Bias in Research:

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Introduction

- This presentation will explain types of bias and their effects on research.
- We want to:
  - Avoid bias in the design of a study
  - Adjust for bias that can't be avoided, and
  - Recognize the effects of bias on study results
- Examples of bias, especially selection bias will be discussed.

Bias in Research

- Is not defined as prejudice or unfairness when discussing research terms
- Is not random error (errors of chance due to sampling variability)
- Is not measured by the *p* value for statistical significance
- Is not an easy question to answer
  - When asking if there is bias in your study, it can't simply be answered yes or no – Instead, ask yourself, *"How much bias is there?"*

Bias is

- In research, bias is the presence of systematic error
  - An influence that distorts the results of a study
  - A qualitative problem that affects conclusions
- Bias can affect:
  - *Which patients in the study population are exposed to treatments?*
  - *Which patients are included in the study?*
  - *How are the assessments and measurements done?*

Avoiding Bias in Study Populations

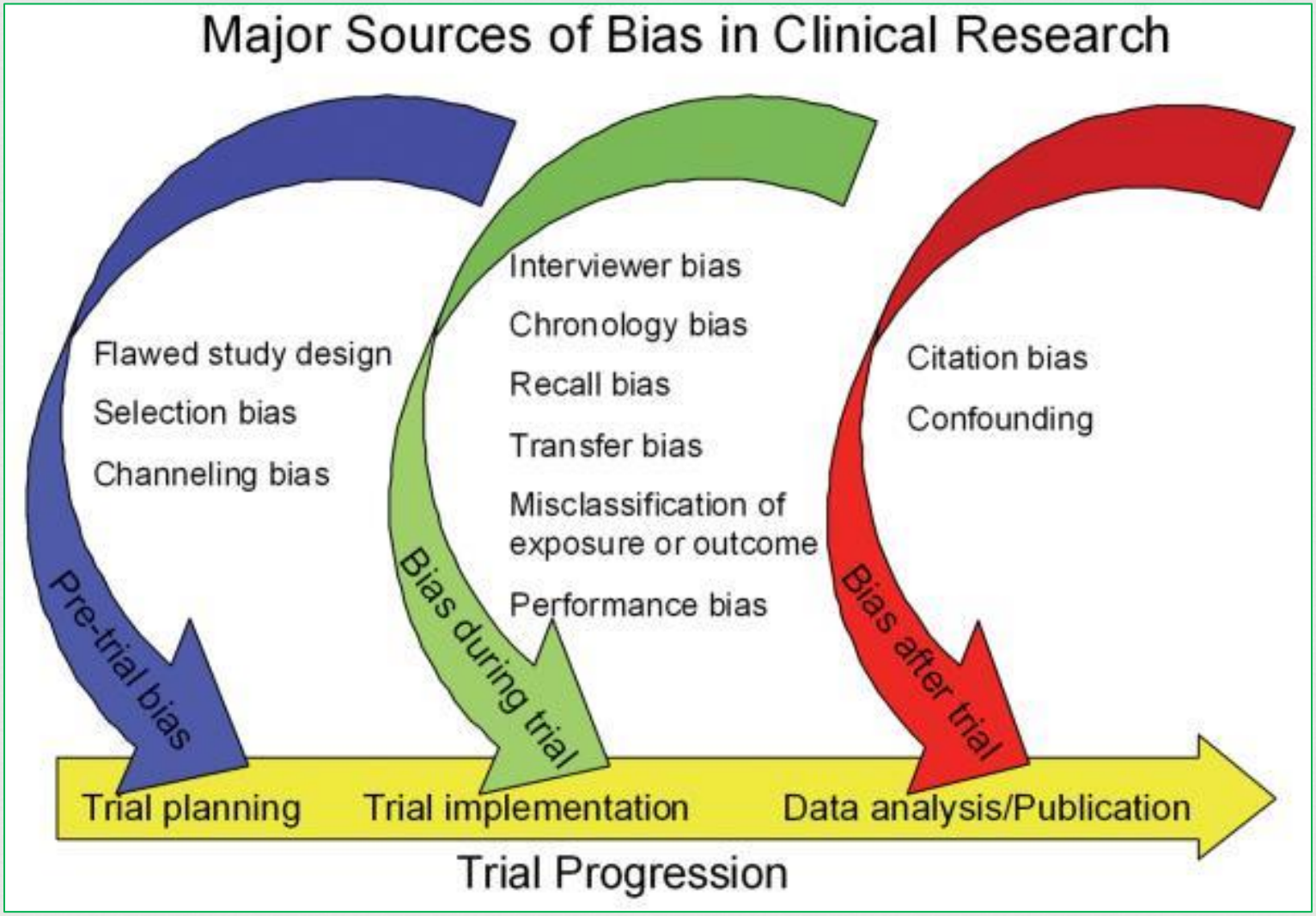
- A study population is the group of subjects included in a study's final analysis, excluding the subjects who dropped out.
- The source population is the group from which the study population originated.

Validity in Research

- When the source population is identical to the study population, you have:
  - Internal validity (absence of bias related to the study's source population)
  - External validity (ability to generalize results to the extended population)
- It is very challenging to make the study population identical to the source population and to avoid bias.
- The following diagram illustrates major sources of bias to be avoided in a valid clinical trial.

Gerhard, T. (2008). Bias: Considerations for research practice. *American Journal of Health System Pharmacists. (65),* 2159-2168.

Identifying & Avoiding Research Bias



Tips to Avoid Bias **Before** a Clinical Trial

- **Flawed study design** – Clearly define risk and outcome, preferably with objective or validated methods. Standardize and blind the data collection.
- **Selection bias** – Select patients using rigorous criteria (to avoid confounding results). Patients should originate from the same general population. Well-designed, prospective studies help to avoid selection bias, because the treatment group outcome is unknown at the time of enrollment.
- **Channeling bias** – Assign patients to the study cohorts using rigorous criteria.

Tips to Avoid Bias **During** a Clinical Trial

- **Interviewer bias** – Standardize the interviewer's interaction with patients. Blind the interviewer to treatment exposure status.
- **Chronology bias** – Do prospective studies. Avoid using historical controls (due to confounding by secular trends).
- **Recall bias** – Use objective data sources whenever possible. If using subjective data sources, corroborate with the medical record. Conduct prospective studies.

Tips to Avoid Bias **During** a Clinical Trial

- **Transfer bias** – Carefully design a plan (before the study) for patients that are lost to follow-up.
- **Exposure misclassification** – Clearly define treatment exposure before the study. Avoid using proxies (assumptions of associations between variables that are not necessarily related).
- **Outcome misclassification** – Use objective diagnostic studies or validated measures as primary outcome.
- **Performance bias** – Consider cluster stratification to minimize variability (i.e. differences in surgical technique).

Tips to Avoid Bias **After** a Clinical Trial

- **Citation bias** – Register the trial with an accepted clinical trials registry. Check registries for similar unpublished or in-progress trials before publication.
- **Confounding bias** – Control any known confounders or extraneous variables with the study design (case control design or randomization). During data analysis, regression can decrease confounding. Unknown confounders can only be controlled with randomization.

Pannucci, C.J. (2010). Identifying and avoiding bias in research. *Plastic and Reconstructive Surgery. 126(2),* 619-25.

Setting Up Valid Research

- To decrease bias, studies can be set up with:
  - Random assignment of treatment
  - Blinding of patients and care providers
  - Intent-to-treat analysis when comparing outcomes between groups
- Randomized controlled trials (RCTs) are the "gold standard" to obtain unbiased results, but that does not mean that all RCTs are free of bias.

Discussion

- What are some examples of bias producing invalid or inaccurate results in clinical trials?

Examples of Research Bias

- Before 1998, many observational studies demonstrated that hormone replacement therapy decreased the risk of heart disease among postmenopausal women.
- More recent studies, rigorously designed to minimize bias, found the opposite effect (an increased risk of heart disease)
- One explanation for the discrepancy is failure to adequately account for differences in lifestyle and socioeconomic status in the women who were observed.

Prentice, R. L. et al. (2005). Combined postmenopausal hormone therapy and cardiovascular disease; Toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *American Journal of Epidemiology. 162, 404-414.*

Focus on Patient Selection

- Ideal study populations are clearly defined, accessible, reliable, and at an increased risk of the outcome of interest.
- Sampling should obtain subjects representative of the population to be studied. Selection bias is more likely:
  - When the criteria used to recruit and enroll patients into separate cohorts are inherently different.
  - In case control studies, by observing groups differing in outcomes for supposed causality.
  - In retrospective cohort studies (looking back at events) in exposed vs non-exposed groups.

Possible Selection Bias

- One day while consenting research patients, the clinic RN said I shouldn't include a patient who had schizophrenia. But, I considered him to be a potential participant. I knew that most patients with mental illnesses are in recovery.
- Since psychiatric patients are a large part of the source population, I didn't exclude him based on his diagnosis - My decision would be based on his functioning.
- I asked the physician, who recommended not approaching him because he was overwhelmed. I accepted that as an appropriate reason to exclude him.

How Much Selection Bias Exists for Psychiatric Patients?

- For valid reasons (such as the need to protect vulnerable populations), studies of psychiatric patients are rare at many organizations.
- However, some patients with psychiatric diagnoses do participate in general research after being screened for cognitive and behavioral ability.
- Anxiety and depression seem to be common psychiatric problems that do not necessarily exclude patients from research studies.
- However, some clinical trials have criteria that specifically exclude certain psychiatric diagnoses.

"Food for Thought" from Literature Search

- In a study, 215 randomly accessed newly admitted cancer patients (in 3 collaborating cancer centers) were examined for the presence of formal psychiatric disorders.
- 44% were diagnosed as manifesting a clinical psychiatric syndrome and 3% with personality disorders. The large majority of conditions were highly treatable disorders.

Derogatis, L.R. et al. (1983). *Journal of American Medical Association. 249(6),* 751-757.

"Food for Thought" from Literature Search

- Phase III clinical trials are needed before a drug receives FDA approval. A long-standing problem exists. – Clinical trials are purposely designed with stringent inclusion criteria that exclude a substantial portion of the population to be studied. In other words, those studies are "stacked" in favor of finding positive results.

Grohol, J. M. (2009). The problem with phase III clinical trials. Retrieved from http://psychcentral.com/blog/archives/2009/05/06/the-problem-with-phase-iii-clinical-trials/

“Food for Thought” from Literature Search

- A crucial issue in assessing mental capacity is not whether a psychiatric diagnosis is present, but whether the patient has the mental abilities required to make the decision in a meaningful way.
- The ethical demands of protection of subjects and stimulation of scientific research may be balanced.

Welie, S.P. & Berghmans, R.L. (2006). Inclusion of patients with severe mental illness in clinical trials: Issues and recommendations surrounding informed consent. 20(1), 67-83.

A Policy Example

- A proposed policy for cognitively impaired research participants is summarized here:
  - All adults are presumed competent to consent unless legally judged to be incompetent or their medical record lists an activated POA for Health Care.
  - Cognitively impaired persons are considered vulnerable because of lower capacity to make an informed decision about participation in research.
  - Investigators interested in enrolling them are required to submit a request to the Human Subjects Committee for review.

A Policy Example (Continued)

- People with Alzheimer's disease, dementia, mental illness and developmental disabilities may be considered cognitively impaired and may not be able to provide informed consent for participation in research.
- For some studies, federal regulations and state statues permit researchers to obtain consent from a legally-authorized representative. If possible, assent should also be obtained from the subject.

Exploring the "Gray Area"

- Including psychiatric patients in research could help to minimize selection bias in your study.
- However, it is vital to ensure informed and voluntary consent.
- When consenting patients, assessment of cognitive and behavioral status will help determine:
  - Ability to give informed consent
  - Ability to follow through with the study

Conclusion

- Even if it isn't possible to avoid all bias, recognizing it is very important.
- Evaluating for bias in research helps to determine its validity.
- Hopefully, the information presented today can help you minimize bias in your studies.

Discussion

- Questions?
- Comments?

References

- Derogatis, L.R., Morrow, G. R., Fetting, J., Penman, D., Plasetsky, S., Schmale, A. M., Henrichs, M. & Carnicke, C. L. (1983). *Journal of American Medical Association. 249(6),* 751-757.
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