I. Research Designs

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Clinical research takes care primarily of the study of groups of diseased individuals in order to establish a diagnosis, estimate a prognosis and start a treatment. With this purpose, it uses the scientific method from different points of view: architectural, which is divided in cause-effect and process studies; methodological, which includes clinical trials, cohort–case-control–studies and surveys; and by objectives, which comprised diagnostic test, prognosis and treatment studies, as well as risk factors or etiologic agent studies. These designs are considered to be primary, i.e., they use information obtained directly from the subject under study; however, there are other that use information from primary studies, which are known as secondary or integration designs.

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research
research projects
clinical trial

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Introduction

Clinical research, known as clinical epidemiology –a term that under the current sense was quoted by Alvan R. Feinstein (previously, it had been used by John R. Paul, to refer to what we currently know as social epidemiology and community-based medicine)– takes care of the study of groups of individuals in order to obtain decision-making evidence in patient care; i.e., it deals with the study of the structure and function of research performed in diseased subjects. However, sometimes it overlaps with classical epidemiology and studies the subject before the development of the disease. On the other hand, knowledge acquired in clinical epidemiology applies to the patient as an individual entity, whereas in most cases, knowledge obtained in classical epidemiology applies to a group of subjects.

The research method in clinical epidemiology is unique and it is consistent with the scientific method. However, for educational purposes, classifications have been made from different points of view, out of which three are the most common.

The first one, called *architectural*, is based on the most accurate description of the real event and includes cause-effect and process studies. The second one, known as *methodological*, is characterized for hierarchically categorizing the quality of the information obtained from the groups under study; it comprises clinical trials, cohort –case-control– studies and surveys. The third one uses the purpose it entails in everyday clinical practice and is known as *approach by objectives*; it is divided in diagnostic, prognostic, treatment and risk factors or causative agent (causality) studies.

Studies not considering a maneuver imposed by the investigator and that, therefore, are not experiments but observations, follow the principles of the scientific method and replace the experimental maneuver with a naturally-occurring or an imposed maneuver with purposes unrelated with the research.

Architectural Approach

When we talk about cause-effect studies, we refer to the change suffered in the subject's baseline state when receiving a maneuver, for example: when estimating, in a previously healthy patient (baseline state) who suffers a head injury (observational maneuver), the probability of dying or being left with sequels (outcome); or when assessing, in a patient with headache (baseline state), if a prescribed analgesic (maneuver) reduced the pain (outcome). This means that cause-effect studies not only include the search

for an etiologic agent or risk factor, but also for prognostic factors and even therapeutic actions. On the other hand, process studies assess the quality of procedures, either by comparing the procedure to be analyzed with a standard or with another execution of it; for example: to estimate the sensitivity and specificity of neck ultrasound (procedure under study) it is compared in patients with carotid obstruction (against carotid arteriography). In cases without gold standard, the study is compared with another execution of the same study assessing the same lesion by two radiologists in order to evaluate the coincidence beyond that expected by chance (Figures 1 and 2).

Methodological Approach

Based on the quality of the obtained information, the methodological approach attempts to hierarchically categorize the different designs in a way that it allows for deciding which study on the same matter is more reliable by being less likely to have biases present and, therefore, in which the decisions related with patients should be based.

It is important to consider that designs in lower hierarchical levels carried out adequately can outperform others with higher levels but poorly structured; furthermore, studies at lower hierarchical levels may be sufficient to answer a research question; moreover, not rarely, these are the only ones that can be performed.

In the description of the designs it is necessary taking into account four basic characteristics and the measurement of the outcome occurrence.

Basic Characteristics

1. Imposition or not of a maneuver with research purposes. A study is considered experimental if the maneuver was imposed by the investigator, and observational when such maneuver is natural (e.g., the presence of some disease) or imposed with purposes unrelated with the research (smoking, alcoholism, etc.).
2. Follow-up of the patient over time or not. A study is considered to be longitudinal when the patient is assessed in some of his/her characteristics of interest over time (more than once); in most cases, the change from baseline state to that of the result or outcome is referred, for example: follow-up of a group of physicians with no history of ischemic heart disease (baseline state) for five years and measurement of the onset of coronary heart disease during this period (outcome). The research is cross-sectional when the patient is assessed in a stationary manner (only on one occasion), for example: measurement of hypertension in a group of diabetic patients trying to find an association of lack of metabolic control with hypertension. While longitudinal studies allow for the assessment of different factors as sources of change from baseline to the subsequent state with certainty of the temporality of exposure to them, in transversal studies, often there is no certainty of a temporal relationship, even when associations are established between variables where which is the maneuver and which the outcome is artificially assumed.
3. Directionality in the collection of information. A study is prolective when the collection of information relates to the baseline state, as well as to the maneuver and the outcome. It is performed in real time with investigational purposes, i.e., simultaneously with the exposure to the maneuver and the occurrence of the outcome. It is retrolective when the information is obtained once the exposure to the maneuver and the outcome have occurred. It is possible for a study to be retro-prolective if at the moment at which the information is obtained the maneuver has already occurred, but not yet the

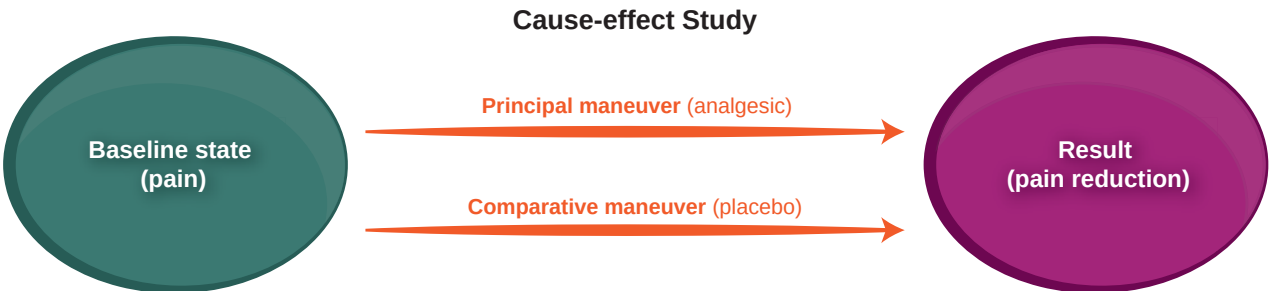

Figure 1 A cause-effect study seeks to establish the association between the maneuver and the change in the subject's baseline state, which generates a result. Three components must be considered: the subject's **baseline state**, **the principal maneuver** and **the outcome or result**; according to the question, the comparative maneuver may be necessary or not.

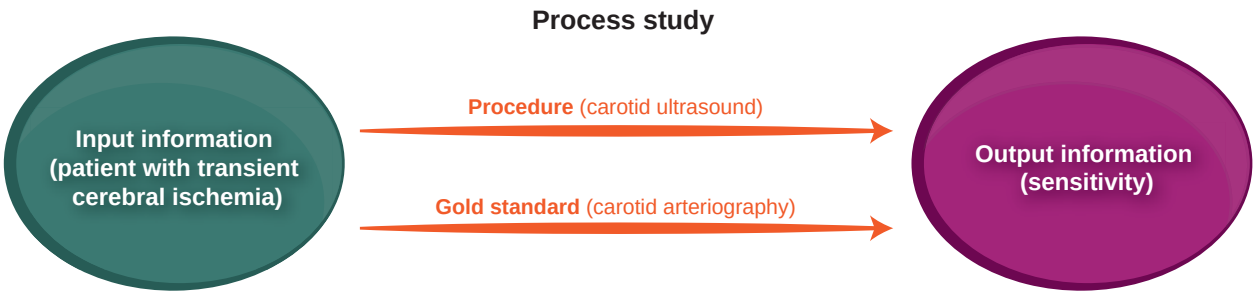

Figure 2 Process studies try to assess the reliability of the procedure, for which input information (substrate) is required, as well as the execution of a procedure to be compared with the gold standard or with other execution of the procedure, which yields as a result output information.

result, and therefore, its measurement is performed at the moment it occurs (Figure 3).

4. Search or not for an association between two variables. A study is descriptive when the purpose is to show the range of characteristics of the group under study. Frequently, the results of descriptive studies are used for comparative purposes; for example: when the prevalence of certain disease in a given population is compared with the prevalence of the same disease in a previously analyzed population. Conversely, a study is comparative when the association between the maneuver and the outcome or between a standard and the quality of a product or procedure (when it is a diagnostic study) is searched. An example of a comparative study is the search for association between obesity (natural maneuver) and insulin resistance (outcome), or when comparing an acute cholecystitis ultrasonographic diagnosis (procedure) with surgical findings (gold standard).

Measurement of Outcome Occurrence

Measurement of the outcome frequency can be performed in two ways according to the methodological design:

1. *Incidence (cumulative incidence)* refers to the number of new cases occurring in a certain period and population; it is characteristic of studies with follow-up, i.e., of cohorts (either observational or experimental). It can have different names: when mortality is studied and not the occurrence of a disease, it is known as mortality rate.
2. *Prevalence* or number of existing cases at a given moment in a given population; it is typical of cross-sectional studies, except for case-control studies.

The *case-control ratio* is not a way to measure the occurrence of the outcome but rather an artificially-created simple case-control relationship.

Basic Designs

Hierarchical order, assigned by the quality of the obtained information, places the *clinical trial* at first place, since it allows for information to be obtained directly and with control over the maneuver and, consequently, with the least amount of errors. It is followed by the cohort study, then the case-control study and, finally, the survey.

The *clinical trial* is characterized for being a prolective and longitudinal study, where the application of the maneuver (experimental) to which the change in the baseline state wants to be attributed to (comparative) is planned; a clinical trial is experimental when it has a comparative group, with randomization to the maneuver and blinded assessment of the outcome. However, sometimes there is no comparative group available, and baseline state is the characteristic that has to be compared with the result (*before-and-after study*), or randomization of the maneuver or a blinded assessment of it are impossible to perform, which defines the clinical trial as being *quasi-experimental*. The clinical trial can be defined as an experimental cohort, since it has all the characteristics of a cohort with allocation of the maneuver. Being a longitudinal study, it allows for the incidence to be estimated as a measure of occurrence of the disease.

The *cohort* is the ideal design among observational studies. It is characterized for having a group of subjects selected according to common characteristics at a given moment and that are followed over time in some of their characteristics (*longitudinal*), where the collection of information (*prolective*, *retrolective* or *retro-prolective*) may or may not coincide with the occurrence of the maneuver or the result, and in which the association between the maneuver and the result is always sought (*comparative*). Even when the design may be retrolective, a situation in which it is termed historical cohort, the direction goes from the cause (maneuver) to the effect (result). For example, a prognostic study can be conducted to find out which

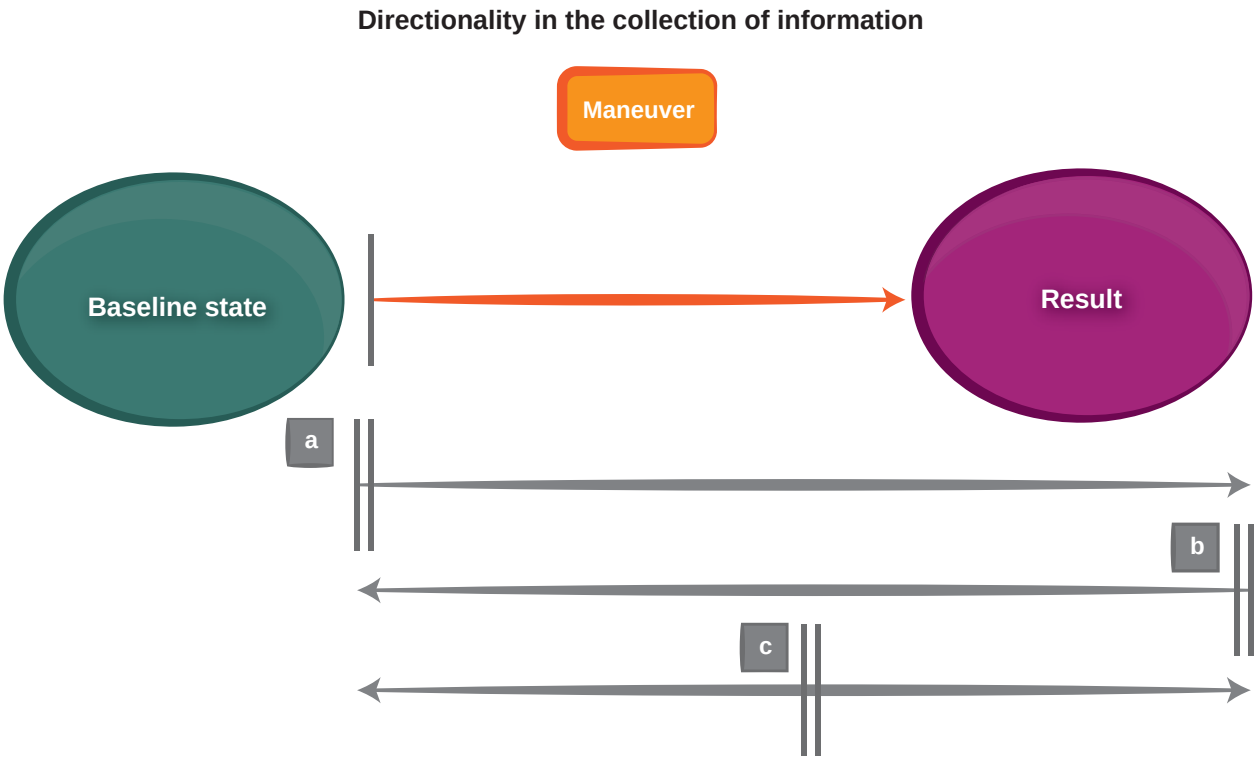

Figure 3 When the capture of information starts at baseline state before the maneuver and the result, the study is considered to be prolective (a); when the capture is carried out once the maneuver and the result have occurred, it is considered to be retrolective (b); and when the capture is performed once the maneuver has occurred but before the result, it is a retro-prolective study (c).

stroke patients will die within the first few days after the event, for which the information on the charts of all patients admitted to the hospital during the year preceding the study is reviewed; since the maneuver (characteristics present within the first hours of the stroke, known as prognostic indicators) and the result or outcome have already occurred (death within the first seven days of the event), it is a retrolective study; however, the analysis and capture of data should be done with all patients, starting with clinical manifestations present at admission and then measuring the outcome. Unlike case-control studies, which may cover these same characteristics, the cohort provides information of all the patients that suffered the stroke during the year and, therefore, the incidence of the outcome is available, whereas in case-control studies, the whole population is not available but rather an artificial rate of case-controls is used, as outlined below.

Conversely to the aforementioned designs, the case-control design is characterized for going from the effect to the cause. It starts with a group of subjects with the outcome of interest (*result*), which corresponds to the cases, and a witness group that did not suffer the outcome (*controls*) is selected; afterwards, the association between the maneuver and the outcome (*comparative*) is searched. Therefore, it is a *retrolective* and *observational* study. There is controversy regarding the follow-up of variables or not, with some authors considering this to be a cross-sectional study, since all the information is obtained at one time-point, whereas for others, it is *longitudinal* because a recapitulation of the maneuver temporality is feasible until the moment of the outcome. In this design, there is no outcome occurrence measurement; there is simply an artificially-created case control relation.

The *survey* is the simplest among observational designs but also the most limited in its assertions; it is carried out on a representative sample of the study population and the most common objective is outlining the population characteristics (*descriptive*); however, it can also be used to establish an association between two or more variables (*comparative*). Frequently, it is impossible to determine whether the maneuver precedes the outcome, since the gathering of information happens after both the maneuver and the outcome have occurred (retrolective) and at one single time (*transversal*). Unlike case-control studies, there is no predetermined ratio of the number of cases and controls; in fact, there is no selection of the population based on the outcome, but instead, once the population is selected (whatever the criteria are), exposure to the maneuver, which in this case is observational, and the

Table I Designs according to the methodological approach

Design	EXP/OBS	LONG/TRANS	PROL/RETROL	COMP/DESC	MEASURE
Clinical trial	Experimental	Observational	Prolective	Comparative	Incidence
Cohort	Observational	Longitudinal	Prol/Retrol/RP	Comparative	Incidence
Case-control	Observational	Long/Trans	Retrolective	Comparative	Prop. C-C
Survey	Observational	Transversal	Retrolective	C/D	Prevalence

The methodological approach considers four features: 1. Imposition or not of the maneuver for investigational purposes: experimental (EXP) or observational (OBS) study, respectively. 2. Patient follow-up (LONG) or not (TRANS) over time. 3. Directionality in the collection of information: prolective (PROL), retrolective (RETROL) and retro-prolective (RP). 4. Search or not of association between two or more variables: comparative (C) and descriptive (D), respectively. Measurement of outcome occurrence (MEASURE), either through incidence, prevalence, or simply the case-control ratio (C-C ratio)

outcome are measured. Therefore, the obtained result is the prevalence of the outcome.

Table I summarizes the distinctive characteristics of each design. It is worth mentioning that there are combinations of these designs and sometimes it is difficult defining them.

Approach by Objectives

The approach based on clinical practice is the one that we are more used to; furthermore, in it, it is possible to distinguish the largest difference between clinical epidemiology and classical epidemiology. In clinical epidemiology, which studies groups of patients, the primary objective is to solve an already existing problem in a group of people for which a diagnosis must be established (diagnostic study), a prognosis has to be estimated (prognostic studies) and a therapeutic maneuver has to be initiated (experimental or quasi-experimental clinical trial). However, as we mentioned earlier, it is common for clinical epidemiology to overlap with classical epidemiology and to address risk factors problems, such as cardiovascular disease (risk factors or etiologic agent study, the latter when the agent is single).

Complementary Studies

So far, we have mentioned only studies that use primary information; however, there is a group known as "integration studies," characterized by the pooling of data obtained in primary studies. These comprise four designs: review studies (meta-analyses and systematic reviews), clinical practice guidelines, decision analyses and economic analyses.

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