EVIDENCE-BASED MEDICINE CORNER

Bias in RCTs: confounders, selection bias and allocation concealment

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The double blind randomized controlled trial (RCT) is considered the gold-standard in clinical research. Evidence for the effectiveness of therapeutic interventions should rely on well conducted RCTs. The importance of RCTs for clinical practice can be illustrated by its impact on the shift of practice in hormone replacement therapy (HRT). For decades HRT was considered the standard care for all postmenopausal, symptomatic and asymptomatic women. Evidence for the effectiveness of HRT relied always on observational studies mostly cohort studies. But a single RCT that was published in 2002 (The women's health initiative trial (1) has changed clinical practice all over the world from the liberal use of HRT to the conservative use in selected symptomatic cases and for the shortest period of time. In other words, one well conducted RCT has changed the practice that relied on tens, and probably hundreds, of observational studies for decades.

But what is the appeal of RCT and why does it have such a place at the very top of the hierarchy of evidence? It is because it is the least design of clinical research that can be affected by bias if it has been conducted properly. Conducting a RCT allows investigators to control many types of bias that are hardly, if ever, controllable in other study designs such as the non-randomized controlled trials, cohort and case-control studies. Thus adequate knowledge of the different types of bias

that may distort a RCT results and how to avoid them is mandatory for researchers who seek conducting proper research of high relevance and validity.

What is bias?

Bias is the lack of neutrality or prejudice. It can be simply defined as "the deviation from the truth". In scientific terms it is "any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth2". Such deviation leads, usually, to over-estimating the effects of interventions making them look better than they actually are.

Bias can occur and affect any part of a study from its planning phase to its publication. It arises mainly due to the adoption of an inadequate design, misconduct of the research methodology or the inadequate analysis of data. As research is important for determining whether a new intervention is effective or not and if effective what is the magnitude of its effectiveness, bias is obviously detrimental to research and hence to clinical practice.

There are many types of bias that affect scientific research. Sackette has identified 35 types of bias2. However, there are major types that drastically affect the conclusion of a study and there are others that are minor ones. Selection bias is one of the major types of bias that can impair the results of a RCT but due to the nature of the design of a RCT it can, and should be, avoided.

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Confounders

Research aims primarily at measuring the association between two variables; an intervention (or exposure) and an outcome. This can be achieved by designing a comparative research with at least two groups; one receiving the intervention under investigation (study group) and another either receiving a placebo or another intervention (a control group). The outcomes in both groups are then compared. But to study the effect of interventions properly one important pre-requisite is that participants in both groups (the study group and the control one) should be similar in all characteristics except for the intervention being studied.

Suppose that a study has been conducted to compare pregnancy rates in patients with anovulatory infertility that are subjected to intrauterine insemination (IUI) after ovarian stimulation either with FSH injections in one group or clomiphene citrate (CC) in the other group. Thus, participants were distributed into two groups; a study group that received FSH and IUI and a control one that received CC and IUI. After 6 months of therapy there was a 32% pregnancy rate in the FSH/IUI group and 24% in the CC/IUI group but during the analysis of data there was a significant difference in the body mass index (BMI) between the two groups with more obese females in the CC/IUI group than in the FSH/IUI one. The question is: "Was the lower pregnancy rate in the CC group due to the inferior effect of CC compared to FSH or due to the higher BMI that is known to affect ovulation and pregnancy rates unfavorably?" We can not precisely know as both factors could be responsible for the results of the research. The same problem would occur if we found a significant difference in the mean age between the two groups with older females in the CC/IUI group than in the FSH/IUI one as age is inversely proportionate to fertility. So, if any factor, that has an effect on the study outcome other than the one studied, prevails in one group more than the other it would negatively affect the study result. Such factors, as obesity and age in regard to fertility in our example, are known as "confounders".

A confounder is defined as "a variable, other than the one studied, that can cause or prevent the outcome of interest." For any outcome in research there are many confounders that should be considered in the planning phase of the trial, reported in the results section (usually table 1 in the manuscript), and analyzed for significant differences between the groups. Any confounding variable should be equally distributed in the two groups to give balanced groups. Some other examples of confounders are the effect of smoking, life style, and dietary habits on bone mineral density and the frequency of sexual intercourse, duration of sexual activity, and number of partners on cancer cervix.

Selection bias

Interferences from researchers to divide patients into groups (select which patient goes to which group) will result in dissimilar or unbalanced groups and would introduce bias into the study. Such type of bias is known as "selection bias."

If investigators "thought wrongly" that they can equally distribute or balance all the basic characteristics and risk factors or confounders between the groups, they definitely can not ensure balancing unknown risk factors or unknown confounders. The best way of eliminating selection bias, then, is by randomizing patients properly into groups.

Randomization is achieved by using any method that gives every participant an equal chance to be allocated into any of the study groups. In other words, after consenting to participate in the study, every participant should have a 50% chance to be allocated to the study group and 50% chance to be allocated to the control group. Such randomization can be achieved by many methods as simple as coin tossing or rolling a dice or better by using random numbers tables or computer generated random numbers. A scheme is then chosen defining what numbers lead to which group (randomization code or sequence). The most important is that once the randomization method and sequence have been determined, they should never be changed and randomization should never be repeated for the same participant for whatever reason. The effect of randomization as a protection

against selection bias was studied in a Cochrane systematic review in which control group patients in non-randomized controlled trials were frequently found to have a worse prognosis than patients in the study group3. This, of course, lead to exaggeration of the treatment effect of studied interventions.

Allocation concealment

Unfortunately, using a perfect randomization method alone does not ensure avoidance of selection bias due to human interference in the procedure. Suppose that during the conduct of the FSH vs. CC trial the researcher who is responsible for randomizing patients into groups found an eligible patient (a patient who meets inclusion criteria) who can not afford for the cost of FSH injections or who refused to take injections and preferred oral CC. On randomizing her, the randomization process directed her to the FSH group! Here the investigator may try to help this participant and solve this problem either by excluding her from the study (and prescribing CC to her) or by repeating the randomization method till she is directed to the CC group. Thus knowing the randomization sequence or code that directs patients to the study or the control groups can affect selection of patients and allows for re-directing them to desired groups. Hiding the randomization sequence or code from those performing the randomization achieves neutrality and ensures that the randomization process is properly applied and not repeated to direct certain participants to certain group in the study. Hiding the allocation sequence from those performing randomization is known as "allocation concealment". Here, after randomization, the randomization code is sent with the patient name to the principal investigator or better, for more neutrality, to a third party who has the randomization codes to decide whether this code directs the patient to the study group or to the control one preventing it from being changed. Failure to apply an adequate method of allocation concealment exaggerates treatment effect by 40%4. Thus, allocation concealment is another important pre-requisite in RCTs to prevent selection bias.

There are methods of randomization that look perfect but in reality can lead to bias as they can never be concealed. Such methods lead to pseudo-randomization or what is known as quasi-randomization. The use of hospital admission numbers, date of birth or day of enrollment into the study as a method of randomization is inadequate as the randomization sequence can not be hidden in such situations and patients can be excluded from the study based on the knowledge of their group assignment or can easily be re-directed to another group. Using such methods makes the trial falls to the category of non-randomized controlled trials.

Moher et al, in 1998, reported that allocation concealment was reported in less than 10% of articles describing RCTs published in prominent journals in five different languages5. Thus randomization and concealment of the randomization sequence became pre-requisites in the CONSORT statement that aims for improving the reporting of randomized controlled trials enabling readers to understand a trial's conduct and to assess the validity of its results (6).

CONCLUSION

In conclusion, selection bias is detrimental to randomized controlled trials. To prevent selection bias, investigators should anticipate and analyze all the confounders important for the outcome studied. They should use an adequate method of randomization and allocation concealment and they should report these methods in their trial. Editors and peer reviewers should enforce the importance of use and reporting these methods before accepting RCTs for publication.

REFERENCES

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women; Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288:321-33.
2. Sackett DL. Bias in analytic research. J Chronic Dis 1979; 32:51-63
3. Kunz R, Vist G, Oxman AD: Randomization to protect against selection bias in healthcare trials. (Cochrane

Database of Methodology Reviews). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.

4. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.

5. Moher D, Fortin P, Jadad AR, Juni P, Klassen T, Le Lorier J, Liberati A, Linde K, Penna A. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. Lancet 1996;347:363-6.

6. Moher D, Schulz K, Altman D (for the CONSORT Group). The CONSORT Statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285:1987-91