Allocation concealment and blinding: when ignorance is bliss

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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” treatments\(^2\) 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 background\(^5\) 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.


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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.”\(^6\) 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).”\(^6\) 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.\(^6\)

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,\(^7\) 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.\(^3\) 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.

4 Berger VW. Quantifying the magnitude of baseline covariate imbalances resulting from selection bias in randomized clinical trials (with discussion). Biometr J 2005; 47: 119-139.

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TO THE EDITOR: In their article on controlled trials, Forder et al\(^1\) described the trial by Karlowsky et al on vitamin C and the common cold\(^2\) 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 Karlowsky 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 Karlowsky 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, a 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 Karlowsky 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). 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 blind is false and should not be reiterated.  


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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 allocation after randomisation.  

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.  


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.  


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 Koczwar and colleagues proposing a national exit examination for all Australian medical school graduates.  

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. 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.