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Short communication

The blind leading the blind: Use and misuse of blinding in randomized controlled trials

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ABSTRACT

The use of blinding strengthens the credibility of randomized controlled trials (RCTs) by minimizing bias. However, there is confusion surrounding the definition of blinding as well as the terms single, double, and triple blind. It has been suggested that these terms should be discontinued due to their broad misinterpretation. We recommend that, instead of abandoning the use of these terms, explicit definitions of blinding should be adopted. We address herein the concept of blinding, propose standard definitions for the consistent use of these terms, and detail when different types of blinding should be utilized. Standardizing the definition of blinding and utilizing proper blinding methods will improve the quality and clarity of reporting in RCTs.

1. What is blinding?

Clinical trial outcomes may be biased by human expectations, especially when treatment allocation, assessment methods, and outcome measures have a subjective component [1]. At a basic level, blinding (also called "masking," especially in ophthalmology studies) is utilized to eliminate or minimize these biases. For example, subjects entering a study might be differentially allocated to unblinded treatment groups such that those deemed most likely to benefit from the active treatment are assigned to receive it, while the remaining subjects are allocated to placebo (selection bias). Even when subjects are randomly allocated to receive active or placebo treatment, those who are knowingly randomized to a treatment that is perceived as superior to a placebo may offer overly optimistic responses that create an exaggerated treatment effect (self-report bias). These subjects may also differ in their tendency to drop out of a trial or in their desire to seek additional and potentially confounding treatments versus those allocated to placebo [2], which complicates the interpretation of clinical trial results.

Investigators and research staff are also prone to bias. A subjective investigator-graded outcome scale is a commonly reported end point in clinical trials and knowledge of a subject's treatment assignment may consciously or unconsciously influence the investigator to assign better evaluations to those who are taking the active test product (observer bias). Unblinded randomized controlled trials (RCTs) result in larger treatment effects compared to blinded studies [3,4] and diagnostic test performance is overestimated when evaluations are made with prior knowledge of the diagnosis [5].

2. Confusion in blinding terminology

The double-blind RCT is widely considered the gold standard study design that most convincingly demonstrates the effectiveness of a product or intervention [6]. However, there is great confusion surrounding the definition of blinding and, specifically, what conditions constitute a single-, double-, or triple-blind trial [7]. A review of 200 double-blind RCTs reported 8 unique combinations of two or more groups

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that were blinded, including subjects, investigators, outcome assessors, data managers, biostatisticians, and (rarely) manuscript writers [8]. Almost 1 in 2 double-blind RCTs do not specify which groups were actually blinded [8]. The definition of blinding is so misunderstood that the most recent CONSORT Statement (CONSORT 2010) recommends that the terms "single blind," "double blind," and "triple blind" be abandoned and, instead, blinded RCTs should only detail who was blinded after treatment allocation and how [9,10]. Given the broad misunderstanding of the concept of blinding, all individuals involved in clinical trial design and conduct should develop a basic understanding of blinding terminology and methods. We briefly address herein the concept of blinding and propose standard definitions for the consistent use of these terms in clinical trials.

3. Types of blinding and the proposed standard definitions

Although the definitions of single, double, and triple blind vary widely among physicians and textbooks [7], the proposed standardized definitions of these terms are offered as follows.

3.1. Single blind

A single-blind trial is traditionally defined as one where only subjects are blinded to treatment allocation, and almost 3 out of 4 clinical research textbooks concur with this definition [7]. Clinical trials that utilize blinding of any single group are sometimes labeled as single blind, but this definition is uncommon. In order to improve clarity in the reporting of clinical trials, we propose that the term "single blind" should be reserved only for studies where subjects, but not investigators or outcome assessors, are blinded. Furthermore, the blinding status of other groups (e.g., data managers and biostatisticians) should be identified but should not impact the designation of "single blind."

3.2. Double blind

The standard definition of double blind is that neither the subjects nor the investigators (including those who administer treatment) and outcome assessors are aware of the treatment assignment, regardless of the blinding status of other groups [7]. We concur with this definition and propose that the term "double blind" should be specifically reserved for trials where these groups are blinded and the blinding status of other groups should also be described.

3.3. Triple blind

There is great disagreement among physicians and textbooks regarding the definition of triple blind and, in fact, no single definition predominates [7]. However, the common thread among most proposed definitions and, as such, our proposed definition of triple blind is blinding of subjects, investigators (including those who administer treatment), outcome assessors, and those involved in data management (i.e., data managers and biostatisticians). Again, the blinding status of all groups should always be specified in accordance with the recommendations of CONSORT 2010 [9,10].

4. Who needs to be blinded?

A rarely discussed aspect of blinding involves *a priori* consideration of which groups involved in a clinical study need to be blinded. Open label, or unblinded, clinical trials are susceptible to self-report and observer bias, although the use of these designs is sometimes unavoidable. For example, a clinical trial comparing the effectiveness of a minimally invasive procedure versus open surgery cannot easily blind subjects or investigators to the assigned treatment. Consequently, studies incorporating sham procedures and inactive devices have become more widespread in order to minimize the confounding effects associated with subject knowledge of treatment assignment [11,12].

The single-blind trial, where only the subjects are blinded to the intervention, is conducted when the investigator requires knowledge of treatment allocation (e.g., sham surgery). This design is effective in preventing the subject knowledge of the treatment assignment from confounding study outcomes. Nonetheless, this design remains prone to bias from the investigator, especially in trials with subjective endpoints, e.g., investigator-graded degree of clinical improvement, since they may harbor a vested interest in a positive subject outcome.

As previously mentioned, the double-blind RCT represents a distinct improvement over open-label and single-blind trials and, when feasible, represents the strongest design for minimizing subject- and investigator-related bias. Double-blind RCTs are often required to attain regulatory approval for new drugs, dietary supplements, and, in some cases, medical devices. The potential bias reduction associated with double blinding is noteworthy as a meta-analysis indicated that some double-blind studies reported 15% lower treatment effects compared to unblinded studies [3].

The rarely utilized triple-blind trial arguably offers only minor advantages beyond that of a double-blind design. Blinding of data managers and biostatisticians is generally less critical than blinding of subjects and investigators, because data management personnel usually have no contact with subjects or site staff and because data analysis is typically conducted only after the database has been locked. Therefore, the risk of introducing significant bias is lower in these groups, especially when pre-defined data management methods and statistical analysis plans are utilized. However, bias may result when statistical analyses are performed in the absence of pre-specified guidelines. The implementation of triple-blind trials also incorporates logistic challenges that must be considered, which partly explains why they are rarely utilized [13]. For example, a requirement for the biostatistician to remain blinded adds a level of complexity to the study implementation since the person who prepares the randomization list would need to be someone other than the study biostatistician.

5. Assessment of blinding success

There has been considerable discussion regarding the value of evaluating blinding success after a study has been completed by asking subjects and/or investigators to guess which treatment each subject was administered [14]. Formal statistical methods for evaluating blinding success have even

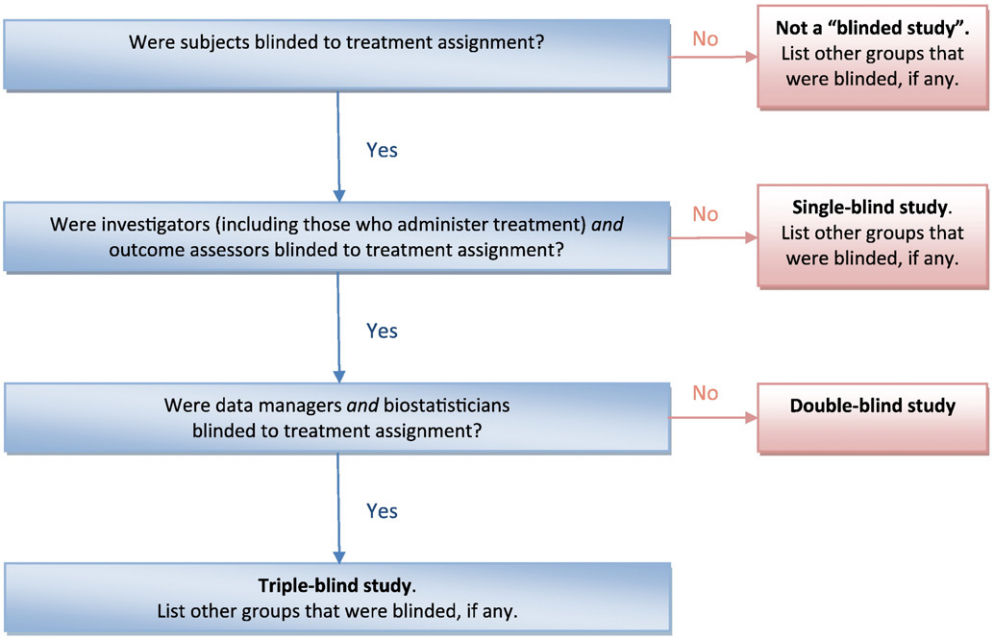

Fig. 1. Blinding definitional flowchart.

been proposed [15]. The evaluation of blinding success is controversial and has generated numerous publications for and against the practice [14,16–25]. Comprehensive coverage of this topic is, therefore, beyond the scope of this brief communication.

6. Conclusion

Although the latest CONSORT statement encourages authors and editors to discontinue use of the term "blinded trial" [9,10], these terms are heavily entrenched in clinical research jargon [26] and their use will likely continue despite this recommendation. Furthermore, specifying the type of blinding used is in agreement with the International Conference on Harmonisation (ICH) guidelines [27]. We therefore propose that, instead of abandoning the use of this term, explicit definitions for these terms should be proposed and advanced, ultimately resulting in the widespread adoption of standardized terminology. We have presented a standard definition of blinding and have created a flowchart to aid in decision-making that identifies the most common groups that are blinded in clinical studies (Fig. 1). Standardizing the definition of blinding and utilizing proper blinding methods will improve the quality and clarity of reporting in RCTs.

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