Reviewer’s report

Title: Assessing and Reporting Heterogeneity in Treatment Effects in Clinical Trials: A Proposal

Version: 1 Date: 15 May 2010

Reviewer: lawrence friedman

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This paper discusses an important issue in interpretation and clinical actions deriving from the results of clinical trials. It is well-written and organized and covers the major points. I have only discretionary comments.

a) Risk models will evolve as more information (presumably primarily genetic) becomes available. One might want to subsequently re-analyze the trial data using the new models (if, for example, DNA was collected and stored, so that new genetic information could be employed). Any implications of such re-analysis might be mentioned.

b) Many outcomes of interest are other than mortality and major morbidity. For example, quality of life and physical functioning are more commonly being used. Few risk models are available for these kinds of endpoints, and validation of models developed from the internal data could be problematic. How might this be addressed?

c) Even for mortality and major morbidity outcomes, the use of risk models assumes that it doesn’t matter how the risk level is obtained. But the balance of benefit and harm from the treatment might be different depending on whether most of the risk for heart disease, for example, comes from elevated blood pressure, elevated LDL-cholesterol, diabetes, advanced age, or other factors. Does that need to be addressed in the risk models, and if so, how?

Level of interest: An exceptional article

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests.