Blinding in Randomized Controlled Trials: What researchers need to know?

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Abstract

Randomized Controlled Trial (RCT) is a classical research design, in which the participants are randomly allocated to one or other treatment conditions under the study. Researchers widely use randomized trials to evaluate the effectiveness of various pharmacological and non-pharmacological interventions. At the outset, randomization minimizes the bias in allocating subjects to the intervention and control group. However, it does not exclude the chances of differential treatment of groups or biased adjudication of outcome variables. Blinding helps in controlling various types of biases that might inadvertently sweep into the study. The two major biases that can be controlled using blinding are the performance bias and the ascertainment bias. The four groups of people blinded in the trial are the study subjects, the research investigator/s, the outcome assessor/s, and the data analyst/s. Based on the number of people blinded, trials are classified as open label trial, single blinded trial, double blinded trial, triple blinded trial, and quadruple blinded trial. Sometimes, it may be difficult or nearly impossible to do blinding because of methodological, technical, or ethical reasons. Researchers must ensure transparency in reporting the blinding. If, blinding was employed, mentioning the study as 'double blinded' or 'triple blinded' may not be sufficient. The researchers must explicitly report, which all individuals were blinded and how. Blinded RCTs can minimize bias to a greater extent. Blinding helps in prevention of biased ascertainment of outcomes and reduce the chance of co-interventions. Researchers must strive to blind as many individuals as practically feasible to limit the bias in RCTs.

Key words: Blinding, masking, randomization, performance bias, ascertainment bias

Introduction

Randomized Controlled Trial (RCT) is a classical research design, in which the participants are randomly allocated to one or other treatment conditions under the study. RCTs help in authentic explanation of causality. Randomization is the cardinal feature of an RCT and it refers to the random allocation of subjects to the study arms. RCTs provide the investigator the assurance that the difference in the outcomes among subjects in study arms was solely caused by the intervention, as randomization equalizes the study group in all other factors. Thus, RCTs set the standard of excellence in undertaking health sciences research (Bench, Day, & Metcalfe, 2013; Polit & Beck 2012; Nelson, 2011 & Kendal, 2003).

Researchers widely use randomized trials to evaluate the effectiveness of various pharmacological and non-pharmacological interventions. In health sciences research, RCTs are usually done to evaluate, whether a treatment or intervention is successful in-bringing about desired changes in behavior, improving the quality of life, or promoting symptom alleviation. Because of its methodological rigor and its ability to ascertain causality, RCTs are considered as the gold standard for conducting medical research. At the outset, randomization minimizes the bias in allocating subjects to the intervention and control group; however, it does not exclude the chances of differential treatment of groups or biased adjudication of outcome variables (Karanicolas, Farrokhyar & Bhandari, 2010). Blinding

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helps in controlling these types of biases that might inadvertently sweep in the study.

The objectives of this article are to introduce the concept of blinding, outline the importance of blinding, discuss the classification of trials based on blinding, and present the potential benefits of blinding.

Blinding

To reduce bias and to ensure the methodological rigor, the investigators should plan the trial in such a way that the study subjects, investigators encountering the study subjects, individuals collecting the outcome measures, and those who are analyzing the data, have no knowledge regarding allocation status of the study participants. Blinding is defined as "Keeping trial participants, investigators (usually health-care providers), or assessors (those collecting outcome data) unaware of the assigned intervention, so that they will not be influenced by that knowledge." (Schulz and Grimes, 2004)

Importance of blinding

Randomization eliminates the influence of confounding factors or biases that are present at the time of allocation. However, it does not eliminate the confounders that may sweep-in after the allocation has taken place. Blinding can play a major role in controlling these post randomization confounders. Hence, blinding is as important as randomization in RCT (Hulley, Cummings, Browner, Grady & Newman, 2013). The absence of blinding can result in various types of biases. The two major biases that can be controlled using blinding are the performance bias and the ascertainment bias.

Performance bias: The differences in care or attention provided, to the subjects in different arms are referred to as performance bias (Polit & Beck, 2012). The extra attention given to the participants, in the intervention arm is referred to as "co-intervention." In an unblinded study, the co-intervention might influence the difference in outcome measures between the study groups. This is also referred as co-intervention bias (Hulley et al., 2013). For example, in an unblinded study to evaluate the effect of counseling on smoking cessation, the investigator's keenness to find the benefit might lead the investigator to 'further motivate' the client to stop smoking. This 'further motivation', which is not part of the intervention, is referred to as co-intervention. The chances of co-intervention can be effectively limited using blinding.

Ascertainment bias: Blinding can reduce the ascertainment bias to a greater extend. If, the researcher has foreknowledge about the treatment assignment of a study participant, it may influence his or her judgment in outcome assessment (Hulley et al., 2013). This foreknowledge may unduly influence the way how outcome variables are measured, verified, or recorded. This kind of a bias is termed as ascertainment bias (detection bias). For example, in an unblinded trial to evaluate the effectiveness of 'nurse-led interventions' in improving the quality of life of patients diagnosed with cancer, the investigator may get biased during the adjudication of outcome variables. Subjective outcome measures such as physical measurements, self-reported scales, and disease diagnoses are all susceptible to ascertainment bias. The ideal method to protect the trial against an ascertainment bias is to keep the individuals involved in the trial (more specifically the outcome assessors) unaware of the allocation status.

Classification of trials based on blinding

The four groups of people blinded in the trial are- the study subject/s, the research investigator/s, the outcome assessor/s, and the data analyst/s. Based on the number of people blinded, trials are classified as open label trial, single blinded trial, double blinded trial, triple blinded trial, and quadruple blinded trial.

Open label trial: When blinding is not used in a trial, the trial is referred to as an 'open label trial.' An open label RCT is also referred to as an open RCT, open trial, non-blinded trial, or unblinded trial. In the case of unblinded trials, all the people involved in the trial will be aware of the group assignment of study participants. An open-label RCT evaluated the effectiveness of music therapy in reducing the anxiety of patients undergoing Micrographic Mohs Surgery (MMS). Subjects were randomly assigned to- with music and without music group. Due to the nature of the intervention (music), it was impossible to blind the subjects as well as the surgeon (Vachiramon, Sobanko, Rattanaumpawan, & Miller, 2013).

Single blinded trial: A single blinded trial involves blinding of any one group of individuals. Usually, the subjects receiving the intervention or the outcome assessors are blinded to the intervention assignments. Polkki and colleagues (2008) tested the effectiveness of an imagery-induced relaxation intervention in reducing post-operative pain among children aged eight to 12 years. In this single blinded study, the nurse who collected the data did not know whether, children were in the treatment group or in the usual care control group.

Double blinded trial: In a double blinded trial, any two groups of individuals are blinded. Double blinding is recommended in drug trials. Usually, the investigators as well as the study participants, are blinded to the allocation status. Noehren et al. (2014) conducted a placebo controlled trial to evaluate the effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS) on outcomes of patients with fibromyalgia. In this double blinded trial, the participants were blinded to the active and placebo TENS treatments and the outcomes assessor was blinded to the group assignments. Blinding of the investigator was not feasible as he administered the TENS intervention for the study subjects.

Triple blinded trial: Three groups of people are blinded to the intervention assignments in a triple blinded study. Usually, the subjects, the investigators, and the outcome assessors are blinded. In RCT, on the efficacy of doxycycline and rifampin for patients with Alzheimer's disease, the researchers utilized a triple blinded design. Patients, investigators, and outcome assessors were blinded to treatment allocation. The three groups of individuals remained blinded during the entire study period, including follow-up (Loeb et al., 2004).

Quadruple blinded trial: If, all four groups of people (study subjects, research investigators, outcome assessor, and data analysts) are blinded to the allocation status of the participants, the trial is referred as a quadruple blinded study. Burns et al. (2005) conducted a study to evaluate the effect of peri-operative n-acetylcysteine in preventing renal dysfunction among high-risk patients undergoing Coronary Artery Bypass Graft (CABG) surgery. In these, placebo-controlled quadruple blinded study patients, clinicians, data collectors, and the data analysts were blinded to the group assignments of the study subjects.

Potential benefits of blinding

The potential benefits of blinding are discussed based on the type of individuals (study subjects, research investigators, outcome assessors, and data analysts) blinded.

Blinding subjects: The participants' knowledge of his or her assignment into the intervention arm may operate a positive response, even if the therapy had no positive clinical effect (Gordis, 2013). If, the participants are not aware that they are getting an experimental drug or placebo, then the clinical outcomes are rarely influenced by their expectations of its efficiency. Thus, blinding subjects helps in reduction of expectation bias. Blinding of subjects is necessary, when the outcomes are subjective in nature (like pain and fatigue, etc.). Subjective outcomes are more prone to expectation bias.

Blinding investigators;Blinding the investigators will help to reduce the differential treatment provided to the subjects in the intervention or control groups. Investigators include doctors or nurses or interventionists, who might interact with the subjects during the trial. Schulz & Grimes (2004) reports that the investigators 'for or against attitude' regarding an intervention can directly be transferred to the study subjects, if the investigators are not blinded. Blinding the investigators thus help in preventing the delivery of supplemental care or co-intervention to subjects in the experimental arm.

Blinding outcome assessors:Blinding the outcome assessor is crucial in ensuring the impartial assessment of outcome variables. In studies involving subjective outcomes, blinding the outcome assessors helps in meticulous evaluation of outcomes. Unblinded outcome assessors tend to register more generous responses for the outcome variables of subjects in the intervention arm (Schulz & Grimes, 2004).

Blinding the data analysts:The bias introduced at the time of statistical analysis such as selective use of

statistical tests as well as selective reporting of outcome variables can be effectively controlled by blinding the data analysts. The data analysts are blinded to the study assignments till the completion of data analysis (Karanicolas et al., 2010).

Trials and blinding: Some practical considerations

Unlike randomization, blinding is always not possible. The ability to blind a trial depends upon the nature of trials and the nature of outcome variables. Sometimes it may be difficult or nearly impossible to do blinding because of methodological, technical, or ethical reasons. In situations when, the subjects are assigned to interventions like surgical, dietary, educational, behavioral, psychological, exercise, or rehabilitation, it is non-feasible to blind the participants.

In a study to evaluate the effectiveness of gait training program for patients with paraplegia, the participants know what intervention they are receiving, and the research interventionist know who received what intervention. In these types of situations, it is nearly impossible to blind the investigators and study subjects. However, the researchers can explore the possibility of blinding the outcome assessors. Blinding outcome assessors are mostly feasible and considerably easy to implement. Even though, blinding procedures help to reduce bias and enhance validity, only 33% of the 199 published RCTs from 2007 to 2009 published in 16 nursing journals, reported using blinding procedures (Polit, Gillespie & Griffin, 2011).

Blinding or masking: Which terminology to use?

'Blinding' or 'Masking' are the two common terminologies used to describe the same procedure. Morris, Fraser, & Wormald (2007) recommends the use of the term 'masking' in trials pertaining to ophthalmology, as the term 'blind' refers to an ophthalmologic condition and as an outcome variable. The majority of health science researchers use the term blinding rather than masking. Since, blinding is predominantly used in medical literature, it is recommended to use the terminology 'blinding' rather than 'masking' (Schulz, Altman, & Moher, 2007; Schulz & Grimes, 2004).

Allocation concealment and blinding

There has been a considerable amount of confusion even among researchers regarding allocation concealment and blinding (Schulz & Grimes, 2004). Both the techniques are used to control confounding variables. Allocation concealment is a part of randomization. Allocation concealment protects the randomization sequence until the subjects are allocated to the study arms, thus preventing selection bias, whereas blinding helps in preventing the ascertainment bias (Figure 1). It is always possible to achieve allocation concealment, whereas the blinding is not.

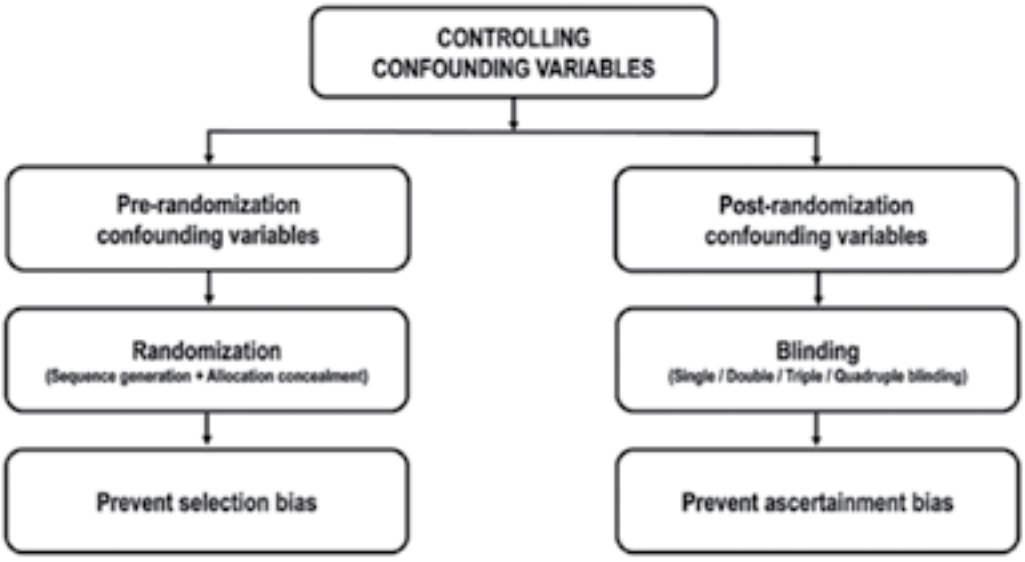

Figure 1: Allocation concealment and blinding

Reporting blinding in research reports

Despite its methodological importance, blinding is often poorly reported in the trial reports (Hróbjartsson et al., 2009). The updated Consolidated Standards of Reporting Trials (CONSORT) guidelines demand transparent reporting of blinding process (Moher et al., 2010). Researchers must ensure transparency in reporting blinding. If, blinding was employed, mentioning the study as 'double blinded' or 'triple blinded' may not be sufficient. The researchers must explicitly report, which all individuals were blinded and how. If, blinding was not possible, the researchers must justify the reason regarding the same. If, blinding was not employed, the researchers may consider it as a limitation and acknowledge it in the report.

CONSORT statement recommends reporting on, "How the success of blinding was evaluated?" Various methods have been proposed to assess the success of blinding in RCTs (Kolahi, Bang, & Park, 2009). The researchers can check the successfulness of blinding by asking the study subjects, research investigator, outcome assessor, and data analysts, which intervention (active intervention or placebo or do not know) they think was administered to a particular group. If the blinding was successful, the individuals will not be able to successfully guess the treatment assignment. A double blinded placebo controlled trial was conducted to evaluate the effectiveness of chlorhexidine (CHX) gluconate chewing gum on anti-plaque activity. In this study, the researchers asked the participants to guess the treatment they received (active or placebo or do not know). The participants' guess for the CHX gum and placebo were not statistically significant, indicating successful blinding (Kolahi, Soolari, Ghalayani, Varshosaz, and Fazilaty, 2008).

Conclusion

Blinding is a significant methodological feature of randomized trials. It involves concealing information regarding group assignment from participants, investigators, outcome assessors, and data analysts. Blinded RCTs can minimize bias to a greater extent. Blinding helps in prevention of biased ascertainment of outcomes and reduce the chance of co-interventions. Researchers must strive to blind as many individuals as practically feasible to limit the bias in randomized controlled trials.

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