Identifying and Eliminating Bias in Interventional Research Studies – A Quality Indicator

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ABSTRACT

This review article deals with highlighting the importance of identification and elimination mechanisms of important biases in interventional research studies.In simple terms, Bias means a systematic error that can occur in the event of any phase of the research, during planning, implementing, data collection, analysis and also during publication stage. An in-depth knowledge regarding the bias allows researchers and readers to critically and independently review the scientific literature and avoid interventions which are suboptimal or potentially harmful. A thorough understanding of bias has a stronger implication towards conducting good research and publishing high quality articles, which are very much essential for the practice of evidence-based practice.

Keyword: Identifying and Eliminating Bias

INTRODUCTION

In scientific terms Bias is "any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth". It can be simply defined as "the deviation from the truth".[1]

Bias is not uncommon in interventional trials, but to a greater extent in Indian studies compared with those western trials, says one of the systematic review and comparative empirical analysis of randomized controlled trial reports published in selected Chinese, Indian, and European or North American medical journals.[2]

The possible reasons for trials appearing biased, which reflect underlying inadequacies in the design and conduct of the trials are:

1. Inadequate knowledge of the researcher in accurate designing and conduction of trials.
2. Indian higher education looks research as a differential component in the academic functioning. It is not considered as a lucrative career option. Apart from this, resource constraints, lack of commitment, lack of proper encouragement, etc., are the impediments that are affecting the quality of research in our institutions of higher education.[3]
3. Career in pharmacology, physiology and other basic sciences are not rewarding in India. So the doctors who opt for these branches are usually from the bottom of the talent pool. That leads to the poor quality of basic medical research in India.
4. Those researchers and journal editors in India not adopting the CONSORT reporting guidelines[4], are sole responsible for the rejection of papers in International Journals and publishing of poor quality trials respectively.
5. Research organizations conducting and reporting a trial in favor of the funder, budgeting their efforts[5] – working more intensely on some research assignments while neglecting others – that tends to report a poor quality or extremely low number of high quality research papers.

Hence, the authors considered to present this review with the following objectives:

- To become familiar with various types of bias in experimental research study.
- To discuss how bias influences experimental research study and highlights some of its sources.
- To use the knowledge of such biases that may help us recognize them and minimize their impact on the planning of research and health-related decisions.

METHODS

A search strategy was done in 04 electronic databases and e-books, for English-language source, published over the period 1995-2015 for the topics of bias in interventional studies, strategies to overcome those biases, strengthening of interventional studies by elimination of bias in experimental research study. Hand searching was additionally conducted in relevant research methodology books. The intent of this literature search was to identify and review the potential sources of bias in interventional studies and methods to overcome for conducting quality based studies in this review.

RESULTS

The different types of biases that occur in interventional studies are broadly categorized into biases in Randomized Controlled Trials [RCT] and Non-Randomized Studies [NRS].

Further, the review deals with discussing different biases in interventional studies, its sources and highlighting elimination strategies of some of the important biases.

I. Biases that can arise, even before the trial is conducted

1. Choice-of-Question Bias

It is one of the most unrecognized types of bias that occur in RCTs. This bias is concealed within the question that the study intends to answer. This bias may not have a stronger impact on the strength of the study but it may affect the generalizability of the study outcomes.[6]

This bias can take many forms:

i. Hidden agenda bias:

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It occurs when a trial is mounted, not in order to answer a question, but rather to demonstrate a pre-required answer.

ii. Cost and convenience bias:
It occurs when a study is done on a basis of what we can afford to study, or what is convenient to study, rather than what we really want to study. It can seriously compromise what we choose to study.

iii. Funding availability Bias:
It occurs where studies tend to concentrate on questions that are more readily fundable, often for a vested or commercial interest.[7]

2. Bureaucracy Bias

- In simple terms it can be called as Institutional Review Board (IRB) bias.
- It most commonly occurs when IRB are unduly constrictive, and non-permissive for the study of important concepts.
- It also occurs when IRB unduly allows and encourages studies which are scientifically invalid, but having the potential hold to get the funds or name to the institution.[6]

II. Biases that can arise, during the actual course of the trial

1. Population Choice Bias

This bias can occur when the sample is drawn multiple times from the same population and it can have profound impact on the external validity of randomized trials.

In certain conditions, the sampling is done with a specific gender predilection (*gender bias*) or towards a particular age group (*age bias*), the outcomes of such study may not be generalizable to the study population.

There are subgroups of population choice bias like *informed consent bias, literacy bias and language bias* wherein the investigators may intentionally avoid eligible patients just because they do not comprehend the consent form.[6]

2. Intervention choice Bias

It occurs when the type of the intervention chosen by the investigator can affect the study outcomes widely.[6]

i. Complexity bias

It can occur when a trial is used to study complex interventions, with a number of components, or where outcomes may depend on multiple contingencies outside of the control of the investigator (e.g. the skill of the surgeons or the resources of the community).

3. Control group bias

This bias may appear when the intervention group is compared with control group of poor design, which may erroneously project the outcomes to be more (or less) effective. Comparing an interventional group with a placebo clarifies the intervention is effective or not. But, it does not reveal the experimental intervention provides better outcomes or not compared to the existing ones.[6] An obvious way to make an intervention appear to be more effective than it really is would be to choose an ineffective comparison group.

4. Outcome choice Bias

i. Measurement bias

It occurs in those RCTs that evaluate outcomes which are easy to measure, rather than the outcomes those are relevant.

ii. Time term bias

It occurs in those RCTs where short-term outcomes are measured rather than the important long-term outcomes.

5. Selection Bias

Randomization is an important protocol in RCTs which ensures that all the study participants are provided with equal opportunity to be selected for each study groups.[8]

Selection bias can occur if some potentially eligible individuals are selectively excluded from the study, because the investigator knows the group to which they would be allocated if they participated.

How can selection bias be reduced?

- Selection bias can be reduced by concealing the randomization sequence from the investigators at the time of obtaining consent from potential trial participants.
- *Allocation concealment* is a very simple maneuver that can be incorporated in the design of any trial and that can always be implemented.
- Allocation concealment defined "as an important technique which protects the randomization mechanism, ensuring that the patient is completely unaware of the treatment been rendered before entering into the study".[9]
- Despite its simplicity as a maneuver and its importance to reduce bias, allocation concealment is rarely reported, and perhaps rarely implemented in RCTs. If, however, allocation concealment was not carried out, the majority of RCTs are at risk of exaggerating the effects of the interventions they were designed to evaluate.
- Sometimes, the researchers do tend to access the allocation codes, which are kept in sealed opaque envelopes. The most commonly used methods are powerful lights or high intense steam to open the envelope and later reseal it, before others notice it. This may cause selection bias into RCTs.[6]

6. Ascertainment Bias

Ascertainment bias occurs when the results or conclusions of a trial are systematically distorted by knowledge of which intervention each participant is receiving.

Ascertainment bias can be introduced by:

- The person administering the interventions,
- The person receiving the interventions (the participants),
- The investigator assessing or analyzing the outcomes,
- The report writer who describes the trial in detail.

i. Participant ascertainment bias: If participants know that they have been allocated to the placebo group, they are likely to feel disappointed and less willing to report improvement at each of the study time points.

ii. Observer bias: If the people in charge of assessing and recording the outcomes know which patients are allocated to each of the study groups, they could, consciously or unconsciously, tend to record the outcomes for patients receiving the new drug in a more favorable way than for patients receiving placebo.

How can Ascertainment bias be reduced?

The best way to protect a trial against ascertainment bias is by keeping the people involved in the trial unaware of the identity of the interventions for as long as possible. This is called blinding or masking.

Ascertainment bias can widely be reduced by blinding all the concerned people involved in the trials: the intervention providers, the interventions receivers and those concerned with

assessment and reporting the outcomes.[7,9]

The strategies that can be used to reduce ascertainment bias can be applied during at least two periods of a trial:

a. During the time of Data collection
b. After data have been collected

Strategies to reduce ascertainment bias during data collection phase

The best strategy to reduce ascertainment bias during data collection is with the use of placebos. *Placebos* are interventions believed to be inactive, but otherwise identical to the experimental intervention in all aspects other than the postulated specific effect. One of the best comparisons in any trials are the Placebos, which are very easy to develop and apply in drug trials, and it is important that the placebo should resemble in taste, smell and appearance of the active drug, and should be delivered using same procedure as for the active drug.

Strategies to reduce ascertainment bias after data collection phase

This bias can occur easily after data collection, which can be controlled by keeping anonymity of the study groups, with the people involved with data analyzing and reporting the trial outcomes.

In any trial, the coding of the study groups should be done prior to the time of providing the data to the statistical analysis, wherein the results thus obtained will contain the same codes and further the similar codes are followed until the trial reporting stage. The codes remain undisclosed until all the process of analysis and reporting of the trial is completed.[6]

Selection Bias [Bias due to lack of allocation concealment]	**Ascertainment Bias** [Bias due to lack of blinding]
Allocation concealment helps to prevent selection bias, protects the randomization sequence *before* and *until* the interventions are given to study participants and can be always implemented.	*Blinding* process helps to prevent ascertainment bias by protecting the randomization mechanism, even after the allocation to the study groups is done. It may or may not facilitate to implement in certain conditions.[7]

7. Contamination Bias

The control group subjects may mistakenly receive the maneuver of interest or be affected by an extrinsic maneuver, which diminishes the differences in outcomes of the experimental and control groups.

8. Compliance Bias

Sometimes, there can be erroneous outcomes which can impact the efficacy of the treatment rendered to the patients, and it could be possibly due to non-compliance to the treatment regimen.[10]

9. Bogus control Bias

When subjects allocated to the experimental maneuver group expire or withdraw before the maneuver is administered and are reallocated to the control group or are omitted, the experimental and control groups are no longer matched and the differences between may be biased toward the experimental group.

10. Proficiency Bias

Absence of establishing the equilibrium with respect to the experimental interventions or treatments rendered to subjects can cause this bias.[10]

I. Biases that occurs during reporting of a trial

1. Withdrawal Bias

- This Bias can happen due to incorrect management of data pertaining to patients' refrainment, withdrawal mechanism and protocol violations.
- Any researcher would expect that all the trial participants should follow the protocol, provide data on all study outcomes at each point in time and ensure to complete the trial. However, dropouts are most commonly encountered in many studies.
- Dropouts can happen because of some participants tend to refrain away from the study before the trial is completed or inappropriate following of the protocol or because certain study outcomes are incorrectly measured or even with the problems of multiple repeated measures.[6]
- On occasion, it is impossible to know the status of participants at the times when the missing information should have been collected. Example: Relocation of participants without informing the investigator or failing to contact for an unknown reason. Those outcomes measured and analyzed excluding these participants, and if it is related to the interventions or the treatment rendered, can cause bias.[6]

Reduction Strategies that can be used to eliminate withdrawal bias

- The first strategy is *intention-to-treat analysis*, which deals with including all the study participants in the data analyses, randomly allocated to their respective groups, irrespective of whether the participants completed the study or not.
- The second strategy is *sensitivity analysis*, which deals with accounting the worst possible outcomes or time points with worst results on one end or similar confinement of best possible outcomes or time points in the group that shows the best results on the other end with reference to the dropouts. This is followed by sensitively analyzing the data for possibility of the results that may support or refute the initial analysis results, which includes the missing data.[11]

2. Selective Reporting Bias

A major and common source of bias in an RCT is selective reporting of results, describing those outcomes with positive results, or which favor the studied intervention.

The sub-categories of this bias are:

- *Social desirability bias* in which the items that are desired, are more likely to be reported.
- *Data dredging bias / Interesting data bias*:Following the data analysis, the researcher may get influenced with those outcomes which are of more concern / interesting to them and subsequently report them, leaving behind the lesser important ones.[6]

Steps to reduce biases that occur during the course and reporting of a trial

- Double blinding subjects and investigators when possible, to prevent knowledge of exposures from influencing the detection of outcome events.
- Robust instrument development and validation process for data collection.
- Hide the identity of the subjects from the data collector

when possible.
- Create a division of labor by having a different person record data than performs the maneuver.
- Maintain good contact to avoid attrition from the study.

IV. Biases that can occur during dissemination of the trials

1. Publication bias

Publication bias may occur if any journal is more inclined to publish only the studies with positive outcomes or those with good study designs. This cannot be identified within a single study but rather it can be elicited better in systematic reviews and meta-analysis. This can lead to over-emphasis of the outcomes and may mislead the readers.[12]

The failure to write and publish negative results is not a random event, but is heavily influenced by the direction and strength of research findings, whereby manuscripts with statistically significant (positive) results are published preferentially over manuscripts reporting non-significant (negative) results.

How to reduce publication bias?
- Publication bias can be eliminated through compulsory registration of trials at inception, and publication of the results of all trials.
- Establishing the equilibrium between numbers of studies published with positive and negative results.
- Sensitization of the researchers should be done regarding the importance of negative studies being published, with journals giving equal space for the publication of the same.
- Evaluation of studies should be based on the internal validity of the study rather than the conclusions.[13]
- Identify funding sources and possible conflicts of interest.

Variants of publication Bias:

i. Language bias

Bias which may arise due to predilection of certain authors for submitting and publishing their papers by journals in different languages, based on the direction of their results. E.g.: Presumption that studies with positive results are more published in English.[6]

ii. Time lag bias

Bias that occurs when the speed of publication depends on the direction and strength of the results of the trial. In general, it seems that trials with 'negative' results take twice as long to be published as 'positive' trials.

V. Biases that can occur during uptake phase of the trials

The following are some of the biases which are most common and pertinent:

1. Relation to the author bias / rivalry Bias

Bias that can occur by under-rating the strengths or exaggerating the weaknesses of studies published by a rival.

2. Clinical practice Bias

It takes place when readers judge a study according to whether it supports or challenges their current or past clinical practice (e.g. a clinician who gives lidocaine to patients with acute myocardial infarction underrating a study that suggests that lidocaine may increase mortality in these patients)[11].

VI. Miscellaneous Types

1. **Technology bias:** Bias which relates to judging a study according to the reader's attraction or aversion for technology in health care.
2. **Resource allocation bias**: It happens when readers' exhibit strong inclination for certain types of provision of resources. It is more widely seen in health care sector, originating from its potential stake holders ranging from consumers to policy makers.[6]
3. **Trial design bias:** It occurs when a study that uses a design supported, publicly or privately, by the reader (e.g. a consumer advocate overrating an RCT that takes into account patient preferences).
4. **Flashy title bias:** It happens when the study results are overvalued based on their attractive titles (especially by the journalists) or undervalued by the academicians, considering as undue sensational in the field.[6]

Bias in Non-Randomized Experimental Studies

Bias may be present in findings from Non-Randomized experimental studies in many of the same ways as in poorly designed or conducted randomized trials. For example, the indistinct exclusion criteria, absence of monitoring the standardized protocols during intervention and outcome assessments and lack of blinding are the most probable causes for bias, irrespective of whether the trial is randomized or non-randomized.[14]
- Non-randomized experimental study are susceptible to the same bias as RCTs.
- Selection Bias – caused by inadequate selection of participants.
- Performance Bias – caused by inadequate measurement of intervention.
- Detection Bias – caused if the assessment of outcomes is not standardized or blinded.
- Attrition biases – caused by inadequate handling of incomplete outcome data because of drop-outs.[15]
- Reporting Bias – caused by selective outcome reporting

The study designs classified as NRS, and their varying susceptibility to different biases, makes it difficult to produce a generic robust tool that can be used to evaluate risk of bias. [16] 19th Cochrane Colloquium and VI International Conference on Patient Safety, held at Madrid during 19 – 22 October 2011 has dealt with development and validation of a new Instrument – Risk of Bias Assessment tool for Non-Randomised Studies (RoBANS). And discussion concluded that RoBANS is a valid tool designed to assess the Risk of Bias of Non-Randomised Studies.

The Cochrane's RoB tool and GRADE (Grading of Recommendations Assessment, Development and Evaluation), endorses RoBANS, henceforth it can be incorporated into RevMan and GRADEpro, which appears to be useful to undertake systematic reviews.[17] A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) is another robust tool that can be used for evaluating the risk of bias in the results of non-randomized studies of interventions that compare the health effects of two or more interventions.[18]

CONCLUSION

Bias is an ever-present and insidious problem in research study design and execution, and while no study design is exempt from bias, some are more prone to particular types.The main reason

of bias is the absence of rigorous methodology or the inability to assess the potential link between the cause and an effect in the target population.

An imperative objective in study outline is that the outcomes are substantial and generalizable to the larger population. Efforts to implicate rigorous statistics to minimize the bias may divert the readers.Better an investigator anticipates the potential areas of bias in every phase of the trial to achieve a much valid results.

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