

## REVIEW ARTICLE

**Blinding in randomized control trials: the enigma unraveled**Vartika Saxena<sup>1</sup>, Manisha Naithani<sup>2</sup>, Anissa Atif Mirza<sup>3</sup><sup>1</sup>Additional Professor, Department of Community & Family Medicine, All India Institute of Medical Sciences, Rishikesh; <sup>2</sup>Assistant Professor, Department of Biochemistry, All India Institute of Medical Sciences, Rishikesh,<sup>3</sup>Associate Professor & Acting Head, Department of Biochemistry, All India Institute of Medical Sciences, Rishikesh

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The search for new treatments and testing of new ideas begins in the laboratory and then established in clinical research settings. Studies addressing the same therapeutic problem may produce conflicting results hence Randomized Clinical Trial is regarded as the most valid method for assessing the benefits and harms of healthcare interventions. The next challenge face by the medical community is the validity of such trials as theses tend to deviate from the truth because of various biases. For the avoidance of the same it has been suggested that the validity or quality of primary trials should be assessed under blind conditions. Thus blinding, is a crucial method for reducing bias in randomized clinical trials. Blinding can be defined as withholding information about the assigned interventions from people involved in the trial who may potentially be prejudiced by this knowledge. In this article we make an effort to define blinding, explain its chronology, hierarchy and discuss methods of blinding, its assessment, its possibility, un-blinding and finally the latest guidelines.

**Key Words**

Randomized Clinical Trial; Blinding; Unblinding

**Introduction**

A clinical trial is one of the final stages of long and vigilant research procedures. Gaining irrefutable knowledge from clinical research data becomes impossible due to studies producing conflicting results; hence there is need of Randomized Clinical Trial (RCT), the most valid method for assessing the benefits and harms of healthcare interventions (1). One challenge to the validity of RCT is the propensity for various biases. It has been suggested that the validity of trials should be assessed under blind conditions.

**Aims & Objectives**

To understand blinding and bring together all the aspects related to it.

**Material and Methods**

As this is a review article, which has used only the information available in public domain, so there is no ethical issues involved.

**Results**

**Definition:** Blinding came into existence in very early in research experiments with the French Academy of Sciences originated the first recorded blind experiments in 1784 (2). First double-blind study was done by Rivers (1908) in experimental psychology. The term "blind test" was first used by Gold 1946 (3). Blinding has been applied since time immemorial, but the enigmatic nature of blinding remains, as it is still a difficult feat to understand or to actually utilize in a RCT.

Blinding is a crucial method for reducing bias in randomized clinical trials. Blinding can be defined as withholding information about the consigned

method of treatment which is likely to prejudice the people involved in the trial. Blinding is prevention of bias in Clinical trials especially when looking at subjective outcomes (4). Simply stating the term blinding refers to keeping all trial participants (the patients, investigators or those collecting and assessing outcome data) unaware of the dispensed intervention, so that this knowledge does not influence them. “Masking” and “blinding” are synonymous terms, although the word masking may sometimes be preferable especially to avoid confusion in ophthalmologic trials where blindness can be an outcome. Though blinding is preferred term because it pervades all guidelines, is universally recognized (5).

### **Chronology of Blinding in RCT**

Blinding is used in research studies that compare two or more types of interventions in same disease. Blinding is usually done after successful randomization and allocation concealment.

### **Randomization**

Creation of an unpredictable allocation series is the first step of randomization which is of paramount importance in a RCT. Randomization is a pre-defined strategy for generating the allocation sequence. To prevent the patients and researchers from anticipating the received treatments and thereby influencing the trial outcome is the primary purpose of randomizing patients.

### **Allocation concealment**

After the creation of an unpredictable allocation series, the next step is to concealing it at least until patients has been assigned to their groups or respective treatment arms. This would prevent the collapse of randomization and has been termed as allocation concealment. Allocation concealment can be confused with blinding, though it's completely different from blinding. It just seeks to eliminate selection bias, that is who is selected as a participant and is assigned which treatment arm. Also, it is possible to conceal the generated randomization in every trial. Blinding on the other hand takes care of what happens after group assignment, what is the treatment being given to respective group. So by contrast, blinding relates to what happens after randomization and seeks to reduce ascertainment bias (assessment of outcome). Unlike allocation concealment blinding is a difficult feat to attain and is not always possible.

### **Types of trials**

The medical trials can be broadly classified into three types viz open trials, partially blind and blind trials (6).

Open trials/open label are where all participants and investigators know who is getting which intervention e.g. medical vs. surgical treatments. Such trials are considered useful for dose ranging studies. For example a randomized, open-label clinical trial on cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder was carried out. In this particular study 498 patients with schizophrenia were randomly assigned to open-label Antipsychotic Drugs (7). Here the participants and the treatment providers knew the treatment being provided to the two groups. Similarly, open trials are used for pilot studies assessing the actual efficacy of medications (8).

A partially blind trial is usually conducted during Phase II, of any vaccine development where participants and providers are blind to vaccine but not to schedule (9). Last in this list is the holy grail of trials -the blind trials. Here we would be discussing more about the blind trials, their history, Hierarchy, why blinding is done, how we accomplish it and how to assess it.

### **Hierarchy of Blinding**

It is advisable for the researcher to blind at least four groups of individuals involved in trials (10). These can be namely the participants, clinicians /surgeons, outcome assessor (data collectors and critical evaluator) and the data analysts.

Hierarchy of Blinding includes the various types based on individuals blinded.

- **Single blind:** where only participant/ only clinician is blinded to assigned intervention or treatment
- **Double blind:** Both participant and clinician/ health care provider are blinded to treatment
- **Triple blind:** participants, clinician and outcome assessors blinded to treatment
- **Quadruple blind:** participants, clinician, outcome assessors and statistical analyst blinded to treatment

In Single blind trial usually participants are blind to the treatment given. When it is unacceptable ethically to give placebo treatment then blinding the treating clinician would serve the purpose. Justification for single blind scenarios is possible only when the carrying out of double-blind becomes unfeasible due to adjustments required in medication dose or potential side effects which are

unknown and non-quantified. For example, in a prospective randomized a comparison between laparoscopic and small-incision cholecystectomy conducted in 200 patients. The patients were randomized in the operating theatre and an aesthetic technique and pain-control methods were standardized and identical wound dressings were applied in both groups. Here it was the patients who were blinded as blinding of surgeons were not possible.

Knowledge of group assignment to participants may affect their conduct in the trial (11). For example, one who is aware of not receiving active treatment may pursue supplementary treatment outside of the trial, may vary his/her responses to subjective measures of outcome and is more inclined to leave the trial. Those receiving an experimental intervention may have preconceived notions about the effects of particular treatment, thus defeating the purpose of trial. This also eliminates Hawthorne Effect (12) which states that attention alone produces results. That is why an equal attention control design is used in clinical trials. To "blind" patient placebo can be used, it is a pill of same size, color, shape as treatment or the other treatments "shammed" as nearly as possible.

In Double blind trial both the participant and clinician are blinded. Patient is given a bar-code or code. The medications also are having a bar-code/ code. Blinding the Investigator/clinician eliminates Investigator bias (13). One very interesting example of a double blinding is trial by Bollinger *et al* (14) which was looking at reduction of smoking using oral nicotine inhalers instead of cigarettes. In this study 400 healthy volunteers were included and provided either active or placebo inhalers by pharmacists (not part of trial) using a computer generated list which has randomized participants. Thus both the both participants and health providers were blinded.

Because of blinding the investigators are also less likely to convey their penchants or attitudes to participants, or to differentially provide additional treatments, or to adjust dose of the treatment being tested and finally influencing which patient should leave or continue in the trial.

In triple blind trial the Participants, clinician and outcome assessors are blinded. One example is a triple-blind, sham-controlled study of Low-level laser therapy facilitates superficial wound healing in humans by Hopkins *et al* (15) where the subject, clinician, and investigator examining the wounds

were blinded as to which treatment group was the sham. The definition of sham is a treatment or procedure that is performed as a control and that is similar to but omits a key therapeutic element of the treatment or procedure under investigation. Here Low level laser beam therapy was given to one group of patients and sham procedure to other group. It was only after the data analysis, the manufacturer revealed the true treatment head. The need of blinding the outcome assessor is eminent since unwittingly (or even intentionally) they may exercise more care about one type of responses or measurements such as those supporting a particular hypothesis.

In Quadruple blind trial the participants, clinician, outcome assessors and statistical analyst are blinded. Until the entire analysis has been completed the data analyst should not be aware of the progression or expected results of intervention. At the level of statistical analysis, a bias may be introduced by the selective use and reporting of various statistical tests, though this may or may not be an unintentional (16,17) nevertheless the effects are manifold. One such example of study using blinding at each stage is an experiment conducted by Ghajari *et al* (18) comparing the radiographic findings and success rates of direct pulp capping with different substances. Radiographic and clinical successes were evaluated at 20-month follow-up by a calibrated dentist, radiologist and a statistician who were also blind to the type of used biomaterial.

#### **Methods of blinding in Pharmacological trials**

Simplest methods for of blinding are possible in Pharmacological trials.

For medications to be applied or taken orally a common preparation can be done to produce similar looking medications (both having active ingredient and those having none) like similar capsules, tablets, or similar bottles are commonly used techniques. Researchers have used specific flavors such as sugar or peppermint masking the characteristic taste of the active ingredients. For treatments administered by care providers, like intravenous injections, preparation of opaque dispensers or containers to adequately conceal different appearances of fluid within can be used. The provided treatment and placebo should have identical appearance (size, color, weight, feel, odor, etc.), same package, same label and same instruction.

It has also been suggested that the injection of placebo or active treatment can be administered by

unblinded operator not involved in any other study procedure.

### **Blinding in Non-Pharmacological trials**

Sham procedures can be used for assessing a device or gauging the success of a surgical procedure. The sham procedures can be simulation of the intervention under consideration; including “standardizing” the postoperative care. It is also recommended that the researcher can use identical inactivated machine, same light noise sensation, same instructions, same duration and frequency, patient’s position, same precautions like protective goggles in both groups.

The sham procedures for studies involving the participation of patients were either an intervention of very similar nature. For example, some studies involved the use of hands-on set of man oeuvres to simulate treatment or others have used sham procedures using identical apparatus or machines such as a switched off machine or use of switched on machine having a barrier to block the treatment or modifying the position of patient in placebo arm so that the targeted area is not exposed to the treatment (19). For example, a study assessing use of high-strength magnetic application for treatment of knee osteoarthritis has used a misdirected magnetic field (facing away from the knee joint) as placebo.

### **Blinding in surgical trials**

Blinding is indisputably more difficult to achieve in surgical trials, since surgical treatments would often result in tell-tale incisions and scars differing between groups or there is simply a comparison between surgical and non-operative intervention. In such scenario it is much advisable to blind the other members of the team including those providing post-operative care like nursing staff and interacting with patients after surgery like dieticians and other doctors. Rationale of using strategies like concealment of scars or digitally varying the radiological features is to masquerade the type of scar/implant.

### **Assessment of Blinding**

Accomplishment of perfect blinding is of fundamental importance in many trials. It is assumed to be so and the results become questionable if this vital assumption is debased. Several ways are proposed in literature to evaluate blinding, but none of the suggested methods are being used commonly or can be regarded as gold standards. But truthfully reporting the blinding efforts used can help the readers to judge those efforts. Some straightforward

steps have been widely quoted in literature including step one of unambiguously stating who was blinded and providing the mechanism used, as was done in a double blind study by Roddy *et al* on use of nonoxynol 9 film, aiming to reduce sexual transmission of diseases male-to-female (20). This publication clearly mentions that neither the women nor the care giving staff knew which group of patients were using appropriated films, and also states that the placebo and treatment films were indistinguishable in appearance. Step two includes assessment of blinding using preformed questionnaires. Lastly one can also use statistical assessment of Blinding (21, 22). The two statistical methods, James' blinding index and Bang's blinding index are currently available.

### **Possibility of Blinding**

Undoubtedly Blinding is not always a possibility. Sometimes single blind trials or even open trials cannot be avoided. Full blinding is often impossible in trials of different approaches of patient management, blinding in a surgical intervention or device study, surgical procedures having characteristic scar, or a treatment having characteristic side effects.

If it is almost impossible to blind the participants or the treating clinician then the researcher should be innovative and do the best they can, promote use of hard outcomes rather than subjective ones like questionnaires. If possible the researcher can Blind outcome assessors, and finally on completion can measure degree of un-blinding and lastly acknowledge the limitations.

### **Un-blinding**

In life threatening situations and emergencies involving trial participants, unblinding can be done. Even for a single subject the blinding of a trial should be done only when knowledge of the treatment assignment is a must for the subject's care. Any breaking of the blind, either intentional or unintentional should be reported correctly mentioning the procedure and timing. For example, in a double-blind randomized trial having 265 subjects conducted by Bisognano *et al* to determine the effect of baro-reflex activation therapy on systolic blood pressure in resistant hypertension, three subjects met the emergency un-blinding criteria of hypertensive emergency with confirmed diastolic BP of 120 mm Hg or greater with evidence of accelerated symptoms of end-organ damage and had their treatment assignment revealed (23).

### Current scenario of Blinding

There has been a lot of debate in the scientific community about the terms. A recent review including 200 trials with a survey of authors was conducted regarding how blinding is reported in clinical trials and how lack of reporting relate to lack of blinding. They found that One-hundred and fifty-six (78%) articles described trials as 'double blind' but only a meagre 3 (2%): explicitly described blinding. They also revealed that twenty (19%) 'Double blind' trials: had not blinded patients, health care providers or data collectors. These results indicate a lack of correct concepts and their faulty implementations.

Consolidated Standards of Reporting Trials (CONSORT) Guidelines were first made available in print in year 1996 and were updated in 2010. The statement provides clear cut checklist and flow diagrams for researchers. The recent consort guidelines suggest that terms like single, double blind etc. are vague and their use should be abandoned. The investigators should rather as to who was blinded and how they achieved the blinding. The guidelines (24) have been formulated to perk up the quality of reporting of various RCTs.

### Implications

Human behavior is known to be swayed by what we discern or believe. In research there is a particular risk of propel particular set of findings, especially when subjective assessment is there resulting in biased outcomes. Blinding is used to eradicate such a bias. The significance of blinding may differ in different circumstances. This paper emphasizes that it may jeopardise results if ample blinding measure and techniques are not used. This seems to be challenging the veracity of researchers, but notably such biases are often subconscious. Trials not using appropriate blinding show larger treatment effects on the other hand good blinding strategies makes less biased outcomes and helps preserve the credibility of results.

### Conclusion

Blinding is critical for Randomized controlled trial (RCTs) for alleviating biases and must be practiced as far as possible for generating the valid data. Latest reports show that currently researchers are neither practicing the binding appropriately nor they are reporting it clearly in their published data.

### Recommendation

Blinding is an important aspect for Randomized controlled trial (RCTs) for removing the biases. Hence while undertaking RCTs researchers must ensure proper allocation concealment (before randomization) and blinding as appropriate. Researchers must also report the process of blinding clearly while publishing the research article.

### Relevance of the study

This article will help the researchers and students to understand the importance and correct process of ensuring blinding in the study. This would further help in generating valid data.

### Authors Contribution

VS & MN: the conceptualization, design and giving recommendations for the article. AAM: critically reviewed the draft article.

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