Letter to the Editor

I refer to the article "Assessment of blinding in clinical trials" by Heejung Bang et al. as published in your journal *Controlled Clinical Trials* 25 (2004) 143–156.

Of course, success of blinding is a fundamental issue in many clinical trials. Bang et al. provide a useful tool for calculating the success of blinding. However, there is a fundamental shortcoming in the basic strategy of questioning. Bang et al. refer to questions to patients who were asked during or at the end of study about the treatment allocation they think they were assigned. To my opinion, this question is only valid before onset of the treatment because of the correlation between efficacy and correct guessing. An effective medication should make the patients feel to be treated effectively which automatically leads to the correct guessing that they were assigned to the treatment. The same holds for medication with a typical safety profile. In conclusion, the method by Bang et al. is only valid to blinding information from participants if they are asked before or very shortly after the onset of the study, about the treatment allocation they think they are assigned.

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Assessment of blinding may be inappropriate after the trial

In their paper discussing the assessment of blinding in clinical trials, Bang et al. [1] based their analysis on the premise that "all participants randomly guess their assignment. . .This is the most ideal scenario in reality" ([1], p. 149). However, this premise makes an implicit assumption that the drug does not differ from placebo in any physiological effects that a person could observe subjectively, which is a very strong assumption. If a drug is truly effective, such as penicillin for pneumococcal pneumonia, both the patient and the physician can infer the treatment with high certainty by subjective observations. Thus, when the drug is truly effective, we are expecting "breaking of blindness".

Bang et al. [1] admit in their discussion, that "it is possible that unsuccessful blindness may not influence statistical analysis in the end." Thereafter they state that "in a well-known trial of vitamin C, the perceptions affected the endpoint concerning cold symptoms," thus providing the Karlowski et al. [2]

trial as the single example of a trial in which breaking of blindness may have caused the observed difference between the study arms.

The Karlowski trial was planned as a double-blind placebo-controlled trial. Because of the shortage of time, no appropriate placebo (e.g. citric acid) was manufactured, and they used lactose-placebo, which is sweet and differs in taste from vitamin C (ascorbic acid). At the end of the trial many participants guessed correctly their treatment, and this led Karlowski to carry out a subgroup analysis by the blindness status of the participants. Vitamin C appeared effective among "unblinded" participants, but no effect was seen among "blinded" participants [2,3]. This subgroup finding was spectacular by indicating that knowledge of treatment explained the differences between the study arms. Therefore the Karlowski trial has been frequently cited as an example of the importance of blinding, e.g., in the CONSORT statement pointing out the importance of trial quality [4], and as the only example by Bang et al. [1].

However, the subgroup analysis by Karlowski et al. [2,3] is not valid. For example, a total of 249 common cold episodes were recorded in the trial, but the subgroup analysis contained only 144 episodes, so that 105 episodes (42% of all) were missing [5]. Karlowski did not mention the exclusion of 105 episodes from their subgroup analysis, nor did they present their rationalization for the greater than average benefit (sic!) in the excluded participants who were neither "blinded" nor "unblinded" [5]. Further problems of the "placebo effect explanation" are detailed elsewhere [5]. Chalmers, the principal author, commented on the re-analysis of the Karlowski trial [6], but his criticism appears to be invalid [7].

Vitamin C has consistently reduced the duration and severity of colds [8,9], and some of the largest trials explicitly reported that vitamin C and placebo tablets looked and tasted the same [10–12]. The validity of the placebo should be determined before the trial. Blindness at the end of the trial may be influenced by the true physiological effects of the drug [5].

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Response to Henneicke-von-Zepelin and Harri Hemilä's comment

We thank Drs. Henneicke-von-Zepelin and Harri Hemilä for their interesting commentaries on our paper. We agree that the blinding effect may be confounded or correlated with the effectiveness or side effects of the study medication if (1) they exist; and (2) the interview is conducted in a later or the end stage of the clinical trial. It is important to note that these two commentaries raised the virtually same concern and suggested the identical solution, i.e., the validity of blindness should be determined before the trial.

It is true that a well-defined statistical test for the hypothesis of successful blinding at the time of randomization is fulfilled by the analysis based on treatment guesses shortly after randomization. However, it does not seem to us to be very interesting to check the blinding at the beginning of the trial, since this serves primarily to show that the treatment was allocated in a blinded manner. When a trial is described as double blind, most readers would understand it to mean that neither the participant nor the clinician knew the treatment assignment during the entire course of the trial.

There is a second reason that an early assessment of blinding is seldom adopted in current practice. A questionnaire asking the participants what treatment they are on at the time of, or shortly after, randomization may cause many to become more curious about the treatment assignment, which could lead to overt attempts to break the blind. Usual practice is to not say anything about blinding beyond the informed consent. If one is still interested in testing blindness before the trial, however, we recommend that a group of individuals who are not participating in the study be used for the assessment. Even this only answers the question whether the identity of the treatments is easily discerned. This is, of course, important per se, but offers limited information with regard to the interpretation of the final results of the trial.

Unblinding can occur at any time and assessment at the end of the study seems to us to be more relevant to the interpretation of the trial results. If unblinding has been detected beyond the level of chance, the investigator should look for possible causes, including (in)efficacy or safety issues as the two commentators point out. We regard this issue as a problem of interpretation of results in the context of the study. If participants and /or investigators are able to determine treatment assignment because of responses or side effects, it does not seem proper to describe the study as a double-blind trial even though it was designed to be double blind.

To the best of our knowledge, no research has been done on how to disentangle unblinding and efficacy. It is an interesting topic for future research, but will likely require additional data to solve the problem adequately. Some insight might be obtained from understanding "blinding assessment"