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Allocation concealment and blinding: when ignorance is bliss : [Letter]

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sonal anecdotes, with a curiously Australian emphasis, suggesting an immuno-modulatory role for naltrexone in MND. A few further clicks of the mouse and the naltrexone ordering site with costings appeared.

Patients with incurable diseases commonly seek "alternative" treatments² at great personal financial cost, calculated at thousands of dollars per patient with MND.³ Often there is insufficient, or, as with naltrexone, no evidence that these treatments are effective.⁴ Most patients with MND will consider alternative therapy, irrespective of their educational background⁵ or understanding of disease pathophysiology. How each physician approaches the use of complementary and alternative therapies by their patients may develop into an important issue in the therapeutic relationship. Certainly, being aware of the possibility may prove critical. In the patient described by Henderson and McCombe, an unfortunate outcome of irreversible liver failure in a patient with NMD was averted through conventional monitoring of liver function.

1 Kiernan MC. Riluzole: a glimmer of hope in the treatment of motor neurone disease. *Med J Aust* 2005; 182: 319-320.

2 MacLennan A, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. *Lancet* 1996; 347: 569-573.

3 Wasner M, Klier H, Borasio GD. The use of alternative medicine by patients with amyotrophic lateral sclerosis. *J Neurol Sci* 2001; 191: 151-154.

4 Dwyer JM. Good medicine and bad medicine: science to promote the convergence of "alternative" and orthodox medicine. *Med J Aust* 2004; 180: 647-648.

5 Dobson R. An exceptional man. *BMJ* 2002; 324: 1478. □

Allocation concealment and blinding: when ignorance is bliss

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TO THE EDITOR: Forder et al conveyed that trials without allocation concealment have the potential to mislead.¹ However, it is not true in any meaningful sense that "Without exception, allocation concealment is achievable in all randomised clinical trials. In contrast, it is not always possible to blind people to study treatments received." Rather, "Masking may be defined as either the process (researchers not revealing treatment codes until the database is locked) or

the result (complete ignorance of all trial participants as to which patients received which treatments). A masking claim indicates only the former... If masking is possible only some of the time, then clearly reference is being made to the result, and not the process. To be fair, then, one would have to ask if the result of allocation concealment is always possible... only the process of allocation concealment, but not its result, can be ensured."²

Forder et al also state that certain methods (including sealed envelopes) are considered to be adequate concealment methods. Sadly, this is true, but only if the emphasis is on the word "considered", because sealed envelopes are both imperfect at preventing direct observation of future allocations and useless at preventing the prediction of future allocations, even without direct observation. Because the extent of prediction depends on the specific restrictions used on the randomisation,³ allocation concealment is not even a binary phenomenon, and so to truly assess allocation concealment in a given trial, one must ask how much prediction is possible in that trial.

Allocation concealment is perfect if no observation or prediction is possible, and only partially effective if some prediction is possible. Many trials use randomised blocks, and smaller block sizes tend to allow for substantial prediction.³⁻⁵ So, while methods aimed only at preventing the direct observations of future allocations may be considered to be adequate, it is clear that in reality they are not.

That the authors failed to use this opportunity to set the record straight indicates their implicit agreement with the incorrect statement that methods aimed only at preventing the direct observations of future allocations are not only considered adequate, but actually are adequate. Pretending that allocation concealment is binary, and hence that it suffices to use methods aimed only at preventing the direct observations of future allocations, represents ignorance that may be bliss, but certainly is not harmless.

1 Forder PM, GebSKI VJ, Keech AC. Allocation concealment and blinding: when ignorance is bliss. *Med J Aust* 2005; 182: 87-89.

2 Berger VW, Christophi CA. Randomization technique, allocation concealment, masking, and susceptibility of trials to selection bias. *J Mod Appl of Stat Methods* 2003 2: 80-86.

3 Berger VW, Ivanova A, Deloria-Knoll M. Minimizing predictability while retaining balance through the use of less restrictive randomization procedures. *Stat Med* 2003; 22: 3017-3028.

4 Berger VW. Quantifying the magnitude of baseline covariate imbalances resulting from selection bias

in randomized clinical trials (with discussion). *Biomet J* 2005; 47: 119-139.

5 Berger VW. Selection bias and covariate imbalances in clinical trials. Chichester: John Wiley & Sons, 2005. □

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TO THE EDITOR: In their article on controlled trials, Forder et al¹ described the trial by Karlowski et al on vitamin C and the common cold² as an example of how patients' or investigators' preconceptions about the value of the treatment may affect a trial's results. However, their presentation of this trial is misleading in two respects.

Firstly, the Karlowski et al trial was reanalysed and the "placebo-effect explanation" of the original authors was shown to be erroneous.³ For example, their subgroup analysis of "blinded" and "non-blinded" participants excluded 42% of all episodes of colds, even though the subgroups were presented as complementary; numerous further problems are detailed elsewhere.³ Thus, the trial by Karlowski and colleagues cannot be seen as an example of the placebo effect in action. The concept of large and omnipresent placebo effects can be traced back to an early article by Beecher, who chose "15 illustrative studies" covering such conditions as, "severe postoperative wound pain, cough, headache, seasickness, etc."⁴ Beecher calculated that the "average placebo-effect" was 35.2% (SE, ± 2.2%). However, these studies did not use a control group. The comparison was "before-after", which is affected by the regression to the mean phenomenon as most of these conditions are self-limiting. Thus, Beecher's studies did not measure the "effect" of placebo. A recent meta-analysis of 114 trials comparing a placebo group with a no-treatment group found no evidence of placebo effect on binary outcomes, and only a rather small effect on pain, thus disproving Beecher's notion of great and universal placebo-effects.⁵ This empirical evidence was disregarded by Forder and colleagues. Although there are reasons to use placebo whenever practicable, the bias caused by the absence of a placebo control should not be exaggerated, and the "placebo effect" should also not be misused to support investigators' own preconceptions.³

Secondly, the trial by Karlowski et al was focused on the effect of vitamin C on the common cold,² and thus the "placebo effect explanation" in this particularly influential trial is crucial to the biological question. A

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recent meta-analysis of 55 placebo-controlled trials found that regular vitamin C supplementation had no effect on the incidence of colds in the general population (relative risk [RR], 0.98; 95% CI, 0.95–1.00), but reduced the incidence of colds in people exposed to substantial physical or cold stress (RR, 0.50; 95% CI, 0.38–0.66).⁶ Also, regular vitamin C intake reduced the duration of colds in adults by 8% (95% CI, 3%–13%) and in children by 13.5% (95% CI, 5%–21%). Although further studies are needed to evaluate the practical significance of these findings, it is evident that the interpretation by Karlowski and colleagues that the effect of vitamin C on the common cold may be explained by the break in the double blind² is false and should not be reiterated.

- 1 Forder PM, GebSKI VJ, Keech AC. Allocation concealment and blinding: when ignorance is bliss. *Med J Aust* 2005; 182: 87–89.
- 2 Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold: a prophylactic and therapeutic trial. *JAMA* 1975; 231: 1038–1042.
- 3 Hemilä H. Vitamin C, the placebo effect, and the common cold: a case study of how preconceptions influence the analysis of results. *J Clin Epidemiol* 1996; 49: 1079–1084; discussion in 1085–1087.
- 4 Beecher HK. The powerful placebo. *JAMA* 1955; 159: 1602–1606.
- 5 Hrobjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001; 344: 1594–1602; discussion in 2001; 345: 1276–1279.
- 6 Douglas RM, Hemilä H, D'Souza R, et al. Vitamin C for preventing and treating the common cold (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2004. Abstract available at: <http://www.cochrane.org/cochrane/revabstr/AB000980.htm> (accessed Apr 2005). □

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IN REPLY: Allocation concealment refers to ignorance of future treatment assignment before randomisation whereas masking or blinding is most commonly used to refer to the concealment of treatment assignment after randomisation.¹

There are two criteria for successful concealment of allocation: (i) physical concealment of the process of random assignment to treatment, and (ii) concealment of any pattern of consecutive assignments. Successful concealment of the process must prevent unauthorised access to randomisation lists, envelopes or algorithms; the best way is to use a centralised or remote service for randomisation, whereby an independent party

other than the clinician or investigator accesses a secure sequence list or a secure computer system to generate the next allocation.^{2,3} Successful concealment of the pattern of random assignments prevents investigators from predicting a future treatment assignment on the basis of pattern recognition of allocations to date. Identifying a pattern of previous allocations can occur in open-label trials, in which all parties are aware of allocated treatments after randomisation, or if the blinding of patients and investigators has been compromised. The likely success of concealing the allocation process can reasonably be judged by its description in most trial reports (usually found in the Methods section). However, it is usually more difficult to assess the likelihood that investigators could have predicted future allocations.

Unsuccessful concealment of treatment assignment after randomisation (masking or blinding) should be detailed in the trial report. In circumstances where the blinding has been substantially compromised, exploring the results of treatment separately among participants who were unblinded and those who remained blinded, should be considered, although these are no longer randomised comparisons. In the study by Karlowski et al,⁴ the placebo did not match the active treatment in taste, which alerted the investigators to the likely occurrence of significant unblinding within the study. To their credit, the investigators sought to quantify the extent of unblinding by means of a questionnaire at study close-out, and reported their findings by results of these responses. The particular grouping of responses, however, has been the subject of some discussion,^{5,6} and while the interpretation of a possible placebo effect has been challenged, it has not necessarily been disproven. (The absence of a placebo effect could be proven only if information concerning perceived benefits of vitamin C related more to cold frequency than cold symptoms. Biologically, it is far more plausible for a placebo effect to result in fewer cold symptoms reported than fewer colds reported.) This trial highlights the impact of compromised blinding in the reporting of trial results, emphasising the importance of maintaining adequate blinding for reliable and unbiased trial results.

Good quality reporting of trials, in accordance with the CONSORT statement,⁷ includes describing the processes in enough detail to assure readers that any pattern of randomisation is not predictable. Authors

should report issues relating to allocation concealment, blinding (where appropriate) and randomisation sufficiently to convey the message that these essential trial principles were successfully achieved.⁸

- 1 Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med* 2002; 136: 254–259.
- 2 Beller EM, GebSKI V, Keech AC. Randomisation in clinical trials. *Med J Aust* 2002; 177: 565–567.
- 3 Forder PM, GebSKI VJ, Keech AC. Allocation concealment and blinding: when ignorance is bliss. *Med J Aust* 2005; 182: 87–89.
- 4 Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold. *JAMA* 1975; 231: 1038–1042.
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- 6 Hemilä H. Discussion. To the dissent by Thomas Chalmers. *J Clin Epidemiol* 1996; 49: 1087.
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- 8 Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002; 359: 614–618. □

Achieving equal standards in medical student education: is a national exit examination the answer?

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TO THE EDITOR: We read with interest the article by Koczwara and colleagues proposing a national exit examination for all Australian medical school graduates.¹ It is refreshing to see interest in educational outcomes, a distinctly different trend from earlier reforms that shifted curricular focus from content to the learning process, exemplified by problem-based learning (PBL). Although the early process-focused programs were based on sound pedagogy current at their time, their educational outcomes have been relatively disappointing, with marginal or no demonstrable improvements in knowledge structures, clinical skills, or generic capabilities such as self-direction.² Rather than an indictment of PBL, the results may reflect what was missing in those programs: explicit focus on educational outcomes, alignment of assessments with outcomes, and attention to the learning environment.