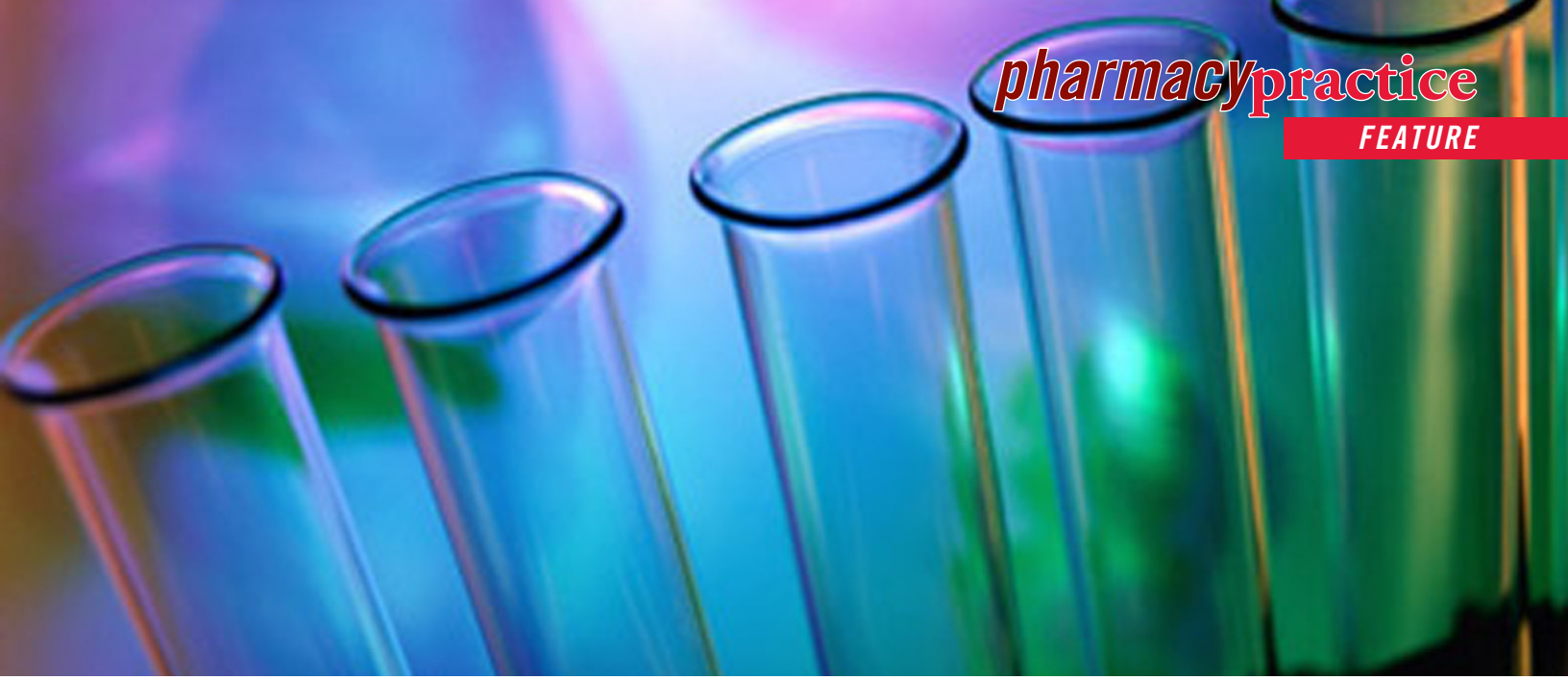

JOURNAL SERIES:

Statistics Review Part 6: Bias in Randomized Controlled Trials

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This article describes the importance of bias in randomized controlled trials, identifies common sources of bias and ways to reduce their impact, and implications for readers of medical literature.

Objectives:

1. Describe the importance of limiting bias in randomized controlled trials
2. Identify common sources and means of limiting bias in randomized controlled trials.
3. Integrate evaluation of bias into future analysis of clinical trials

Bias in clinical research refers to a distortion of the truth (see Table 1. for a glossary of terms used throughout this article).[1] This misrepresentation of data or flaw in study design, whether intentional or unintentional, lessens the validity of the study undertaken and hinders a reader's ability to provide patients with sound, evidence-based medical care. However, clinical research is inherently subject to many forms of bias, and it is impossible to conduct a "perfect" clinical trial completely devoid of systematic errors.[1-3] In fact, attempting to do so may lead to trial designs so unachievable in real-world practice that the generalizability suffers as a consequence. Moreover, setting such lofty standards would discourage the publication of small, imperfect studies which may still contain relevant information. More realistic goals are not to completely eliminate bias, but to conduct research in such a way as to minimize potential sources as much as possible and, perhaps equally important, present data in a comprehensive, transparent manner that allows for adequate scrutiny of the results. Additionally, readers must be able to identify potential sources of bias in order to draw appropriate conclusions before applying research findings to patient care.[1-6]

While the randomized controlled trial (RCT) is considered the gold standard in evidence-based medicine, every type of clinical research is subject to bias, even RCTs.[1] Bias may be introduced intentionally in an attempt to bestow greater clout to study findings or place a positive spin on negative results, but more commonly is introduced unintentionally due to shortcomings that may arise from various aspects of the research process. Thus, in order to limit bias in clinical research, it is crucial to be able to identify potential sources of bias and understand methods to reduce systematic error.

Pre-Trial Bias

Proper planning is essential in limiting flaws in trial design. Prior to study outset, it is imperative that protocols are developed in extensive detail such that the execution and analysis of the trial is not left to interpretation amongst investigators.

A common example of bias introduced prior to trial onset is selection bias (i.e., the groups to be compared differ at baseline in their susceptibility to the outcomes being measured).[1] This may result in a cohort containing patients more or less likely to benefit from therapy due to confounding factors, and is thus misrepresentative of the broader population.[1-4] Similarly, improper randomization of patients can lead to significant dissimilarities between treatment arms at baseline, which can influence the efficacy of an intervention.

Selection bias can be limited by choosing clearly defined inclusion and exclusion criteria that ensure the results are as generalizable as possible while maximizing safety and internal validity. Similarly, inclusion of a sufficiently large sample size, collection of detailed baseline information, appropriate randomization, and stratification of patients based on potential confounding factors can help to reduce differences between treatment arms.[1,4] Furthermore, patients should be

TABLE 1. Glossary of Terms

Term	Definition
Bias	Distortion of the truth; a trend in the collection, analysis, interpretation, publication or review of data that can lead to systematic error[1,4]
Confounding	An association within a trial that is true but potentially misleading[4]
Inclusion and Exclusion Criteria	Specific guidelines dictating trial eligibility of patients screened
Internal Validity	The extent to which systematic error is reduced
External Validity	The generalizability of trial results to a patient population outside of the trial
Randomization	A process of allocating study assignments in such a way that each patient is equally likely to be assigned to any of the possible arms[11]
Stratification	An attempt to control for possible confounding factors through the randomization or analysis of data with patients grouped based on these potential confounding factors
a priori	Prior to beginning the trial
post-hoc	A change made after beginning the trial
Blinding	Concealing which intervention each patient is receiving[1]
Double-blind	Concealment of treatment allocation to both the patient and treating physician[1]
Inter-rater Reliability	Consistency in assessment amongst investigators
Recall Bias	Systematic error based on inaccuracy of information derived from memory of a situation or event

consecutively recruited and researchers should have no influence as to which treatment arms specific patients enter into.

It should be noted that limitation of bias throughout the course of a study starts with the development of the study protocol prior to initiation of the trial (or *a priori*). It is imperative that a sufficiently detailed hypothesis is formed and every aspect of the methods and analysis is generated *a priori* in order to limit the need to make decisions regarding study design once the trial is underway.

Within-Trial Bias

While some biases may stem initially from the study design, many come to fruition during the execution of a clinical trial. For example, when assessing interventions requiring proficiency in certain techniques (e.g., surgical trials), the skill of the practitioner may come into play.[1,3] Thus, varying practitioners within the study could potentially confound results. Likewise, conducting the trial in different areas of the country or world may introduce discrepancies if treatments are not standardized. Inconsistent measuring of results is another source of bias that may arise when comparing trials or even study sites within the same trial.[1,3] Many factors can lead to such differences including failing to standardize definitions, utilizing measurements lacking the sensitivity to detect differences, relying on subjective and/or patient-reported data, or failing to blind the practitioner assessing outcomes.

Patient-related factors may similarly impact the results of a trial.[1-4] For example, poor compliance may reduce the efficacy of a study medication, whereas strict protocols to ensure a level of compliance unachievable in the general population may limit the generalizability of the results. Furthermore, patient drop-out rates must be taken into account, as it is possible that the patients who remain in the trial to completion may be less indicative of the general population (i.e., better able to tolerate the side effects of, or gain greater benefit from, the treatment), or that those who drop out may be too sick to continue.

Appropriate blinding is one means of reducing bias during a trial; ideally all parties involved (e.g., patients, providers, researchers, etc.) should be blinded.[1,3,7] However, this may be challenging in some cases. One way to minimize the impact of less-than-ideal blinding is to divide the labor such that different investigators are responsible for randomization, intervention, and assessment. Additionally, whether blinded or not, prospectively developing detailed methods of intervention administration, data collection, and inference of results reduces inconsistency in measurement. Employing objective, as opposed to subjective, outcomes minimizes inter-rater variability and reduces recall bias. Likewise, choosing gold standard primary outcomes when possible allows for better comparison to similar trials. Measuring compliance, maintaining close contact with subjects, and detailing reasons for patient attrition may reduce the confounding effects of non-adherence and loss-to-follow-up.

Post-Trial Bias

In addition to properly designing and executing the trial, it is essential that analysis and presentation of data be impartial, transparent, and complete to allow the research to be appropriately scrutinized before it is applied to practice. In preparing research for publication, the CONSORT guidelines have been developed to standardize reporting of clinical research and serve as an excellent reference for composing unbiased manuscripts.[8]

Once again, clearly explaining methods for trial analysis *a priori* and avoiding changes in these methods is crucial. For example, alterations to planned sample size, post hoc data analyses, exclusion of data interpreted as outliers, or mishandling of unavailable data may all contribute to bias in analysis and should be fully explained within the text if performed.[1-4]

Perhaps the most easily identified form of bias in clinical research can be seen in the interpretation and discussion of data in a written manuscript. This may be intentional (e.g., to enhance probability of publication or place a positive spin based on conflicts of interest) or unintentional (e.g., over-emphasizing a statistical difference that may not be clinically relevant).[1,3-4] In general, bias in research can occur any time conclusions are not substantiated by results demonstrated in the trial.

Means of limiting bias in this stage can be considered from three perspectives: that of the researchers, publishers, and readers. Researchers can limit biases by basing conclusions on hypothesis-driven data collection and appropriate methods of statistical analysis, while avoiding inferences based on preconceived assumptions.[1-4] Additionally, researchers must present methods and data in as clear a fashion as

possible without excluding pertinent data. Study limitations and potential confounding factors should also be clearly stated in the discussion in addition to impartial comparisons to previous studies in the field.

From the publisher perspective, bias in research includes publication of all trials, regardless of significant findings. A preference towards publication of trials displaying positive outcomes (i.e., publication bias) has been observed in current literature.[1,3-4,9-10] This may become even more pronounced when studies are pooled, for instance in a meta-analysis, without the inclusion of negative data. It is the responsibility of both researchers and publishers to reduce publication bias within the medical literature.

Readers must also assume responsibility for careful analysis of the medical literature in order to appropriately deliver evidence-based medical care to their patients.[1-6] For example, readers should evaluate the validity of studies independently of author conclusions, identify possible conflicts of interest, assess the timeliness of the research, and evaluate all literature published on the subject as opposed to only the trials that support their opinions.

Role of Funding Sources

A final source of bias that should be mentioned is the potential impact the funding source may impart on clinical research. Its influence may be seen in any or all of the previous sections. For example, multiple systematic reviews have noted greater rates of statistically significant pro-industry findings in industry funded research.[1,9] However, discounting all trials funded by drug companies would severely limit the number of large-scale clinical trials conducted and unfairly assume that any such trial was inherently biased. Nevertheless, such potential bias is not limited solely to industry-funded trials. It is imperative that companies funding clinical research fully disclose all conflicts of interest. If such conflicts are present, the funding source should abstain from developing or overseeing the trial and clarify any role undertaken in the final manuscript, thus allowing readers to evaluate the impact of this funding source.

Summary

This article provides a broad overview of potential sources of biases in RCTs. For further reading on the subject, several articles are available that document the biases found in medical literature in greater detail.[1-4] Awareness of potential sources of bias will assist researchers in developing sound study designs and allow practitioners to adequately scrutinize medical literature to improve patient care.

Practice Questions

1. Which of the following would not be expected to reduce selection bias?
   a. Recruiting specific patients for inclusion in a specific arm of the study based on desired characteristics
   b. Clearly defining inclusion and exclusion criteria *a priori*
   c. Matching treatment groups based on potential confounding factors
   d. Randomization of patients to treatment arms

2. A trend leading to greater numbers of articles in the medical literature displaying statistically significant outcomes is termed _____.
   a. Selection bias
   b. Popularity bias
   c. Publication bias
   d. Statistical significance bias

3. Which of the following would be most likely to introduce bias into a randomized controlled trial?
   a. Each patient is assessed by the same physician
   b An objective measure is chosen as the primary outcome
   c. The physician assessing the study participants is blinded to the treatment the patient has received
   d. Trial coordinators perceive a lack of compliance among patients in the treatment arm and decide post hoc to distribute a survey to all patients to assess compliance

Answers:

1. **a** This increases the risk of selection bias, as preferentially including more patients with a specific feature would skew the baseline characteristics of the cohort from that seen in the general population.

2. **c** Publication bias arises when journals trend towards publishing studies with positive, statistically significant results while rejecting studies showing no difference.

3. **d** Methods and statistical analyses performed should be determined *a priori*. Altering the protocol of a study after it has begun increases the risk of bias being introduced from researchers making adjustments to the protocol based on early observations in order to show more significant results.

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