

Introduction to Research Methodology & Terminology

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WHAT IS RESEARCH?

It is a process of finding a reliable answer to a simple question. In medicine, research represents an important tool for detected various health related issues and explaining them. Also, the new treatments-pharmaceutical agents, devices, and surgical procedures-which being developed every day are subjected for analysis and revision. How do we know if there is any benefit to patients of these new treatments? Sometimes, new treatments are introduced into practice with very little scientific evidence that they are better than current practice. Patients' lives may be risked and money spent on therapies that may be no better, or may even be worse, than current available therapies. In this brief article, there is a summary of most common methods and terms used in medical research.

TYPES OF RESEARCH STUDIES

1. Quantitative studies:

Things are measured, counted and numerically compared with a view to confirming or refuting a specific hypothesis.

2-Qualitative studies:

Adept social science to gain in depth but non numerical understanding of a particular topic and perhaps generates a hypothesis that can be tested in a quantitative study.

RESEARCH DESIGNS

1- Observational: Observe the natural process over a period of time and events of interest are recorded: patient characteristics, occurrence, incidence, complications, hospital readmission, and death. It is subjected to bias. Observational study can be used to estimate the risk of outcome in patients who are exposed to risk function versus none exposed. In prospective cohort study it is called Risk ratio or relative risk:

-If exposure is not associated with the outcome: risk ratio equals one.

-If exposure is associated with increased risk: risk ratio will be more than one.

-If exposure is associated with reduced risk: risk ratio will be less than one.

It can be expressed with confidence interval (CI), if this interval does not include the value of one: the association of exposure and the outcome is significant ($p < 0.05$).

Odds ratio is used to estimate the risk in case control studies which can also be expressed with 95 % CI.

Observational studies may be:

A) Retrospective: looks backwards in time and records events that have already occurred. Major drawback is incomplete and inaccurate data (Bias).

B) Cross Sectional study

- Records observation at specific point in time.
- Used to establish prevalence rate.
- Survey is a typical cross sectional study.
- Prevalence: is the proportion of population who has a disease at one period of time.

C) **Prospective study:** looks forwards in time. It is preplanned; it maximizes data accuracy. Used to test an intervention.

2 - Experimental research:

Best method to evaluate established treatment or investigation and the potential benefit of a proposed new treatment. Clinical trial: trial that uses human as the experimental subject. Experimental studies are classified to: Controlled studies and uncontrolled studies.

RESEARCH CATEGORIES

A) Primary research evidence: original and first hand

1-Randomized controlled trials:

Most common (gold standard). Compare effect of the drug, treatment, therapy, with that of a placebo or a competitor.

2-Cohort studies:

Prospective, more reliable, require large number of patients and long periods. It studies exposed group of subjects to a drug, toxin, and environmental factors, follow up to see the effects of this exposure cohort. It provides information about incidence of a disease. It can be also retrospective.

3- Case control studies (Observational study):

May be prospective or retrospective. Subjects that have developed a disease (cases) as well as subjects who have not (control) are studied and asked about their past exposure to a particular causative agent. The control subjects are matched to cases on some criteria: age, gender to equalize the base line characteristics.

To decrease the confounding factors:

- Matching
- Use of multivariate statistics
- Increase the sample size by increasing ratio of control to the cases, hence 2:1, 3:1, and 4:1

To decrease the Bias:

- Standardize of exposure, outcome, before data collection
- Accuracy in acquiring data for both cases and control

4-Case reports and case series: the most useful for generating hypotheses that can be tested in a comparative study. Case series and case reports are observational study in which story about a particular event is told, adverse effect of drug or therapy. As there is no control group; case reports and case series provide weak evidence and do little more than to show that an outcome is possible. In order to claim that a new treatment is better, you must be able to answer the question, "better than what?"

5-Survey: something measured in a group of patients (their blood pressure) or a group of healthy persons (it may include their knowledge or attitudes).

B) Secondary research evidence: Summaries and draw conclusions from primary studies:

1-Non systematic review (Journalist review):

Some (not all) primary evidence in a topic. Interlaced with the author's personal opinion. Written by experts in certain fields.

2-Systematic review:

All the evidence on a topic via a systematic search of literature and unpublished sources. Evaluated using predefined quality criteria

3-Meta Analysis:

Numerical results of different studies are combined using standard statistical techniques. More precise and more definitive. More confident about the results either positive or negative i.e. true reflection of the effect studied rather than due to the play of chance.

4-Guidelines:

Systematically developed statements to assist practitioners' decision about appropriate care for specific clinical circumstances.

5-Economic analysis:

Use of mathematical techniques to define choices in resource allocation.

CLINICAL TRIALS

We usually think of using clinical trials in the context of evaluating new treatments (drugs, surgery, devices, etc.). The clinical trial model is the best method for clarifying the safety and efficacy of an experimental treatment before it is approved and before it becomes the standard of care in the community. In this same context, in recognition of the truism that 'medical practice does not change on the basis of one study, clinical trials may be useful in providing confirmatory evidence of safety and efficacy after the new treatment has been introduced. The methodology is also suited to evaluating many other aspects of health care, including prevention strategies, public health screening programs for disease, and methods of distribution of health resources. The clinical trial method provides the scientific basis for evaluation of the benefits as well as the risks of new health care technology.

The primary outcome in a clinical trial is a measure that is easy to assess in all patients. In general, "objective" or "hard" outcome measures that are well-defined and can be observed directly are preferred. Examples include death (or survival), disease recurrence, change in blood pressure, etc. More "subjective" outcome measures, such as pain reduction, quality of life, psychological status, and the like may be equally important but are more subject to bias when the patient or the investigator knows (or thinks he knows) which treatment the patient received. The primary outcome should be one that is clinically relevant; for example, although change in lipid profile may be an objective, easily measured outcome in a trial for a lipid lowering agent, it may be of little relevance to patients or clinicians

if there is no concomitant change in risk of heart disease or death.

TYPES OF CLINICAL TRIALS

Uncontrolled trials: For evaluation of new drug, mode of therapy. Usually less seriously ill patients are selected for the study, so they will do well compared with the generally accepted management. To avoid the distorted view of therapy, a control group is chosen; patients with the same condition matched as far as possible for major prognostic indicators

Controlled trials: May be randomized or none randomized. The control may be no treatment control, placebo controlled (negative control) or conventional therapy control (positive control). Control may be:

1-Historical control:

Most common, Compares retrospectively one's current patients on the new treatment with previous patients who received standards treatment. It is subjected to bias because of the patient selection, experimental environment; inclusion criteria are not the same quality of recorded data of historical control will be poorer.

2- Self controlled

Patients act as their own control. All patients' characteristics affecting the outcome of interest are equalized i.e. before and after drug.

3-Cross - over trials:

When two or more interventions are to be compared in patients who act as their own control, they need to be exposed to each of the treatment; this requires them to be crossed over from one treatment to the next: It has the following steps:

- Randomization of patients to each treatment
- Measuring the effects

-Wash out period: enabling the effects of the 1st treatment to dissipate before testing the second treatment. After this period giving them the alternate treatment

-Another set of measurements. It is very powerful, avoids confounding, maximize likelihood of detecting treatment effect.

4- Concurrent control:

Randomization may be viewed that it is unethical if proven efficacy was known, to hold the treatment from a group of patients to be treated as control

RANDOMIZED CONTROLLED TRIALS (RCT)

It is the gold standard as it provides the most valid basis for the comparison of intervention in health care. It minimizes the bias and allows small but clinically significant difference in benefit and harm to be detected provided that the number is large enough. Allows relied inference about cause and effect provided that the number is large enough. It avoids: bias, over optimistic expectations of new therapy. It gives the patient 50% chance to receive the more effective treatment which one is valuable if the new therapy is expensive, so equal chance of each patient to receive it (FAIR) and also the potential of harm

Randomization:

Randomization is the usual method of allocating treatment to two or more groups of subjects in a clinical trial. "Random" does not mean haphazard. The randomization process is documented so that it is reproducible.

Requirements of RCT:

- 1-The primary measurement(s) should be clearly identified.
- 2-A clinically important treatment effect should be specified.
- 3-The treatment effect should be clearly indicated as being absolute or relative difference.
- 4-Statistical test and power to estimate sample size should be reported.

RANDOM ALLOCATION AND BLINDING

1- Simple design:

patients are randomly allocated to one of two groups (treatment and control) using random table or computer generated list. So, no systematic differences between control and intervention group in factors known or unknown that may affect the outcome.

Randomization is not necessarily 1:1. If the study group is large, so both groups will be similar in all aspects at the start of the trial (balance of those prognostic variables). Because randomization does not guarantee that the treatment groups will be identical in terms of baseline characteristics, stratification before randomization (e.g. by gender, age group, disease stage, or other prognostic factor) may be used as an additional means of ensuring balance in the treatment groups for known variables. Stratification is usually used when there is an important known prognostic factor, such as tumor stage, that can be measured before randomization. In smaller trials, it may be necessary to stratify according to several characteristics (minimization method).

Allocation can be done by:

-Date of birth, date of presentation: but can lead to unbalanced selective recruitment. Sequentially numbered sealed opaque envelop: potential of bias if envelop is opened, not used or lost.

-Ideally by random number tables (two groups: even number and odd number groups), computer allocation, central randomization (telephone link to a trial office), pharmacy, numbered or coded containers. Other methods such as shuffled cards, tossed coins, minimization.

Blindness or masking which may be:

- Single blindness : patients should remain unaware to which group treatment is given
- Double blindness : patients and trialist should remain unaware to which group treatment is given

➤ Triple blindness: outcome taken by an observer blind to the original treatment and allocation.

Partially Randomized Study (patient preference trial):

It allows patients with strong preference to receive their chosen treatment while the remainders are randomized (BIAS)

2- Zelen randomization method:

Half of the patients are randomized to the current standard therapy (no consent). The other half are randomized to the new treatment (consented). If patients decline to participate, then they simply go back to receive the current therapy.

3- cluster randomization trial:

Randomizing intact social groups or clusters to different intervention; Logistic and administrative convenience. Reduces the treatment contamination that is measured in individual outcomes.

CLINICAL STUDIES CATEGORIES

Phase I study: generally establish whether a treatment is safe and what is the dosage. Usually done in vitro or in animals before human study

Phase II study: studies the efficacy of treatment after safety studies in phase I

Phase III study: Compares effective treatments from phase II studies. A new drug or drug combination may be tested against one of proven efficacy.

Phase IV study: collect and compare data on established treatment.

Factorial trials: Allow the simultaneous analysis of any number of factors of interest. The simplest design is 2 X 2 factorial experiments, consider two factors (two different treatments); it can detect interaction between the two factors.

Early Stopping Rules:

During the clinical trial the treatment is halted if too many patients experience un acceptable or

unexpected toxicity or if the treatment is less or more effective than expected.

Placebo:

If the objective is to evaluate a new drug in comparison with no treatment, a placebo is used for the comparison group. A placebo is an inactive agent made to seem identical to the active agent in terms of appearance and mode of administration.

Sham surgery for clinical trials:

Comparing two groups, one has real surgery and the other has simulated surgery. Like placebo in medical trials usually done on animals.

Bias and confounding:

In a research study an observed difference between groups may be a result of:

1-Treatment effect: a true difference

2-Random variation: chance, or

3- A deficiency in research design which enables systematic difference to exist in the groups' characteristics, measurements, data collection or analysis: BIAS

BIAS:

Is systematic deviation from the truth?

Sources of bias:

1-Selection bias: improved outcome because one group is healthier or at low risk than the other.

2-Detection bias: measurement or observations in one group are not as significantly sought as in the other.

3-Observation bias: personal judgment as to whether an event occurred or not or determines its extent.

4-Reporting bias : Recall bias : where a person , group identity influence their likelihood of accurately reporting previous experience, symptom or outcome

5- Response bias: when patients enrollment in a trial differ from those in the population of interest.

6-Publication bias: where negative results are less likely to be submitted or accepted for publication.

As bias is systematic error, other clinical variable can lead to random error and can be eliminated by increasing the number of patients

How to reduce bias?

1-Randomization

2- Blinding

Confounding:

When baseline characteristics of the group being compared are unequally distributed and this also has an effect on the outcome of interest. In this situation it is difficult to attribute the difference in the outcome to the treatment effect.

Baseline characteristics = confounding variables = covariates

Such as age, risk factors can be eliminated by:

- a. Increasing the number of the patients
- b. Randomization
- c. Stratifying randomization
- d. Adjustment using multivariate statistical techniques.

Sample size:

Too small sample is one of the most common problems seen in clinical trials. Sample size goes hand-in-hand with power: if no difference between treatments is seen, it could be because there was not enough power to detect a true difference.

It is important scientifically and ethically to estimate sample size when planning a trial:

- 1- If a trial with negative results has insufficient power, a clinically important but statistically non significant effect is usually ignored or worse is taken to mean that the treatment under the study made no difference
- 2- Over sized trial make unnecessary cost and involve additional patients.
- 3- Vary small trial may be scientifically useless and hence unethical in its use of subjects and other resources.

Sample size calculation should be carried out before starting the study.

Non Compliance:

A commonly encountered complication in many clinical trials is that of treatment cross-over or noncompliance with assigned treatment. How should these patients be counted in the data analysis? Should they be discarded? Should they be included according to the treatment they actually received?

The preferred method of handling treatment cross-overs in such a study is to analyze the data according to the assigned treatment ("intention to treat analysis"). The reason for this principle is that crossover to unassigned treatments is not random. Patients may have varying reasons for opting for a particular treatment, and if the treatment selection is related to the study outcome, analysis according to treatment received would yield a biased estimate of treatment effect. Although the primary analysis always should be according to "intention to treat analysis", secondary analyses may be included to evaluate treatment effect in patients receiving the assigned treatment only. This may be appropriate in trials in which a relatively large proportion of patients do not receive the assigned treatment.

It is important in all clinical trials to try to minimize noncompliance with assigned treatments. It is imperative to monitor treatments in order to estimate the impact of noncompliance.

Loss to follow-up:

Loss to follow-up usually refers to loss of contact with a patient so that there is no opportunity to assess outcomes. A large proportion of participants lost to follow-up can invalidate the findings from a clinical trial.

Validity:

When a clinical trial is technically well-designed, is conducted properly, and analyzed correctly, it can be said that there is high internal validity. This means that the results are valid within the context of the clinical trial and any differences can be attributed to the treatment under investigation.

However, the objective of a trial is usually to generate inferences about the efficacy of a treatment among a larger group of similar patients. If we were investigating the effect of a new treatment on survival in disease X but in our clinical trial we were able to include only a very narrowly-defined group of patients with disease X (perhaps only in men over the age of 21 who attend a particular clinic), we might be concerned that the results are not applicable to the general population of patients with disease X (which might be 50% female, with many patients under 21 years of age).

By definition, all clinical trials populations are selected, as only those who agree to participate may be included. Therefore, the representativeness of the trial population should always be questioned. In general, the results of clinical trials that are valid may be said to be generalizable to other patients who meet the eligibility criteria for the trial.

Patient issues:

Is it ethical to randomize patients to treatment? Is it ethical NOT to randomize when a promising new treatment is available but has unknown efficacy? Can truly informed consent ever be obtained? When is the use of a placebo appropriate? Should treatment effects (beneficial and/or adverse) be monitored during the trial and how should interim results be used?

In many countries, research is not considered ethical unless it has been approved by an external review group charged with ensuring adherence to ethical standards (often referred to as an institutional review board or an ethics review committee). In most cases, participants must be informed about the nature of the trial as well as the potential risks and benefits of participating, and generally explicit consent for participation must be granted. The issue of when it is ethical to use a placebo (untreated group) for comparison is currently being debated.

In some cases, the interests of science conflict with those of community ethics. A case in point is the current requirement for gender and racial/ethnic

"representativeness" in clinical trials sponsored by the U.S. National Institutes of Health. These and many other ethical issues are inherent in the design and conduct of clinical trials. Discussions of these topics are available in the current literature and in many internet sites.

In brief as the clinical trials involves human, patient issues are of importance. In particular, any clinical trial must be passed by an ethical committee who judge that the trial does not contravene the Declaration of Helsinki. Informed patient consent must be obtained from each of the patient or from the legal guardian or parent if the patient is a minor before he or she is entered into the trial.

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