Identifying Bias In Clinical Cancer Research

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BIAS: WHAT IS IT?

- Having a preference to one particular person/ group/ point of view: being inclined to one sided opinion
- Prejudice is tendency to be biased negatively
- Statistically bias means that the processes involved are not uniformly random and one outcome is favoured over the other

FACTORS THAT MAY INFLUENCE TRIAL RESULTS

- These are factors other than the intervention being tested
- Include: random error (natural variation) and systemic error (bias)
- Make efforts to reduce both type of errors by careful statistical assessment and planning of study parameters and expectations

RANDOM ERROR

- This type of error is due to natural/ biological/ random variation or distribution in the occurrence of events studies
- May be on either side of the true value.
- Usually is normally distributed (exceptions: skewed distributions)

SYSTEMIC ERROR (i.e. BIAS)

- Difference between true value and observed value due to all causes other than random variation
- Maybe a flaw in either the study design or data analysis
- Leads to consistently erroneous result, usually on one side of normal value
- Intentional or unintentional

BIAS IN CLINICAL TRIALS

- The control and intervention groups must be similar enough so that any differences detected in patient outcomes can reasonably be attributed only to the intervention under study.

- If systematic differences exist between the control and intervention groups then it is possible that the results of the study are biased

TYPES OF BIAS

1. Sampling bias
2. Comparator bias
3. Selection bias
4. Expectation bias
5. Analysis bias
6. Reporting bias

1. SAMPLING BIAS

- Systematic error due to study of a non random sample of a population

- Sample is not a random sample when some individuals are more likely than others to be chosen

Example if you want to look as to how much time a person spends on weight lifting exercises on a daily basis and if you happen to chose only males in a gym as a sample the error in assessment can occur as males in the gym are more likely to spend less on cardio and more on weights than females

SAMPLING BIAS

- A special kind of sampling bias is non response bias

- Happens when subjects have a choice of whether or not to respond. If a significant number of subjects choose not to respond, a response bias tends to be very likely as non responders may very frequently be those who do not agree rather than those who agree.

For example NOTA option: a serious problem as then the results are skewed towards the most passionate responders and far from the reality of agreement

SOURCES OF SAMPLING BIAS

- Failure to adhere to random sampling procedures
- Omission of specific subgroups of the population from the sampling frame and therefore from the sample
- Faulty measuring devices

This may be in terms of specific questions used in a questionnaire and may also arise in a survey that involves taking physical measurements, when the measuring device is incorrect e.g a defective BP machine so that all measurements are low/high

- Non-response to a survey by specific subgroups of the population that are relevant to the measures of concern in the survey

PREVENTING SAMPLING BIAS

- Random sampling
- Sampling all obvious and potential subgroups (representative sampling)
- Accurate measurements
- Taking into account non-responders in a survey

2.COMPARATOR BIAS

- Not using control treatment known to be beneficial/ standard

For example even though erythropoietin is known effective in preventing anemia in cancer patients as shown in many controlled trials, some researchers may choose to compare their drug with placebo.

- Comparator bias is introduced when patients are denied effective treatments and the effective treatments studied in the trial will give an unfair advantage.

COMPARATOR BIAS

- Giving an inappropriately low dose of a treatment

This has occurred in comparisions of a new NSAID for arthritis with older drugs of the same class

Inappropriately low dose can also result from giving a treatment by inappropriate route, for example comparing intravenous with oral route in a drug that is poorly absorbed from the GI tract

- Giving an inappropriately high dose of a treatment

Similar lines to accentuate the side effect of the older drug to show factitious safety profile of the investigational drug

COMPARATOR BIAS: HOW TO MINIMIZE

- Appropriate choice of comparator group by systematic review of existing evidence in literature etc
- Use of placebo only when essential
- Using appropriate dose and route of administration of comparator drug
- Evaluation of net effects of treatments (benefits vs risks; profile of side effects too are frequent study points in drug studies)

3. SELECTION BIAS

" Example of Selection Bias at its worst: Give the new drug to the rich, anyway the poor won't even afford it if it comes out to be effective!!!"

- Selecting and allocating participants to treatment groups depending upon investigator's beliefs about safety/ efficacy of treatments or other subjective reasons

- Results in "dissimilar and obviously unmatched" groups with different baseline characteristics

SELECTION BIAS: HOW TO MINIMIZE

- Use randomization: single most effective way to reduce selection/allocation bias
- Every subject has equal chance of receiving test/ investigational treatment
- Results in similar intervention and control groups
- Provides a basis and foundation to draw logical and realistic statistical inference

RANDOMIZATION

- Alternate allocation to groups (e.g. one to control group and one to treatment group
- Tossing a coin (simplest and satisfactory but difficult to justify fairness to skeptics, so not favored)
- Randomization tables
- Computerized randomization (patients stratified in blocks and then randomized considering different characteristics; simplest: female or male?; age group?)
- There are other advanced methods (e.g. concealed randomization)

4. EXPECTATION BIAS

- Both the investigator's and subjects expectations can influence the results of a clinical trial

(For example, investigator believes that a pain medication MUST decrease pain; how come the pain not relieved in a study subject? Investigator repeatedly stresses to elicit a positive response from the subject by asking multiple LEADING QUESTIONS)

- BLINDING helps reduce this bias: LET NO ONE KNOW WHICH TREATMENT IS BEING GIVEN TO WHOM

BLINDING TECHNIQUES

- Single blind: patient doesn't know which group they're in
- Double blind: patient and assessor both don't know this
- Triple blind: patient, assessor and investigator don't know

But investigators in ophthalmology trials hate to use this terminology! ? Reason.

❖Lookalike trial medications/placebo:
made such that feels, tastes, smells, looks the same to active agent

❖Sham techniques (but may be a difficulty in surgical trials. Why?)

5. ANALYSIS BIAS

- Analysing only select groups or subgroups that show positive response to the study
- Not including the drop-outs (might have dropped out due to adverse reactions!) or withdrawn subjects in the final analysis
- Multiple unplanned subgroup analyses (in pursuit of ANYTHING that comes positive: data dredging): multiple subgroups mean fewer subject numbers in each subgroup and hence reduced power
- Confounding variables: factors other than intervention eg age, degree of severity of disease, previous treatments that may affect outcome (for e.g. concurrent radioimmunotherapy trials)

ANALYSIS BIAS: HOW TO MINIMIZE

- Always know beforehand and be sure what statistical analysis to be used in a particular study and include this in study protocol
- Utilize stratified design for significant variables
- Analyse using *intention to treat* to account for drop-outs and withdrawn cases: *ERR ON THE SIDE OF CAUTION*
- Have separate subgroup analysis for significant variables
- Account for confounding variables and use multivariate analysis

6. REPORTING BIAS

- Only reporting studies with good outcome
- Not reporting/ publishing studies with unfavorable results: file drawer problem
- Hiding evidence of negative outcomes

Remember negative studies are similarly welcome, if not more, as positive ones because they provide evidence of WHAT NOT TO DO!

REPORTING BIAS: HOW TO MINIMIZE

- First and foremost: change in mindset and attitude is needed
- Clinical trial registry: registering all clinical trials on new investigational agents
- Compulsion to submit results of all studies to regulatory authority
- Publishing results of all clinical trials on websites and online
- Well recognised journals to encourage negative studies (which they now do very very often!)

Thank you and good luck..

Questions..?