I welcome the opportunity to respond to the letter from Hemilä (1) on my paper on bias in clinical trials (2) published in the Journal. In that paper, I reviewed the potential bias that may be related to lack of adequate blinding. I referred to previously published randomized trials in which blinding was broken because the active treatment and the placebo were not sufficiently similar (3, 4). One of these “double-blind” trials evaluated the effect of ascorbic acid on common cold. As Chalmers (5) pointed out, several participants (employees of the National Institutes of Health) opened their capsules and were able to guess whether they had been allocated vitamin C.
or placebo (lactulose) because the taste was clearly different. The same problem occurred in a randomized trial on smoking cessation because the taste of the active treatment, nicotine gum, was clearly different from that of the placebo consisting of Wrigley’s chewing gum (4). Unfortunately, many published reports of randomized trials do not provide the necessary details regarding the methods used to maintain blinding. This limitation makes it impossible for the reader to assess whether blinding was adequate.

Previous empirical studies have stressed the potential influence of adequate blinding on the control of bias in randomized trials (2). The results of the studies vary. The reason for the variation may be that the effect of blinding depends on other aspects of the trials such as the choice of outcome measure. The influence of placebo might depend on the characteristics of the outcome measure (6, 7). Subjective continuous outcomes (e.g., pain) may be more susceptible to bias than objective binary outcomes (e.g., mortality). Other important questions include the influence of blinded outcome assessment in trials on interventions that are not possible to blind and the relation between the efficacy of blinding and the estimated intervention effect. Pretrial evaluation of whether participants will be able to differentiate active medication from placebo has also been suggested (8). Additional methodological studies on these and similar questions seem warranted.

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References


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