

## An Analysis of Blinding Success in a Randomised Controlled Trial of Fish Oil Omega-3 Fatty Acids

Jean CJ Liu,<sup>1,2</sup> PhD, Adrian Raine,<sup>3</sup> DPhil, Rebecca P Ang,<sup>4</sup> PhD, Daniel SS Fung,<sup>2,5</sup> MBBS, MMed (Psychiatry), FAMS

### Abstract

**Introduction:** Incidental reports collected in clinical trials suggest that amongst participants, omega-3 fatty acids derived from fish oil ('omega-3') may be difficult to blind. **Materials and Methods:** We conducted a systematic evaluation of blinding success in a 24-week trial of omega-3 versus an oil-based placebo. Within 1 week of supplement commencement (Week 1), a blinding questionnaire was completed by 131 children enrolled in a trial of omega-3 for the treatment of disruptive behaviour disorders. A version of the questionnaire was also completed by their parents at Week 1, and by the children at the end of supplement administration (Week 24). **Results:** Participants were unable to differentiate omega-3 from placebo, and accuracy did not improve as a function of: the confidence of guesses, reason for guesses, notice of any change, beliefs about what should change, or time. Child and parent guesses also showed high concordance. **Conclusion:** Taken together, these data provide strong evidence that the identity of omega-3 can be blinded to participants.

Ann Acad Med Singapore 2015;44:85-91

**Key words:** ADHD, Child, Clinical trials, Psychiatry

### Introduction

There has been growing interest in the use of dietary supplementation to treat psychiatric disorders. In particular, supplementation of omega-3 fatty acids has been researched as a potential means of preventing and managing psychopathology.<sup>1,2</sup> These fatty acids are ingested through dietary sources (e.g. fish), with inadequate concentrations implicated in psychiatric morbidity.<sup>2</sup> This has given rise to clinical trials that evaluate the supplementation of omega-3 fatty acids.

However, one research challenge is blinding the identity of omega-3 to participants. To evaluate efficacy, clinical trials need to assess whether supplementation results in symptomatic improvements over and above the effects of time (spontaneous recovery) and of psychological expectations associated with receiving treatment (placebo

effects).<sup>3,4</sup> This is possible in trials employing placebo-controlled designs,<sup>5</sup> where participants receive either an omega-3 supplement or a matching placebo without a significant active component; if successful, participants would be blind to which substance they receive, allowing researchers to isolate pharmacological effects from those of spontaneous recovery and placebo effects. This design is of particular importance for psychiatric trials, where outcomes involve a high degree of rater subjectivity.<sup>6</sup>

At present, it is unclear as to what extent blinding can be carried out for omega-3 fatty acids derived from fish oil ('omega-3'), as these have a strong odour and a fishy taste that are difficult to mask.<sup>7,8</sup> For example, in a clinical trial for the treatment of adult bipolar disorder, Stoll et al<sup>9</sup> reported a higher incidence of fishy aftertaste experienced by omega-3 than by placebo participants. Similarly, Grenyer et al<sup>10</sup> found

<sup>1</sup>Division of Social Sciences, Yale-NUS College, Singapore

<sup>2</sup>Neuroscience and Behavioral Disorders Program, Duke-NUS Graduate Medical School, Singapore

<sup>3</sup>Departments of Criminology, Psychiatry, and Psychology, University of Pennsylvania, Philadelphia, USA

<sup>4</sup>Psychological Studies Academic Group, National Institute of Education, Singapore

<sup>5</sup>Department of Child and Adolescent Psychiatry, Institute of Mental Health, Singapore

Address for Correspondence: A/Prof Jean CJ Liu, Division of Social Sciences, Yale-NUS College, 6 College Avenue East, Singapore 138614.

Email: jeanliu@yale-nus.edu.sg

that at the end of a trial for adult major depression, 90% of omega-3 and 64% of placebo participants identified which supplement they had received; participants cited taste as the reason for their guess. Whereas both of these studies used an oil-based placebo without a fishy taste, Lesperance et al<sup>11</sup> added a fish flavour to their placebo; even so, they found that omega-3 participants experienced a fishy aftertaste more frequently than the placebo participants did. Thus, incidental reports collected during clinical trials suggest that omega-3 may be difficult to blind.

Where blinding integrity cannot be established, conclusions about omega-3 efficacy are limited. Accordingly, Liu et al<sup>7</sup> called for evidence that omega-3 can be disguised to participants. Studies of this nature have been conducted for zinc gluconate and for oral antibiotics, where taste likewise was implicated in possible blinding compromise.<sup>12,13</sup>

In this paper, we report a systematic analysis of blinding success in a psychiatric trial of omega-3. This was assessed in a “best-case scenario”, where fish flavour was added to the placebo (to match the omega-3 supplements by taste; following Lesperance et al).<sup>11</sup> In this analysis, we measured accuracy—participants’ ability to distinguish omega-3 from placebo—as well as possible predictors of accuracy: participants’ confidence in their guesses, the reason for their guesses, whether they noticed any change, and whether they believed anything should change. We focused on blinding data collected within a week of supplement administration, after participants had consumed the supplements but during the latency period before behavioural effects are reported.<sup>14</sup> This was to ensure participants’ guesses were not due to actual pharmaceutical effects observed or lack thereof;<sup>15,16</sup> however, we also tracked whether accuracy changed over time. Finally, while we focused on child participants who consumed the supplements, we also examined whether their guesses related to those of their parents, who were additional outcome assessors in the trial.

## Materials and Methods

### Participants

Participants were 131 children aged between 7 and 16, enrolled in a stratified (by age and diagnosis, with equal randomisation [1:1]), placebo-controlled trial of omega-3 and social skills training for the treatment of disruptive behaviour disorders (ClinicalTrials.gov identifier: NCT00819429). Trial procedures were approved by both institutional and hospital group review boards (CRC 240/2008; DSRB A/08/410).

All participants had been attending an outpatient psychiatric clinic (the Child Guidance Clinic) during the recruitment period of September 2009 to July 2012, and had

been diagnosed with a disruptive behaviour disorder (attention deficit hyperactivity disorder (ADHD); oppositional defiant disorder (ODD); and/or conduct disorder (CD)) through the Computerized Diagnostic Interview Schedule for Children (C-DISC). Exclusion criteria were intelligence quotient score below 70, and pre-existing brain pathology (e.g. serious head injury, epilepsy).

Following screening procedures for inclusion criteria, participants were randomly allocated to receive either omega-3 or placebo: 63 participants received omega-3, whereas 68 participants received placebo. Table 1 shows the participants’ baseline demographic and clinical characteristics.

### Supplements

Omega-3 supplements were 500 mg of white-coloured soft gelatine oval capsules filled primarily with marine fish oil concentrate and 5.6 mg vitamin E (fatty acid profile: 32.9% 20:5 (n-3); 22.4% 22:6 (n-3); 6.5% 18:1; 5.8% 22:5 (n-3); ≤5% other fatty acids; and 6.4% minor components); as participants consumed 4 supplements each day, the daily dosage was 2 g of the active supplements. Placebo capsules were matched for colour, size, and texture, and were filled primarily with high oleic sunflower oil and 5.7 mg vitamin E (fatty acid profile: 74.4% 18:1 (n-9); 11.7% 18:2 (n-6); ≤5% other fatty acids including 18:3 (n-3), 18:4 (n-3), 20:5 (n-3), 22:5 (n-3), 22:6 (n-3); and 0.2% minor components). Note that the placebo contained 1.3% marine fish oil (0.8% 20:5 (n-3), 0.5% 22:6 (n-3)); this was added to provide a fish odour and taste, but at trace levels was not expected to have significant physiological effects. Both omega-3 and placebo capsules were purchased from Efamol Limited (Surrey, United Kingdom), with capsules prepared in unlabelled, unit-dose blister packs.

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Characteristic	Actual Supplement Received	
	Omega-3 (n = 63)	Placebo (n = 68)
Age in years*	10.65 (1.70)	10.76 (2.05)
Gender		
Male	56	54
Female	7	14
Disruptive behaviour disorder		
ADHD	23	26
ODD/CD	6	9
ADHD and ODD/CD	34	33

ADHD: Attention deficit hyperactivity disorder; CD: Conduct disorder; ODD: Oppositional defiant disorder

\*Data reported as means (standard deviation).

Participants' supplements were pre-allocated by a study administrator based on a computer-generated randomisation list. The randomisation sequence was stratified by age (7 to 12 and 13 to 16 years) and diagnosis (ADHD only; ODD/CD only; ADHD and ODD/CD), with a 1:1 allocation and a block size of 10. Following randomisation, blister packs were labelled with participants' study identifiers.

Details of each participant's group allocation were kept in a locked facility by the study administrator who was not involved in data collection; all persons involved in data collection or outcome reporting were blind to this allocation.

### Blinding Questionnaire

Based on research addressing the placebo effect,<sup>4,17</sup> a 5-item blinding questionnaire was created. As a preamble, printed instructions reminded participants that they had been taking 4 beige-coloured capsules every day, and that "for some people, the capsule mainly contains fish oil" (omega-3) whereas "for other people, the capsule mainly contains sunflower oil" (placebo).

The first item was a forced-choice question asking participants to guess whether they had been taking omega-3 or placebo. The subsequent 2 items asked participants to rate the confidence of their guess (on a 5-point scale anchored on one end with "1: No idea at all" and on the other with "5: Absolutely sure it's the one"; Item 2), and to state the reason for this guess (Item 3). Finally, Items 4 and 5 asked participants to describe anything that changed or happened to them after they consumed the capsule ('notice of change'; Item 4), or anything they thought should change or happen to them ('belief about change'; Item 5).

The parent version of the questionnaire was identical, except that parents were asked to guess what they thought their child had been taking (Item 1), and to report notice of or belief about changes in their child (Items 4 and 5).

## Procedure

### Supplement Administration

As part of the trial, participants consumed 4 capsules daily for 6 months (Weeks 0 to 24). During the first visit, caregivers were instructed to give participants 4 capsules each day—2 in the morning and 2 in the evening (before or after food); caregivers were also advised to refrigerate the capsules to reduce odours. Compliance was verified through caregivers' reports, and by requesting for used blister packaging to be returned. No enquiry was made as to participants' swallowing ability.

### Blinding Assessment

Within a week of supplement administration (Week 1),

participants returned to complete the blinding questionnaire. Participants were required to respond to the questions independently, without the assistance of caregivers.

At the end of supplement administration (Week 24), participants were asked again to complete the blinding questionnaire. Additionally, at both time-points (Weeks 1 and 24), parents were contacted over the phone or in person to complete the parent version of the questionnaire.

### Data Analyses

Statistical analyses were conducted using SPSS & R, with Type 1 Decision Wise Error Rate controlled at  $\alpha = 0.05$ . Refer to Figure 1 for a flowchart indicating the number of participants included in each analysis.

## Results

### Measures of Blinding Integrity

To assess blinding success, a chi-square analysis was run with actual supplement received (omega-3 vs placebo) cross-tabulated against participants' Week 1 guesses about which supplement they had received (omega-3 vs placebo). As shown in Table 2, there was no significant difference in participants' guesses as a function of actual supplement received:  $\chi^2(1, n = 121) = 0.66, P = 0.42$ .

As blinding integrity requires evidence for equivalence (and not merely lack of evidence for a difference), an additional 2 one-sided test was run.<sup>18,19</sup> With this test, the proportion of participants who guessed that they had received omega-3 was found to be statistically equivalent—defined as less than 20% difference—amongst both groups of participants (90% CI for difference in proportion = -0.07 to 0.19).

### Degree of Blinding Success

The degree of blinding success was quantified by computing: overall accuracy (number of correct guesses divided by total number of guesses), and James'<sup>20</sup> and Bang's<sup>21</sup> blinding indices. As James' and Bang's indices weights responses of participants who report they "don't know" what they received, those who answered "1: No idea at all" in Item 2 (when asked how sure they were

Table 2. Participants' Guesses at Week 1 as a Function of Actual Supplement Received

Supplement Guess	Actual Supplement Received		
	Omega-3	Placebo	Total
Omega-3	50	49	99
Placebo	9	13	22
Total	59	62	121

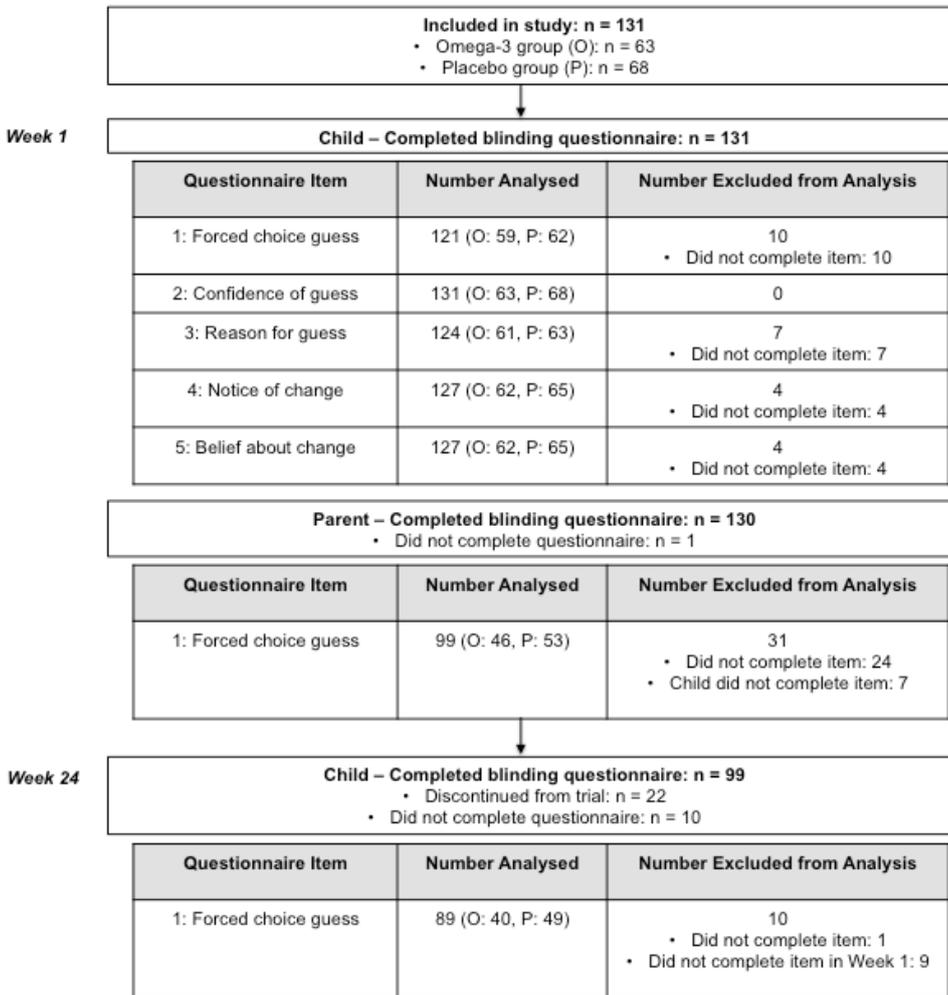


Fig. 1. Flowchart indicating the number of participants included in each analysis.

of their guesses) were scored as “don’t know”, in place of their original guess of having received omega-3 or placebo (Item 1). (Note: 10 participants did not respond to the forced-choice question (Item 1), and responded “1: No idea at all” to Item 2; these responses were scored as “don’t know” for this analysis.)

Overall, participants’ accuracy was 52.07% (95% CI, 42.84% to 61.16%)—no better than chance. James’s blinding index was 0.62 (95% CI, 0.56 to 0.69); this indicates a state between random guessing and perfect blindness.<sup>20</sup> Bang’s blinding index was 0.56 (95% CI, 0.40 to 0.71) amongst participants who received omega-3, and -0.51 (95% CI, -0.65 to -0.38) amongst participants who received placebo; as the sum of the 2 indices does not differ from 0, these highlight participants’ response bias<sup>21</sup>—that is, the majority of participants had guessed that they had received omega-3.

### Predicting Accuracy

We further analysed whether participants’ accuracy in supplement guesses at Week 1 were related to these factors: the confidence of their guesses, the reason for their guesses, their notice of any change, and their beliefs about changes. For the open-ended questions (reason for their guesses, notice of change, beliefs about changes), a list of response categories was created for each question. Participants’ responses were then grouped into these categories by 2 independent raters—the first-named investigator (JL), and a rater blind to both study aims and participants’ supplement allocation. Inter-rater agreement was high ( $\kappa = 0.80, P < 0.001$ ).

Participants’ confidence in their ratings did not differ as a function of which supplement they received:  $F(1, 119) = 2.25, P = 0.14$ ; nor of whether they were wrong or correct

in their guesses:  $F(1,119) = 0.61, P = 0.44$ . Tables 3 to 5 indicate how many participants cited each response category when asked about: the reasons for their guess (Table 3), any change they noticed following supplement consumption (Table 4), and their beliefs about what should change (Table 5); for each of these factors, the distribution of response categories did not differ as a function of supplement received (largest  $\chi^2 = 4.67, P = 0.32$ ).

Accordingly, a logistic regression model with participants' guesses and either one of confidence scores, reasons for guess, notice of change, or belief about change did not significantly predict the actual supplement participants were given (largest  $\chi^2 = 1.07, P = 0.59$ ).

**Accuracy Over Time**

To track accuracy over time, we cross-tabulated participants' guesses at Week 1 versus those at Week 24 (Table 6). There was a significant relation between guesses at both time-points ( $\chi^2(1, n = 89) = 13.03, P < 0.001$ ), with 83.1% of guesses unchanged; accuracy did not change as a function of time (McNemar's  $\chi^2 = 0.27, (1, n = 89), P = 0.61$ ).

*Child-parent Guesses*

Finally, Table 7 provides a count of participants who guessed that they received omega-3 versus placebo, as a function of what his or her parent guessed (both measured at Week 1). Again, there was a significant relation between the guesses of both respondents ( $\chi^2(1, n = 99) = 4.77, P = 0.03$ ), with 75.8% of guesses identical.

Table 3. Reason for Participants' Guesses as a Function of Supplement Received

Reason for Guess*	Actual Supplement Received	
	Omega-3	Placebo
Odour or taste		
Smells or tastes fishy	17	21
Does not smell or taste fishy	4	5
Smell or taste (unspecified)	14	12
Appearance or texture	2	4
Behavioural differences		
Behavioural differences observed	0	1
No behavioural differences observed	2	0
Other comment about behavioural difference	1	1
Someone told them so	9	8
Unsure/guessing	11	9
Others	1	2

\*Responses from participants who made a guess (n = 121).

Table 4. Participants' Notice of Change as a Function of Supplement Received

Nature of Change Noticed*	Actual Supplement Received	
	Omega-3	Placebo
Concentration- or academic-related	10	7
Behaviour-related	4	6
Physical change	5	3
Unsure/unable to explain	0	2
Others	3	1

\*Responses from participants who reported noticing change (n = 41).

Table 5. Participants' Beliefs about Change as a Function of Supplement Received

Nature of Belief about Change*	Actual Supplement Received	
	Omega-3	Placebo
Concentration- or academic-related	11	15
Behaviour-related		
Social or emotional	3	3
Other behaviours	6	2
Unsure/unable to explain	1	4
Others	2	1

\*Responses from participants who reported a belief that something should change (n = 48).

Table 6. Participants' Guesses at Weeks 1 versus 24

Supplement Guess at Week 1	Supplement Guess at Week 24		
	Omega-3	Placebo	Total
Omega-3	67	7	74
Placebo	8	7	15
Total	75	14	89

Table 7. Participants' Guesses versus Parents' Guesses (at Week 1)

Participants' Guess	Parents' Guess		
	Omega-3	Placebo	Total
Omega-3	68	13	81
Placebo	11	7	18
Total	79	20	99

## Discussion

The current study was designed to examine blinding success in a psychiatric trial of omega-3. Using an oil-based placebo with a fish flavour, and assessing child participants within 1 week of trial commencement, we found strong evidence of blinding integrity. First, participants were unable to guess which supplement they had received; their accuracy was no better than chance, with most participants perceiving that they had received omega-3 regardless of actual supplement received. Parents' guesses also showed agreement with those of child participants, with a similar response bias for omega-3. Second, child participants' accuracy did not improve as a function of: the confidence of their guess, the reason for their guess, notice of any change, or beliefs about what should change. Finally, participants' guesses corresponded to those made 6 months into the trial; accuracy did not improve over time. Taken together, our findings suggest it is possible to blind the identity of omega-3 to participants. Symptomatic changes found in the trial can then be said to result from the pharmacological effects of omega-3.

Our data further highlight the importance of odour or taste in blinding omega-3, as this was the most cited reason when participants justified their guess. That many participants noticed a fishy taste—regardless of whether they actually received omega-3 or placebo—likely contributed to the observed response bias for omega-3. Nonetheless, further methodological studies are needed where blinding choices are systematically varied and participants' guesses examined; for example, it is still unclear which mode of delivery (e.g. capsule, liquid) or type of flavouring (e.g. adding fish odour to the placebo, or adding peppermint flavour to both omega-3 and placebo) best promotes blinding integrity.

Another novel feature of our data is that we assessed supplement guesses not only from participants who consumed the supplements, but also of parents, who were additional outcome assessors in the trial. We found correspondence between guesses, with parents likewise showing a response bias for omega-3.

Finally, although we report strong evidence of blinding success, it remains unclear whether our findings generalise to trials of other designs. We note that Lesperance et al<sup>11</sup> likewise added a fish flavour to their placebo, but still found that omega-3 participants experienced a fishy aftertaste more frequently than did placebo participants. (We note, however, that the supplement formulation in this trial differed from ours.) As the risk of unblinding is real, and outcomes—particularly those in psychiatric trials—may involve a high degree of subjectivity, we recommend that each trial administer our blinding questionnaire to accrue trial-level evidence.<sup>7,22</sup>

## Conclusion

To conclude, our study represents the first in-depth study of blinding integrity in a clinical trial of omega-3. Based on a questionnaire administered within 1 week of trial commencement, we found clear evidence that the identity of omega-3 can be blinded to participants.

## Acknowledgements

*This research was funded by a grant awarded to AR, RPA, and DSSF from the National Medical Research Council of Singapore (grant number: NMRC 1170/2008); and by a grant awarded to JCJL from Yale-NUS College (start-up grant number: R-607-264-057-121). The authors gratefully acknowledge Tan Yan Lin and Jolly Chua for their assistance in data management, and Zhou Mingyi for coding the data.*

## REFERENCES

1. Politi P, Rocchetti M, Emanuele E, Rondonelli M, Barale F. Randomized placebo-controlled trials of omega-3 polyunsaturated fatty acids in psychiatric disorders: a review of current literature. *Curr Drug Discov Technol* 2013;10:245-53.
2. Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, et al. Omega-3 fatty acids: Evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry* 2006;67:1954-67.
3. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686-95.
4. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008;59:565-90.
5. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). E10: Choice of control group and related issues in clinical trials. Geneva: ICH; 2000. Available at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E10/Step4/E10\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf). Accessed 1 November 2011.
6. Boutron I, Estellat C, Guittet L, Dechartres A, Sackett DL, Hrobjartsson A, et al. Methods of blinding in reports of randomized controlled trials assessing pharmacologic treatments: a systematic review. *PLoS Med* 2006;3:e425.
7. Liu JC, Ang RP, Fung DS. Something fishy: The issue of omega-3 blinding in psychiatric clinical trials. *Aust N Z J Psychiatry* 2013;47:201-5.
8. Sontrop J, Campbell MK. Omega-3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. *Prev Med* 2006;42:4-13.
9. Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407-12.

10. Grenyer BF, Crowe T, Meyer B, Owen AJ, Grigonis-Deane EM, Caputi P, et al. Fish oil supplementation in the treatment of major depression: a randomised double-blind placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:1393-6.
  11. Lesperance F, Frasare-Smith N, St-Andre E, Turecki G, Lesperance P, Wisniewski SR. The efficacy of omega-3 supplementation for major depression: A randomized controlled trial. *J Clin Psychiatry* 2011;72:1054-62.
  12. Farr BM, Gwaltney JM Jr. The problems of taste in placebo matching: an evaluation of zinc gluconate for the common cold. *J Chronic Dis* 1987;40:875-9.
  13. Walter SD, Awasthi S, Jeyaseelan L. Pre-trial evaluation of the potential for unblinding in drug trials: a prototype example. *Contemp Clin Trials* 2005;26:459-68.
  14. Gertsik L, Poland RE, Bresee C, Rapaport MH. Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. *J Clin Psychopharmacol* 2012;32:61-4.
  15. Sackett DL. Turning a blind eye: why we don't test for blindness at the end of our trials. *BMJ* 2004;328:1136.
  16. Sackett DL. Clinician-trialist rounds: 6. Testing for blindness at the end of your trial is a mug's game. *Clin Trials* 2011;8:674-6.
  17. Colagiuri B, Morley K, Boakes R, Haber P. Expectancy in double-blind placebo-controlled trials: an example from alcohol dependence. *Psychother Psychosom* 2009;78:167-71.
  18. Chen JJ, Tsong Y, Kang SH. Tests for equivalence or noninferiority between two proportions. *Drug Inf J* 2000;34:569-78.
  19. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987;15:657-80.
  20. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation—a VA cooperative study. *Stat Med* 1996;15:1421-34.
  21. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;25:143-56.
  22. Sackett DL. Commentary: Measuring the success of blinding in RCTs: don't, must, can't or needn't? *Int J Epidemiol* 2007;36:664-5.
-