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Measuring the success of blinding in placebo-controlled trials: should we be so quick to dismiss it?

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1 **Measuring the success of blinding in placebo-controlled trials: should we be so quick to**
2 **dismiss it?**

3 Running head: Measuring blinding success in placebo-controlled trials

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28 **1 Background**

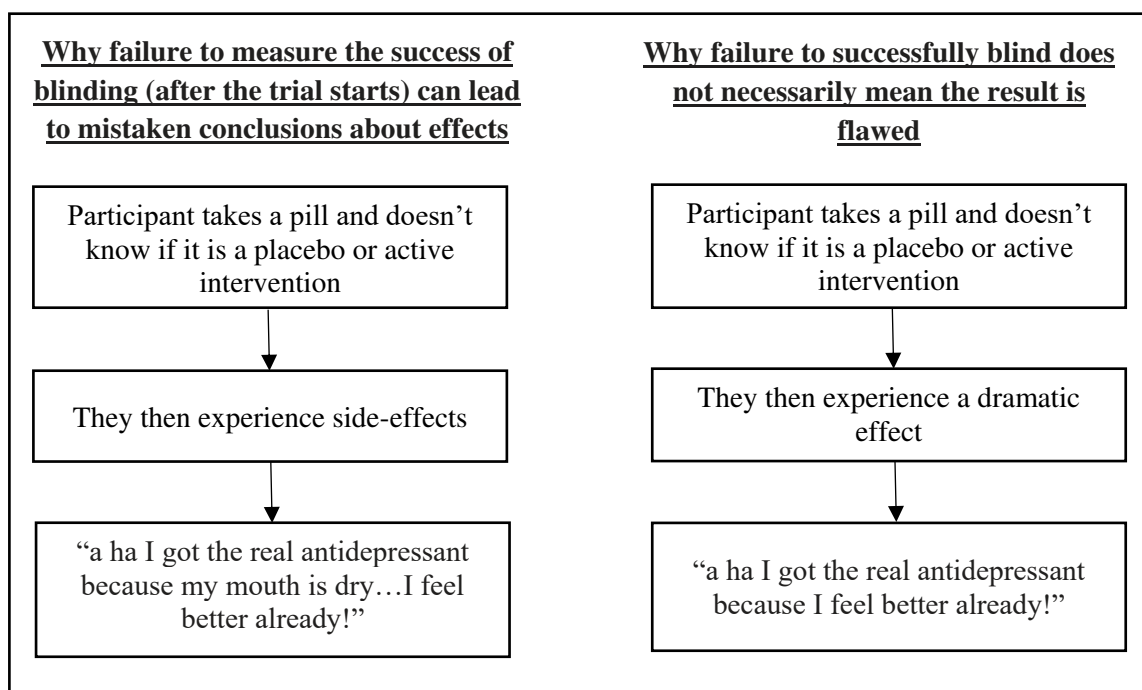
29 From being almost universally regarded as a methodological virtue of clinical trials and being
30 included in the original 2001 Consolidated Standards of Reporting Trials (CONSORT)
31 statement (1), measuring the success of blinding has fallen out of fashion. Subsequent
32 versions of CONSORT removed this recommendation based on the correct view that it can
33 lead to misleading inferences about causes of the failure to blind. (2, 3) In addition, Anand, et
34 al. (4) recently questioned the need to blind patients and clinicians or measure and report
35 whether blinding was done successfully. While critics are correct to point out problems with
36 the view that blinding is a universal methodological virtue, and to point out that measuring
37 the success of blinding is not straightforward, they are too quick to dismiss the value of
38 testing and reporting on the success of blinding. This is reflected in our findings extending
39 the Template for Intervention Description and Replication (TIDieR) statement for
40 placebo/sham control components, in which almost all Delphi respondents recommended that
41 trials should measure and report whether blinding was successful. (5)

42 We are not aware of any publications that set out the case for and against measuring blinding
43 success, or that provide mitigating positions. Our experience suggests that confusion about
44 blinding inhibits reasonable debates in this area. Here, we attempt to clarify some of the
45 confusions surrounding blinding and measuring its success, before providing the case for and
46 against, reporting measures of the success of blinding, and suggesting a ‘middle road’ which
47 takes both sides of the debate into account.

48 **2 Measuring blinding success: the case for**

49 Blinding involves concealing knowledge of treatment assignment to one or more groups
50 involved in clinical trials (participants, intervention providers, data collectors, outcome
51 assessors, statisticians, and manuscript authors). (6) Trials can be described in a number of
52 ways including open (unblinded), single-blind, double-blind or triple-blind. The terminology
53 can be confusing however, as a random sample of 200 trials has shown that the term double
54 blind can be used to describe blinding up to 18 different combinations of trial personnel. (7)
55 As noted in CONSORT, it is important to specify who was blinded in a trial, (2) as blinding
56 different people may affect outcomes, especially those which are subjective. For example, if
57 participants and data collectors were not blinded this may have more of an impact than an
58 unblinded statistician who may have less influence on the outcomes.

59 Measuring whether blinding was successful involves asking patients and clinicians about
 60 their treatment assignment beliefs before the trial is officially unblinded. Successful blinding
 61 occurs when there is a balance of expectations and beliefs related to the assigned
 62 intervention, demonstrating that those who are blinded are not aware of the (active or
 63 inactive) intervention that has been assigned. However, blinding can fail when participants,
 64 caregivers, or other groups involved in a trial deduce the intervention allocation at the
 65 beginning of the trial (e.g. due to inadequate matching between the placebo and active
 66 intervention), or during the trial (e.g. due to adverse events). (8-10) Since the function of
 67 blinding is to reduce the impact of expectations, unsuccessful blinding is problematic, as
 68 beliefs and expectations of those who correctly guess the intervention allocation *could* then
 69 influence the outcome of the trial. (11-14) As such a trial that was designed blinded but in
 70 which attempts to blind were unsuccessful may approach the quality of a trial where
 71 (complete, double) blinding is ethically and feasibly possible, but is not blinded (see Fig 1).



80 **Fig 1. Why measuring blinding success is important and why it is not**

81 A number of meta-epidemiological studies have investigated differences between trials
 82 (reported as) blinded and those that are not (reported as) blinded. (15-24) Some (but not all)
 83 of those found that lack of reporting of blinding led to larger effect sizes. Recently,
 84 Moustgaard, et al. (15) found inconsistent effects of blinding on treatment effect sizes.
 85 However, there are methodological concerns regarding the study's sample selection and
 86 classifications of reporting of blinding. (25) Like randomisation and allocation concealment,
 87 blinding can reasonably be expected to have a small average effect, possibly with an

88 unpredictable direction. (26, 27) In an era when marginal gains from many of our medical
89 interventions suffice to change policy and practice, (28) ruling out small biases or errors is
90 becoming more important. In addition, small average effects are compatible with larger
91 effects in some instances, for example trials of treatments for disorders that are placebo
92 responsive, such as pain. Additional meta-epidemiological studies with large sample sizes,
93 together with well-defined outcomes, disease areas, and classifications of reporting of
94 blinding are required to address this important issue. Such studies cannot be conducted unless
95 trials report whether blinding was successful (where this is feasible).

96 Aside from the importance of blinding itself, the importance of measuring (see Box 1) and
97 reporting blinding success is apparent in various trials. For example, Karlowski, et al. (29)
98 compared Vitamin C with placebo for treating the common cold, and found Vitamin C to be
99 apparently effective. However, because of the sour taste of Vitamin C and sweet taste of the
100 lactose placebo pills, the trial was not successfully blinded. When the authors carried out a
101 subgroup analysis in which they divided participants into those who remained blinded and to
102 those who were not, they found that there was no benefit of Vitamin C in the blinded group.
103 Although ideally the authors should have ensured both placebo and active intervention were
104 adequately matched, this example still shows the importance of measuring and reporting
105 blinding success. Otherwise, it would have been mistakenly concluded that Vitamin C was
106 superior.

107 More recently, a unsuccessfully blinded trial of zinc for treating common cold symptoms
108 found that zinc significantly reduced the duration of cold symptoms compared to placebo.
109 (30) Whereas, another trial with successful blinding, found that zinc did not reduce symptom
110 duration. (31) This difference may be due to significantly more side-effects being reported to
111 Zinc than placebo in the first trial, (30) which led to unblinding and subsequent bias. As such
112 the success of blinding reported in these studies could be useful for those appraising them and
113 looking for reasons for their discrepant results.

114

115 A common approach to measuring the success of blinding uses chi-square tests of independence,
116 where successful blinding is indicated by a null finding (patient guesses are not related to their
117 intervention allocation). (32) However, this lacks sensitivity and does not provide any directional
118 information about the pattern of participant guesses. (33) James' (34) and Bang's (33) blinding index
119 (BI) have addressed some of these concerns by asking participants to guess their intervention
120 assignment using three responses (active, placebo or do not know). James' provides a single value that
121 combines data from all arms ranging from 0 to 1, 0 being total lack of blinding, 1 being complete
122 blinding and 0.5 being completely random blinding. Bang's BI aims to provide a more sensitive
123 measure of blinding within each experimental arm compared to James' by calculating a score from -1
124 to 1, 1 being complete lack of blinding, 0 being consistent with perfect blinding and -1 indicating
125 opposite guessing which may be related to unblinding. (33) As such, it can be used to detect where
126 blinding may have failed, while still assessing overall success. An even newer method is the use of
127 video surveillance. This involves video-recording procedures in the trial and asking a professional
128 familiar with the procedure to guess the intervention allocation. (35) However, in practice, blinding
129 success is rarely measured, with only 2-24% of trials reporting the success of blinding. (36, 37). In
130 addition, these methods fall short as they do not consider why unblinding may have occurred.

131 **Box 1. How to measure blinding success?**

132 **3 Measuring blinding success: the case against**

133 The case against measuring the success of blinding can be traced to Dave Sackett, who cited
134 a 2x2 factorial trial of aspirin and sulfinpyrazone for stroke prevention. In the trial, blinded
135 clinicians largely distinguished aspirin from sulfinpyrazone. (38) But, because of prior
136 'hunches' that sulfinpyrazone would be more effective, they mistakenly believed that patients
137 with better outcomes had received sulfinpyrazone, when in fact the trial showed aspirin was
138 more effective. In this example, the results of tests for blinding can be ambiguous. Hence,
139 Sackett and others following him argued that tests for the success of blinding should not be
140 conducted.

141 Sackett is correct that in this example (and perhaps others like it), that the test for the success
142 of blinding was confounded by mistaken beliefs about which intervention was effective (or a
143 misattributed response to treatment). However, if these (mistaken) hunches about efficacy
144 were *different* (unbalanced) in the intervention and control groups, then they could have
145 confounded the study no matter how mistaken they were. Or, their beliefs were the same
146 (balanced) across the groups, in which case there was no confounding (even if the beliefs
147 were mistaken). Either way, the test for the success of blinding will reveal useful information,
148 namely about whether expectations might have confounded the results.

149 There are some cases in which failure to successfully blind does not imply that the study was
150 methodologically lacking. For example, a dramatically effective treatment can cause
151 unblinding, however it should not lead us to conclude that a trial of the treatment was

152 methodologically lacking. On the contrary, as Senn (39) argued: ‘The whole point of a
153 successful double-blind trial is that there should be unblinding through efficacy.’ The
154 problem remains however, that if a trial reports that the cause of unblinding was dramatic
155 effectiveness, a report of ‘failed’ blinding could mislead some into thinking the trial was less
156 trustworthy.

157 Secondly, measuring the success of blinding at the wrong time (for example before follow-
158 up or trial completion) may raise suspicion among participants and cause the problem it is
159 intended to prevent. (40) (41)

160 Thirdly, some trials cannot feasibly or ethically be blinded, for example, non-drug
161 interventions such as exercise, behavioural therapy and nutritional advice. (Aside: trials of
162 these interventions can be rigorous by using other methodological tools to reduce bias (42),
163 such as pre-registering trials, following a pre-specified analysis plan, adequate sample size
164 and using randomisation, to reach the best achievable research practice.) Also, in some cases
165 unblinding is an ethical requirement, for example due to hypothesized toxicity, and blinding
166 itself could increase research waste, with some evidence indicating that patients are less
167 likely to enrol in blinded trials. (4)

168 **4 Discussion**

169 Demanding that all trials attempt to use and measure the success of blinding is too strong
170 because blinding is sometimes impossible, unethical, or misleading. Future research is
171 required to determine how to best interpret findings from assessing the success of blinding.
172 On the other hand, blinding has the potential to rule out bias, and failure to recommend that
173 the success of blinding be reported when it is measured, seems like wilful withholding of
174 information that potentially useful.

175 In addition, the change in the CONSORT recommendation from asking researchers to report
176 on success of blinding (if measured) to not asking, seems to have been based on arguments
177 that may deserve revisiting. Of course, the fact that CONSORT does not explicitly
178 recommend reporting on the success of blinding does not prevent reviewers from reporting it.
179 However, the fact that CONSORT cites a paper by Sackett as the reason for removing it, in
180 which he claims that testing the success of blinding is a ‘mug’s game’ could be interpreted as
181 a reason to avoid reporting on the success of blinding.

182 Also, while measuring the success of blinding at many (or the wrong) points may cause some
183 problem, this does not imply that measuring success of blinding at a single (roughly) correct

184 point is not useful. Moreover, empirical research suggests that getting the ‘correct’ point may
185 not be required. Rees, et al. (43) have shown that the difference between a six-point
186 assessment of blinding success during a trial and a two-point model is not significant.

187 Overall, the fact that difficulties, ethical problems, or ambiguity in measuring its success does
188 not imply that it should be given up altogether.

189 **5 Conclusion and recommendation? A middle ground**

190 While we acknowledge there are a dearth of studies that have investigated this issue, more
191 definitive evidence can only come from studies that measure the success of blinding. We
192 recognise that some trials cannot feasibly or ethically be blinded, but it is important that trials
193 that *could have* introduced blinding and measured its success, are distinguished from trials
194 that could not have. Our suggestion for a way forward considers the current state of evidence
195 for and against measuring the success of blinding. We hope this stimulates further discussion,
196 and that future iterations of CONSORT reflect on our arguments and revisits this issue.

197 We suggest that:

- 198 **1. Authors should make every attempt to match the placebo and active intervention to**
199 **avoid unblinding at the start of the trial and subsequent research waste.**
- 200 **2. When authors have measured the success of blinding they should report the results.**
- 201 **3. Critical appraisers should consider reasons why unblinding may have arisen before**
202 **condemning a trial as having a high risk of bias, or if blinding success has not been**
203 **reported, they should assess whether it is possible that blinding has been compromised.**
- 204 **4. Future development of measures to assess the success of blinding should ask those**
205 **intended to be blinded what their intervention allocation beliefs were and why.** This
206 can help disentangle the reasons (dramatic effects or side-effects), although the reason
207 may not always be known for sure.

208 **Competing interests**

209 Declarations of interest: none

210 **Contributor statement**

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