What is Scientific Research and How Can it be Done?

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Abstract

Scientific researches are studies that should be systematically planned before performing them. In this review, classification and description of scientific studies, planning stage randomisation and bias are explained.

Keywords: Scientific researches, clinic researches, randomisation

Research conducted for the purpose of contributing towards science by the systematic collection, interpretation and evaluation of data and that, too, in a planned manner is called scientific research: a researcher is the one who conducts this research. The results obtained from a small group through scientific studies are socialised, and new information is revealed with respect to diagnosis, treatment and reliability of applications. The purpose of this review is to provide information about the definition, classification and methodology of scientific research.

Before beginning the scientific research, the researcher should determine the subject, do planning and specify the methodology. In the Declaration of Helsinki, it is stated that 'the primary purpose of medical researches on volunteers is to understand the reasons, development and effects of diseases and develop protective, diagnostic and therapeutic interventions (method, operation and therapies). Even the best proven interventions should be evaluated continuously by investigations with regard to reliability, effectiveness, efficiency, accessibility and quality' (1).

The questions, methods of response to questions and difficulties in scientific research may vary, but the design and structure are generally the same (2).

Classification of Scientific Research

Scientific research can be classified in several ways. Classification can be made according to the data collection techniques based on causality, relationship with time and the medium through which they are applied.

1. According to data collection techniques:
   • Observational
   • Experimental
2. According to causality relationships:
   • Descriptive
   • Analytical
3. According to relationships with time:
   • Retrospective
   • Prospective
   • Cross-sectional
4. According to the medium through which they are applied:
   • Clinical
   • Laboratory
   • Social descriptive research (3)

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Another method is to classify the research according to its descriptive or analytical features. This review is written according to this classification method.

I.   Descriptive research
    a. Case series
    b. Surveillance studies

II. Analytical research
    a. Observational studies: cohort, case control and cross-sectional research
    b. Interventional research: quasi-experimental and clinical research

I. Descriptive Research: in this type of research, the participant examines the distribution of diseases according to their place and time in society. It includes case reports, case series and surveillance studies.

a. Case Report: it is the most common type of descriptive study. It is the examination of a single case having a different quality in the society, e.g. conducting general anaesthesia in a pregnant patient with mucopolysaccharidosis.

b. Case Series: it is the description of repetitive cases having common features. For instance; case series involving interscapular pain related to neuraxial labour analgesia. Interestingly, malignant hyperthermia cases are not accepted as case series since they are rarely seen during historical development.

c. Surveillance Studies: these are the results obtained from the databases that follow and record a health problem for a certain time, e.g. the surveillance of cross-infections during anaesthesia in the intensive care unit.

II. Analytical Scientific Research: the most important difference of this and the descriptive research is the presence of a comparison group. They are categorised as observational and interventional research.

a. Observational Research: the participants are grouped and evaluated according to a research plan or protocol. Observational research is more attractive than other studies: as necessary clinical data is available, coming to a conclusion is fast and they incur low costs (4). In observational studies, the factors and events examined by the researcher are not under the researcher's control. They cannot be changed when requested. All the variables, except for the examined factor or event, cannot be kept constant. Randomisation can be restrictedly used in some cases. It might not be always possible to apparently and completely detect a cause and effect relationship. The results are considerably similar to real-life situations since the events are examined as they are and special conditions are not created. Since the repetition of the observed cases is impossible most of the times, it may not be possible to recreate the same conditions (5).

Moreover, some studies may be experimental. After the researcher intervenes, the researcher waits for the result, observes and obtains data. Experimental studies are, more often, in the form of clinical trials or laboratory animal trials (2).

Analytical observational research can be classified as cohort, case-control and cross-sectional studies.

• Cohort Studies (Prospective, Retrospective and Ambidirectional): A cohort is a group formed by patients having common characteristics. A cohort study is the one in which a group of patients is followed-up in time, e.g. comparison of academic performances of children (who underwent anaesthesia in their neonatal period) in their adolescence.

Firstly, the participants are controlled with regard to the disease under investigation. Patients are excluded from the study. Healthy participants are evaluated with regard to the exposure to the effect. Then, the group (cohort) is followed-up for a sufficient period of time with respect to the occurrence of disease, and the progress of disease is studied. The risk of the healthy participants getting sick is considered an incident. In cohort studies, the risk of disease between the groups exposed and not exposed to the effect is calculated and rated. This rate is called *relative risk.* Relative risk indicates the strength of exposure to the effect on the disease.

Cohort research may be observational and experimental. The follow-up of patients prospectively is called a *prospective cohort study.* The results are obtained after the research starts. The researcher's following-up of cohort subjects from a certain point towards the past is called a *retrospective cohort study.* Prospective cohort studies are more valuable than retrospective cohort studies: this is because in the former, the researcher observes and records the data. The researcher plans the study before the research and determines what data will be used. On the other hand, in retrospective studies, the research is made on recorded data: no new data can be added.

In fact, retrospective and prospective studies are not observational. They determine the relationship between the date on which the researcher has begun the study and the disease development period. The most critical disadvantage of this type of research is that if the follow-up period is long, participants may leave the study at their own behest or due to physical conditions. Cohort studies that begin after exposure and before disease development are called *ambidirectional studies.* Public healthcare studies generally fall within this group, e.g. lung cancer development in smokers.

• Case-Control Studies: these studies are retrospective cohort studies. They examine the cause and effect relationship from the effect to the cause. The detection or determination of data depends on the information recorded in the past. The researcher has no control over the data (2).

• Cross-Sectional Studies: in cross- sectional studies, the patients or events are examined at a particular point in time.

Prevalence studies (the percentage of a population having a disease at a certain time) are the ones in which the diagnosis and disease mechanism are detected and the cause and effect relationship is examined at the same level.

Cross- sectional studies are advantageous since they can be concluded relatively quickly. It may be difficult to obtain a reliable result from such studies for rare diseases (2).

Cross-sectional studies are characterised by timing. In such studies, the exposure and result are simultaneously evaluated. While cross-sectional studies are restrictedly used in studies involving anaesthesia (since the process of exposure is limited), they can be used in studies conducted in intensive care units.

b. Interventional Research (Experimental Studies): in this type of research, there is a control group aimed to be tested. The researcher decides upon which effect the participant will be exposed to in this study. Post-intervention, the researcher waits for the result, observes and obtains the data. Interventional studies are divided into two: quasi-experimental and clinical research.

• **Quasi-Experimental Research:** they are conducted in cases in which a quick result is requested and the participants or research areas cannot be randomised, e.g. giving hand-wash training and comparing the frequency of nosocomial infections before and after hand wash.

• **Clinical Research:** they are prospective studies carried out with a control group for the purpose of comparing the effect and value of an intervention in a clinical case. Clinical study and research have the same meaning. Drugs, invasive interventions, medical devices and operations, diets, physical therapy and diagnostic tools are relevant in this context (6).

Clinical studies are conducted by a responsible researcher, generally a physician. In the research team, there may be other healthcare staff besides physicians. Clinical studies may be financed by healthcare institutes, drug companies, academic medical centres, volunteer groups, physicians, healthcare service providers and other individuals. They may be conducted in several places including hospitals, universities, physicians' offices and community clinics based on the researcher's requirements. The participants are made aware of the duration of the study before their inclusion. Clinical studies should include the evaluation of recommendations (drug, device and surgical) for the treatment of a disease, syndrome or a comparison of one or more applications; finding different ways for recognition of a disease or case and prevention of their recurrence (7).

Clinical Research

In this review, clinical research is explained in more detail since it is the most valuable study in scientific research.

Clinical research starts with forming a hypothesis. A hypothesis can be defined as a claim put forward about the value of a population parameter based on sampling. There are two types of hypotheses in statistics.

• H_0 hypothesis is called a control or null hypothesis. It is the hypothesis put forward in research, which implies that there is no difference between the groups under consideration. If this hypothesis is rejected at the end of the study, it indicates that a difference exists between the two treatments under consideration.

• H_1 hypothesis is called an alternative hypothesis. It is hypothesised against a null hypothesis, which implies that a difference exists between the groups under consideration. For example, consider the following hypothesis: drug A has an analgesic effect. Control or null hypothesis (H_0): there is no difference between drug A and placebo with regard to the analgesic effect. The alternative hypothesis (H_1) is applicable if a difference exists between drug A and placebo with regard to the analgesic effect.

The planning phase comes after the determination of a hypothesis. A clinical research plan is called a *protocol*. In a protocol, the reasons for research, number and qualities of participants, tests to be applied, study duration and what information to be gathered from the participants should be found and conformity criteria should be developed.

The selection of participant groups to be included in the study is important. Inclusion and exclusion criteria of the study for the participants should be determined. Inclusion criteria should be defined in the form of demographic characteristics (age, gender, etc.) of the participant group and the exclusion criteria as the diseases that may influence the study, age ranges, cases involving pregnancy and lactation, continuously used drugs and participants' cooperation.

The next stage is methodology. Methodology can be grouped under subheadings, namely, the calculation of number of subjects, blinding (masking), randomisation, selection of operation to be applied, use of placebo and criteria for stopping and changing the treatment.

I. Calculation of the Number of Subjects
The entire source from which the data are obtained is called a *universe or population*. A small group selected from a certain universe based on certain rules and which is accepted to highly represent the universe from which it is selected is called a *sample* and the characteristics of the population from which the data are collected are called *variables*. If data is collected from the entire population, such an instance is called a *parameter*. Conducting a study on the sample rather than the entire population is easier and less costly. Many factors influence the determination of the sample size. Firstly, the type of variable should be determined. Variables are classified as categorical (qualitative, non-numerical) or numerical

(quantitative). Individuals in categorical variables are classified according to their characteristics. Categorical variables are indicated as nominal and ordinal (ordered). In nominal variables, the application of a category depends on the researcher's preference. For instance, a female participant can be considered first and then the male participant, or vice versa. An ordinal (ordered) variable is ordered from small to large or vice versa (e.g. ordering obese patients based on their weights-from the lightest to the heaviest or vice versa). A categorical variable may have more than one characteristic: such variables are called binary or dichotomous (e.g. a participant may be both female and obese).

If the variable has numerical (quantitative) characteristics and these characteristics cannot be categorised, then it is called a numerical variable. Numerical variables are either discrete or continuous. For example, the number of operations with spinal anaesthesia represents a discrete variable. The haemoglobin value or height represents a continuous variable.

Statistical analyses that need to be employed depend on the type of variable. The determination of variables is necessary for selecting the statistical method as well as software in SPSS. While categorical variables are presented as numbers and percentages, numerical variables are represented using measures such as mean and standard deviation. It may be necessary to use mean in categorising some cases such as the following: even though the variable is categorical (qualitative, non-numerical) when Visual Analogue Scale (VAS) is used (since a numerical value is obtained), it is classified as a numerical variable: such variables are averaged.

Clinical research is carried out on the sample and generalised to the population. Accordingly, the number of samples should be correctly determined. Different sample size formulas are used on the basis of the statistical method to be used. When the sample size increases, error probability decreases. The sample size is calculated based on the primary hypothesis. The determination of a sample size before beginning the research specifies the power of the study. Power analysis enables the acquisition of realistic results in the research, and it is used for comparing two or more clinical research methods.

Because of the difference in the formulas used in calculating power analysis and number of samples for clinical research, it facilitates the use of computer programs for making calculations.

It is necessary to know certain parameters in order to calculate the number of samples by power analysis.

a. Type-I (α) and type-II (β) error levels

b. Difference between groups (d-difference) and effect size (ES)

c. Distribution ratio of groups

d. Direction of research hypothesis (H1)

a. Type-I (α) and Type-II (β) Error (β) Levels

Two types of errors can be made while accepting or rejecting H_0 hypothesis in a hypothesis test. Type-I error (α) level is the probability of finding a difference at the end of the research when there is no difference between the two applications. In other words, it is the rejection of the hypothesis when H_0 is actually correct and it is known as α error or p value. For instance, when the size is determined, type-I error level is accepted as 0.05 or 0.01.

Another error that can be made during a hypothesis test is a type-II error. It is the acceptance of a wrongly hypothesised H_0 hypothesis. In fact, it is the probability of failing to find a difference when there is a difference between the two applications. The power of a test is the ability of that test to find a difference that actually exists. Therefore, it is related to the type-II error level.

Since the type-II error risk is expressed as β, the power of the test is defined as $1-\beta$. When a type-II error is 0.20, the power of the test is 0.80. Type-I (α) and type-II (β) errors can be intentional. The reason to intentionally make such an error is the necessity to look at the events from the opposite perspective.

b. Difference between Groups and ES

ES is defined as the state in which statistical difference also has clinically significance: ES$\geq$0.5 is desirable. The difference between groups is the absolute difference between the groups compared in clinical research.

c. Allocation Ratio of Groups

The allocation ratio of groups is effective in determining the number of samples. If the number of samples is desired to be determined at the lowest level, the rate should be kept as 1/1.

d. Direction of Hypothesis (H1)

The direction of hypothesis in clinical research may be one-sided or two-sided. While one-sided hypotheses hypothesis test differences in the direction of size, two-sided hypotheses hypothesis test differences without direction. The power of the test in two-sided hypotheses is lower than one-sided hypotheses.

After these four variables are determined, they are entered in the appropriate computer program and the number of samples is calculated. Statistical packaged software programs such as Statistica, NCSS and G-Power may be used for power analysis and calculating the number of samples. When the samples size is calculated, if there is a decrease in α, difference between groups, ES and number of samples, then the standard deviation increases and power decreases. The power in two-sided hypothesis is lower. It is ethically appropriate to consider the determination of sample size, particularly in animal experiments, at the beginning of the study. The phase of the study is also important in the determination of number of subjects to be included in drug studies. Usually, phase-I stud-

ies are used to determine the safety profile of a drug or product, and they are generally conducted on a few healthy volunteers. If no unacceptable toxicity is detected during phase-I studies, phase-II studies may be carried out. Phase-II studies are proof-of-concept studies conducted on a larger number (100–500) of volunteer patients. When the effectiveness of the drug or product is evident in phase-II studies, phase-III studies can be initiated. These are randomised, double-blinded, placebo or standard treatment-controlled studies. Volunteer patients are periodically followed-up with respect to the effectiveness and side effects of the drug. It can generally last 1–4 years and is valuable during licensing and releasing the drug to the general market. Then, phase-IV studies begin in which long-term safety is investigated (indication, dose, mode of application, safety, effectiveness, etc.) on thousands of volunteer patients.

II. Blinding (Masking) and Randomisation Methods

When the methodology of clinical research is prepared, precautions should be taken to prevent taking sides. For this reason, techniques such as randomisation and blinding (masking) are used. Comparative studies are the most ideal ones in clinical research.

Blinding Method

A case in which the treatments applied to participants of clinical research should be kept unknown is called the *blinding method*. If the participant does not know what it receives, it is called a *single-blind* study; if even the researcher does not know, it is called a *double-blind* study. When there is a probability of knowing which drug is given in the order of application, when uninformed staff administers the drug, it is called *in-house blinding*. In case the study drug is known in its pharmaceutical form, a double-dummy blinding test is conducted. Intravenous drug is given to one group and a placebo tablet is given to the comparison group; then, the placebo tablet is given to the group that received the intravenous drug and intravenous drug in addition to placebo tablet is given to the comparison group. In this manner, each group receives both the intravenous and tablet forms of the drug. In case a third party interested in the study is involved and it also does not know about the drug (along with the statistician), it is called *third-party blinding*.

Randomisation Method

The selection of patients for the study groups should be random. Randomisation methods are used for such selection, which prevent conscious or unconscious manipulations in the selection of patients (8).

No factor pertaining to the patient should provide preference of one treatment to the other during randomisation. This characteristic is the most important difference separating randomised clinical studies from prospective and synchronous studies with experimental groups. Randomisation strengthens the study design and enables the determination of reliable scientific knowledge (2).

The easiest method is simple randomisation, e.g. determination of the type of anaesthesia to be administered to a patient by tossing a coin. In this method, when the number of samples is kept high, a balanced distribution is created. When the number of samples is low, there will be an imbalance between the groups. In this case, stratification and blocking have to be added to randomisation. Stratification is the classification of patients one or more times according to prognostic features determined by the researcher and blocking is the selection of a certain number of patients for each stratification process. The number of stratification processes should be determined at the beginning of the study.

As the number of stratification processes increases, performing the study and balancing the groups become difficult. For this reason, stratification characteristics and limitations should be effectively determined at the beginning of the study. It is not mandatory for the stratifications to have equal intervals. Despite all the precautions, an imbalance might occur between the groups before beginning the research. In such circumstances, post-stratification or restandardisation may be conducted according to the prognostic factors.

The main characteristic of applying blinding (masking) and randomisation is the prevention of bias. Therefore, it is worthwhile to comprehensively examine bias at this stage.

Bias and Chicanery

While conducting clinical research, errors can be introduced voluntarily or involuntarily at a number of stages, such as design, population selection, calculating the number of samples, non-compliance with study protocol, data entry and selection of statistical method. Bias is taking sides of individuals in line with their own decisions, views and ideological preferences (9). In order for an error to lead to bias, it has to be a systematic error. Systematic errors in controlled studies generally cause the results of one group to move in a different direction as compared to the other. It has to be understood that scientific research is generally prone to errors. However, random errors (or, in other words, 'the luck factor'-in which bias is unintended-do not lead to bias (10).

Another issue, which is different from bias, is chicanery. It is defined as voluntarily changing the interventions, results and data of patients in an unethical manner or copying data from other studies. Comparatively, bias may not be done consciously.

In case unexpected results or outliers are found while the study is analysed, if possible, such data should be re-included into the study since the complete exclusion of data from a study endangers its reliability. In such a case, evaluation needs to be made with and without outliers. It is insignificant if no difference is found. However, if there is a difference, the results with outliers are re-evaluated. If there is no error, then the outlier is included in the study (as the outlier may be a result). It should be noted that re-evaluation of data in anaesthesiology is not possible.

Statistical evaluation methods should be determined at the design stage so as not to encounter unexpected results in clinical research. The data should be evaluated before the end of the study and without entering into details in research that are time-consuming and involve several samples. This is called an *interim analysis*. The date of interim analysis should be determined at the beginning of the study. The purpose of making interim analysis is to prevent unnecessary cost and effort since it may be necessary to conclude the research after the interim analysis, e.g. studies in which there is no possibility to validate the hypothesis at the end or the occurrence of different side effects of the drug to be used. The accuracy of the hypothesis and number of samples are compared. Statistical significance levels in interim analysis are very important. If the data level is significant, the hypothesis is validated even if the result turns out to be insignificant after the date of the analysis.

Another important point to be considered is the necessity to conclude the participants' treatment within the period specified in the study protocol. When the result of the study is achieved earlier and unexpected situations develop, the treatment is concluded earlier. Moreover, the participant may quit the study at its own behest, may die or unpredictable situations (e.g. pregnancy) may develop. The participant can also quit the study whenever it wants, even if the study has not ended (7).

In case the results of a study are contrary to already known or expected results, the expected quality level of the study suggesting the contradiction may be higher than the studies supporting what is known in that subject. This type of bias is called *confirmation bias.* The presence of well-known mechanisms and logical inference from them may create problems in the evaluation of data. This is called *plausibility bias.*

Another type of bias is *expectation bias.* If a result different from the known results has been achieved and it is against the editor's will, it can be challenged. Bias may be introduced during the publication of studies, such as publishing only positive results, selection of study results in a way to support a view or prevention of their publication. Some editors may only publish research that extols only the positive results or results that they desire.

Bias may be introduced for advertisement or economic reasons. Economic pressure may be applied on the editor, particularly in the cases of studies involving drugs and new medical devices. This is called *commercial bias.*

In recent years, before beginning a study, it has been recommended to record it on the Web site *www.clinicaltrials.gov* for the purpose of facilitating systematic interpretation and analysis in scientific research, informing other researchers, preventing bias, provision of writing in a standard format, enhancing contribution of research results to the general literature and enabling early intervention of an institution for support. This Web site is a service of the US National Institutes of Health.

The last stage in the methodology of clinical studies is the selection of intervention to be conducted. Placebo use assumes an important place in interventions. In Latin, placebo means 'I will be fine'. In medical literature, it refers to substances that are not curative, do not have active ingredients and have various pharmaceutical forms. Although placebos do not have active drug characteristic, they have shown effective analgesic characteristics, particularly in algology applications; further, its use prevents bias in comparative studies. If a placebo has a positive impact on a participant, it is called the *placebo effect*; on the contrary, if it has a negative impact, it is called the *nocebo effect*. Another type of therapy that can be used in clinical research is *sham* application. Although a researcher does not cure the patient, the researcher may compare those who receive therapy and undergo sham. It has been seen that sham therapies also exhibit a placebo effect. In particular, sham therapies are used in acupuncture applications (11). While placebo is a substance, sham is a type of clinical application.

Ethically, the patient has to receive appropriate therapy. For this reason, if its use prevents effective treatment, it causes great problem with regard to patient health and legalities.

Before medical research is conducted with human subjects, predictable risks, drawbacks and benefits must be evaluated for individuals or groups participating in the study. Precautions must be taken for reducing the risk to a minimum level. The risks during the study should be followed, evaluated and recorded by the researcher (1).

After the methodology for a clinical study is determined, dealing with the 'Ethics Committee' forms the next stage. The purpose of the ethics committee is to protect the rights, safety and well-being of volunteers taking part in the clinical research, considering the scientific method and concerns of society. The ethics committee examines the studies presented in time, comprehensively and independently, with regard to ethics and science; in line with the Declaration of Helsinki and following national and international standards concerning 'Good Clinical Practice'. The method to be followed in the formation of the ethics committee should be developed without any kind of prejudice and to examine the applications with regard to ethics and science within the framework of the ethics committee, Regulation on Clinical Trials and Good Clinical Practice *(www.iku.com)*. The necessary documents to be presented to the ethics committee are research protocol, volunteer consent form, budget contract, Declaration of Helsinki, curriculum vitae of researchers, similar or explanatory literature samples, supporting institution approval certificate and patient follow-up form.

Only one sister/brother, mother, father, son/daughter and wife/husband can take charge in the same ethics committee. A rector, vice rector, dean, deputy dean, provincial healthcare director and chief physician cannot be members of the ethics committee.

Members of the ethics committee can work as researchers or coordinators in clinical research. However, during research meetings in which members of the ethics committee are researchers or coordinators, they must leave the session and they cannot sign-off on decisions. If the number of members in the ethics committee for a particular research is so high that it is impossible to take a decision, the clinical research is presented to another ethics committee in the same province. If there is no ethics committee in the same province, an ethics committee in the closest settlement is found.

Thereafter, researchers need to inform the participants using an informed consent form. This form should explain the content of clinical study, potential benefits of the study, alternatives and risks (if any). It should be easy, comprehensible, conforming to spelling rules and written in plain language understandable by the participant.

This form assists the participants in taking a decision regarding participation in the study. It should aim to protect the participants. The participant should be included in the study only after it signs the informed consent form; the participant can quit the study whenever required, even when the study has not ended (7).

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