of clinical importance and benefit of having the same vaccine made with thimerosal rather than without.

7. Listing of potential sources of bias, including sources of funding, and their potential impacts on estimating the relation of the exposure measures to the outcome measures.

8. Data and methods shown in detail according to thimerosal or ethyl mercury exposure and outcomes, by age and sex at a minimum.

9. All analysis methods including rationale for method, potential biases in method, adjustments for each bias, and rationale for each adjustment.

10. Bias-adjusted interval estimates that fall entirely below the declared margin of safety for the potential effects among the major potentially most vulnerable subgroups, including infants and children exposed in utero via maternal vaccination, and those that might be genetically predisposed to organic mercury toxicity.

The panel emphasizes that any sound assessment of thimerosal safety will need to integrate information across human, animal, and *in vitro* data. Methods for such integration will thus need to be spelled out in detail along the lines given above, with particular attention to validity and generalizability or transportability issues.